Sudhansu Chokroverty
Editor

Sleep Disorders Medicine

Basic Science, Technical Considerations and Clinical Aspects

Fourth Edition

Springer

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Preface

A spectacular progress in uncovering the mysteries of sleep took place in the twentieth century which is continuing in the twenty-first century. What once remained shrouded in mystery and in the realm of vivid imagination of writers, scholars, artists, philosophers, poets, and religious leaders is now finding its rightful place beyond the fantasy of dreamers in the real world of neuroscience. We now know a great deal about neurobiology of sleep and dream, but much remains to be solved. Why do we remain awake? What happens if we are sleep deprived? Why do we need sleep? These questions keep popping up without a satisfactory answer. Sleep is an indispensable state of human existence and is noted in all mammalian and non-mammalian including avian and reptilian species. We have learned a lot from the animal kingdom. We know that the newborn dolphins continue to swim immediately after birth along with mother dolphins (to protect the newborn), totally sleep deprived for weeks without any long-term adverse effects on the brain or the body. In contrast, sleep deprivation experiments of Rechtschaffen and co-workers in rats on a carousel ("the disk-over-water" technique) produced emaciated animals despite increased food intake but with eventual death. Later sleep deprivation experiments using different techniques failed to reproduce similar results. Of course, it is not possible to perform complete sleep deprivation experiments on humans. Another mysterious finding is unihemispheric sleep in dolphins, porpoise, and pilot whales. This is thought to represent adaptation to life in water. Do humans have similar asymmetric or unihemispheric sleep? There are indications from polysomnographic recordings of severe obstructive sleep apnea (OSA) patients with hypoxemia using sophisticated computerized coherence analysis that such interhemispheric slow wave sleep asymmetry is also present in human maximally during apneic arousals and REM sleep, probably related to some brain stress or some unknown physiological adaptive mechanism. Another notable feature is the coexistence of sleeping and waking brain regions in arousal parasomnias which is reminiscent of sleeping brain in one half and waking brain in the other half of the cetaceans. Another example of such similarity is simultaneous presence of local sleep and waking regions during normal human sleep.

Sleep has been described in all different ways by poets and writers.

"What is more gentle than a wind in summer?
...What is more tranquil than a musk-rose blowing?
...What, but thee Sleep? Soft closer of our eyes!
...Thee for enlivening all the cheerful eyes
That glance so brightly at the new sun-rise.

—John Keats, *"Sleep and Poetry"*

"Not poppy nor mandragora
Nor all the drowsy syrups of the world,
Shall ever medicine thee to that sweet sleep
Which thou owedst yesterday."

—William Shakespeare, *Othello*
Act iii, Scene 3

"Sleep…
The death of each day's life, sore labour's bath,
Balm of hurt minds, great nature's second course,
Chief nourisher in life's feast."

—William Shakespeare, *Macbeth*
Act ii, Scene 2

Famous novelists of the past centuries have on occasion given colorful descriptions of characters seemingly having symptoms of sleep disorders long before these entities entered into the scientific literature. A case in point is a description of narcolepsy-like symptoms in Edgar Allan Poe's "Premature Burial" (published in 1844, 36 years before Gelineau's introduction of the term narcolepsy in 1880). There are other examples: A description of sleep paralysis in the character "Ishmael" in Herman Melville's "Moby-Dick" published in 1851 (25 years before the use of the term "night palsy" by Weir Mitchell in 1876); a description of RBD-like symptoms in Don Quixote by Miguel Cervantes in "Man of La Mancha" published in 1605 (381 years before the clinical description of RBD in 1986); and William Shakespeare's description of sleep walking of Lady Macbeth around 1606 long before scientific studies to characterize this arousal parasomnia were performed in the twentieth century.

Despite electrifying progress in sleep research, the public and profession alike are still not sufficiently cognizant of the fact that "sleep attack" or sleep deprivation (especially when combined with alcohol) can be as lethal as a "heart attack" or "brain attack" (stroke).

Most of the sleep problems do not present acutely (but some may initiate acute and emergent events triggering as much drama as a heart attack or stroke; for example, there are reports of sudden cardiac arrhythmias or even sudden death associated with OSA and severe hypoxemia).

Unquestionably, considerable progress has been made in the last three to four decades encompassing basic science, technical, clinical, and therapeutic aspects of sleep medicine. Dedicated sleep scientists and clinicians, many organizations and foundations (regional, national, and international) should be credited for pushing the topic of sleep medicine forward. Sleep medicine is now recognized to be an independent specialty with its own training program. We are all dreaming and eagerly awaiting the day when sleep medicine will be considered an independent department with its own administrative, clinical, and research staff similar to other disciplines (e.g., departments of medicine, surgery, obgyn, and others).

Since the publication of the first edition in 1994, the second edition in 1999, and the third edition in 2009, many new advances have been made and hence the need for this fourth edition. There are 19 new chapters in this edition to address new advances (Chaps. 4, 9, 10, 12, 15, 16, 25, 31, 33, 35, 40, 42, 43, 49, 55, 56, 57, 58) including some topics (e.g., Chaps. 25, 33, and 36) which had not been addressed in depth in the last edition. I will highlight a few of these new chapters (numbers 10, 15, 16, 35, 43, 58). These are unique chapters and are highly relevant to the science and practice of sleep medicine, but unfortunately, not addressed adequately in most of the available standard textbooks of sleep medicine. There are considerable similarities and differences between altered consciousness induced by anesthetic agents and sleep, and sleep clinicians and scientists must be aware of these facts (Chap. 10). Anyone involved in clinical trial must have some basic knowledge about statistical principles, and hence, a new chapter (no. 15) is devoted to this topic, outlining the principles in a lucid and easily comprehensible manner. A sleep clinician involved in interpretation and recording of polysomnographic and other technical recordings should have some fundamental knowledge about instrumentation and signal analysis (Chap. 16) to appreciate the fallacies and pitfalls of such recordings. Occult sleep disordered breathing (SDB) may pose imminent danger to any patient about to undergo a surgical procedure. It is, therefore, important to be aware of the presence of SDB in the preoperative, perioperative, and postoperative periods (Chap. 35). Another important topic for sleep clinicians and scientists to understand is the difference among sleep, coma, and vegetative and minimally conscious states, but again these topics are

not addressed in the standard textbooks of sleep medicine. I am fortunate and grateful to have the world's leading expert, Dr. Steven Laureys, addressing these subjects as the lead author (Chap. 43). Complementary and alternative medicine (CAM; Chaps. 56 and 57) is increasingly becoming popular although valid scientific data after randomized control trials (RCTs) are not available for most of the CAM therapies. Finally, a fascinating topic (Chap. 58) is sleep in extreme environment (e.g., space travel) for which we have some limited data but which, I believe, will be a hot topic in future sleep medicine. Chap. 40 dealing with evaluation and management of PLMS and RLS written by a leading authority on these topics is a new chapter in this edition but was included in the chapter on "Motor function and dysfunction of sleep" by Wayne Henning as the lead author in the third edition. The other three new chapters in this edition address Phylogeny of Sleep (Chap. 9), Sleep and Immune Regulation (Chap. 12), and Fatigue in Clinical Practice (Chap. 42). The chapter on the phylogeny of sleep is important to understand evolution of sleep from inframammalian to mammalian species which may help understand the function of and need for sleep. The role of sleep in immune regulation and fatigue, noted in many neurological and other conditions, and often mistaken for sleep or secondary to sleep deprivation is included in two new chapters in this edition. REM behavior disorder (RBD) is addressed as part of parasomnia chapter (no. 50), but in this edition, I have also included RBD as a separate chapter (no. 49) because of its increasing recognition as a forerunner to a neurodegenerative disease and the exciting possibilities of finding a biomarker for this. New authors and co-authors have been invited for several chapters (number 1, 4, 5, 6, 7, 8, 13, 14, 18, 23, 24, 28, 32, 34, 38, 39, 41, 44, and 54). Clifford Saper, a leading neuroscientist and researcher in basic science of sleep, replaced William Dement in writing the introductory chapter (no. 1). For the circadian timing and sleep–wake regulation chapter (6), Philip Boudreau and co-authors replaced Robert Y. Moore. For Chap. 14 (Dreaming and Sleep Disorder), James. F. Pagel and Seithikurippu R. Pandi-Perumal replaced Rosalind Cartwright.

The basic layout of the fourth edition remains same as in the third edition, dividing the book into three major sections: basic science, technical considerations, and clinical aspects. However, because of increased size of this edition to conform to the policy of Springer, the fourth edition of the book is published in two volumes (volume one dealing with basic science and technical aspects and volume two dealing with clinical consideration). As in the third edition, the purpose of this edition remains the same, namely to provide a comprehensive text for both the beginners and seasoned practitioners of sleep medicine. Hence, the book is directed at neurologists, internists (especially those specializing in pulmonary, cardiovascular, gastrointestinal, and renal and endocrine medicine), family physicians, pediatricians, psychiatrists, psychologists, otolaryngologists, dentists, neurosurgeons, neuroscientists, and intensivists, as well as those interested in advancing their knowledge in sleep and its disorders (e.g., technologists, nurses, and other healthcare professionals).

I end this preface by announcing with heavy heart and profound sadness the death of three giants in contemporary sleep medicine since the publication of the third edition, Professor Elio Lugaresi, Professor Pasquale Montagna, and Professor Arthur Spielman. These three distinguished scholars made robust scientific contributions in sleep medicine and sleep science. Their scholarly contributions left indelible marks in the scientific world. I dedicate this book to these three gentlemen and scholars. Their memory will remain forever with us. They are not physically present today, but their souls are indestructible, unvanquished, and eternal. May they rest in peace. We shall never forget what they have done as living mortals to promote sleep science.

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Sudhansu Chokroverty

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Part I
Basic Science of Sleep

Introduction to the Topic

1

Clifford B. Saper

While sleep occupies almost a third of our lives (and half or more of the lives of many animals), the processes that go on in the brain during sleep remain mysterious and in the realm of basic investigation. On the other hand, we have made enormous strides in recent years in identifying the cellular basis that underlies many of the phenomena of sleep and circadian rhythms, and in the process are beginning to frame some cogent ideas about the ultimate function of sleep. The chapters that follow in this section provide a detailed look at the basic science of sleep, from the perspectives of anatomy, physiology, pharmacology, and behavior.

Our understanding of the basic brain circuitry that regulates sleep and wakefulness has advanced considerably in recent years and continues to grow as this work remains at the cutting edge of the field [1, 2]. Although the outlines of the classic cholinergic and monoaminergic wake-promoting systems have been known since the 1980s, studies that have placed lesions in these pathways have demonstrated disappointingly little effect on amounts of baseline wake–sleep [3–5]. Recent studies have uncovered additional components of the ascending arousal system, including the parabrachial nucleus [6] and portions of the basal ganglia [7, 8], that have augmented our understanding of it and have added new pieces to the puzzle.

Similarly, our understanding of the sleep-promoting circuitry of the brain has progressed enormously in recent years. In addition to the contribution of the ventrolateral preoptic nucleus to causing sleep [2], evidence has emerged for the role of the median preoptic nucleus in accumulating sleep need [9]. Other neurons in the nucleus accumbens and in the parafacial zone in the medulla have been described [8, 10, 11], which also appear to promote sleep. Sleep-active neurons that are putatively inhibitory have been identified in the cerebral cortex [12] as well as the melanin-concentrating hormone cell group in the lateral hypothalamus [13, 14]. Their respective roles in sleep promotion are only now being explored.

There have also been major gains in our understanding of both the homeostatic and circadian regulation of sleep. Studies have uncovered the role of adenosine in causing sleepiness [15] and have identified the site in the nucleus accumbens at which caffeine acts on A2A receptors to combat sleepiness [11]. The immune interactions with sleep promotion have also been studied, identifying the role for prostaglandin D2 as a somnogen [16]. At the same time, the pathways have been worked out by which the suprachiasmatic nucleus influences wake–sleep cycles [17].

In addition to understanding the basic neuronal mechanisms that regulate sleep–wake, there has been substantial progress in understanding the interactions between sleep and a myriad of other physiological processes that it affects. These range from interactions with basic physiological systems, such as autonomic, respiratory, and immune systems [18, 19], to the effect of sleep fragmentation or loss on cognitive processes, ranging from attention to memory [20]. In particular, there is an emerging consensus that loss of specific stages of sleep may impair specific types of memory formation [21]. Understanding the cellular mechanisms that underlie this vulnerability will be critical to determining the biological function of sleep.

Finally, as our understanding of sleep neuroscience has broadened, we have come to understand how disruption of this delicate physiological mechanism can produce the range of sleep disorders that we see as clinicians. For example, the effects of stress-induced insomnia on wake–sleep circuitry support insomnia being a distinct state, neither wake nor sleep, with activation of both sleep-promoting and limbic and arousal systems at the same time [22, 23]. Our knowledge about the mechanisms of atonia during REM sleep has illuminated our understanding of both cataplexy and REM behavior disorder [24, 25]. In patients with sleep apnea, we

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are beginning to understand the arousal mechanisms that lead to frequent arousals [26], and how these interact with the control of the upper airway muscles that are necessary for ventilation.

Our ultimate goal as sleep clinicians is to improve the lot of our patients. As we better understand the diseases we treat, we are able to come up with novel therapies that are informed by the underlying pathophysiology. For example, the current development of orexin antagonists as sleep-promoting drugs is based upon our understanding of the biology of orexins and their contribution to maintaining wakefulness [27]. Conversely, the development of H3 antagonists as wake-promoting drugs depends upon our understanding of the histamine arousal system and its pharmacology [28].

The ideal situation in basic science is for our most basic observations to inform our bedside diagnosis and treatment abilities and to carry back information from the bedside that stirs the next generation of basic science questions. This has certainly been the case in the sleep field, as the chapters that follow in this basic science section demonstrate, and the ones in succeeding in the clinical sections emphasize.

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Overview of Normal Sleep

2

Sudhansu Chokroverty

Historical Perspective

The history of sleep medicine and sleep research is a history of remarkable progress and remarkable ignorance. In the 1940s and 1950s, sleep had been in the forefront of neuroscience, and then again in the late 1990s, there has been a resurgence of our understanding of the neurobiology of sleep. Sleeping and waking brain cycles can now be studied by sophisticated neuroimaging techniques which have shown remarkable progress by mapping different areas of the brain during sleep states and stages. Electrophysiological research has shown that even a single neuron sleeps as evidenced by the electrophysiological correlates of sleep–waking at the cellular (single cell) level. Despite recent progress, we are still groping for answers to two fundamental questions: What is sleep? and why do we sleep? Sleep is not simply an absence of wakefulness and perception nor is it just a suspension of sensorial processes but is a result of a combination of a passive withdrawal of afferent stimuli to the brain and functional activation of certain neurons in selective brain areas. The more important question, however, is "How do we stay awake?" In the mother's womb, we were all asleep, and we wake up the moment we are born. But even in the newborn, sleep occupies 16 out of 24 h. Therefore, the fundamental inquiry should be directed at the mechanism of wakefulness.

Since the dawn of civilization, the mysteries of sleep have intrigued poets, artists, philosophers, and mythologists. The fascination with sleep is reflected in the literature, folklore, religion, and medicine. *Upanishad* [1, 2] (circa 1000 B.C.), the ancient Indian textbook of philosophy, sought to divide human existence into four states: the waking, the dreaming, the deep dreamless sleep, and the superconscious ("the very self"). This is reminiscent of modern classification of three states of existence (see later). One finds the description of pathologic sleepiness (possibly a case of Kleine–Levin syndrome) in the mythologic character Kumbhakarna in the great Indian epic *Ramayana* [3, 4] (circa 1000 B.C.). Kumbhakarna would sleep for months at a time, then get up to eat and drink voraciously before falling asleep again (Fig. 2.1). The ancient Chinese believed in two basic principles of life: *yang*, the active, light, and positive; and *yin,* the passive, dark, and negative. The *yin–yang* concept, originated with *Fu Hsi* (circa 2900 B.C.), has since become a symbol for sleep and wakefulness [5].

Throughout the literature, a close relationship between sleep and death has been perceived, but the rapid reversibility of sleep episodes differentiates sleep from coma and death. There are myriad references to sleep, death, and dream in poetic and religious writings, including the following quotations: "The deepest sleep resembles death" (*The Bible*, I Samuel 26:12); "sleep and death are similar … sleep is one-sixtieth [i.e., one piece] of death" (*The Talmud*, Berachoth 576); "There she [Aphrodite] met sleep, the brother of death" (Homer's *Iliad*, circa 700 B.C.); "To sleep perchance to dream … For in that sleep of death what dreams may come?" (Shakespeare's *Hamlet*); "How wonderful is death; Death and his brother sleep" (Shelly's "Queen Mab").

The 3 major behavioral states in human—wakefulness, non-rapid eye movement (NREM), and rapid eye movement (REM) sleep—are three basic biological processes that have independent functions and controls. The reader should consult Borbely's monograph *Secrets of Sleep* [2] for an interesting historical introduction to sleep.

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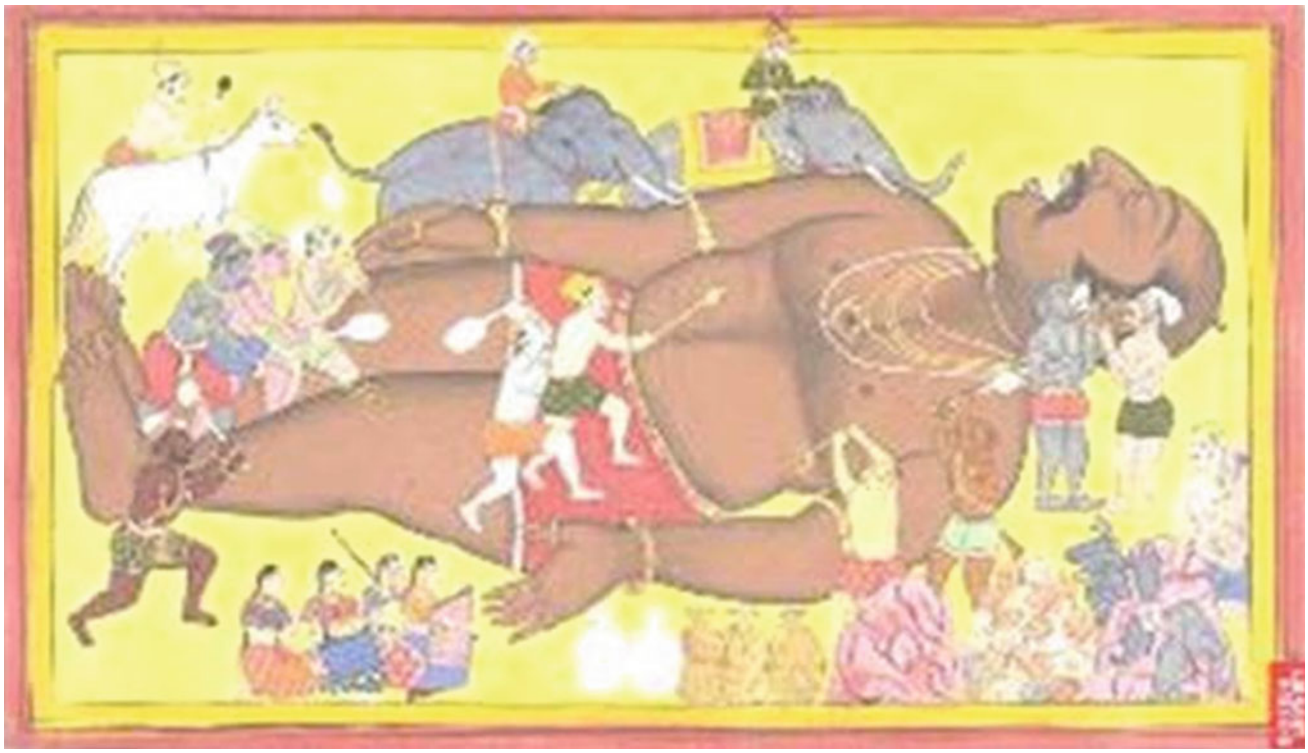

Fig. 2.1 Waking up of the giant Kumbhakarna, brother of Ravana in the great Indian epic Ramayana (circa 1000 B.C.) by hitting him with weapons and clubs, and shouting in his ear. This is a historical example of pathologic sleepiness resembling contemporary Kleine-Levin syndrome

What is the origin of sleep? The words *sleep* and *somnolence* are derived from the Latin word somnus; the German words *sleps*, *slaf*, or *schlaf*; and the Greek word *hypnos*. Hippocrates, the father of medicine, postulated a humoral mechanism for sleep and asserted that sleep was caused by the retreat of blood and warmth into the inner regions of the body, whereas the Greek philosopher Aristotle thought sleep was related to food, which generates heat and causes sleepiness. Paracelsus, a sixteenth-century physician, wrote that "natural" sleep lasted 6 h, eliminating tiredness and refreshing the sleeper. He also suggested that people not sleep too much or too little, but awake when the sun rises and go to bed at sunset. This advice from Paracelsus is strikingly similar to modern thinking about sleep. Views about sleep in the seventeenth and eighteenth centuries were expressed by Alexander Stuart, the British physician and physiologist, and by the Swiss physician, Albrecht von Haller. According to Stuart, sleep was due to a deficit of the "animal spirits"; von Haller wrote that the flow of the "spirits" to the nerves was cut off by the thickened blood in the heart, resulting in sleep. Nineteenth-century scientists used principles of physiology and chemistry to explain sleep. Both Humboldt and Pfluger thought that sleep resulted from a reduction or lack of oxygen in the brain [2].

Ideas about sleep were not based on solid scientific experiments until the twentieth century. Ishimori [6] in 1909, and Legendre and Pieron [7] in 1913, observed sleep-promoting substances in the cerebrospinal fluid of animals during prolonged wakefulness. The discovery of the EEG waves in dogs by the English physician Caton [8] in 1875 and of the alpha waves from the surface of the human brain by the German physician Berger [9] in 1929 provided the framework for contemporary sleep research. It is interesting to note that Kohlschutter, a nineteenth-century German physiologist, thought sleep was deepest in the first few hours and became lighter as time went on [2]. Modern sleep laboratory studies have generally confirmed these observations.

The golden age of sleep research began in 1937 with the discovery by American physiologist Loomis et al. [10] of different stages of sleep reflected in EEG changes. Aserinsky and Kleitman's [11] discovery of REM sleep in the 1950s at the University of Chicago electrified the scientific community and propelled sleep research to the forefront. Observations of muscle atonia in cats by Jouvet and Michel in 1959 [12] and in human laryngeal muscles by Berger in 1960 [13] completed the discovery of all major components of REM sleep. Following this, Rechtschaffen and Kales produced the standard sleep scoring technique monograph in 1968 (R–K

scoring technique) [14] which remained the gold standard until now. Recently, the American Academy of Sleep Medicine (AASM) published the AASM manual for the scoring of sleep and associated events [15] which modified the R–K technique and extended the scoring rules. The other significant milestone in the history of sleep medicine was the discovery of the site of obstruction in the upper airway in obstructive sleep apnea syndrome (OSAS) independently by Gastaut et al. [16] in France as well as Jung and Kuhlo [17] in Germany in 1965, followed by the polygraphic observations in the same year by Lugaresi et al. [18] of obstructive central and mixed apnea in these patients associated with periodic fall of blood pressure (BP) during apnea and rise above the baseline on resumption of breathing. The next milestone was the demonstration of dramatic relief of symptoms in these patients following tracheostomy (which bypasses the upper airway obstruction) by Kuhlo et al. [19]. In 1969 in a brief polygraphic report, Chokroverty et al. [20] made two important observations in patients with obesity hypoventilation syndrome (Pickwickian syndrome): Oxygen inhalation produced more prolonged and frequent episodes of apneas–hypopneas indicating the importance of peripheral chemoreceptor-driven hypoxemia causing respiratory stimulation and arousal in the presence of chronic daytime hypercapnia (these findings were later confirmed by other investigators [21]); the other observation is that following weight loss of 100–150-pound patients' symptoms improved, daytime arterial carbon dioxide normalized but apneas–hypopneas persisted, though these were less frequent than before weight loss. Subsequently, numerous papers were published by Guilleminault et al. [22] who coined the term *sleep apnea syndrome*. Then came the seminal paper by Sullivan and associates in 1981 [23] of continuous positive airway pressure (CPAP) titration to eliminate such obstruction as the standard treatment modality for moderate-to-severe OSAS. Finally, identification of 2 neuropeptides, hypocretin 1 and 2 (orexin A and B) in the lateral hypothalamus and perifornical regions [24, 25] followed by an animal model of a human narcolepsy phenotype in dogs by mutation of hypocretin 2 receptors ($HCTR_2$) by Lin et al. [26], the creation of similar phenotype in pre-prohypocretin knockout mice [27] and transgenic mice, [28] documentation of decreased hypocretin 1 in the cerebrospinal fluid in humans, [29] and decreased hypocretin neurons in the hypothalamus at autopsy [30, 31] in human narcolepsy patients opened a new and exciting era of sleep research.

Definition of Sleep

Sleep is "…great nature's second course, chief nourisher in life's feast" (Wm. Shakespeare).

The definition of sleep and a description of its functions have always baffled scientists. Moruzzi [32] while describing the historical development of the deafferentation hypothesis of sleep quoted the concept Lucretius articulated 2000 years ago—that sleep is the *absence of wakefulness*. A variation of the same concept was expressed by Hartley [33] in 1749, and again in 1830 by Macnish [34] who defined sleep as *suspension of sensorial power*, in which the voluntary functions are in abeyance, but the involuntary powers, such as circulation or respiration, remain intact. It is easy to comprehend what sleep is if one asks oneself that question as one is trying to get to sleep. Human sleep can be defined as an altered state in which there is impaired conscious awareness of the external world with different controls, rhythms, emotions, and dreams. It is a transient natural, periodic, physiologic phenomenon which is reversible, thus differentiating it from irreversible coma and death. Consciousness requires two components: awareness (function of cerebral cortex) and arousal (function of ascending reticular activating system). Sleep differs from unconscious state or coma (a pathological state) in the following manner: Sleep besides being a reversible physiological state also shows differences from coma in terms of brain metabolism and circulation which show marked depression and impairment in coma but slight alterations in sleep. Persistent vegetative state, minimally conscious state, and coma are distinctly different from sleep state although superficially may resemble those other states (see Chap. 43). Modern sleep researchers define sleep on the basis of both behavior of the person while asleep and the related physiologic changes that occur to the waking brain's electrical rhythm in sleep [35–38]. The behavioral criteria (Table 2.1) include lack of mobility or slight mobility, closed eyes, a characteristic species-specific sleeping posture, reduced response to external stimulation, quiescence, increased reaction time, elevated arousal threshold, impaired cognitive function, and a reversible unconscious state. Sleep is an active anabolic state (e.g., promoting growth, stimulating immune system) and is observed in all mammals, birds, reptiles, amphibians, and fish. The physiologic criteria (see Sleep Architecture and Sleep Profile) based on the findings from electroencephalography (EEG), electrooculography (EOG), and electromyography (EMG) as well as other physiological changes in ventilation and circulation. While trying to define the process of falling asleep, we must differentiate sleepiness from fatigue or tiredness. Fatigue (see also Chap. 41) can be defined as a state of sustained lack of energy coupled with a lack of motivation and drive but does not require the behavioral criteria of sleepiness such as heaviness and drooping of the eyelids, sagging or nodding of the head, yawning, and an ability to nap given the opportunity to fall asleep. On the other hand, fatigue is often a secondary consequence of sleepiness.

Table 2.1 Behavioral criteria of wakefulness and sleep

Criteria	Awake	Non-rapid eye movement sleep	Rapid eye movement sleep
Posture	Erect, sitting, or recumbent	Recumbent	Recumbent
Mobility	Normal	Slightly reduced or immobile; postural shifts	Moderately reduced or immobile; myoclonic jerks
Response to stimulation	Normal	Mildly to moderately reduced	Moderately reduced to no response
Level of alertness	Alert	Unconscious but reversible	Unconscious but reversible
Eyelids	Open	Closed	Closed
Eye movements	Waking eye movements	Slow rolling eye movements	Rapid eye movements

The Moment of Sleep Onset and Offset

There is no exact moment of sleep onset—there are gradual changes in many behavioral and physiological characteristics including EEG rhythms, cognition, and mental processing including reaction time. Sleepiness begins at sleep onset even before reaching stage 1 NREM sleep (as defined later) with heaviness and drooping of the eyelids; clouding of the sensorium; and inability to see, hear, or perceive things in a rational or logical manner. At this point, an individual trying to get to sleep is now entering into another world in which the person has no control and the brain cannot respond logically and adequately. This is the stage coined by McDonald Critchley as the "Pre-Dormitum" [39] who also mentioned that Gowers used "sleepening" for this stage, and this is opposite of "awakening." Slow rolling eye movements (SEMs) begin at sleep onset and continue through stage 1 NREM sleep. At sleep onset, there is a progressive decline in thinking process, and sometimes there may be hypnagogic imagery and hypnic myoclonus [40].

Similar to sleep onset, the moment of awakening or sleep offset (post-dormitum) is also a gradual process from the fully established sleep stages. This period is sometimes described as manifesting sleep inertia or sleep drunkenness. There is a gradual return to a state of alertness or wakefulness.

Sleep Architecture and Sleep Profile

Based on three physiologic measurements (EEG, EOG, and EMG), sleep is divided into two states [41] with independent functions and controls: NREM sleep and REM sleep. Table 2.2 lists the physiologic criteria of wakefulness and sleep and Table 2.3 summaries NREM and REM sleep states. In an ideal situation (which may not be seen in all

Table 2.2 Physiologic criteria of wakefulness and sleep

Criteria	Awake	Non-rapid eye movement sleep	Rapid eye movement sleep
Electroencephalography	Alpha waves; desynchronized	Synchronized	Theta or saw tooth waves; desynchronized
Electromyography (muscle tone)	Normal	Mildly reduced	Moderately to severely reduced or absent
Electrooculography	Waking eye movements	Slow rolling eye movements	Rapid eye movements

Table 2.3 Summary of non-rapid eye movement and rapid eye movement sleep states

Sleep state	Sleep time (%)
NREM sleep	75–80
N1	3–8
N2	45–55
N3	15–23
REM sleep	20–25
Tonic stage	–
Phasic stage	–

NREM Non-rapid eye movement; *REM* Rapid eye movement

normal individuals), NREM and REM alternate in a cyclic manner, each cycle lasting on an average from 90 to 110 mins. During a normal sleep period in adults, 4–6 such cycles are noted. The first two cycles are dominated by slow-wave sleep (SWS) (R–K stages 3 and 4 NREM and AASM stage N3 sleep); subsequent cycles contain less SWS, and sometimes SWS does not occur at all. In contrast, the REM sleep cycle increases from the first to the last cycle, and the longest REM sleep episode toward the end of the night may last for an hour. Thus, in human adult sleep, the first third is dominated by the SWS and the last third is dominated by REM sleep. It is important to be aware of these facts because certain abnormal motor activities are characteristically associated with SWS and REM sleep.

Non-rapid Eye Movement (NREM) Sleep—NREM sleep accounts for 75–80 % of sleep time in an adult human. According to R–K scoring manual, [14] NREM sleep is further divided into four stages (stages 1–4), and according to the recent AASM scoring manual, [15] this is subdivided into three stages (N1, N2, and N3), primarily on the basis of EEG criteria. Stage 1 NREM (N1) sleep occupies 3–8 % of sleep time; stage 2 (N2) comprises 45–55 % of sleep time; and stage N3 or SWS makes up 15–23 % of total sleep time. The dominant rhythm during adult human wakefulness consists of the alpha rhythm (8–13 Hz) noted predominantly in the posterior region intermixed with small amount of beta rhythm (>13 Hz) seen mainly in the anterior head regions (Fig. 24.1). This state called stage W may be accompanied by conjugate waking eye movements (WEMs) which may comprise vertical, horizontal, oblique, slow, or fast eye movements. In stage 1 NREM sleep (stage N1), alpha rhythm diminishes to less than 50 % in an epoch (i.e., a 30-second segment of the polysomnographic tracing with the monitor screen speed of 10 mm/s) intermixed with slower theta rhythms (4–7 Hz) and beta waves (Fig. 24.2). Electromyographic activity decreases slightly, and slow eye movements (SEMs) appear. Toward the end of this stage, vertex sharp waves are noted. Stage 2 NREM (stage N2) begins after approximately 10–12 min of stage 1. Sleep spindles (11–16 Hz, mostly 12–14 Hz) and K-complexes intermixed with vertex sharp waves herald the onset of stage N2 sleep (Fig. 24.3). Sleep spindles could be divided into two types: fast spindles (13–15 Hz) seen predominantly in the centroparietal region and slow spindles (11 ≤ 13 Hz) seen mostly in the frontal region. EEG at this stage also shows theta waves and slow waves (0.5–2 Hz) that occupy less than 20 % of the epoch. After about 30–60 mins of stage 2 NREM sleep (stage N2), stage 3 sleep begins and slow waves comprise 20–100 % of the epoch (Fig. 24.4). As stated above, R–K stages 3 and 4 NREM are grouped together as SWS and are replaced by stage N3 in the new AASM scoring manual. Body movements often are recorded as artifacts in PSG recordings toward the end of SWS as sleep is lightening. Stage N3 is briefly interrupted by stage 2 NREM (stage N2), which is followed by the first REM sleep approximately 60–90 mins after sleep onset.

Rapid Eye Movement (REM) Sleep—REM sleep accounts for 20–25 % of total sleep time. Based on EEG, EMG, and EOG characteristics, REM can be subdivided into two stages (tonic and phasic). This subdivision is not recognized in the recent AASM scoring manual. A desynchronized EEG, hypotonia or atonia of major muscle groups with the exception of the diaphragm and the oculomotor muscles, and depression of monosynaptic and polysynaptic reflexes are characteristics of tonic REM sleep. This tonic stage persists throughout the REM sleep, whereas the phasic stage is discontinuous and superimposed on the tonic stage. Phasic REM sleep is characterized by bursts of rapid eye movements (REMs) in all directions, in singlets or clusters. Phasic swings in blood pressure and heart rate, irregular respiration, spontaneous middle ear muscle activity (MEMA), periorbital integrated potentials (PIPs) [42], and myoclonic twitching of the facial and limb muscle and tongue movements [43] are all characteristics of phasic REM sleep (Fig. 2.2). These and other phasic phenomena of REM sleep are listed in Box 2.1. A few periods of apnea or hypopnea may occur during REM sleep. Electroencephalographic tracing during REM sleep consists of low-amplitude fast pattern in the beta frequency range mixed with a small amount of theta rhythms, some of which may have a "saw tooth" appearance (Fig. 2.2). Saw tooth waves are trains of sharply contoured, often serrated, 2–6 Hz waves usually with rapid ascent and slow descent seen maximally over the central regions and are thought to be the gateway to REM sleep, often preceding a burst of REMs. PIPs are seen during REMs (Fig. 2.2) but not all REMs are accompanied by PIPs. During REM sleep, there may be some intermittent intrusions of alpha rhythms in the EEG lasting for a few seconds. The first REM sleep lasts only a few minutes. Sleep then progresses to stage 2 followed by stage N3 before the second REM sleep begins.

Box 2.1. Lists of Phasic Events of REM Sleep

- Rapid eye movements (REMs)
- Phasic muscle bursts (myoclonic or transient muscle bursts)
- Phasic tongue movements
- Periorbital integrated potentials (PIPS)
- Middle ear muscle activity (MEMA)
- Ponto-geniculo-occipital waves (PGO or P waves) [rats and cats; also reported in human during corticography while performing epilepsy surgery]
- Phasic alterations of breathing (brady-tachypnea)
- Phasic swings of BP (up and down)
- Phasic swings of heart rate (brady-tachyarrhythmia)
- Hippocampal theta waves (rhythms) [animal study]

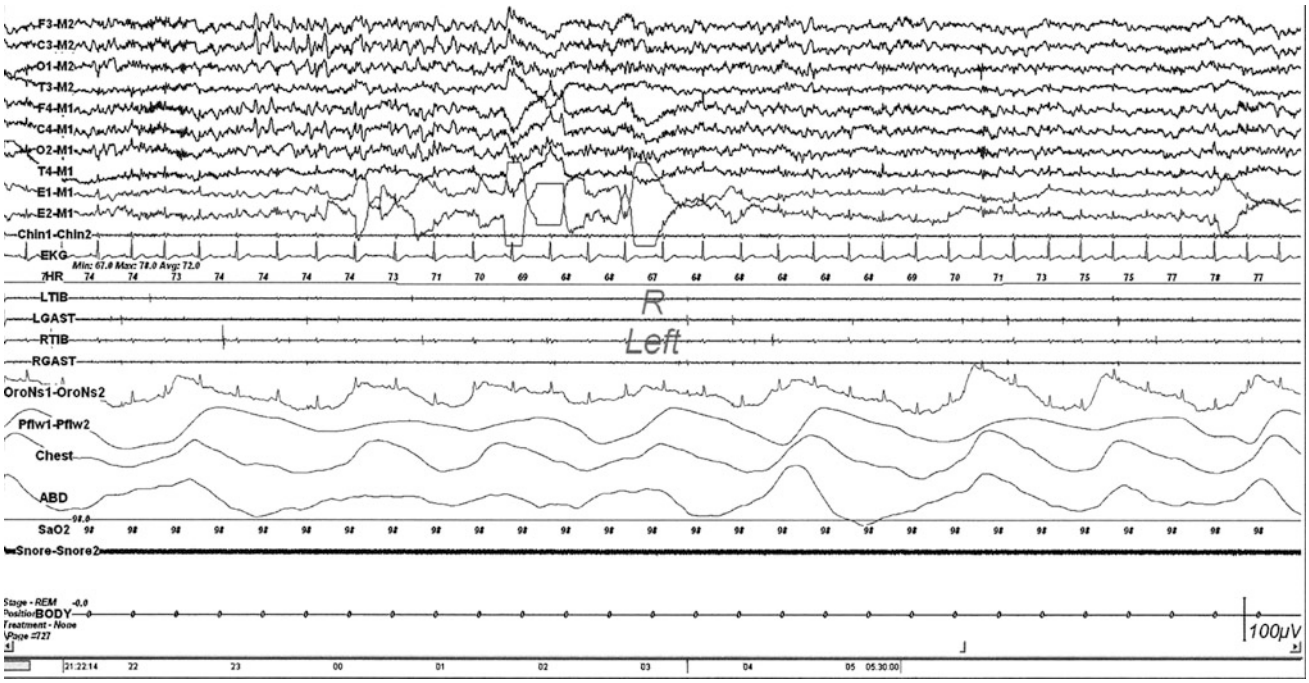

Fig. 2.2 Polysomnographic recording shows rapid eye movement (REM) sleep in an adult. EEG (top 8 channels) shows mixed-frequency theta, low-amplitude beta, and a small amount of alpha activity. Note the characteristic sawtooth waves (seen prominently in channels, 1, 2, 5, and 6 from the *top*) of REM sleep preceding bursts of REMs in the electrooculograms (E1-M1; E2-M2). Chin EMG shows marked hypotonia, whereas TIB and GAST EMG channels show very low-amplitude phasic myoclonic bursts. Reprinted from Chap. 2, 3rd edition

- Saw tooth waves in the EEG
- Alpha bursts in the EEG during REM sleep
- Phasic increase in brain intracellular firing rates during REM sleep
- Penile erections in men and clitoral tumescence in women in REM sleep
- Phasic increase in myocardial oxygen demand in REM sleep
- Phasic vivid dreaming in REM sleep
- Phasic suppression of REM muscle atonia
- Phasic pupillary dilation and constriction
- Phasic fractionations of diaphragmatic activity (pauses of 40–80 ms occurring in clusters) correlating with PGO waves which are phasic events of REM sleep

In summary, during normal sleep in adults, there is an orderly progression from wakefulness to sleep onset to NREM and then to REM sleep. Relaxed wakefulness is characterized by behavioral state of quietness and physiological state of alpha and beta frequency in the EEG, WEMs, and increased muscle tone. NREM sleep is characterized by progressively decreased responsiveness to external stimulation accompanied by SEMs, followed by electroencephalographic slow-wave activity associated with spindle and K-complexes, and decreased muscle tone. REMs markedly reduced or absent muscle tone and low voltage fast electroencephalographic activity mixed with distinctive saw tooth waves and PIPs characterize REM sleep.

The R–K system addresses normal adult sleep and macrostructure of sleep. In patients with sleep disorders such as sleep apnea, parasomnias, or sleep-related seizures, it may be difficult to score sleep according to R–K criteria. Furthermore, the R–K staging system does not address the microstructure of sleep. The recent AASM sleep scoring criteria with a brief reference to R and K system have been outlined in Chap. 24. The macrostructure of sleep is summarized in Box 2.2. There are several endogenous and exogenous factors, which will modify sleep macrostructure (Box 2.3).

Box 2.2: Sleep Macrostructure

Sleep states and stages
Sleep cycles
Sleep latency
Sleep efficiency (the ratio of total sleep time to total time in bed expressed as a percentage)
Wake after sleep onset

Box 2.3: Factors Modifying Sleep Macrostructure

- **Exogenous**
  - **Noise**
  - **Exercise**
  - **Ambient temperature**
  - **Drugs and alcohol**

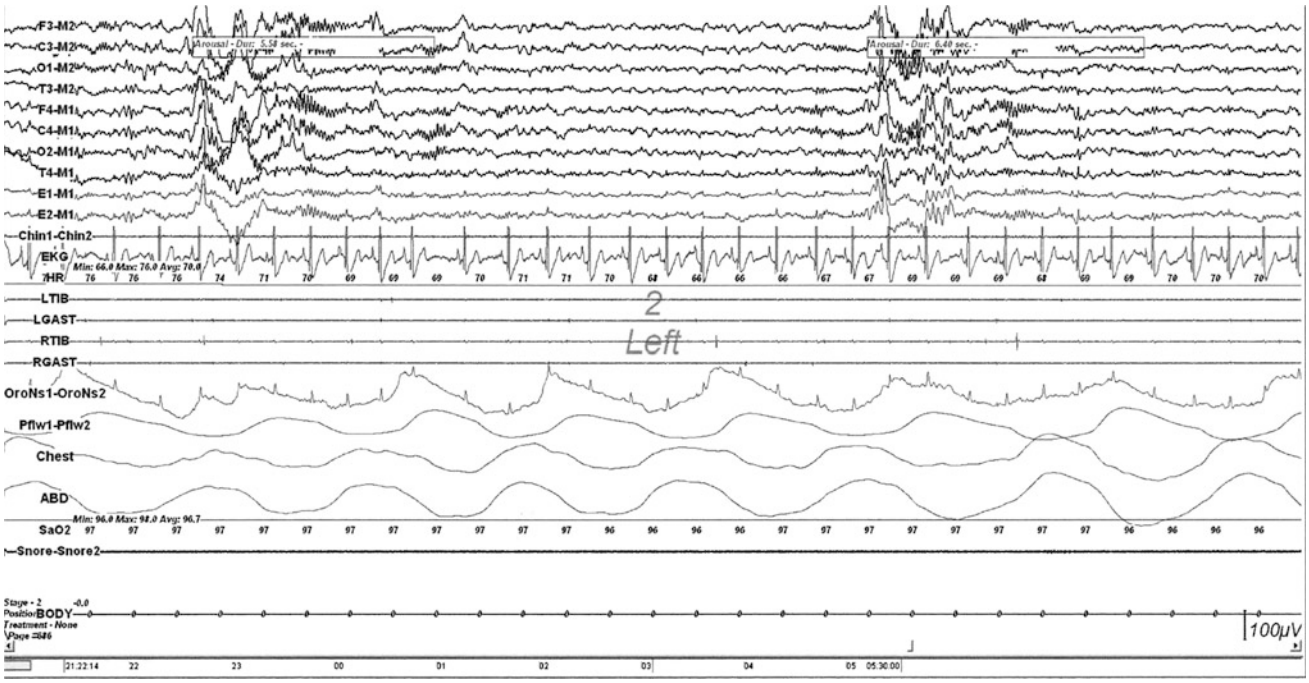

Fig. 2.3 Polysomnographic recording shows two brief periods of arousals out of stage N2 sleep in the left- and right-hand segments of the recording, lasting for 5.58 and 6.40 s and separated by more than 10 s of sleep. Note delta waves followed by approximately 10-Hz alpha activities during brief arousals. Reprinted from Chap. 2, 3rd edition

- **Endogenous**
  - **Age**
  - **Prior sleep–wakefulness**
  - **Circadian phase**
  - **Sleep pathologies**

Sleep Microstructure—Sleep microstructure includes momentary dynamic phenomena such as arousals, which have been operationally defined by the Task Force of the American Sleep Disorders Association (now called American Academy of Sleep Medicine) [44] which has remained essentially unchanged in the recent AASM scoring manual, [15] and the cyclic alternating pattern (CAP), which has been defined and described in various publications by Terzano and co-investigators [45–47]. Other components of microstructure include K-complexes and sleep spindles (Box 2.4).

Box 2.4: Sleep Microstructure

Arousals
Cyclic alternating pattern
Sleep spindles
K-complexes

Arousals are transient phenomena resulting in fragmented sleep without behavioral awakening. An arousal is scored during sleep stages N1, N2, N3 (or REM sleep) if there is an abrupt shift in EEG frequency lasting from 3 to 14 s (Fig. 2.3) and including alpha, beta, or theta activities but not spindles or delta waves. Before an arousal can be scored, the subject must be asleep for 10 consecutive seconds. In REM sleep, arousals are scored only when accompanied by concurrent increase in segmental EMG amplitude. K-complexes, delta waves, artifacts, and only increased segmental EMG activities are not counted as arousals unless these are accompanied by EEG frequency shifts. Arousals can be expressed as number per hour of sleep (an arousal index), and up to 10 arousal index can be considered normal.

The Cyclic Alternating Pattern—The CAP (Fig. 2.4) indicates sleep instability, whereas frequent arousals with or without stage shifts signify sleep fragmentation [47]. A fragmentation index (number of arousals and stage shifts per hour) can also be calculated to indicate sleep instability. Sleep microstructure is best understood by the CAP, wherein an EEG pattern that repeats in a cyclical manner is noted mainly during NREM sleep. This is a promising technique in evaluating both normal and abnormal sleep, as well as in

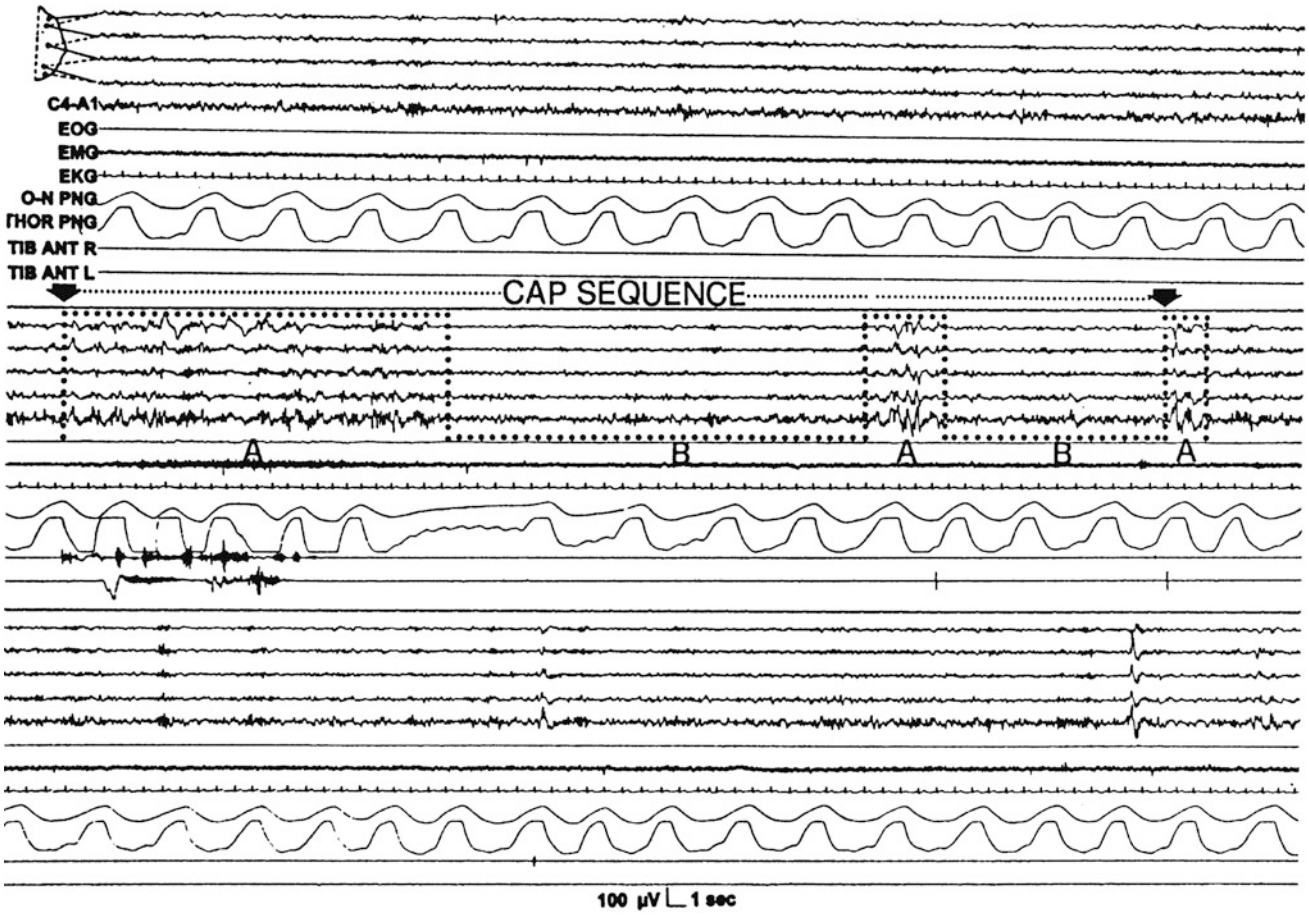

Fig. 2.4 Polysomnographic recording showing consecutive stretches of non-cyclic alternating pattern (non-CAP) (*top*), cyclic alternating pattern (CAP) (*middle*), and non-CAP (*bottom*). The CAP sequence, confined between the two *black arrows*, shows three phase As and two phase Bs, which illustrate the minimal requirements for the definition of a CAP sequence (at least three phase As in succession). Electroencephalographic derivation (top 5 channels in *top* panel): FP2-F4, F4-C4, C4-P4, P4-02, and C4-A1. Similar electroencephalographic derivation is used for the *middle* and *lower* panels. From Terzano et al. [48]. Reprinted from Chap. 2, 3rd edition

understanding the neurophysiologic and neurochemical basis of sleep. A CAP cycle [48] consists of an unstable phase (Phase A) and relatively stable phase (Phase B) each lasting between 2 and 60 s. Phase A of CAP is marked by an increase in EEG potentials with contributions from both synchronous high amplitude and slow, and desynchronized fast rhythms in the EEG recording standing out from a relatively low-amplitude slow background. The A phase is associated with an increase in heart rate, respiration, blood pressure, and muscle tone. CAP rate (total CAP time during NREM sleep) and arousals both increase in older individuals and in a variety of sleep disorders including both diurnal and nocturnal movement disorders. Non-CAP (sleep period without CAP) is thought to indicate a state of sustained stability.

In summary, sleep macrostructure is based on cyclic patterns of NREM and REM states, whereas sleep microstructure mainly consists of arousals, periods of CAP, and periods without CAP. An understanding of sleep macrostructure and microstructure is important because emergence of abnormal motor activity during sleep may be related to disturbed macrostructure and microstructure of sleep.

The Ontogeny of Sleep

Evolution of EEG and sleep states (see also Chap. 52) from the fetus, preterm, and term infant, early childhood, adolescence to adulthood follows in an orderly manner depending upon the maturation of the central nervous system (CNS) [49–52]. Neurological, environmental, and genetic factors as well as comorbid medical or neurological conditions will have significant effects on such ontogenetic changes. Sleep requirements change dramatically from infancy to old age. Newborns have a polyphasic sleep pattern, with 16 h of sleep per day. This sleep requirement decreases to approximately 10 h per day by 3–5 years of age. In preschool children, sleep assumes a biphasic pattern.

Adults exhibit a monophasic sleep pattern, with an average duration from 7.5 to 8 h per night. This returns to a biphasic pattern in old age.

Upon falling asleep, a newborn baby goes immediately into REM sleep, or active sleep, which is accompanied by restless movements of the arms, legs, and facial muscles. In premature babies, it is often difficult to differentiate REM sleep from wakefulness. Sleep spindles appear from 6 to 8 weeks and are well formed by 3 months (may be asynchronous during the first year and by age 2 are synchronous). K-complexes are seen at 6 months but begin to appear at over 4 months. Hypnagogic hypersynchrony characterized by transient bursts of high amplitude waves in the slower frequencies appears at 5–6 months and is prominent at one year. By 3 months of age, the NREM/REM cyclic pattern of adult sleep is established. However, the REM/NREM cycle duration is shorter in infants, lasting for approximately 45–50 mins and increasing to 60–70 mins by 5–10 years and the normal adult cyclic pattern of 90–100 mins by age of 10 years. A weak circadian rhythm is probably present at birth, but by 6–8 weeks, it is established. Gradually, the nighttime sleep increases and daytime sleep decreases and the number of naps decreases. By 8 months, the majority take two naps (late morning and early afternoon). The first 3 months is a critical period of CNS reorganization, and striking changes occur in many physiological responses. In newborns, total sleep time is about 16 h. The total sleep time decreases to 14 h at 4 months and to 13 h at 6–8 months. By 3–6 months, major concentration of sleep occurs at night.

Sleep onset in the newborn occurs through REM sleep. During the first three months, sleep onset REM begins to change. In the newborn, active sleep (REM) occurs 50 % of the total sleep time. This decreases during the first 6 months of age. By 9–12 months, REM sleep occupies 30–35 % of sleep and by 5–6 years, REM sleep decreases to adult levels of 20–25 %. The napping frequency continues to decline, and by age 4–6 years, most children stop daytime naps. Nighttime sleep patterns become regular gradually, and by age 6, nighttime sleep is consolidated with few awakenings. At 9–10 years of age, most children sleep for 10 h at night. Pre-adolescents are highly alert during the day with multiple sleep latency test (MSLT) showing a mean sleep latency of 17–18 min. In summary, the multiphasic sleep pattern of newborns and infants gradually changes to biphasic sleep in preschool children, and finally to monophasic sleep in adults [49, 50]. Sleep reverts to biphasic pattern in the elderly.

There are two other important changes that occur in the sleep pattern in old age: repeated awakenings throughout the night, including early morning awakenings that prematurely terminate the night sleep, and a marked reduction of the amplitude of the slow waves resulting in a decreased percentage of slow-wave sleep (SWS) in this age group. The

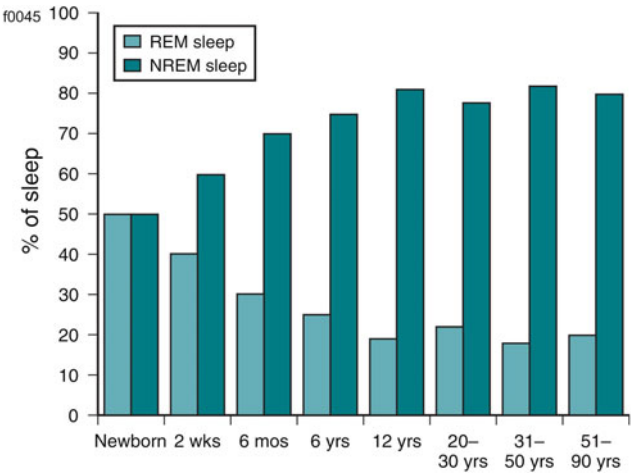

Fig. 2.5 Graphic representation of percentages of REM and NREM sleep at different ages. Note the dramatic changes in REM sleep in the early years. Adapted from Roffwarg et al. [49]. Reprinted from Chap. 2, 3rd edition

percentage of REM sleep in normal elderly individuals remains relatively constant, and the total duration of sleep time within 24 h is also no different from that of young adults; however, elderly individuals often nap during the daytime compensating for lost sleep during the night. Figure 2.5 shows schematically the evolution of sleep step distribution in newborns, infants, children, adults, and elderly adults. Night sleep histograms of children, young adults, and of elderly adults are shown in Fig. 2.6.

The significant evolutionary changes in the respiratory and cardiovascular functions [51, 53]. Respiratory controllers are immature and not fully developed at birth. Respiratory mechanics and upper airway anatomy are different in newborns than in adults contributing to breathing problems, particularly during sleep in newborn infants. Brief periods of respiratory pauses or apneas lasting for 3 s or longer, periodic breathing and irregular breathing may be noted in newborns, especially during active (REM) sleep. According to the National Institutes of Health, Consensus Development Conference on Infantile Apnea, [54] the term periodic breathing refers to respiratory pauses of at least 3 s with less than 20 s of normal breathing in between the pauses. Cheyne–Stokes breathing is periodic waxing and waning of respiration accompanied by central apneas and may be noted in preterm infants. Periodic breathing and occasional central apneas of up to 15 s duration in newborns may be noted without any clinical relevance unless accompanied by bradycardia or cyanosis. These breathing events gradually disappear during the first few weeks of life. The respiratory rate also gradually slows during the first few years of life. Another important finding in the newborn, particularly during active sleep is paradoxical inward motion of the rib cage. This occurs because of

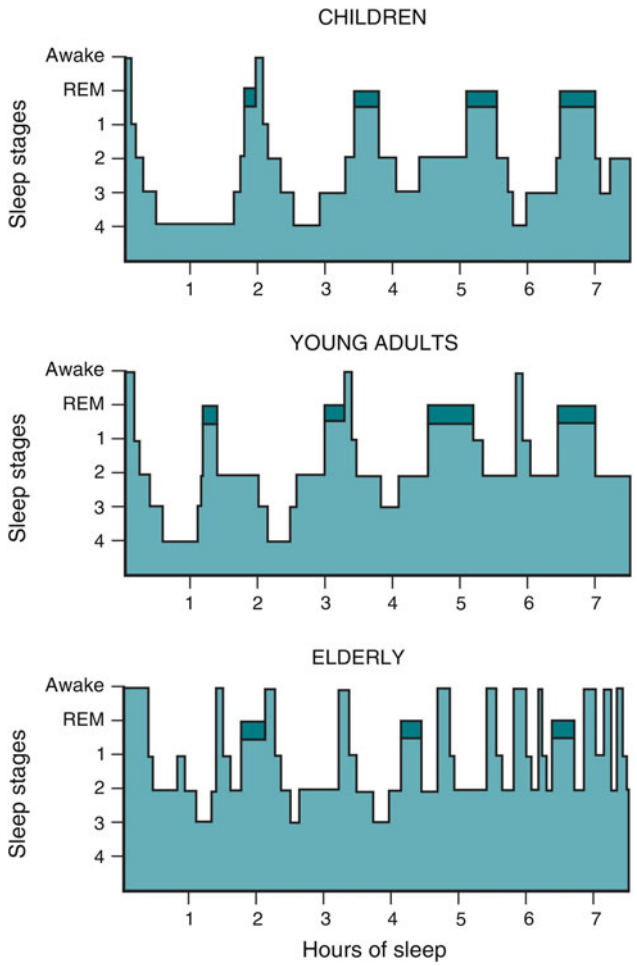

Fig. 2.6 Night sleep histogram from a child, a young adult, and an elderly person. Note significant reduction of stage 4 NREM sleep as one grows older. From Kales and Kales [238]. Reprinted from Chap. 2, 3rd edition

high compliance of the rib cage in newborns, circular rather than elliptical thorax and decreased tone of the intercostal and accessory muscles of respiration. This paradoxical breathing causes hypoxia and reduced diaphragmatic efficiency. Similar breathing in adults occurs during diaphragmatic weakness. At term, posterior cricoarytenoyd muscles which assist in maintaining upper airway patency are not adequately coordinated with diaphragmatic activity causing a few periods of obstructive apneas especially during active sleep. Ventilatory responses to hypoxia are also different in newborns than in adults. In quiet sleep, hypoxia stimulates breathing as in adults, but in active sleep after the initial period of stimulation, there is ventilatory depression. Laryngeal stimulation in adults causes arousal, but in infants, this may cause an apnea. Breathing becomes regular, and the respiratory control is adequately developed by the end of the first year. Changes in cardiovascular function indicate changes in the autonomic nervous system (ANS) during infancy and early childhood. There is greater parasympathetic control for children than infants (as assessed by heart rate low-frequency [LF] and high-frequency [HF] analysis (see also Chap. 11): 0.15–0.5 Hz [HF] indicates parasympathetic and 0.04–0.15 Hz [LF] indicates sympathetic activity). The better parasympathetic control for children than infants indicates ANS maturity. Respiratory heart rate modulation is variable in newborns as assessed by LF and HF heart rate spectral analysis. In active sleep, most of the power is in LF. In older infants and children, there is significant respiratory heart rate modulation termed normal sinus arrhythmia. Respiratory rate during quiet sleep decreases, and the respiratory variability decreases with age.

Sleep Habits

Sleep specialists sometimes divide people into two groups: "evening types" (owls) and "morning types" (larks). The morning types wake up early feeling rested and refreshed and work efficiently in the morning. These people get tired and go to bed early in the evening. In contrast, evening types have difficulty getting up early and they feel tired in the morning; they feel fresh and energetic toward the end of the day. These people perform best in the evening. They go to sleep late at night and wake up late in the morning. The body temperature rhythm takes on different curves in these two types of people. The body temperature reaches the evening peak an hour earlier in morning types than in evening types. What determines a morning or evening type is not known, but heredity may play a role. Katzenberg et al. [55] using the 19-item Horne–Ostberg questionnaire to determine morningness/eveningness in human circadian rhythms discovered a clock gene polymorphism associated with human diurnal preference. One of two H clock alleles (3111C) is associated with eveningness. These findings have been contradicted by later studies [56]. There is a third type (intermediate type) not conforming to either morning or evening type [57].

Sleep Need and Requirement

Sleep requirement or sleep need is defined as the optimum amount of sleep required to remain alert and fully awake and to function adequately throughout the day. Sleep debt is defined as the difference between the ideal sleep requirement and the actual duration of sleep obtained. There are two divergent views: Harrison and Horner [58] concluded that society is not sleep deprived, whereas Bonnet and Arand [59] stated that modern society is chronically sleep deprived. Between 1910 and 1963, there was a mean reduction of 1.5 h of sleep in adolescents aged 8–17 years [60].

However, there may be a significant sampling error in this survey. A study by Bliwise and associates [61] in healthy adults aged 50–65 years showed a reduction of about one hour of sleep between 1959 and 1980 surveys.

It has been traditionally stated that women need more sleep than men, but this has been questioned in a recent field study [62]. There is also a general perception based on questionnaire, actigraphy, and PSG studies that sleep duration decreases with increasing age [63, 64]. This relationship, however, remains controversial. Older adults take naps, and these naps may compensate for nighttime sleep duration curtailment. Sleep is regulated by homeostasis (increasing sleep drive during continued wakefulness) and circadian factors (the sleep drive varying with time of the day). The influence of these factors is reduced in older adults but is still present. Older adults are also phase advanced (e.g., internal clock set earlier yielding early bedtime and early morning awakenings).

Sleep requirement for an average adult is approximately 7½–8 h regardless of environmental or cultural differences [65]. Most probably whether a person is a long or a short sleeper and sleep need are determined by heredity rather than by different personality traits or other psychological factors. Sleep behavior is regulated by genetics. Sleep duration is influenced by the gene DEC2, mutation of which in some people may reduce sleep duration. Social (e.g., occupational) or biological (e.g., illness) factors may also play a role. Sleep need is genetically determined, but its physiologic mechanism is unknown. Slow-wave activity (SWA) in sleep EEG depends on sleep need and homeostatic drive. Adenosine, a peptide, seems to have a direct role in homeostasis. Prolonged wakefulness causes increased accumulation of adenosine which decreases during sleep. SWA increases after sleep loss. Long sleepers spend more time asleep but have less SWS [66] and more stage 2 NREM sleep than do short sleepers [67]. An early important epidemiological study [68] found that the chances of death from coronary arterial disease, cancer, or stroke are greater for adults who sleep less than 4 h or more than 9 h when compared to those who sleep an average of 7½–8 h. There have been some more recent studies by Kripke et al. [69] and others [70–72] confirming these observations. In later studies, other factors such as sleeping medications may have confounded these issues. There is no clear-cut conclusion yet.

There is controversy whether a person can extend sleep beyond the average requirement. Early studies by Taub and Berger [73, 74] showed that sleep extension beyond the average hours may cause exhaustion and irritability with detriment of sleep efficiency. The authors refer to this as the "Rip Van Winkle" effect [74]. Sleep extension studies in the past reported conflicting results regarding MSLT scores, vigilance, and mood ratings [75]. When subjects are challenged to maximum sleep extension, there is substantial improvement in daytime alertness, reaction time, and mood [75]. Most individuals carry a large sleep debt and as extra sleep reduces carryover sleep debt, it is then no longer possible to obtain extra sleep [76].

Sleep and Dreams

Freud [77] called dreams the "Royal Road to the Unconscious" in his seminal book, The Interpretation of Dreams, published in 1900. The Freudian theory postulated that repressed feelings are psychologically suppressed or hidden in the unconscious mind and often manifested in dreams. Sometimes those feelings are expressed as mental disorders or other psychologically determined physical ailments, according to this psychoanalytic theory. In Freud's view, most of the repressed feelings are determined by repressed sexual desires and appear in dreams or symbols representing sexual organs. In recent times, Freudian theory has fallen in disrepute. The modern sleep scientists try to interpret dreams in anatomic and physiologic terms. Nevertheless, we still cannot precisely define what is "dream" and why we dream. The field of dream research took a new direction since the existence of REM sleep was first observed by Aserinsky and Kleitman [11] in 1953. It is postulated that approximately 80 % of dreams occur during REM sleep and 20 % occur during NREM sleep [78]. It is easier to recall REM dreams than NREM dreams. It is also easier to recall dreams if awakened immediately after the onset of REM dreams rather than trying to remember them the next morning upon getting out of bed. REM dreams are often vivid, highly emotionally charged, unrealistic, complex, and bizarre. In contrast, dream recall which sometimes may partially occur upon awakening from the NREM dream state is more realistic. People are generally oriented when awakening from REM sleep but are somewhat disoriented and confused when awakened from NREM sleep. Most of all, dreams take place in natural color, rather than black and white. In our dreams, we employ all five senses. In general, we use mostly the visual sensations, followed by auditory sensation. Tactile, smell, and taste sensation are represented least. Dreams can be pleasant, unpleasant, frightening, or sad. They generally reflect one's day-to-day activities. Fear, anxiety, and apprehension are incorporated into our dreams. In addition, stressful events of past or present may occupy our dreams. The dream scenes or events are rarely rational but often occur in an irrational manner with rapid change of scene, place, or people or a bizarre mixture of these elements. Sometimes, lucid dreams may arise in which the dreamer seems to realize vividly that he or she is actually dreaming [79].

The neurobiologic significance of dreams remains unknown. Sleep scientists try to explain dreams in the terms

of anatomical and physiological interpretation of REM sleep. During this state, the synapses, nerve cells, and nerve fibers connecting various groups of nerve cells in the brain become activated. This activation begins in the brainstem, and the cerebral hemisphere then synthesizes these signals and creates colorful or black and white images giving rise to dreams. Similarly, signals sometimes become converted into auditory, tactile, or other sensations to cause dream imagery. Why the nerve circuits are stimulated to cause dreaming is not clearly understood. Some suggestions to explain significance of dreams include activation of the neural networks in the brain, [80] restructuring and reinterpretation of data stored in memory [81]. This resembles Jouvet's hypothesis of a relationship between REM sleep and recently acquired information [82]. According to molecular biologist and Nobel laureate Crick and Mitchison [83], the function of dreaming is to unlearn, that is, to remove unnecessary and useless information from the brain. Some have also suggested that memory consolidation takes place during the dream stage of sleep (see Chap. 13). In addition, stories abound regarding artists, writers, and scientists who develop innovative ideas about their art, literature, and scientific projects during dreams. Dream-enacting behavior associated with abnormal movement during sleep (REM behavior disorder) and frightening dreams called nightmares or dream anxiety attacks constitute two important REM parasomnias.

Phylogeny of Sleep

Studies have been conducted to find out whether, like humans, other mammals have sleep stages [1, 84–87]. The EEG recordings of mammals show similarities to those of humans. Both REM and NREM sleep stages can be differentiated by EEG, EMG, and EOG in animals. Dolphins and whales are the only groups of mammals showing no REM sleep on recordings [1, 88, 89]. Although initially thought to have no REM sleep, [90] some recent evidence suggests that Australian spiny anteaters (the monotremes, or egg-laying mammals, *echidna*) do have REM sleep [91–93]. Siegel and colleagues [94] suggest that the echidna combines REM and NREM aspects of sleep in a single sleep state. These authors further suggest that REM and NREM sleep evolved from a single, phylogenetically older sleep state.

Like humans, mammals can be short or long sleepers. There are considerable similarities between sleep duration and length of sleep cycles in small and large animals. Small animals with a high metabolic rate have a shorter life span and sleep longer than larger animals with lower metabolic rates [95]. Smaller animals also have a shorter REM–NREM cycle than larger animals. The larger the animal, the less it sleeps; e.g., elephants sleep 4–5 h and giraffes sleep even less than that.

A striking finding in dolphins is that during sleep, half the brain shows the characteristic EEG features of sleep while the other half shows the EEG features of waking [96]. Each sleep episode lasts approximately 30–60 mins; then, the roles of the two halves of the brain reverse. Similar unihemispheric sleep episodes with eye closure contralateral to the sleeping hemisphere are known to occur in the pilot whale and porpoise [35]. It is of interest to note that there are indications from computerized coherence analysis of such interhemispheric SWS asymmetry even in human with severe OSA during apneic arousals [97, 98].

Both vertebrates and invertebrates display sleep and wakefulness [99]. Most animals show the basic rest–activity rhythms during a 24-h period. There is behavioral and EEG evidence of sleep in birds but the avian REM–NREM cycles are very short [99, 100]. Although birds are thought to have evolved from reptiles, the question of the existence of REM sleep in reptiles remains somewhat controversial [99]. The absence of REM sleep in reptiles and the presence of NREM and REM sleep in both birds and mammals would be in favor of REM sleep being a more recent development in the phylogenetic history of land-dwelling organisms [99]. Sleep has also been noted in invertebrates, such as insects, scorpions, and worms, based on behavioral criteria [100].

In conclusion, the purpose of studying the phylogeny of sleep is to understand the neurophysiologic and neuroanatomic correlates of sleep as one ascends the ladder of phylogeny from inframammalian to mammalian species. Tobler [35] concluded that sleep is homeostatically regulated, in a strikingly similar manner, in a broad range of mammalian species. These similarities in sleep and its regulation among mammals suggest common underlying mechanisms that have been preserved in the evolutionary process.

Circadian Sleep–Wake Rhythm

The existence of circadian rhythms has been recognized since the eighteenth century, when the French astronomer de Mairan [101] noted a 24-hr rhythm in heliotrope plants. The plants closed their leaves at sunset and opened them at sunrise, even when they were kept in darkness, shielded from direct sunlight. The discovery of 24-h rhythm in the movements of plant leaves suggested to de Mairan an "internal clock" in the plant. Experiments by chronobiologists Pittendrigh [102] and Aschoff [103] in 1960 clearly proved the existence of 24-h rhythms in animals.

The term *circadian rhythm*, coined by chronobiologist Halberg [104], is derived from the Latin circa, which means *about*, and *dian*, which means *day*. Experimental isolation from all environmental time cues (German *Zeitgebers*) has clearly demonstrated the existence of a circadian rhythm in humans independent of environmental stimuli [105, 106].

Earlier investigators suggested that the circadian cycle is closer to 25 h than 24 h of a day–night cycle; [1, 107–109] however, recent research points to a cycle near 24 h (approximately 24.2 h). Ordinarily, environmental cues of light and darkness synchronize or entrain the rhythms to the night–day cycle; however, the existence of environment-independent, autonomous rhythm suggests that the human body also has an internal biological clock [1, 105–108].

The experiments in rats in 1972 by Stephan and Zucker [110] and Moore and Eichler [111] clearly identified the site of the biological clock, located in the paired suprachiasmatic nucleus in the hypothalamus, above the optic chiasm. Experimental stimulation, ablation, and lesion of these nuclei altered circadian rhythms. The existence of a circadian pacemaker in the suprachiasmatic nuclei (SCN) in humans was confirmed by Lydic and colleagues [112]. There has been clear demonstration of the neuroanatomic connection between the retina and the suprachiasmatic nuclei—the retinohypothalamic pathway [113]—that sends the environmental cues of light to the SCN. The SCN serves as a pacemaker, and the neurons in the SCN are responsible for generating the circadian rhythms [106, 114–117]. The master circadian clock in the SCN receives afferent information from the retinohypothalamic tract which sends signals to multiple synaptic pathways in other parts of the hypothalamus, plus superior cervical ganglion and pineal gland where melatonin is released. The SCN contains melatonin receptors, and there is a feedback loop from the pineal gland to the SCN. Several neurotransmitters have been located within terminals of the SCN afferents and interneurons, including serotonin, neuropeptide Y, vasopressin, vasoactive intestinal peptide, and γ-aminobutyric acid [106, 116, 118].

Time isolation experiments have clearly shown the presence of daily rhythms coordinated by the master clock, the SCN in many physiological processes such as the sleep–wake cycle, body temperature, and neuroendocrine secretion. Body temperature rhythm is sinusoidal, whereas cortisol and growth hormone secretion rhythms are pulsatile. It is well known that plasma levels of prolactin, growth hormone, and testosterone are all increased during sleep at night (see Chap. 11). Melatonin, the hormone synthesized by the pineal gland (see Chap. 11), is secreted maximally during night and may be an important modulator of human circadian rhythm entrainment by the light–dark cycle. Sleep decreases body temperature, whereas activity and wakefulness increase it. It should be noted that internal desynchronization occurs during free-running experiments, and the rhythm of body temperature dissociates from the sleep rhythm as a result of that desynchronization [2, 106–108] (see Fig. 11.10). This raises the question of whether there is more than one circadian (or internal) clock or circadian oscillator [1]. The existence of two oscillators was postulated by Kronauer and colleagues [119]. They suggested that a 25-h rhythm exists for temperature, cortisol, and REM sleep and that the second oscillator is somewhat labile and consists of the sleep–wake rhythm. Some authors, [120] however, have suggested that one oscillator could explain both phenomena. Recent development in circadian rhythm research has clearly shown the existence of multiple circadian oscillators (peripheral clocks) functioning independently from the SCN [121–124] (Fig. 2.7).

The molecular basis of the mammalian circadian clock has been the focus of much recent circadian rhythm research [125–128] (see Chap. 6). The paired SCN are controlled by a total of 8 or more genes (e.g., Clock, Bmal, Per, Cry, and Tim), and their protein products and regulatory enzymes (e.g., casein kinase 1 epsilon and casein kinase 2 delta), and this knowledge is still evolving. By employing "forward genetics" approach, remarkable progress has been made in a few years in identifying key components of the circadian clock in both the fruit flies (Drosophila) and mammals [125–127]. It has been established that the circadian clock gene of sleep–wake cycle is independent of other circadian rhythm functions. There is clear anatomical and physiological evidence to suggest a close interaction between the SCN and the regions regulating sleep–wake states [128, 129]. There are projections from SCN to wake promoting hypocretin (orexin) neurons (indirectly via dorsomedial hypothalamus) and locus coeruleus as well as to sleep-promoting neurons in ventrolateral and median preoptic neurons. Physiological evidence of increased firing rates in single neuron recordings from the appropriate regions during wakefulness or REM sleep and decreased neuronal firing rates during NREM sleep complement anatomical evidence of such interaction between SCN and sleep–wake regulating systems [129, 130]. Based on the studies in mice (e.g., knockout mice lacking core clock genes and mice with mutant clock genes), it has also been suggested that circadian clock genes may affect sleep regulation and sleep homeostasis independent of circadian rhythm generation in other process [131].

Molecular mechanisms applying gene sequencing techniques have been found to play a critical role in uncovering the importance of clock genes, at least in two human circadian rhythm sleep disorders. Mutation of hPer 2 gene (a human homologue of period gene in Drosophila) causing advancing of the clock (alteration of the circadian timing of sleep propensity) and polymorphism in some familial advanced sleep phase state (ASPS) [132–134] and polymorphism in hPer 3 genes in some subjects with delayed sleep phase state (DSPS) [135, 136] suggest genetic control of the circadian timing of the sleep–wake rhythm. Kolker et al. [137, 138] have shown reduced 24-h expression of BMAL1 and clock genes in the SCN of old golden hamsters pointing to a possible role for the molecular mechanism in understanding age-related changes in the circadian clock.

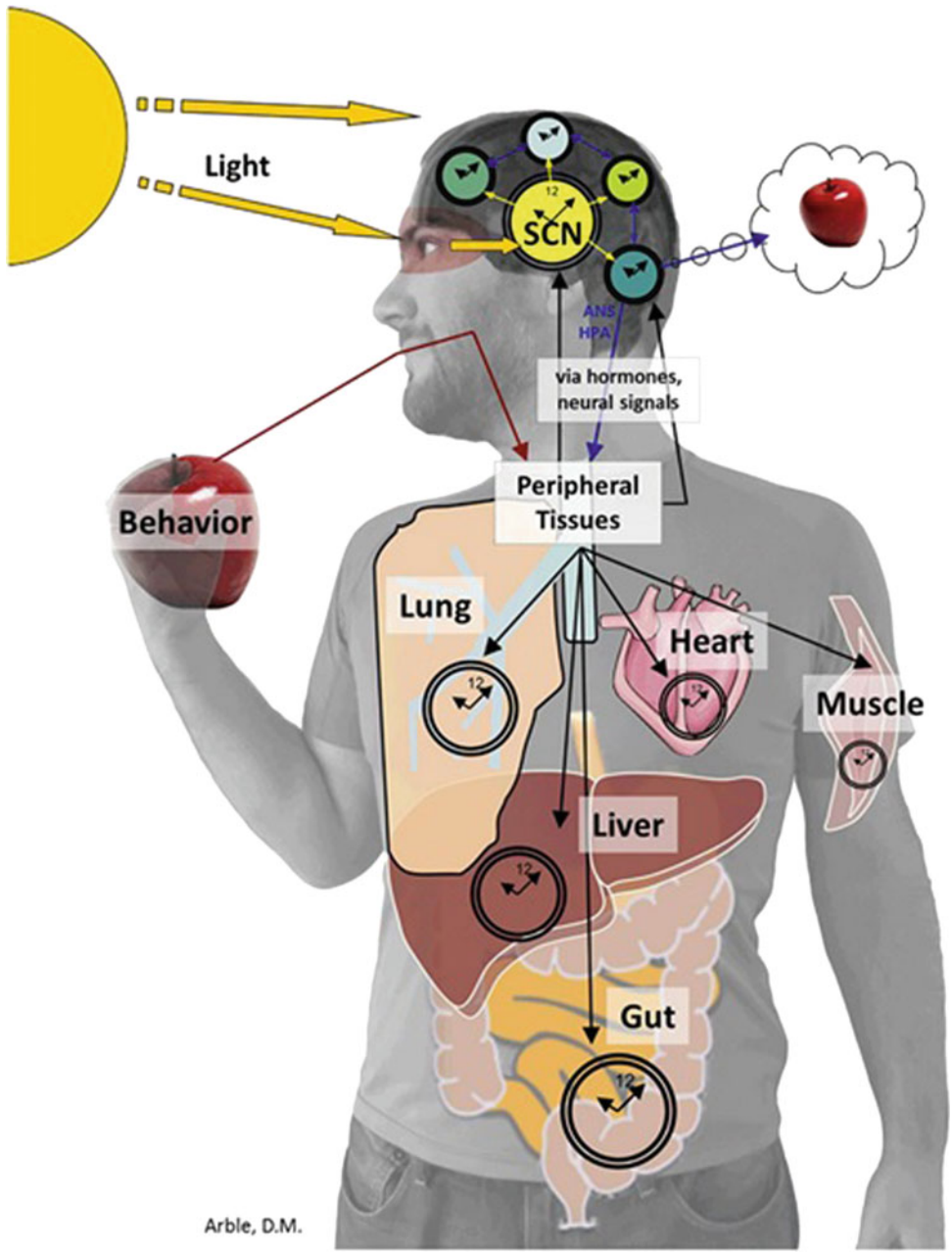

Fig. 2.7 The retinal ganglion cells transmit information about "time of day" via the retinohypothalamic tract to the suprachiasmatic nuclei (SCN), which conveys timing information to the brain including the paraventricular (PVN), arcuate (ARC) nuclei subparaventricular zone (SPZ), medial preoptic area (MPOA), intergeniculate leaflet (IGL), and paraventricular nucleus of the thalamus. The SCN also relays timing cues to peripheral tissues (peripheral oscillators) via the autonomic nervous system and hormones, which together organize complex behaviors. Reproduced with permission from Arble and Sandoval [239]

Kondratov et al. [139] reported that mice deficient in the circadian transcription factor BMAL1 have reduced life span and display a premature aging phenotype. Later, Antoch et al. [140] corroborated these findings by showing that clock mutant mice respond to low-dose irradiation by accelerating this aging process and developing phenotype that are reminiscent of those in BMAL1-deficient mice. It is important to be aware of circadian rhythms, because several other sleep disturbances are related to alteration in them, such as those associated with shift work and jet lag.

Chronobiology, Chronopharmacology, and Chronotherapy

Sleep specialists are becoming aware of the importance of chronobiology, chronopharmacology, and chronotherapy; [141–147] however, studies are spares in these fields. *Chronobiology* refers to the study of the body's biological responses to time-related events. All biological functions of the cells, organs, and the entire body have circadian (approximately 24 h), ultradian (<24 h), or infradian (>24 h) rhythms. It is important, therefore, to understand how the body responds to treatment at different times throughout the circadian cycle and that circadian timing may alter the pathophysiologic responses in various disease states (e.g., exacerbation of bronchial asthma at night and a high incidence of stroke late at night and myocardial infarction early in the morning; see Chap. 47).

Biological responses to medications may also depend on the circadian timing of administration of the drugs. Potential differences of responses of antibiotics to bacteria, or of cancer cells to chemotherapy or radiotherapy, depending on the time of administration, illustrate the importance of chronopharmacology, which refers to pharmacokinetic or pharacodynamic interactions in relation to the timing of the day.

Circadian rhythms can be manipulated to treat certain disorders, a technique called *chronotherapy*. Examples of this are phase advance or phase delay of sleep rhythms and application of bright light at certain periods of the evening and morning.

Cytokines, Immune System, and Sleep Factors

Cytokines are proteins produced by leukocytes and other cells functioning as intercellular mediators that may play an important role in immune and sleep regulation [148–156] (see also Chap. 12). Several cytokines such as interleukin (IL), interferon alpha (IF-α), and tumor necrosis factor (TNF) have been shown to promote sleep. There are other sleep-promoting substances called sleep factors which increase in concentration during prolonged wakefulness or during infection and enhance sleep. These other factors include delta sleep-inducing peptides, muramyl peptides, cholecystokinin, arginine vasotocin, vasoactive intestinal peptide, growth hormone-releasing hormone (GHRH), somatostatin, prostaglandin D_2 nitric oxide (NO), and adenosine. The role of these various sleep factors in maintaining homeostasis has not been clearly established [148]. It has been shown that adenosine in the basal forebrain can fulfill the major criteria for the neural sleep factor that mediates these somnogenic effects of prolonged wakefulness by acting through A1 and A2a receptors [157, 158].

The cytokines play a role in the cellular and immune changes noted during sleep deprivation [148, 149, 159–163]. The precise nature of the immune response after sleep deprivation has, however, remained controversial, and the results of studies on the subject have been inconsistent. These inconsistencies may reflect different stress reactions of subjects and different circadian factors (e.g., timing of drawing of blood for estimation of plasma levels) [148, 159, 164].

Infection (bacterial, viral, and fungal) enhances NREM sleep but suppresses REM sleep. It has been postulated that sleep acts as a host defense against infection and facilitates the healing process [148, 159, 163, 165–168]. It is also believed that sleep deprivation may increase vulnerability to infection [169]. The results of experiments with animals suggest that sleep deprivation alters immune function [1, 159, 160, 165]. Sleep thus has a profound impact on the immune system. It has been shown [170] that following sleep deprivation (e.g., sleeping four hours per night for four nights), there was a delay in immune response 10 days after flu vaccination.

There is evidence that cytokines play an important role in the pathogenesis of excessive daytime sleepiness in a variety of sleep disorders and in sleep deprivation [170–173]. Sleep deprivation causing excessive sleepiness has been associated with increased production of proinflammatory cytokines IL-6 and TNF-α [172, 173]. Viral or bacterial infections causing excessive somnolence and increased NREM sleep are associated with increased production of TNF-α and IL-B [174–176]. In other inflammatory disorders such as HIV infection and rheumatoid arthritis, increased sleepiness and disturbed sleep are associated with increased amount of circulating TNF-α [177–180]. Several authors suggested that excessive sleepiness, in OSAS, narcolepsy, insomnia, or idiopathic hypersomnia may be mediated by cytokines such as IL-6 and TNF-α [181–187]. In a recent review, Kapsimalis et al. [170] concluded that cytokines are mediators of sleepiness and implicated in the pathogenesis of symptoms of OSAS, narcolepsy, sleep deprivation, and insomnia and indirectly play an important role in the pathogenesis of the cardiovascular complications of OSAS.

Theories of the Function of Sleep

The function of sleep remains the greatest biologic mystery of all times. Several theories of the function of sleep have been proposed (Box 2.5). None of the theories are satisfactory to explain the exact biologic functions of sleep. Sleep deprivation experiments in animals have clearly shown that sleep is necessary for survival, but from a practical point of view, complete sleep deprivation for a prolonged period cannot be conducted in humans. Sleep deprivation studies in humans have shown an impairment of performance which demonstrates the need for sleep (see also Chap. 3). The

performance impairment of prolonged sleep deprivation results from a decreased motivation and frequent "micro-sleep." Overall, human sleep deprivation experiments have proven that sleep deprivation causes sleepiness and impairment of performance, vigilance, attention, concentration, and memory. Sleep deprivation may also cause some metabolic, hormonal, and immunologic affects. Sleep deprivation causes immune suppression, and even partial sleep deprivation reduces cellular immune responses. Studies by Van Cauter's group [188, 189] include a clearly documented elevation of cortisol level following even partial sleep loss suggesting an alteration in the hypothalamic–pituitary–adrenal (HPA) axis function. This has been confirmed even in chronic sleep deprivation which causes impairment of glucose tolerance. Glucose intolerance may contribute to memory impairment as a result of decreased hippocampal function. Chronic sleep deprivation may also cause a detriment of thyrotropin concentration, increased evening cortisol level, and sympathetic hyperactivity which may serve as risk factors for obesity, hypertension, and diabetes mellitus. It should, however, be noted that in all of these sleep deprivation experiments, stress has been a confounding factor, raising a question about whether all these undesirable consequences relate to sleep loss only or a combination of stress and sleeplessness.

Box 2.5: Theories of Sleep Function

- Restorative theory
- Energy conservation theory
- Adaptive theory
- Instinctive theory
- Memory consolidation and reinforcement theory
- Synaptic and neuronal network integrity theory
- Thermoregulatory theory
- Immune and endocrine regulation
- Metabolic homeostasis theory

Restorative Theory

Proponents of the restorative theory ascribe body tissue restoration to NREM sleep and brain tissue restoration to REM sleep [190–193]. The findings of increased secretion of anabolic hormones [194–196] (e.g., growth hormone, prolactin, testosterone, luteinizing hormone) and decreased levels of catabolic hormones [197] (e.g., cortisol) during sleep, along with the subjective feeling of being refreshed after sleep, may support such a contention. Increased SWS (rebound) after sleep deprivation [1] further supports the role of NREM sleep as restorative. The critical role of REM sleep for the development of the CNS of young organisms is cited as evidence of restoration of brain functions by REM sleep [198]. Several studies of brain basal metabolism suggest an enhanced synthesis of macromolecules such as nucleic acids and proteins in the brain during sleep, [199] but the data remain scarce and controversial. Protein synthesis in the brain is increased during SWS [200]. Confirmation of such cerebral anabolic processes would provide an outstanding argument in favor of the restorative theory of sleep. Recent work in animals suggests formation of new neurons during sleep in adult animals and this neurogenesis in dentate gyrus may be blocked after total sleep deprivation [201].

Energy Conservation Theory

Zepelin and Rechtschaffen [95] found that animals with a high metabolic rate sleep longer than those with a slower metabolism, suggesting that energy is conserved during sleep. There is an inverse relationship between body mass and metabolic rate. Small animals (e.g., rats and opossum) with high metabolic rate sleep for 18 h per day, whereas large animals (e.g., elephants and giraffes) with low metabolic rates sleep only for 3–4 h. It has been suggested that high metabolic rates cause increased oxidative stress and injury to self-leading to the hypothesis [202] that higher metabolic rates in the brain require longer sleep time to counteract the cell damage by free radicals, and facilitate synthesis of molecules protecting brain cells from this oxidative stress. During NREM sleep, brain energy metabolism and cerebral blood flow decrease, whereas during REM sleep, the level of metabolism is similar to that of wakefulness and the cerebral blood flow increases. In summary, sleep-related reduction in general metabolism including metabolic heat production, lowering of core body temperature, and certain behavioral signs (e.g., immobile posture minimizing heat exchange) conserve energy. Although these findings might suggest that NREM sleep helps conserve energy, the fact that only 120 calories are conserved in 8 h of sleep makes the energy conservation theory less than satisfactory. Considering that humans spend one-third of their lives sleeping, [203] one would expect far more calories to be conserved during an 8-h period if energy conservation was the function of sleep.

Adaptive Theory

In both animals and humans, sleep is an adaptive behavior that allows the creature to survive under a variety of environmental conditions [204, 205].

Instinctive Theory

The instinctive theory views sleep as an instinct [190, 206], which relates to the theory of adaptation and energy conservation.

Memory Consolidation and Reinforcement Theory

The sleep–memory consolidation hypothesis is a hotly debated issue with both proponents and opponents with proponents

outnumbering the opponents. In fact, McGaugh et al. [207] earlier suggested that sleep- and waking-related fluctuations of hormones and neurotransmitters may modulate memory processes. Crick and Mitchison [83] suggested that REM sleep removes undesirable data from the memory. In a later report, these authors hypothesized that the facts that REM deprivation produces a large rebound and that REM sleep occurs in almost all mammals make it probable that REM sleep has some important biological function [208].

The theory that memory reinforcement and consolidation take place during REM sleep has been strengthened by scientific data provided by Karni et al. [209]. These authors conducted selective REM and SWS deprivation in six young adults. They found that perceptual learning during REM deprivation was significantly less compared with perceptual learning during SWS deprivation. In addition, SWS deprivation had a significant detrimental effect on a task that was already learned. These data suggest that REM deprivation affected the consolidation of the recent perceptual experience, thus supporting the theory of long-term consolidation during REM sleep. Recent studies by Stickgold and Walker [210] and Walker and Stickgold [211] strongly supported the theory of sleep–memory consolidation (see Chap. 13). There is further suggestion by Hu et al. [212] that the facilitation of memory for emotionally salient information may preferentially develop during sleep. Stickgold's group concluded that unique neurobiological processes within sleep actively promote declarative memories [213]. Several studies in the past decade have provided evidence to support the role of sleep in sleep-dependent memory processing which include memory encoding, memory consolidation and reconsolidation, and brain plasticity (see review by Kalia) [214]. Hornung et al. [215] using a paired associate word list to test declarative memory and mirror-tracking tasks to test procedural learning in 107 healthy older adults aged 60–82 years concluded that REM sleep plays a role in procedural memory consolidation. Walker's group [216] concluded after sleep deprivation experiments that sleep before learning is critical for human memory consolidation. Born et al. [217] concluded that hippocampus-dependent memories (declarative memories) benefit primarily from SWS. They further suggested that the different patterns of neurotransmitters and neurohormone secretion between sleep stages may be responsible for this function. Backhaus and Junghanns [218] randomly assigned 34 young healthy subjects to a nap or wake condition of about 45 mins in the early afternoon after learning procedural and declarative memory tasks. They noted that naps significantly improved procedural but not declarative memory, and therefore, a short nap is favorable for consolidation of procedural memory. Goder et al. [219] tested the role of different aspects of sleep for memory performance in 42 consecutive patients with non-restorative sleep. They used Rey–Osterrieth Complex Figure Test and the paired associative word list for declarative memory function and mirror-tracking tasks for procedural learning assessment. The results supported the contention that visual declarative memory performance is significantly associated with total sleep time, sleep efficiency, duration of NREM sleep, and the number of NREM–REM sleep cycles but not with specific measures of REM sleep or slow-wave sleep. In contrast to all these studies, Vertes and Siegel [220–223] took the opposing position contending that REM sleep is not involved in memory consolidation or at least not in humans citing several lines of evidence. Vertes and Siegal [220] cited the work of Smith et al. [224, 225] that REM sleep is not involved with memory consolidation. Schabus et al. [226] agreed that declarative material learning is not affected by sleep. In their study, subjects showed no difference in the percentage of word pairs correctly recalled before and after 8 h of sleep. The strongest evidence cited by Vertes and Siegel [220] includes examples of individuals with brain stem lesions with elimination of REM sleep [227] or those on antidepressant medications suppressing REM sleep exhibiting no apparent cognitive deficits. Vertes and Siegel [220] concluded that REM sleep is not involved in declarative memory and REM sleep is not critical for cognitive processing in sleep.

In summary, based on recent studies in our understanding of molecular mechanisms of memory, it can be stated reasonably that sleep strengthens new memories, i.e., sleep can rescue memories that are lost during wakefulness requiring synthesis of new proteins and ribonucleic acid (RNA) by the neurons. Memory consolidation and reconsolidation require both NREM (sleep spindles and SWS) and REM sleep.

Synaptic and Neuronal Network Integrity Theory

There is a new theory emerging that suggests the primary function of sleep is the maintenance of synaptic and neuronal network integrity [203, 228–230]. According to this theory, sleep is important for the maintenance of synapses that have been insufficiently stimulated during wakefulness. Intermittent stimulation of the neural network is necessary to preserve CNS function. This theory further suggests that NREM and REM sleep serve the same function of synaptic reorganization [228]. This emerging concept of the "dynamic stabilization" (i.e., repetitive activations of brain synapses and neural circuitry) theory of sleep suggests that REM sleep maintains motor circuits, whereas NREM sleep maintains nonmotor activities [228, 230]. Gene expression [231] studies using the DNA microarray technique identified sleep- and wakefulness-related genes (brain transcripts) subserving different functions (e.g., energy metabolism, synaptic excitation, long-term potentiation, and response to cellular stress during wakefulness; and protein synthesis, memory consolidation, and synaptic downscaling during sleep).

Thermoregulatory Function Theory

The thermoregulatory function theory is based on the observation that thermoregulatory homeostasis is maintained during sleep, whereas severe thermoregulatory abnormalities follow total sleep deprivation [232]. The preoptic anterior hypothalamic neurons participate in thermoregulation and NREM sleep (see also Chap. 11). These two processes are closely linked by preoptic anterior hypothalamic neurons but are clearly separate. Thermoregulation is maintained during NREM but suspended during REM sleep. Thermoregulatory responses such as shivering, piloerection, panting, and sweating are impaired during REM sleep. There is a loss of thermosensitivity in the preoptic anterior hypothalamic neurons during REM sleep.

Role of Sleep in Immune and Endocrinal Regulation

This has been briefly outlined above

Metabolic Homeostasis Theory

Recent discovery of a new metabolic waste clearing pathway (equivalent to the lymphatic system in the body) in the CNS of mice directs our attention to a new understanding of the function of sleep. This also is beginning to answer a long-standing question of mechanism of clearing of metabolic byproducts of the brain in the absence of a lymphatic system. This pathway was termed "the glymphatic system" by the original researchers led by Nedergaard [233–235] because of its dependence on glial cells (astrocytes) performing a "lymphatic"-like cleansing of the brain interstitial fluid in the perivascular space between the brain blood vessels and leptomeningeal sheathes surrounding these vessels. These researchers have shown that this extracellular space expanded by about 60 % along with shrinkage of the glial cells in the sleeping brain as compared with that in the waking brain to promote clearance of interstitial waste products [234] (Fig. 2.8). Sleep, therefore, restores the function of the brain by promoting glymphatic clearance of neural metabolic waste products accumulated in the waking brain. The investigators have further shown the ability of this system to remove misfolded or aggregated proteins by experimental injection of labeled beta amyloid proteins into the brains of sleeping and awake mice [236, 237]. Cerebrospinal fluid cleared these proteins outside of the cells twice as fast during sleep as during wakefulness. These findings may revolutionize our understanding of sleep dysfunction in many neurodegenerative diseases resulting from proteinopathies (e.g., Alzheimer's disease, Parkinson's disease, and others). Once these findings are replicated in humans using sophisticated neuroimaging techniques, this discovery will electrify the scientific world of sleep toward drug development to prevent or halt the progression of these neurodegenerative diseases.

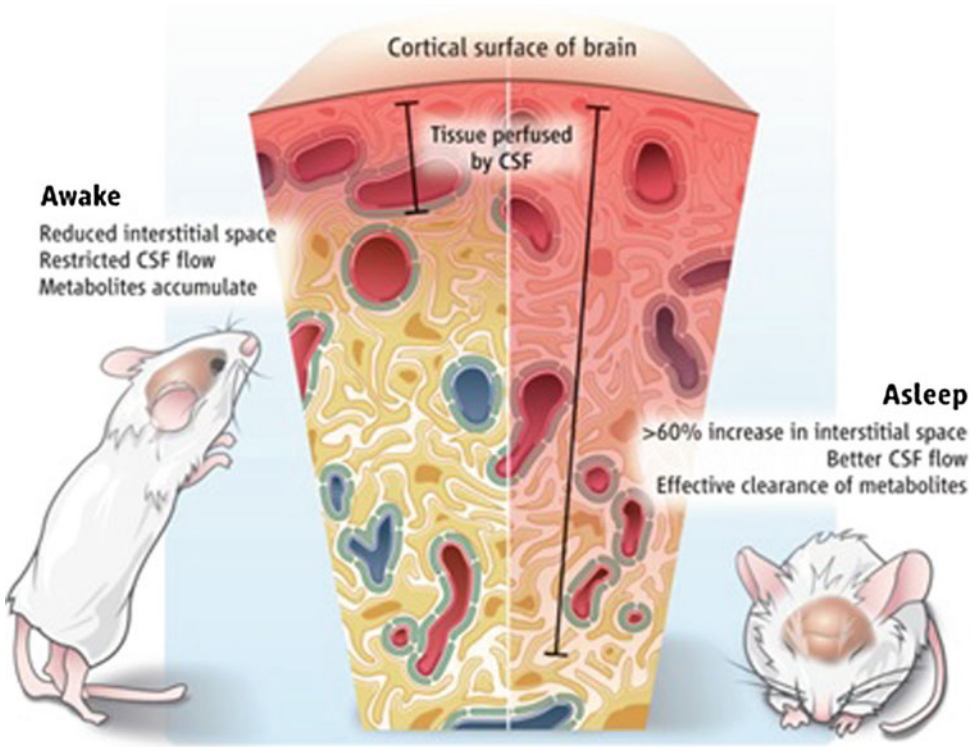

Fig. 2.8 Physiological differences in cerebrospinal fluid (CSF) flow between the awake and the sleeping states in mice. The tissues perfused by CSF including blood vessels are indicated in *red* (arteries) and *blue* (veins). The interstitial space in the mouse cerebral cortex, through which cerebrospinal fluid moves, increases from 14 % in the awake to 23 % in the sleeping animal, an increase that allows the faster clearance of metabolic waste products. Reproduced with permission from Herculano-Houzel [240]

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Sleep Deprivation and Excessive Daytime Sleepiness

3

Sudhansu Chokroverty

Circadian Rhythm and Homeostasis

Sleep and wakefulness are controlled by both homeostatic and circadian factors. The duration of prior wakefulness determines the propensity to sleepiness (homeostatic factor) [1], whereas circadian factors [2] determine the timing, duration, and characteristics of sleep. There are two types of sleepiness: physiologic and subjective [3]. Physiologic sleepiness is the body's propensity to sleepiness. There are two highly vulnerable periods of sleepiness: 2:00–6:00 A.M. (particularly 3:00–5:00 A.M.) and 2:00–6:00 P.M. (especially 3:00–5:00 P.M.). The propensity to physiologic sleepiness (e.g., mid-afternoon and early morning hours) depends on circadian and homeostatic factors [4]. The highest number of sleep-related accidents has been observed during these periods. Subjective sleepiness is the individual's perception of sleepiness; it depends on several external factors, such as a stimulating environment and ingestion of coffee and other caffeinated beverages. Homeostasis refers to a prior period of wakefulness and sleep debt. After a prolonged period of wakefulness, there is an increasing tendency to sleep. The recovery from sleep debt is aided by an additional amount of sleep, but this recovery is not linear. Thus, an exact number of hours of sleep are not needed to repay a sleep debt; rather, the body needs an adequate amount of slow-wave sleep (SWS) for restoration. The circadian factor determines the body's propensity to maximal sleepiness (e.g., between 3:00 and 5:00 A.M.). The second period of maximal sleepiness (3:00–5:00 P.M.) is not as strong as the first. Sleep/wakefulness and the circadian pacemaker have a reciprocal relationship; the biological clock can affect sleep and wakefulness, and sleep and wakefulness can affect the clock. The neurologic basis of this interaction is, however, unknown. In this chapter, I briefly review experimental sleep deprivation, the population at risk of sleep deprivation, and the causes and consequences of excessive sleepiness (Box 3.1).

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Sleep Deprivation and Sleepiness

Many Americans (e.g., doctors, nurses, firefighters, interstate truck drivers, police officers, overnight train drivers and engineers) work irregular sleep–wake schedules and alternating shifts, making them chronically sleep deprived [5, 6]. A survey study [5] found that, compared with the population at the turn of the century (1910–1911), American adolescents aged 8–17 years in 1963 were sleeping 1.5 h less per 24-h period. This does not mean we need less sleep today but that people are sleep deprived. That there may, however, be a sampling error in these surveys (e.g., approximately 2000 people were surveyed in 1910–1911, vs. 311 in the later survey). A study by Bliwise et al. [7] in healthy adults aged 50–65 years showed a reduction of about 1 h of sleep per 24 h between 1959 and 1980 surveys. Factors that have been suggested to be responsible for this reduction of total sleep include environmental and cultural changes, such as increased environmental light, increased industrialization, growing numbers of people doing shift work, and the advent of television and radio. A review of the epidemiologic study by Partinen [8] estimated a prevalence of excessive sleepiness in Westerners at an average of 5–15 % of the total population. In contrast, Harrison and Horne [9] argued that most people are not chronically sleep deprived but simply choose not to sleep as much as they could.

What are the consequences of sleep deprivation? This question has been explored in studies of total, partial, and selective sleep deprivation (e.g., SWS or rapid eye movement [REM] sleep deprivation). These studies have conclusively proved that sleep deprivation causes sleepiness; decrement of performance, vigilance, attention, and concentration; and

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Box 3.1 Causes of excessive daytime sleepiness

Physiologic causes
Sleep deprivation and sleepiness related to lifestyle and irregular sleep–wake schedule
Pathologic causes
Primary sleep disorders
Obstructive sleep apnea syndrome
Central sleep apnea syndrome with or without Cheyne–Stokes breathing
Sleep-related hypoventilation disorders
Sleep-related hypoxemia disorder
Circadian rhythm sleep disorders
Jet lag
Delayed sleep phase syndrome
Irregular sleep–wake pattern
Shift work sleep disorder
Non-24-h sleep–wake disorders
Central disorders of hypersomnolence
Narcolepsy (type 1 and type 2)
Idiopathic hypersomnolence
Kleine–Levin syndrome
Hypersomnia due to a medical disorder
Hypersomnia associated with a psychiatric disorder
Insufficient sleep syndrome
Medication-related hypersomnia
Benzodiazepines
Nonbenzodiazepine hypnotics (e.g., phenobarbital, zolpidem)
Sedative antidepressants (e.g., tricyclics, trazodone)
Antipsychotics
Nonbenzodiazepine anxiolytics (e.g., buspirone)
Antihistamines
Narcotic analgesics, including tramadol (Ultram)
Toxin and alcohol-induced hypersomnolence
General medical disorders
Hepatic failure
Renal failure
Respiratory failure
Electrolyte disturbances
Cardiac failure
Severe anemia
Endocrine causes
Hypothyroidism
Acromegaly
Diabetes mellitus
Hypoglycemia
Hyperglycemia
Psychiatric or psychological causes
Depression
Psychogenic unresponsiveness or sleepiness
Neurologic causes
Brain tumors or vascular lesions affecting the thalamus, hypothalamus, or brain stem
Post-traumatic hypersomnolence
Multiple sclerosis
Encephalitis lethargica and other encephalitides and encephalopathies, including Wernicke's encephalopathy
Cerebral trypanosomiasis (African sleeping sickness)
Neurodegenerative disorders
Alzheimer's disease
Parkinson's disease
Multiple system atrophy
Myotonic dystrophy and other neuromuscular disorders causing sleepiness secondary to sleep apnea
Miscellaneous
Periodic limb movements disorder
Restless legs syndrome
Insufficient sleep syndrome
Inadequate sleep hygiene

increased reaction time. The performance decrement resulting from sleep deprivation may be related to periods of microsleep. *Microsleep* is defined as transient physiologic sleep (i.e., 3- to 14-second electroencephalographic patterns change from those of wakefulness to those of stage I nonrapid eye movement [NREM] sleep) with or without rolling eye movements and behavioral sleep (e.g., drooping or heaviness of the eyelids, slight sagging and nodding of the head).

The most common cause of excessive daytime sleepiness (EDS) today is sleep deprivation. In the survey by Partinen [8], up to one-third of young adults have EDS secondary to chronic partial sleep deprivation, and approximately 7 % of middle-aged individuals have EDS secondary to sleep disorders and 2 % secondary to shift work. Sleep deprivation poses danger to the individuals experiencing it as well as to others, making people prone to accidents in the work place, particularly in industrial and transportation work. The incidence of automobile crashes increases with driver fatigue and sleepiness. Fatigue resulting from sleep deprivation may have been responsible for many major national and international catastrophes [10]. Although both sleep deprivation (SD) and sleep fragmentation (SF) may cause EDS, they are two different phenomena [11]. SD (total, partial, selective) determines sleep duration, whereas SF denotes an interruption of normal continuity of sleep with frequent and transient arousals (e.g., OSAS, RLS/WED-PLMS).

Sleep Deprivation Experiments

Although neither humans nor animals can do without sleep, the amount of sleep necessary to individual people or species varies widely. We know that a lack of sleep leads to sleepiness, but we do not know the exact functions of sleep. Sleep deprivation experiments in animals have clearly shown that sleep is necessary for survival. The experiments of Rechtschaffen et al. [12] with rats using the carousel device have provided evidence for the necessity of sleep. All rats deprived of sleep for 10–30 days died after having lost weight, despite increases in their food intake. The rats also lost temperature control. Rats deprived only of REM sleep lived longer. Complete sleep deprivation experiments for prolonged periods (weeks to months) cannot be conducted in humans for obvious ethical reasons.

Total Sleep Deprivation

One of the early sleep deprivation experiments in humans was conducted in 1896 by Patrick and Gilbert [13] who studied the effects of a 90-h period of sleep deprivation on three healthy young men. One reported sensory illusions, which disappeared completely when, at the end of the experiment, he was allowed to sleep for 10 h. All subjects had difficulty staying awake, but felt totally fresh and rested after they were allowed to sleep.

A spectacular experiment in the last century was conducted in 1965. A 17-year-old California college student named Randy Gardner tried to set a new world record for staying awake. Dement [14] observed him during the later part of the experiment. Gardner stayed awake for 264 h and 12 min and then slept for 14 h and 40 min. He was recovered fully when he awoke. The conclusion drawn from the experiment is that it is possible to deprive people of sleep for a prolonged period without causing serious mental impairment. An important observation is the loss of performance with long sleep deprivation, which is due to loss of motivation and the frequent occurrence of microsleep.

In another experiment, Johnson and MacLeod [15] showed that it is possible to intentionally reduce total sleeping time by 1–2 h without suffering any adverse effects. The experiments by Carskadon and Dement [16, 17] showed that sleep deprivation increases the tendency to sleep during the day. This has been conclusively proved using the Multiple Sleep Latency Test with subjects [17, 18].

During the recovery sleep period after sleep deprivation, the percentage of SWS (stages 3 and 4 NREM sleep using Rechtschaffen–Kales scoring criteria) increases considerably. Similarly, after a long period of sleep deprivation, the REM sleep percentage increases during recovery sleep. (This increase has not been demonstrated after a short period of sleep deprivation, that is, up to 4 days.) These experiments suggest that different mechanisms regulate NREM and REM sleep [19].

Partial Sleep Deprivation

Measurements of mood and performance after partial sleep deprivation (e.g., restricting sleep to 4.5–5.5 h for 2–3 months) showed only minimal deficits in performance, which may have been related to decreased motivation. Later, studies have conclusively proven that total and partial sleep deprivation produce deleterious effects in humans (see under summary).

Selective REM Sleep Deprivation

Dement [20] performed REM sleep deprivation experiments (by awakening the subject for 5 min at the moment the polysomnographic recording demonstrated onset of REM sleep). Polysomnography results showed increased REM pressure (i.e., earlier and more frequent onset of REM sleep during successive nights) and REM rebound (i.e., quantitative increase of REM percentage during recovery nights). These findings were subsequently replicated by Borbely [19] and others [21, 22], but Dement's third observation—a psychotic reaction following REM deprivation—could not be replicated in subsequent investigations [21].

Stage 4 Sleep Deprivation

Agnew et al. [23] reported that, after stage 4 NREM sleep deprivation for 2 consecutive nights, there was an increase in stage 4 sleep during the recovery night. Two important points were raised by this group's later experiments: (1) REM rebound was more significant than stage 4 rebound during recovery nights, and (2) it was more difficult to deprive a person of stage 4 sleep than of REM sleep [22].

Summary

The effects of total sleep deprivation, as well as of REM sleep deprivation, are similar in animals and humans, suggesting that the sleep stages and the fundamental regulatory mechanisms for controlling sleep are the same in all mammals. These experiments and later human studies have proven conclusively that sleep deprivation causes sleepiness and impairment of performance, vigilance, attention, and

concentration, causing serious consequences involving many body systems as well as affecting short- and long-term memories [24–27]. One problem with these SD experiments is the introduction of the confounding factor of stress, and therefore, these experiments may not ideally reproduce the human sleep deprivation conditions.

Consequences of EDS Resulting from Sleep Deprivation or Sleep Restriction

EDS adversely affects performance and productivity at work and school, higher cerebral functions, and quality of life and social interactions and increases morbidity and mortality [24–37].

Performance and Productivity at Work or School

Impaired performance and reduced productivity at work for shift workers; reduced performance in class for school and college students; and impaired job performance in patients with narcolepsy, sleep apnea, circadian rhythm disorders, and chronic insomnia are well-known adverse effects of sleep deprivation and sleepiness. Sleepiness and associated morbidity are worse in night-shift workers, older workers, and female shift workers.

Higher Cerebral Functions

Sleepiness interferes with higher cerebral functions, causing impairment of short-term memory, concentration, attention, cognition, and intellectual performance. Psychometric tests [3, 25] have documented increased reaction time in patients with excessive sleepiness. These individuals make increasing numbers of errors, and they need increasing time to reach the target in reaction time tests [3, 25]. Sleepiness can also impair perceptual skills and new learning. Insufficient sleep and excessive sleepiness may cause irritability, anxiety, and depression. There is a U-shaped relationship between sleep duration and depression similar to that between sleep duration and mortality [38]. Both short (<6 h) and long (>8 h) sleep durations are associated with depression. Learning disabilities and cognitive impairment with impaired vigilance also have been described [36]. This adverse impact of sleep deprivation on cognition may lead to increased number of failures to carry out intended actions causing serious consequences for safety in critical situations [39].

Quality of Life and Social Interaction

People complaining of EDS are often under severe psychological stress. They are often lonely and perceived as dull, lazy, and downright stupid. Excessive sleepiness may cause severe marital and social problems. Narcoleptics with EDS often have serious difficulty with interpersonal relationships, as well as impaired health-related quality of life, and are misunderstood because of the symptoms [40]. Shift workers constitute approximately 20–25 % of the workforce in America (i.e., approximately 20 million). The majority of them have difficulty with sleeping and sleepiness as a result of insufficient sleep and circadian dysrhythmia. Many of them have an impaired quality of life, marital discord, and gastrointestinal problems.

Increased Morbidity and Mortality

Short-term Consequences

Persistent daytime sleepiness causes individuals to have an increased likelihood of accidents. A study by the US National Transportation Safety Board (NTSB) found that the most probable cause of fatal truck accidents was sleepiness-related fatigue [41]. In another study by the NTSB [42], 58 % of the heavy-truck accidents were fatigue related and 18 % of the drivers admitted having fallen asleep at the wheel. The NTSB also reported sleepiness- and fatigue-related motor coach [43, 44] and railroad [45] accidents. New York State police estimated that 30 % of all fatal crashes along the New York throughway occurred because the driver fell asleep at the wheel. Approximately 1 million crashes annually (one-sixth of all crashes) are thought to be produced by driver inattention or lapses [46, 47]. Sleep deprivation and fatigue make such lapses more likely to occur. Truck drivers are especially susceptible to fatigue-related crashes [41, 42, 48–51]. Many truckers drive during the night while they are the sleepiest. Truckers may also have a high prevalence of sleep apnea [52]. The US Department of Transportation estimated that 200,000 automobile accidents each year may be related to sleepiness. Nearly one-third of all trucking accidents that are fatal to the driver are related to sleepiness and fatigue [53]. A general population study done by Hays et al. [54] involving 3962 elderly individuals reported an increased mortality risk of 1.73 in those with EDS, defined by napping most of the time. The presence of sleep disorders (see section "Primary Sleep Disorders Associated with EDS" later in this chapter) increases the risk of crashes. Individuals with untreated

insomnia, sleep apnea, or narcolepsy and shift workers—all of whom may suffer from excessive sleepiness—have more automobile crashes than other drivers [55].

A telephone survey [56] of a random sample of New York State licensed drivers by the State University of New York found that 54.6 % of the drivers had driven while drowsy within the past year, 1.9 % had crashed while drowsy, and 2.8 % had crashed when they fell asleep. Young male drivers are especially susceptible to crashes caused by falling asleep, as documented in a study in North Carolina [57] in 1990, 1991, and 1992 (e.g., in 55 % of the 4333 crashes, the drivers were predominantly male and 25 years of age or younger). Surveys in Europe also noted an association between crashes and long-distance automobile and truck driving [50, 58–61]. A 1991 Gallup organization [62] national survey found that individuals with chronic insomnia reported 2.5 times as many fatigue-related automobile accidents as did those without insomnia. The same 1991 Gallup survey found serious morbidity associated with untreated sleep complaints, as well as impaired ability to concentrate and accomplish daily tasks, and impaired memory and interpersonal discourse. In a 1999 Gallup Poll [63], 52 % of all adults surveyed said that, in the past year, they had driven a car or other vehicle while feeling drowsy, 31 % of adults admitted dozing off while at the wheel of a car or other vehicle, and 4 % reported having had an automobile accident because of tiredness during driving. A number of national and international catastrophes [10] involving industrial operations, nuclear power plants, and all modes of transportation have been related to sleepiness and fatigue, including the Exxon Valdez oil spill in Alaska; the nuclear disaster at Chernobyl in the former Soviet Union; the near-nuclear disaster at 3-Mile Island in Pennsylvania; the gas leak disaster in Bhopal, India, resulting in 25,000 deaths; and the Challenger space shuttle disaster in 1987.

Long-term Consequences

In addition to these short-term consequences, sleep deprivation or restriction causes a variety of long-term adverse consequences affecting several body systems and thus increasing the morbidity and mortality [24–37, 64].

Sleep Deprivation and Obesity

The prevalence of obesity in adults in the United States was 15 % in 1970 and increased to 31 % in 2001 [65]. In children, the figures for obesity were 5 % in 1970 and went up to 15 % in 2001. In the Zurich study [66], 496 Swiss adults followed for 13 years showed a body mass index (BMI) of 21.8 at age 27 that increased to 23.3 at the age of 40, with concurrent decrease in sleep duration from 7.7 to 7.3 h in women and 7.1 to 6.9 h in men. This longitudinal study confirms the cross-sectional studies in adults [67] and children [68]. In the Wisconsin sleep cohort study [69] (a population-based longitudinal study) using 1024 volunteers, short sleep was associated with reduced leptin and elevated ghrelin contributing to increased appetite, causing increased BMI. Several other more recent studies using various approaches have also documented the association of obesity or weight gain with short sleep duration [29, 30, 70–72]. In the study by Altman et al. [72], sleep duration of less than five hours was associated with an additional BMI point of 2.7 and this strong association was not accounted for perceived insufficient sleep. A large-scale prospective study found that the incidence of obesity at one-year follow-up was higher among Japanese men sleeping five hours or less compared with those sleeping seven hours [28].

Sleep Duration and Hypothalamo-pituitary Hormones

Elevated evening cortisol levels, reduced glucose tolerance, and altered growth hormone secretion after experimental acute sleep restriction by Spiegel et al. [73, 74] suggest that participation of the hypothalamic–pituitary axis may contribute toward obesity after sleep deprivation by leading to increased hunger and appetite. There is epidemiologic evidence of reduced sleep duration associated with reduced leptin (a hormone in adipocytes stimulating the satiety center in the hypothalamus), increased ghrelin (an appetite stimulant gastric peptide), and increased BMI [75, 76]. Spiegel et al. [73] in studies using sleep restriction (4 h per night for 6 nights) and sleep extension (12 h per night for 6 nights) experiments in healthy young adults found increased evening cortisol, increased sympathetic activation, decreased thyrotropin activity, and reduced glucose tolerance in the sleep-restricted group. Rogers et al. [77] found similar elevation of evening cortisol levels following chronic sleep restriction. In recurrent partial sleep restriction studies in young adults, the following endocrine and metabolic alterations have been documented [78]: (1) decreased glucose tolerance and insulin sensitivity and (2) decreased levels of the anorexigenic hormone leptin and increased levels of the orexigenic peptide ghrelin. A combination of these findings caused increased hunger and appetite leading to weight gain. Because of these changes, short sleep duration is a risk factor for diabetes and obesity.

Several epidemiologic studies have shown an association between sleep duration and type 2 diabetes mellitus [79]. Ayas et al. [80] found an association between long sleep duration (>9 h) and diabetes mellitus. Yaggi et al. [81] reported an association between diabetes and both short (<5 h) and long (>8 h) sleep duration. Several other reviews [82–85] including some recent studies [29, 30, 32, 83, 86–90] supported a link between sleep duration, particularly short sleep duration and diabetes mellitus. Buxton and

Marcelli [29] used the 2004–2005 National Health Interview Survey (NHIS), and Shankar et al. [30] used the 2008 Behavioral Risk Factor Surveillance System (BRFSS) to find a positive correlation between short sleep duration and diabetes. Hancox and Landhuis [90] from a study conducted in New Zealand found an association between short sleep duration and prediabetes as well as an association between HgA1C and sleep duration.

Sleep Duration and Mortality

Epidemiologic studies by Kripke et al. [91, 92] and Hublin et al. [93] showed increased mortality in short sleepers (also in relatively long sleepers). There is a U-shaped association between sleep duration (both long and short) and mortality [27, 38, 94–96]. The earliest study was by Hammond in 1964 [97]. Another significant early study by Kripke et al. [91, 92] in 1979 found that the chances of death from coronary artery disease, cancer, or stroke are greater for adults who sleep less than 4 h or more than 9 h when compared to those who sleep an average of 7½–8 h. The latest studies by Kripke et al. in 2002 [98] confirmed the earlier observations and documented an increased mortality in those sleeping less than 7 h and those sleeping more than 7½ h. Other factors, such as sleeping medication, may have confounded these issues. In more recent studies, Gallicchio and Kalesan [95] conducted meta-analysis using 23 studies from 2007 to 2009 and Cappuccio et al. [27] using 16 studies from 1993 to 2009 a relationship between sleep duration (both long and short) and all-cause mortality emerged. There is, however, insufficient evidence to make a definite conclusion about sleep duration and mortality. The underlying etiologic factors remain to be determined. One possibility is a common pathway of increased risk of cardiometabolic disease [24].

Sleep Duration and Abnormal Physiologic Changes

Several studies documented abnormal physiologic changes after sleep restriction as follows: reduced glucose tolerance [73], increased blood pressure [99], sympathetic activation [100], reduced leptin levels [101], and increased inflammatory markers (e.g., an increased C-reactive protein, an inflammatory myocardial risk after sleep loss) [102].

Sleep Restriction and Immune Responses

Limited studies in the literature suggest the following responses following sleep restriction: (1) decreased antibody production following influenza vaccination in the first 10 days [103]; (2) decreased febrile response to endotoxin (*Escherichia coli*) challenge [104]; and (3) increased inflammatory cytokines [105] (e.g., interleukin-6 and tumor necrosis factor-α), which may lead to insulin resistance, cardiovascular disease, and osteoporosis.

Sleep Restriction and Cardiovascular Disease

Studies by Mallon et al. [106] in 2002 addressed the question of sleep duration and cardiovascular disease. They did not find increased risk of cardiovascular disease-related mortality associated with sleep duration, but found an association between difficulty falling asleep and coronary arterial disease mortality. However, several other more recent studies found a relationship between increased risk of cardiovascular disease and sleep duration [29, 72, 99, 107–109]. In a 12-year prospective study covering 20,432 men and women with no prior history of cardiovascular disease investigators from the Netherlands [108] observed that short sleepers (≤ 6 h) had higher risk of cardiovascular disease than those sleeping 7–8 h. These findings agree with the observations made by Altman et al. [72], Buxton and Marcelli [29], Cappuccio et al. [109].

Kripke et al. [98] and Newman et al. [107] in their studies concluded that daytime sleepiness and reduced sleep duration predict mortality and cardiovascular disease in older adults. What is the mechanism of increased cardiovascular risk after chronic sleep deprivation? This is not exactly known but may be related to increased C-reactive protein, an inflammatory marker found after sleep loss. In many of the sleep restriction experiments in humans, however, an added stress may have acted as a confounding factor, and therefore, some of the conclusions about sleep restriction regarding mortality, cardiovascular disease, diabetes mellitus, and endocrine changes may have been somewhat flawed.

Summary

Sleep restriction and sleep deprivation are associated with short-term (e.g., increased traffic accidents, EDS, daytime cognitive dysfunction as revealed by reduced vigilance test and working memory) and long-term (e.g., obesity, cardiovascular morbidity and mortality, memory impairment) adverse effects. Thus, chronic sleep deprivation caused either by lifestyle changes or by primary sleep disorders (e.g., obstructive sleep apnea syndrome [OSAS], chronic insomnia) is a novel risk factor for obesity and insulin-resistant type 2 diabetes mellitus.

Causes of Excessive Daytime Sleepiness

Excessive sleepiness may result from both physiologic and pathologic causes (Box 3.1), the latter of which include neurologic and general medical disorders as well as primary sleep disorders and medications and alcohol [110].

Physiologic Causes of Sleepiness

Sleep deprivation and sleepiness because of lifestyle and habits of going to sleep and waking up at irregular hours can be considered to result from disruption of the normal circadian and homeostatic physiology. Groups who are excessively sleepy because of lifestyle and inadequate sleep include young adults and elderly individuals, workers at irregular shifts, healthcare professionals (e.g., doctors, particularly the house staff, and nurses), firefighters, police officers, train drivers, pilots and flight attendants, commercial truck drivers, and those individuals with competitive drives to move ahead in life, sacrificing hours of sleep and accumulating sleep debt. In 2009, the Institute of Medicine (IOM) issued a report on "Resident Duty Hours" focusing on their working hours which predispose them to health and safety issues [111]. Based on this report, the Accreditation Council for Graduate Medical Education (ACGME) implemented new work hours schedule in 2010 which went into effect in July 2011 [112]. Among young adults, high school and college students are particularly at risk for sleep deprivation and sleepiness. The reasons for excessive sleepiness in adolescents and young adults include both biological and psychosocial factors. Some of the causes for later bedtimes in these groups include social interactions with peers, homework in the evening, sports, employment or other extracurricular activities, early wake-up times to start school, and academic obligations requiring additional school or college work at night. Biological factors may play a role but are not well studied. For example, teenagers may need extra hours of sleep. Also, the circadian timing system may change with sleep phase delay in teenagers.

Pathologic Causes of Sleepiness

Neurologic Causes of EDS

Tumors and vascular lesions affecting the ascending reticular-activating arousal system (ARAS) and its projections to the posterior hypothalamus and thalamus lead to daytime sleepiness. Such lesions often cause coma rather than just sleepiness. Brain tumors (e.g., astrocytomas, suprasellar cysts, metastases, lymphomas, and hamartomas affecting the posterior hypothalamus; pineal tumors; astrocytomas of the upper brain stem) may produce excessive sleepiness. Prolonged hypersomnia may be associated with tumors in the region of the third ventricle. Symptomatic narcolepsy resulting from craniopharyngioma and other tumors of the hypothalamic and pituitary regions has been described [113]. Cataplexy associated with sleepiness, sleep paralysis, and hypnagogic hallucinations has been described in patients with rostral brain stem gliomas with or without infiltration of the walls of the third ventricle. Narcolepsy–cataplexy syndrome also has been described in a human leukocyte antigen DR2-negative patient with a pontine lesion documented by magnetic resonance imaging.

Other neurologic causes of EDS include bilateral paramedian thalamic infarcts [114], post-traumatic hypersomnolence, and multiple sclerosis. Narcolepsy–cataplexy syndrome has been described in occasional patients with multiple sclerosis and arteriovenous malformations in the diencephalons [113, 115].

EDS has been described in association with encephalitis lethargica and other encephalitides as well as encephalopathies, including Wernicke's encephalopathy. It was noted that the lesions of encephalitis lethargica described by von Economo [116] in the beginning of the last century, which severely affected the posterior hypothalamic region, were associated with the clinical manifestation of extreme somnolence. These lesions apparently interrupted the posterior hypothalamic histaminergic system as well as the ARAS projecting to the posterior hypothalamus. Encephalitis lethargica is now extinct. Cerebral sarcoidosis involving the hypothalamus may cause symptomatic narcolepsy [117]. Whipple's disease [118] of the nervous system involving the hypothalamus may occasionally cause hypersomnolence. Cerebral trypanosomiasis [119], or African sleeping sickness, is transmitted to humans by tsetse flies: *Trypanosoma gambiense* causes Gambian or West African sleeping sickness, and *Trypanosoma rhodesiense* causes Rhodesian or East African sleeping sickness.

Certain neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and multiple system atrophy also may cause EDS [120, 121]. The causes of EDS in Alzheimer's disease include degeneration of the suprachiasmatic nucleus resulting in circadian dysrhythmia, associated sleep apnea/hypopnea, and periodic limb movements in sleep. In Parkinson's disease, excessive sleepiness may be due to the associated periodic limb movements in sleep, sleep apnea, and depression. EDS in multiple system atrophy associated with cerebellar parkinsonism or parkinsonian cerebellar syndrome and progressive autonomic deficit (Shy–Drager syndrome) may be caused by the frequent association with sleep-related respiratory dysrhythmias and possible degeneration of the ARAS [122].

Sleep disorders are being increasingly recognized as a feature of Parkinson's disease and other parkinsonian disorders. Although some studies have attributed the excessive daytime drowsiness and irresistible sleep episodes ("sleep attacks") to antiparkinsonian medications [123], sleep disturbances are also an integral part of Parkinson's disease [124]. In one study of 303 patients with Parkinson's disease, 22.6 % reported falling asleep while driving [123]. Several studies also reported a relatively high prevalence (20.8–21.9 %) of symptoms of restless legs syndrome in patients with Parkinson's disease [125, 126]. There is also

increasing awareness about the relationship between parkinsonian disorders and REM sleep behavior disorder, which may be the presenting feature of Parkinson's disease, multiple system atrophy, and other parkinsonian disorders [127–137].

The relationship between hypocretin and sleep disorders associated with Parkinson's disease is currently being explored [138].

Myotonic dystrophy (types 1 and 2) and other neuromuscular disorders may cause EDS due to associated sleep apnea/hypopnea syndrome and hypoventilation [139–141]. In addition, in myotonic dystrophy, there may be involvement of the ARAS as part of the multisystem membrane defects noted in this disease.

EDS Associated with General Medical Disorders

Several systemic diseases such as hepatic, renal, or respiratory failure and electrolyte disturbances may cause metabolic encephalopathies that result in EDS. Patients with severe EDS drift into a coma. The other medical causes for EDS include congestive heart failure and severe anemia. Hypothyroidism and acromegaly also may cause EDS due to the associated sleep apnea syndrome. Hypoglycemic episodes in diabetes mellitus and severe hyperglycemia are additional causes of EDS.

Primary Sleep Disorders Associated with EDS

A number of primary sleep disorders cause excessive sleepiness (see Box 3.1). The most common cause of EDS in the general population is insufficient sleep syndrome associated with sleep deprivation. The next most common cause is OSAS; narcolepsy and idiopathic hypersomnolence are other common causes of EDS. Most patients with EDS referred to the sleep laboratory have OSAS. Other causes of EDS include circadian rhythm sleep disorders, restless legs syndrome-periodic limb movements in sleep, some cases of chronic insomnia, and inadequate sleep hygiene.

Substance-induced Hypersomnia Associated with EDS

Many sedatives and hypnotics cause EDS. In addition to the benzodiazepine and nonbenzodiazepine hypnotics and sedative antidepressants (e.g., tricyclic antidepressants and trazodone) as well as nonbenzodiazepine neuroleptics (e.g., buspirone), antihistamines, antipsychotics, and narcotic analgesics (including tramadol [Ultram]) cause EDS (see Chaps. 37 and 55).

Toxin and alcohol-related hypersomnolence can occur as well [142]. Many industrial toxins such as heavy metals and organic toxins (e.g., mercury, lead, arsenic, copper) may cause EDS. These may sometimes also cause insomnia. Individuals working in industrial settings using toxic chemicals routinely are at risk. These toxins may also cause systemic disturbances such as alteration of renal, liver, and hematologic function. There may be an impairment of nerve conduction. Chronic use of alcohol at bedtime may produce alcohol-dependent sleep disorder. Usually this causes insomnia, but sometimes the patients may have excessive sleepiness in the daytime. Many of these patients suffer from chronic alcoholism. Acute ingestion of alcohol causes transient sleepiness.

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Effects of Sleep Deprivation and Sleepiness on Society and Driving

4

Michael A. Grandner and Raza Mian

Introduction

Sleep deprivation has been identified by the Institute of Medicine as "an unmet public health problem [1]." Sleep deprivation among medical residents was featured in a second Institute of Medicine report [2] that eventually led to changes in rules governing medical residencies. Increasing the proportion of the population that achieves adequate sleep has become a national health priority, featured as a goal in the Healthy People 2020 initiative [3]. The joint task force of the American Academy of Sleep Medicine and the Sleep Research Society identified critical research goals and listed as first the goal to better understand the public health implications of sleep deficiency and circadian disruption [4]. Taken together, these and other initiatives show that the public health relevance of sleep loss is recognized, if not completely understood. There has been a dramatic increase in attention to this area, and there has been much that has been learned regarding the implications of sleep for public health. This review aims to briefly describe a way to conceptualize sleep from a public health perspective using a social–ecological approach. Then, the chapter will briefly outline some of the literature linking sleep to health outcomes of societal relevance and how sleep loss may play a role in segments of society along age, gender, race/ethnicity, relationship status, and occupational lines. Then, there is a brief discussion of the role of sleep loss in driving accidents and a section for conclusions and future directions.

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Conceptualizing the Effects of Sleep in the Context of Society

As research has increasingly focused on the role of healthy sleep in the general population, it may be useful to conceptualize the role of sleep in health, taking into account the contextual factors from which sleep arises. One such conceptualization, introduced by Grandner, Hale, Moore, and Patel, is the social–ecological model of sleep and health [5]. This model is built on the social–ecological framework originally proposed by Bronfenbrenner in the 1970s [6].

Briefly, this framework describes how an individual's behavior with respect to health exists in the context of that individual, but also in relation to various social systems. Bronfenbrenner proposed that the individual exists in the context of a "microsystem," a social layer with which the individual is in direct contact. This includes the individual's family, school, and church. These are systems that the individual is a part of and are represented by one-on-one interactions. The next level up is the "mesosystem" which refers to connections that link aspects if the microsystem together, such as factors that connect a person's family to their job. The "exosystem" is the next layer of abstraction and refers to the systems that the individual does not interact with but affects the microsystem/mesosystem. For example, this could be a spouse's work schedule, which affects the individual indirectly. Beyond the exosystem is the "macrosystem" which refers to more abstract systems within which the other systems are a part. For example, this could represent societal norms, laws, and the global environment. See Fig. 4.1 for a general schematic of this framework.

The social–ecological model of sleep and health is based on this approach. The model, presented in Fig. 4.2, conceptualizes sleep in the context of both upstream and downstream factors. Downstream of sleep duration and quality lies adverse health outcomes of poor sleep. These may include weight gain/obesity, metabolic dysregulation, cardiovascular disease, inflammation, psychological disturbances, stress, and performance deficits. It is hypothesized

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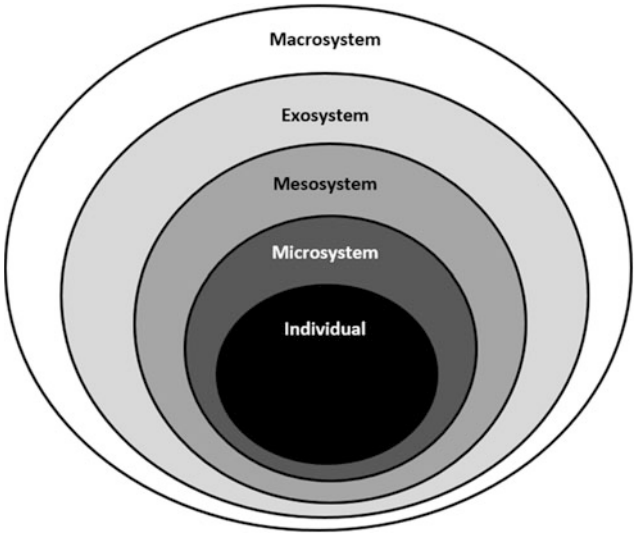

Fig. 4.1 Social–ecological framework

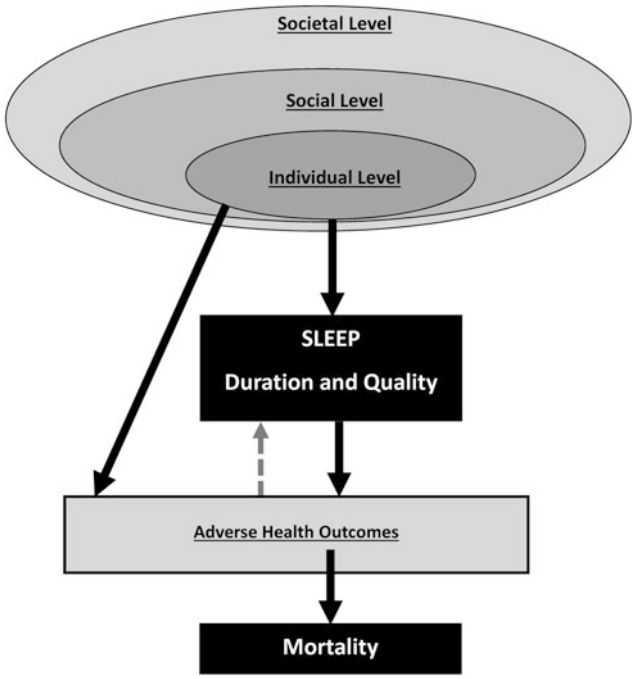

Fig. 4.2 Social–ecological model of sleep and health. Adapted from Grandner, Hale, Moore, and Patel

that these, in aggregate, not only exacerbate each other but eventually contribute to overall morbidity and eventually mortality risk. Upstream of sleep lies the portion of the model that borrows heavily from the social–ecological framework. The model posits that sleep, as experienced by an individual, is best conceptualized in the context of three levels. First is the individual level. These are the individual's own genetics, health, beliefs, choices, etc. These are the proximal causes of sleep experienced by that individual. Beyond the individual level, though, is the social level. This level, which borrows aspects of the microsystem, exosystem, and mesosystem, represents the immediate context of that individual. Factors at this level include neighborhood, culture, social networks, friends, and other systems that exist outside of the individual but to which the individual belongs. Two factors specifically stand out at this level and bridge most directly to the individual level. These include work/school and family/home. These two domains are hypothesized to exert the most influence (above individual-level factors) on sleep at the individual level. The third level is the societal level, within which the social level is situated. This borrows elements of the exosystem and macrosystem. Factors at this level represent structures that the elements at the social level are a part of, but exist outside of those factors. For example, factors at the societal level that influence sleep may include globalization, 24/7 society, public policy, and national geography.

Taken together, this model spells out the role of sleep on health, taking into account the individual and the social–environmental context. This way of thinking may be particularly useful about sleep. For example, when conceptualizing healthy sleep duration and quality, it is difficult to form a comprehensive understanding without taking into account work, family, and other contextual factors.

Health Effects of Sleep Deprivation

Sleep deprivation, whether in the laboratory or in "real-world" settings, is associated with a myriad of adverse outcomes. Any comprehensive summary would be beyond the scope of any single chapter. Of the outcomes that have been studied, effects can be generally conceptualized as neurocognitive (including stress, emotional processing, decision making, attention, and memory) and/or cardiometabolic (including obesity, cardiovascular disease, and diabetes).

Sleep-deprived persons report increased stress, and it is believed that both sleep loss and stress impact mood and emotion. Minkel et al. [7] compared stress handling in sleep-deprived participants with rested controls and reported greater subjective stress, anxiety, and anger in sleep-deprived participants than in rested controls following exposure to a low-stressor condition. High-stressor conditions did not produce varied response. Sleep deprivation may thus lower the psychological threshold for perception of stress from cognitive demands but does not selectively increase response magnitude to high stress performance demands [7]. In an earlier study, the same group had demonstrated that sleep-deprived healthy adults have less emotional expressiveness, especially in response to positive stimuli [8].

Van der Helm et al. investigated the impact of sleep deprivation on the ability to recognize the intensity of human facial emotions [9] in 37 healthy participants and randomly assigned them to total sleep-deprived (TSD) and sleep control (SC) group. This study found that sleep deprivation selectively impairs the accurate judgment of human facial emotions, especially threat relevant (anger) and reward relevant (happy) categories. This study suggests that sleep loss impairs discrete affective neural systems, disrupting the identification of salient affective social cues [9].

Many studies have examined the relationship between habitual short sleep duration and cardiometabolic disease [10, 11]. For example, a number of studies have found associations with obesity [10, 12–14], cardiovascular disease [10, 12, 15–18], stroke [12, 19], and diabetes [11, 12, 20–25]. Proposed mechanisms for these relationships include behavioral and physiological factors. Regarding behavioral factors, short sleep has been associated with overall unhealthy lifestyle choices [26–29] that could predispose to these conditions. Regarding physiological factors, four potential mechanistic pathways linking short sleep to cardiometabolic disease have been identified, representing metabolic, inflammatory, and sympathetic.

The metabolic pathway is represented by studies that have focused on food intake, insulin/glucose function, and secretion of hormones that play important roles in hunger and satiety [30]. Several studies have examined the role of sleep in food intake [31]. Overall, studies of laboratory samples have shown that acute sleep deprivation associated with an increase in energy intake of about 500 kcal per day [32–35]. In particular, the increase in energy intake seems largely confined to after dinner [34, 35]. Some studies have shown that acute sleep deprivation is associated with decreased leptin secretion and elevated ghrelin secretion. Leptin is a hormone secreted by adipose tissue and can be used as a marker of adiposity [36–38]. Some population-level studies have found that short sleepers secrete less leptin [39–44]. But this is complicated by the finding that short sleepers are more likely to be obese, thereby secreting more leptin due to more adipose tissue. This may explain why some studies have shown that short sleepers secrete more leptin overall [45, 46]. Ghrelin, a complement to leptin, is a hormone secreted by the stomach and tends to signal hunger [47–51]. Studies in the population have shown mixed results, perhaps due to a lack of sampling across the day and night [40, 41, 44, 52, 53]. The leptin/ghrelin system represents one aspect of the proposed metabolic pathway. The other main component is the insulin/glucose system. Studies in the laboratory show that acute sleep deprivation leads to temporary insulin resistance [54–60]. In addition, population-level studies have shown that habitual short sleepers are more likely to have diabetes, even using objective criteria including impaired fasting glucose [61].

The inflammatory pathway may also be relevant for the development of cardiometabolic disease. Inflammatory process contributes to all stages of cardiovascular disease, from the development of atherosclerostic plaques in the vascular wall to end-stage thrombotic complications [62]. Several studies have shown that acute sleep deprivation results in a pro-inflammatory state; in particular, studies have shown that sleep deprivation is associated with elevated levels of tumor necrosis factor alpha (TNF-α) [63, 64], interleukin-6 (IL-6) [63, 65, 66], and C-reactive protein (CRP) [66, 67]. Population-level studies have also shown short sleep to be associated with elevated TNF-α [68], IL-6 [69, 70], and CRP [15, 71].

The role of the sympathetic nervous system in the development of cardiovascular disease is well described [72, 73]. One of the primary mechanisms is through the hypothalamic–pituitary–adrenal (HPA) axis, which represents the regulatory/secretory system that induces the release of corticosteroids such as cortisol and catecholamines such as epinephrine (EPI) and norepinephrine (NE). For example, this is key in regulation of blood pressure [74, 75]. Several studies have shown that short sleep is associated with increased blood pressure [76, 77], and this may be reflected in 24-h blood pressure variability [78], which may represent downstream effects of HPA axis activation. A recent study showed that one of the mechanisms by which sleep deprivation disrupts insulin signaling is via alterations in protein kinase B phosphorylation in adipocytes [58]; it should be noted that the primary upstream signal for this process is sympathetic nervous system. In addition, several studies have shown that insufficient sleep is associated with increased HPA axis activity [79–84].

For example, Robertson and colleagues showed that even minor reductions in sleep duration lead to changes in insulin sensitivity, body weight, and other metabolic parameters which vary during the exposure period [85]. Further, short sleep duration is a significant independent risk factor for hypertension [86] and diabetes [87], perhaps because short sleepers demonstrate elevated ghrelin, and reduced leptin, which are likely to increase appetite, thus possibly explaining weight gain associated with short sleep duration [41].

Other systems have been implicated as well. For example, Specker and colleagues investigated the effect of chronic sleep deprivation on bones in 1146 individuals by performing bone measurements on distal radius, spine, and hip [88]. The study then compared bone measurements between sleep-deprived and sleep adequate individuals after controlling covariates. The study found that sleep-deprived women had lower bone mineral density than sleep adequate women

and sleep-deprived men had lower levels of torsional bending strength, relative to than sleep adequate men.

Effects Across Age Groups

Sleep deprivation has implications across the age spectrum. For example, sleep-deprived adults manifest symptoms including daytime sleepiness, psychomotor slowing to impaired cognition, and memory. In contrast, children are more likely to present with emotional and behavioral symptoms, including aggressive and delinquent behaviors, attention and social problems, anxiety/depression, and hyperactivity. A number of studies have tried to elucidate the impact of sleep deprivation on children. Fallone and colleagues studied children aged 6–12 years and found a direct effect on academic performance and attention problems associated with reduced in sleep opportunity, even among students that had no prior history of behavioral or academic problems [89]. Touchettte and colleagues found that patterns of persistent short sleep duration or tendency for short sleep duration in childhood (2.5–6 years) predict high hyperactivity and impulsivity scores and poor performance on neurodevelopmental tasks at time of school entry (ages 5–6 years) [90]. A subsequent study aimed at investigating risk factors associated with short nighttime sleep duration and hyperactivity between ages 1.5 and 5 years using a large database of 2057 children found that children with high hyperactivity scores had a higher risk of short nocturnal sleep time (OR 5.1, 95 % CI [3.2–7.9]) than risk of finding high hyperactivity scores in short sleepers (OR 4.2, 95 % CI [2.7–6.6]). This, it may be the case that it is more plausible that hyperactivity may interfere with nighttime sleep duration rather than short sleep resulting in higher hyperactivity scores. Risk factors for having short sleep duration and high hyperactivity scores included male sex, low household income, lower maternal education and a pattern of receiving comfort outside the bed during nocturnal wakings at 1.5 years of age.

The trajectories of sleep problems between ages 4 and 16 years of age also correlate with general executive function at age 16 years [91]. Individuals whose sleep problems decrease more across time show better general executive control in late adolescence [91]. These findings suggest a probable critical period during childhood when disruptions to the stabilization and consolidation of sleep could very well result in the development of hyperactivity.

Other problems in children have been well documented. For example, the association between autism spectrum disorders (ASDs), attention deficit hyperactivity disorders (ADHDs), and disordered sleep has been commonly reported. Corkum and colleagues reported sleep problems in 25–50 % of children with ADHD [92]. Sleep problems are endemic to children with ASDs with a prevalence ranging from 40 to 86 % [93–96]. The prevalence of sleep disorders among children with ASD is higher than children with other development delays [97, 98] and is unrelated to intellectual quotient [99] or age [100]. In addition to these behavioral issues, several studies have documented poor health outcomes in sleep-deprived children, including metabolic syndrome [101] and visceral adiposity [102].

Questions regarding healthy adolescent sleep date back to 1975, when Webb and Agnew [103, 104] showed that on average, young people between the ages of 8 and 17 were getting 1.5 h less sleep per night than their counterparts did in 1910 and 1911. Since then, various studies and surveys have reported some degree of disrupted or deficient sleep in adolescents. According to the National Sleep Foundation, teens need between 8.5 and 9.25 h of sleep per night, with some laboratory data indicating that 9.2 h is optimal; thus, sleep deprivation can be defined as anything under about nine hours per night. Yet experts generally agree that most adolescents achieve less sleep. After analyzing data from a 2007 Youth Risk Behavior Survey data of US high school students, McKnight-Eily and colleagues found that nearly 70 % reported getting less than eight hours of sleep on school nights [105]. Emphasizing the value of awareness of the impact of sleep insufficiency, the authors agreed with other experts that chronic sleep deprivation in adolescents stems from "social, employment, recreational, and academic pressures as well as biologic changes" in the sleep–wake cycle.

Sleep needs do not markedly decline after puberty, perhaps because of the increased metabolic expenditures associated with growth during adolescence [106]. Yet Wolfson and colleagues, in a study of 3120 American high school students, reported a reduction in total sleep time of 40–50 min and a decline in the average amount of sleep on school nights from about 7.7 h for younger students to about seven hours for older ones [107]. The same study found that 26 % reported that they "usually" sleep less than 6.5 h per night [107]. The sleep loss was due to increasingly later bedtimes, while rise times were reported to be more consistent across ages (likely due to standard school start times). Not surprisingly, in surveys, 13–24 % of adolescents have reported falling asleep in class at least once [107]. Although one recent study concluded that US children and adolescents do get between nine and 10 h per night, as recommended, [108], an accompanying editorial cautioned, "We are still far from understanding what a 'normal,' 'ideal,' or 'adequate' sleep duration is for an individual child to promote optimal health and functioning." [109]

Sleep time restores the neurocognitive functioning of brain [110, 111]. Curcio et al. [112] asserted that insufficient sleep in adolescence impairs behavioral, physiological, and neurocognitive processes vital for learning capacity and

academic performance. Several studies involving actual manipulation of sleep in teenagers and college students have documented the effects of lack of sleep on cognitive functioning, showing impairment of psychomotor abilities, increase in sleepiness, poor memory and computational speed, reduced cognitive achievement, reduced awareness of cognitive impairments, and impaired performance on verbal creativity and abstract thinking [112]. Although the relationship between compromised neurobehavioral functioning and insufficient or disrupted sleep has been well studied in adults, relevant literature on children and adolescents is limited. That said, sleep disruptions in adolescents have also been associated with memory and attention deficits and declines in academic performance [107, 113]. McKnight-Eily and colleagues found that insufficient sleep was associated with many high-risk behaviors; for example, sleep-deprived teens were more likely to engage in physical fighting; seriously consider suicide; and use cigarettes, alcohol, and marijuana [105].

The response to a life stressor may be different among sleep-deprived adolescents. Talbot et al. investigated the impact of sleep deprivation in adolescents and adults on affective functioning and found that participants reported a greater increase in anxiety during a catastrophizing task when sleep deprived than when rested [114]. Further, chronic sleep restriction among adolescents may increase suicidal risk. Lee et al. [115] recruited 8530 students to investigate the association between behaviorally induced insufficient sleep and suicidality. They reported that adolescents with behaviorally induced insufficient sleep syndrome (BISS) had higher SSI score than those who slept 7 h or more on weekdays. They also found that weekend oversleep was associated with suicidality independently of depression, daytime sleepiness, snoring, and insomnia.

Effects Across Racial/Ethnic Groups

Several studies have attempted to understand whether habitual sleep patterns differ according to race/ethnicity group. Ruiter and colleagues [116] conducted a meta-analysis that found that Blacks/African-Americans obtained approximately 28 min less polysomnographic sleep than Whites; they also obtained less slow-wave sleep. These findings are consistent with those of other studies, who found that Blacks/African-Americans obtained less slow-wave sleep [117–121] and had a poorer sleep efficiency [119, 121] than non-Hispanic Whites. This suggests that, on average, for Blacks/African-Americans, sleep is less deep and less restful. Similarly, this meta-analysis evaluated 6 studies of subjective sleep duration [116] that found a similar pattern, with Blacks/African-Americans reporting less sleep on average than Whites (15.1 min less, $p < 0.05$) [116]. A few studies compared sleep among racial/ethnic groups using wrist actigraphy. Several studies reported significantly shorter mean sleep duration and poorer sleep quality for minorities compared to Whites [122–124]. Many of these effects persist after adjustments for socioeconomic factors.

Another approach that has been taken is to evaluate whether people of various groups are more or less likely to report sleep duration by category (usually short or long, relative to normative [7–8 h]). Hale and Do [125] found that, relative to non-Hispanic White Americans, Blacks/African-Americans, non-Mexican Hispanics, and those in the "Other" category were more likely to be short sleepers. Regarding long sleep duration, the only group that was more likely than non-Hispanic Whites to be long sleepers (9 or more hours) was Blacks/African-Americans. Similarly, Nunes and colleagues found that Blacks/African-Americans were less likely to report sleep of 7–8 h, versus non-Hispanic Whites, with increased likelihood of both short and long sleep [126] and Stamatakis and colleagues [127] found that African-Americans were about twice as likely to be short sleepers, and those in the "Other" category were approximately 50 % more likely.

In a more recent study, Whinnery and colleagues examined nationally representative data from the 2007–2008 National Health and Nutrition Examination Survey [128]. The sleep duration categories examined were very short sleep (less than 5 h), short sleep (5–6 h), and long sleep (9 or more hours), compared to normal sleep duration (7–8 h). Those who identified as Black/African-American were approximately 3 and a half times as likely to be a very short sleeper; similarly, non-Mexican Hispanics/Latinos were approximately 3.5 times as likely and Asians/Others were approximately 5 times as likely to be a very short sleeper. Regarding short sleep, those who identified as Black/African-American were about twice as likely to be short sleepers, and those who identified as Asian/Other were approximately 2 and a half times as likely. Mexican–Americans were 60 % less likely to be long sleepers.

This study also examined the degree to which these relationships are attenuated by other factors, including age, sex, relationship status, primary language spoken at home, immigration status, education, income, access to health insurance, home ownership, and food security. Self-identified Blacks/African-Americans were approximately 2.5 times as likely to be very short sleepers and approximately twice as likely to be short sleepers. Mexican–Americans were approximately 60 % less likely to be long sleepers. Non-Mexican Hispanics/Latinos were approximately 2.7

times as likely to be very short sleepers, and Asians/Others were approximately 4 times as likely to be very short sleepers and twice as likely to be short sleepers [128].

It is possible that sleep plays an important role in health disparities. Knutson and colleagues [129] found that racial differences in 5-year change in blood pressure were mediated by differences in sleep duration. In another study, Grandner and colleagues [15] found that the relationship between sleep duration and C-reactive protein (a cardiovascular risk marker) differed by race. Grandner and colleagues also examined whether the relationship between sleep duration and cardiometabolic disease risk depended on race/ethnicity [61]. For all outcomes (self-reported and objectively determined hypertension, hyperlipidemia, diabetes, and obesity), race/ethnicity by sleep duration interactions was significant (all $p < 0.0001$). <Query ID="Q2" Text="The significance of symbol P has been represented by both P and p, and needs to be consistent throughout the text. Please check and amend as necessary".–> When the sample was stratified by self-identified race/ethnicity, different patterns emerged.

Effects for Men and Women

Though the response to altered sleep homeostasis is uniform in general, variation based on gender has been studied across different age groups. In a study aimed at examining gender differences in sleep habits in 11–13 year olds, Natal et al. [130] studied a cohort of 200 students based on a questionnaire. The authors found that girls displayed longer sleep duration over the weekend in comparison with boys.

Arber et al. [131] studied gender and socioeconomic patterning of self-reported sleep problems in Britain using the British Psychiatric Morbidity Survey 2000. The authors report that women reported significantly more sleep problems than men, as did the divorced and widowed compared with married respondents. After adjusting for socioeconomic characteristics, the sleep problems were halved, suggesting a major role for socioeconomic status in these gender differences.

Rodriguez-Munoz et al. [132] studied 240 physicians in Madrid with the aim to assess insomnia and sleep quality in primary care physicians. The study reported a higher frequency of insomnia among women (23 %) compared to men (9.6 %). This relationship between gender and insomnia remained significant even after controlling sociodemographic variables. In terms of sleep quality, as defined by Pittsburgh Sleep Quality Index (PSQI) score of 5 or more than 5, the study reported women scored significantly higher than men on global sleep quality. Sleep problems were more prevalent among women than men (40 vs. 25.3 %).

Goel et al. [133] studied gender differences in polysomnographic sleep in 31 young men and women over a three consecutive overnight sessions in a sleep laboratory. They concluded that women have better sleep quality (shorter sleep onset latency, higher sleep efficiency) compared with men. Yet women of all adult age groups have been found to report more sleep problems, such as inadequate sleep duration and insomnia [134, 135].

Similarly, the susceptibility to various sleep disorders and their consequences differ among men and women. Morrish et al. [136] compared the mortality risk of men and women who were diagnosed with obstructive sleep apnea and were receiving treatment with CPAP between 1995 and 1998 by reviewing hospital records of 292 men and 47 women. Eighty percent of men died compared to 23 % of women ($p = 0.003$). There was a 3.44 greater mortality risk of women diagnosed with OSA and treated with CPAP, mostly due to greater comorbidity. Also, Johnson et al. [137] studied 1014 adolescents from a random sample of an urban health maintenance organization population and found no difference in risk of insomnia in prepubertal girls compared with boys—but the onset of menses in girls conferred a 2.75-fold increased risk of insomnia.

Effects According to Relationship Status

Sleep and spousal relationship/cohabitational status have been a topic of much recent interest. Various studies have tried to decipher the exact nature of such relationship. Troxel et al. [138] conducted an observational longitudinal study aimed at finding associations between marital status and cohabitation history and sleep in midlife women. The authors reported that at the time of the study, partnered women had better sleep quality than unpartnered women; however, with covariate adjustment, most of these associations become nonexistent. Additionally, the prior history showed advantages in sleep for women who were consistently partnered versus women who weren't consistently partnered. This association persisted even after covariate adjustment.

Research suggests that divorced individuals, particularly women, have higher rates of sleep disturbances as compared to married individuals [139]. However, all marriages and marital relations are not equal. So does marital quality translate into better sleep? This was explained by Troxel et al. [140] in a multi-site, multiethnic, community-based study that examined the association between marital happiness and self-reported sleep disturbances in a sample of 2148 midlife women drawn from the Study of Women's Health Across the Nation (SWAN). The Dyadic Adjustment Scale was used to assess marital happiness, and sleep disturbance was assessed using 4 items from the Women's Health Initiative Insomnia Rating Scale (WHIIRS). After controlling for relevant covariates, maritally happy women reported fewer sleep disturbances, with the association evident among Caucasian women and to a lesser extent among

African-American women. In an earlier study, Troxel et al. in 2007 [141] had found that women with bed partners display better sleep efficiency and that married women have shorter sleep latencies as compared with never-married women.

Effects Across Different Occupations

A number of epidemiological studies have suggested [142] an association between shift work and various health problems, such as heart disease [143], ischemic stroke [144], depression [145], metabolic syndrome [146], gastrointestinal ulcers [147], cancer, [148, 149] obesity [150], gastrointestinal dysfunction [147], reproductive problems [151], and some of the adverse pregnancy outcomes [152]. Evidence for the strength of causality of shift work per se for some of these health consequences has been challenged [143]. Translating these studies to predict individual risk of these consequences is required.

Shift work is a stressor that may result in the expression of physiological and psychological vulnerabilities specific to the individual. These vulnerabilities are likely associated with the individuals' genetic and environmental risk of impairment, disability, or disease expression. Further prospective research studies have been sought to clarify the strength of the association between shift work and chronic disease [142]. Furthermore, additional research on the mechanisms underlying reported increased health risks is needed. Among the variety of possible mechanisms and plausible explanations for such an association, which includes vulnerability to circadian rhythm disorder, reduced circadian amplitude, light exposure at night, food intake at inappropriate internal biological times, misalignment of circadian clocks in brain and peripheral tissues, and interactions among the above and with individual differences in disease risk, deficient and discrepant sleep lies at the forefront. Sleepiness, fatigue, cognitive impairment, and impaired sleep have been reported as the immediate consequences of shift work that impact workers simultaneously [153, 154].

Sleepiness and fatigue may reach clinically significant levels thoroughly effecting job performance and predisposing to accidents. Involuntary sleep episodes are more common during the night shift. Risks of errors and accidents appear to be higher among shift workers. Nearly a threefold increased risk of occupational accidents has been reported in shift workers compared with day workers, with increased risk of accidents reported in healthcare workers, police, and commercial drivers, and in all shift workers on the job and during the commute home. The risk of vehicle, aviation, and industrial accidents is highest at night, especially in the early-morning hours.

Shift workers may also underestimate their level of cognitive impairment, providing false confidence as demonstrated by findings of cumulative impairment in performance with little change in subjective alertness during circadian misalignment. Johnson et al. [155] in a study examined how sleep deprivation influenced psychomotor performance of a sample of 289 nurses who worked the night shift. Fifty six percent of the sample was sleep deprived, and a significant inverse relationship between psychomotor performance and hours of sleep was found.

Impact on Driving Accidents

Acute sleepiness in car drivers significantly increases the risk of a crash in which a car occupant is injured or killed. Reductions in road traffic injuries may be achieved if fewer people drive when they are sleepy or have been deprived of sleep or drive between 2 a.m. and 5 a.m. Connor et al. [156] examined the contribution of driver sleepiness to the causes of car crash injuries and assessed the risk of serious injury to car occupants in a case–control study. They reported a strong association between measures of acute sleepiness and the risk of an injury crash. Increased risk was associated with drivers who identified themselves as sleepy (Stanford sleepiness score 4–7 v 1–3; OR 8.2, 95 % CI 3.4–19.7); with drivers who reported 5 h or less of sleep in the previous 24 h compared with more than 5 h (OR 2.7, CI 1.4–5.4); and with driving between 2 a.m. and 5 a.m. compared with other times of day (OR 5.6, 1.4–22.7). No increase in risk was associated with measures of chronic sleepiness. The population attributable risk of driving with one or more of the acute sleepiness risk factors was 19 % (15–25 %).

Howard et al. studied the cumulative effect of extended wakefulness and low-dose alcohol on simulated driving and vigilance and found that both had significantly bad effects on reaction time and concentration lapse, as well as variation in lane position and speed, with extended wakefulness (18–21 h) combined with low-dose alcohol (0.03 % BAC) resulted in greater variation in more lapses ($t = -2.75$, $P < 0.05$) and greater variation in lane position ($t = -3.94$, $P < 0.01$) and speed ($t = -2.79$, $P < 0.05$) than did a BAC of 0.05 % in a rested state. Thus, avoiding alcohol even in lesser concentration after prolonged wakefulness may reduce accident risk.

The risk of human error-related accidents has been reported to increase with sleep deprivation [157]. The overall prevalence of insufficient sleep in adults has been estimated at 20 % [158]. The most common measure in population-based studies is daytime sleepiness. Breslau et al. in a study to determine the prevalence of daytime sleepiness, using interviews over 5.5 years to follow 1007 randomly selected young adults age 21–30 years, was performed in

southeast Michigan [159]. They found the average nocturnal sleep time during weekdays was 6.7 h and on weekends was 7.4 h. Daytime sleepiness was inversely proportional to hours slept, and difficulty falling asleep was more prevalent in single adults with a full-time job.

Studies in young adults indicate that 8–9 h of extended nocturnal sleep is needed to resolve sleepiness caused by decreased sleep time [160, 161]. The apparent chronic partial sleep deprivation of the young adults surveyed in 1997 complements statistics that find young drivers, especially males, at much higher risk of drowsy driving and sleep-related crashes [162]. Accidents related to sleep deprivation have been estimated to have an annual economic impact of $43 to $56 billion [163]. Motor vehicle accidents related to fatigue, drowsy driving, and falling asleep at the wheel are particularly common but often underestimated [164, 165]. Increased time awake, nocturnal circadian phase, reduced sleep duration, prolonged driving duration, and use of soporific medications have all been found to contribute to the occurrence of drowsy driving and fatigue-related motor vehicle crashes [162, 166, 167]. Studies of shift workers, truck drivers [168–170], medical residents [171, 172], and airline pilots [173–176] show an increased risk of crashes or near misses due to sleep deprivation. Sleepiness-related motor vehicle crashes have a fatality rate and injury severity level similar to alcohol-related crashes [162]. Sleep deprivation has been shown to produce psychomotor impairments equivalent to those induced by alcohol consumption at or above the legal limit [177]. For example, in a study of simulated driving performance, impairments in lane-keeping ability after a night without sleep were equivalent to those observed at blood alcohol content (BAC) of 0.07 % [178]. Similarly, a study of professional truck drivers found that deficits in performance accuracy and reaction time at 28 h of sleep deprivation were equivalent to those found after alcohol intoxication (BAC at 0.1 %) [179]. It appears that as continuous daytime waking exceeds 16 h, psychomotor performance deficits increase to levels equivalent to BACs between 0.05 and 0.1 % [177, 179]. Sleep deprivation poses a risk to safe operation in all modes of transportation and to performance in other safety-sensitive activities.

A recent study by Maia and colleagues sheds some light on the potential for sleep deprivation to be involved in driving accidents in the general population [180]. It should be noted that there are no published reports linking objective habitual sleep data to actual driving records. But data from the Behavioral Risk Factor Surveillance System examined drowsy driving behaviors in a population sample. The study by Maia and colleagues found that increased rates of drowsy driving were seen among those reportedly getting 6 h of sleep (per 24 h) or less. This study also allowed for the analysis of an important potential mediating factor: perceived sleep insufficiency. This survey also included an item evaluating how many days in the past month the respondent did not feel that they got enough rest or sleep. It was hypothesized that when the analysis was constrained to only examine individuals who said that they were always fully rested (i.e., 0 nights of insufficient sleep), that these effects would be mitigated. However, the opposite was true. Even in those who felt fully rested, those reporting habitual sleep duration of 6 h or less were approximately 3 times as likely to also endorse reports of drowsy driving. Thus, drowsy driving is not only more common among those who sleep 6 h or less on average, but this risk is not mitigated by feeling fully rested. This is in line with laboratory research studies, which have shown that subjective levels of impairment are not well correlated with objective levels and often underestimate impairment [181].

Conclusions and Future Directions

Sleep deprivation remains an important, unmet public health problem. The effects of sleep deprivation and sleepiness (which often results) are wide ranging. The review in this chapter is only a brief overview of some of the important findings in this area. Individuals who are sleep deprived are more likely to be in poor health demonstrate neurocognitive deficits, have decreased longevity, and experience problems in many functional domains. One of the most salient of these is in driving accidents, many of which are at least partially caused by sleep deprivation. These are issues of not only public health, but also public safety [182] and economic productivity [183]. The consequences of sleep loss are felt across the population. Across the age spectrum, there are unique issues that face children, adolescents, adults, and the elderly [184, 185]. Unique problems also exist for both men and women [186, 187]. The effects of sleep loss may particularly be salient for racial/ethnic minorities, who may be at greater risk of sleep problems [128, 188]. And the social role of sleep is one that is being explored in both quantitative [189–191] and qualitative [192] domains.

The social–ecological model of sleep and health has emerged as a useful framework for conceptualizing the role of sleep at the nexus of physiology and the social environment. It conceptualizes downstream adverse effects of insufficient sleep duration and/or inadequate sleep quality as interconnected risk factors that eventually reduce longevity. And it conceptualizes sleep in the context of individual-level factors, which are embedded within social-level factors, which themselves are embedded within societal-level factors [5].

Still, there are many unanswered questions. The downstream mechanistic pathways linking sleep and important outcomes still need to be clarified. The potentially interactive roles of insufficient sleep duration and inadequate sleep

quality need to be discerned. Further, important social–environmental modifiers of these pathways such as race/ethnicity will aid in the understanding of why certain groups are at increased risk. These and other questions can be addressed, but will require innovative thinking that bridges the population-level experimental studies.

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Neurobiology of REM Sleep, NREM Sleep Homeostasis, and Gamma Band Oscillations

5

James T. McKenna, Mark R. Zielinski, and Robert W. McCarley

Introduction

In modern times, sleep disturbance and disorders are an extremely relevant public health issue [1, 2]. Sleep disturbance due to vocational demands contributes to decreased work performance, as well as increased accident rates and health costs. Sleep disorders including insomnia, narcolepsy, restless leg syndrome, and sleep apnea impact much of the population. Understanding the basic neural mechanisms and circuitry involved in the regulation of vigilance states [wake, non-rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep] has led to the development of pharmacological and behavioral treatments for sleep pathologies. Scientific investigations conducted in the last century have begun to describe molecular, cellular, and complex neural systems responsible for regulating the vigilance states. Much of what we know is due to investigations in animals employing cortical electroencephalogram (EEG) recordings, as well as pharmacological, electrophysiological, optogenetic, and molecular techniques. Furthermore, advances in neuroimaging, in addition to cortical EEG recording, have accelerated the investigation of sleep pathologies in clinical settings.

In this chapter, we present an overview of the circuitry and physiology involved in vigilance state regulation. Each of the three vigilance states is reviewed, focusing on investigations describing electrophysiological characteristics, relevant brain nuclei/regions, neuroanatomical interconnections, and neurotransmitters. We pay particular attention to the role of NREM sleep in homeostasis and review the two-process model of sleep regulation, in which sleep is influenced by both homeostatic (Process S) and circadian (Process C) processes. Herein, we review recent interest in the gamma band oscillation (i.e., ~40 Hz EEG frequency range), a particular high-frequency cortical oscillatory potential seen largely during wake and REM sleep, which plays a major role in attention and memory processing.

Wakefulness

EEG Profile of Wakefulness

In the 1920–1930s, the EEG profile of wakefulness and sleep was first described as changes of electrical cortical amplitude and frequency reflected in wakefulness or sleep [3–5]. Wake characteristics in the EEG largely include low-voltage, high (fast) -frequency activity indicative of cortical activation (Fig. 5.1). Wakefulness is also associated with relatively high muscle tone and movement assessed by electromyogram (EMG) recordings, and eye movements revealed by the electrooculogram (EOG). Wake-indicative cortical activation in humans consists of predominant frequency wave bands in the alpha (8–13 Hz), beta (>13–20 Hz), and gamma (usual EEG frequency around 40 Hz) range. Theta field oscillations in the 4 ≤ 8 Hz range are also seen in the cortical EEG during wake, usually accompanying movement, attention, and cognitive processing.

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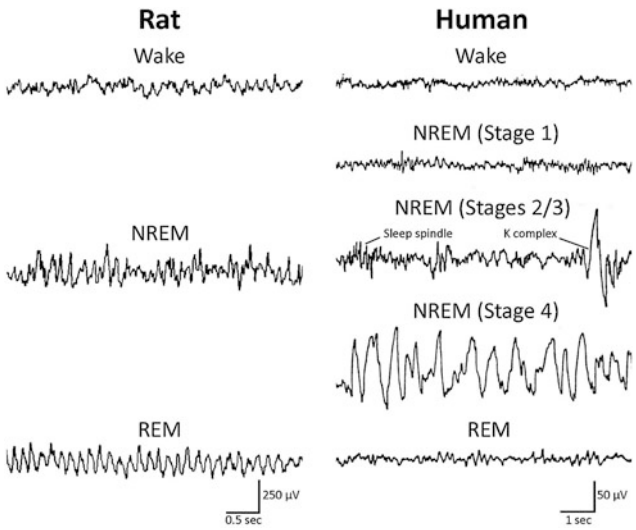

Fig. 5.1 Electroencephalographic (EEG) recordings of vigilance states (wake, NREM sleep, and REM sleep) in the rat and human. Wake in both species is characterized by cortical activation, of largely low-amplitude/fast-frequency activity. NREM sleep in the rodent is usually not differentiated between stages and exhibits large-amplitude delta (1–4 Hz) EEG activity. NREM sleep in humans is classified into 4 stages. In the first stage, the EEG frequency begins to slow, exhibiting alpha and theta activity. Both sleep spindles (7–14 Hz) and K-complexes are seen in NREM stage 2, as EEG amplitude increases and frequency further slows. In NREM sleep stage 4, also known as slow wave sleep, strong delta (1–4 Hz) activity of large amplitude is seen. During REM sleep, the EEG returns to a profile similar to wakefulness, with low-amplitude and high-frequency activity. In the rodent, the EEG exhibits strong theta (5–8 Hz) activity, most likely generated by the hippocampus. Human EEG recordings adapted [366]

Recent Neuroscience Technologies for Sleep Investigations

In recent years, new technologies in the field of neuroscience have been developed that are excelling our understanding of sleep and sleep-related disorders. The advent of optogenetic technologies now allows neurotransmitter-specific excitation and inhibition of neuronal populations [6, 7]. Light-activated ion channels (opsins) packaged in viruses (e.g., adeno-associated) are first intracerebrally injected in mice expressing Cre in specific populations of neurons. The neurotransmitter-select neuronal population of interest may then be excited or inhibited by means of light stimulation at the scale of millisecond precision. An alternative novel technique is the pharmacogenetic excitation or inhibition of select neuronal populations by means of Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), in which cell type-specific expression of G-protein coupled receptors may be excited or inhibited by means of injection of select ligands such as inert clozapine-*N*-oxide [8, 9]. Cellular activation employing this technique, though, does not allow such precise temporal resolution as with optogenetics.

Gamma Band Oscillations (GBO)

Recent evidence points to the importance of GBO in the activated cortical EEG. During wake, the cortical EEG exhibits a predominance of low-amplitude beta (15–30 Hz) and gamma (30–120 Hz) cortical EEG activities. Neural signal transmission is enhanced as GBO occur, produced by the synchronized firing of cortical neuronal populations, providing a mechanism for coding information [10–12]. GBO abnormalities are symptomatic in various pathologies including schizophrenia, autism, and sleep disorders, and a strong association has been established between GBO and attention, perception, and memory [10, 13–15]. Moreover, GBO are enhanced after sleep deprivation largely in the prefrontal and frontal cortices of humans, suggesting an important sleep-related role of gamma rhythms [16].

Neural Mechanisms of GBO

Gamma rhythms are generated locally in the cortex by neural networks in which gamma-aminobutyric acid (GABA)ergic cortical interneurons containing the calcium binding protein parvalbumin (PV) interact with glutamatergic pyramidal cells (Fig. 5.2). Rhythmic fast-spiking inhibition of pyramidal cells produces GBO in the cortical EEG, and GBO frequency is set by the rate of depolarization and hyperpolarization of cortical PV and pyramidal neurons [17]. Electrophysiological investigations have shown that cortical PV neurons fire in phase with cortical EEG field oscillatory activity, especially GBO [18, 19]. GABA-A receptor antagonists applied to the hippocampal and cortical slice block GBO [20, 21]. Optogenetic excitation of cortical PV interneurons promoted GBO, and inhibition reduced GBO [13, 15, 22]. In magnetic resonance spectroscopy neuroimaging studies, cortical GABA levels increased during performance of a GBO-eliciting visual task [23, 24].

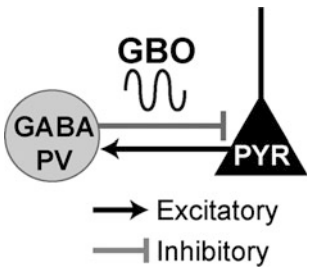

Fig. 5.2 Cortical circuitry generating gamma band oscillations (*GBO*). GBO are generated in the cortex by rhythmic fast-spiking GABAergic, parvalbumin (*PV*) cortical interneuronal inhibition of glutamatergic pyramidal cells. Returning glutamatergic projections excite PV GABAergic interneurons, enhancing oscillatory activity. Interneuronal–interneuronal mutual inhibitory connections between PV neurons, as well as electrical synapses and gap junctions, further promote synchrony (not illustrated)

Gamma band oscillations rhythmic activity is influenced by glutamatergic input from pyramidal cells back to GABA/PV neurons, as well as GABA/PV interneuronal–interneuronal interactions. Furthermore, synchronous PV rhythmic activity is promoted by gap junctions between cortical PV interneurons [25, 26]. In vitro investigations were able to elicit gamma oscillations in cortical slices, indicating that gamma oscillations are generated locally within the cortex [21, 27], and in vivo investigations also indicated that gamma oscillations are locally generated [28].

GBO During Wake

Many investigations indicate that synchronization of GBO between cortical subregions during wake provides a neural mechanism for intracortical communication [29–35]. The amplitude and synchrony of GBO correlated with the challenge/level of difficulty in a working memory task [36]. Recently, a strong correlation has been established between functional magnetic resonance imaging (fMRI) blood oxygen level-dependent (BOLD) signals and local GBO oscillatory activity [37, 38]. Although the temporal resolution of the BOLD signal is too slow to demonstrate GBO, these studies suggest that during select tasks that involve GBO, co-activation of cortical subregions occurs, possibly by means of direct anatomical connections, as well as synchronization by slower hippocampal and cortical oscillations, including theta and delta activity (also referred to as slow wave activity) [17].

Early Investigations of Wake-Regulating Neural Circuitry

During the 1920s, a worldwide epidemic of encephalitic lethargica led to many patients suffering from hypersomnia (i.e., excessive sleepiness). Von Economo analyzed the postmortem tissue of these patients and reported pathological damage in brain tissue located just posterior to the hypothalamus, at the junction of the mesencephalon and diencephalon [39]. A smaller subpopulation of encephalitic lethargica patients exhibited excessive wake, producing profound insomnia, and neurodegeneration was particularly noted in the hypothalamus. It was therefore concluded that an ascending system that involved subcortical projections to the cortex was involved in promotion of wake, and a sleep-inducing brain region resided in the hypothalamus. Later studies confirmed that these same brain regions play a role in the neural circuitry of the ascending reticular activating system (ARAS), reviewed below.

Frederick Bremer in the 1930s performed transection studies in the cat to identify brain regions that promote wakefulness [40, 41]. In one investigation, a particular transection/cut was made in the lower part of the medulla, termed *encéphale isolé*, which did not affect the cortical EEG profile. In another preparation, called *cerveau isolé*, a transection was made at the intercollicular region of the midbrain, rendering the animal in a sleep-like state. These findings suggest that the transition to and maintenance of sleep involve a disconnection of subcortical and cortical brain regions.

Moruzzi and Magoun demonstrated that stimulation of the brainstem reticular formation was very effective in eliciting a cortical EEG profile indicative of wake [42]. The concept of the ascending reticular activating system (ARAS) (Fig. 5.3) was then developed, describing the ascending circuitry originating in the reticular formation that is responsible for wakefulness [43–45]. The ARAS includes a dorsal and ventral pathway, both of which originate in the reticular formation, particularly the rostral pontis oralis (RPO). The dorsal pathway involves reticular formation input to thalamic nuclei that, in turn, strongly project to much of the cortex. Most of the ascending projections for this pathway are excitatory/glutamatergic, including reticular formation input to the thalamus and thalamocortical projections. The ventral pathway again involves projections originating in the reticular formation, now projecting to regions in the hypothalamus, namely the basal forebrain. The basal forebrain in turn sends direct connections to the cortex, again promoting wake. A number of studies have described strong input from the basal forebrain to widespread regions of the cortex, including cholinergic, GABAergic, and, to a lesser extent, glutamatergic basal forebrain input [43–45]. In addition, the medial septum/vertical limb of the diagonal band of Broca of the basal forebrain sends GABAergic and cholinergic input to the hippocampus. GABAergic input paces theta frequency oscillatory activity, seen during wake-related movement and select memory processing, as well as throughout REM sleep [46–48]. The ventral pathway involves glutamatergic output from the reticular formation, as well as basal forebrain glutamatergic projections terminating on the cortex. In addition, a multitude of other neurotransmitters, including acetylcholine, serotonin, noradrenaline, and the neuropeptide orexin, are involved.

Wake-Promoting Neurotransmitters

Acetylcholine

The excitatory neurotransmitter acetylcholine is localized in two essential brain nuclei significantly involved in wake promotion. The first brain region is located in the midbrain tegmentum, including the laterodorsal tegmental (LDT) and pedunculopontine (PPT) tegmental nuclei. The second region is the basal forebrain and includes the medial septum/vertical limb of the diagonal band of Broca,

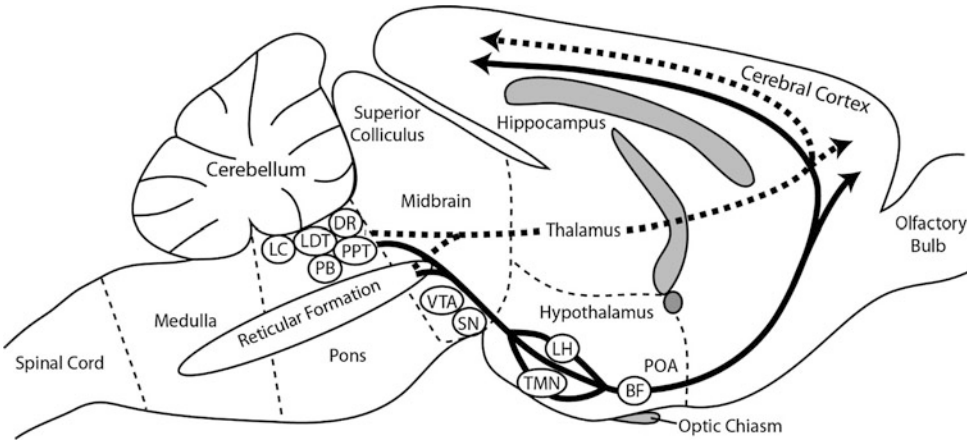

Fig. 5.3 Ascending reticular activating system (*ARAS*) promotes wakefulness. The dorsal pathway (*dashed*) originates in the reticular formation and neighboring dorsal raphe (*DR*), locus coeruleus (*LC*), parabrachial (*PB*), and laterodorsal (*LDT*) and pedunculopontine (*PPT*) tegmental nuclei. These regions project to thalamic nuclei that in turn send widespread projections to the cortex. The ventral pathway (*solid*) also originates in these same pontine and midbrain nuclei, which project directly to the basal forebrain (*BF*) of the hypothalamus, as well as indirectly through the lateral hypothalamic (*LH*) and tuberomammillary (*TMN*) nuclei. BF in turn projects diffusively to the cortex, promoting wakefulness. *POA* preoptic area; *SN* substantia nigra; *VTA* ventral tegmental area

horizontal limb of the diagonal band, magnocellular preoptic nucleus, substantia innominata, and nucleus basalis. Neurochemical measurement revealed increased levels of acetylcholine in the thalamus and cortex during both wake and REM sleep [49–52].

Electrophysiological recordings have revealed a significant association of basal forebrain neuronal activity with cortical activation [44, 45]. Investigations employing post hoc juxtacellular labeling and single unit recording in the head-restrained rat demonstrated that basal forebrain cholinergic neuronal activity was significantly elevated during wake and REM sleep, when compared to NREM sleep [53–56]. Due to optogenetic excitation of basal forebrain cholinergic neurons, there was an increase in transitions from NREM sleep to wake or REM sleep, overall amounts of wake increased, and stimulation during wake and REM sleep sustained cortical activation [57, 58], although recent optogenetic studies indicate that the wake-promoting effect of basal forebrain cholinergic neurons is less potent than that of basal forebrain GABAergic PV populations (see below).

Labeling of c-Fos, an immediate early gene, and its related protein in the brain is a useful tool to document neuronal activation associated with calcium influx [59, 60]. c-Fos activation was documented in basal forebrain cholinergic neurons immediately after the animal was sleep deprived, indicating that these neurons were indeed activated by sleep deprivation [61–63]. Furthermore, the amount of c-Fos activation correlated with the amount of wake observed in the preceding hour before sacrifice [61, 62]. Specific lesions of basal forebrain cholinergic neurons employing the neurotoxin saporin decreased wakefulness and cortical activation [45, 64–68]. Although various wake EEG indices were affected following basal forebrain lesions, wake state total amounts remained intact. Presumed GABAergic and glutamatergic cell populations in the basal forebrain remain following cholinergic-specific lesioning, suggesting that non-cholinergic basal forebrain neurons may also play a role in promotion of wake. Furthermore, alternative ascending systems that do not involve the basal forebrain also promote wake, such as the dorsal ARAS pathway.

LDT/PPT cholinergic neurons send extensive projections to the basal forebrain, thalamus, and cortex, providing multiple routes to influence cortical activation. Numerous electrophysiological studies have shown tegmental neuronal firing in relation to wake and REM sleep [45, 69, 70]. In a recent study employing juxtacellular labeling and single unit recordings, identified cholinergic LDT/PPT neurons exhibited increased firing in relation to cortical EEG during wake and REM sleep [71].

Serotonin

Most of all nuclei in the ARAS receive a serotonergic innervation originating in select brainstem/midbrain raphe nuclei, particularly the dorsal and median raphe [72–75]. Due to the variety of serotonergic receptors (14 subtypes at last count), the role of serotonin in the ARAS is quite complicated. Early work by Jouvet and colleagues reported that depletion of serotonin by means of *p*-chlorophenylalanine (PCPA) produced insomnia, leading to the initial proposal that serotonin is sleep promoting [76, 77]. Later investigations revealed that such serotonergic depletion also influenced body temperature and movement, hence promoting insomnia. Still later investigations concluded that serotonin acts to promote wake and inhibit REM sleep (our

current understanding). Brainstem dorsal raphe neurons are most active during wake, significantly decrease their activity during NREM sleep, and largely cease activity during REM sleep [78, 79]. Notably, juxtacellular labeling and single unit recordings revealed that most dorsal raphe neurons fire during wake, yet a smaller population were sleep active [80, 81], demonstrating the complex heterogeneity of serotonergic cell populations. Optogenetic cell-specific activation of dorsal raphe serotonergic neurons promoted wakefulness, at the expense of NREM sleep amounts [82].

Numerous pharmacological and genetic knockout investigations have also suggested a role of serotonin in wake promotion. Neurochemical measurement revealed that serotonin levels were highest during wake in the dorsal raphe, as well as many of its efferent targets including the anterior hypothalamus, basal forebrain/preoptic region, hippocampus, and frontal cortex [83–87]. Nevertheless, some studies were unable to demonstrate changes in serotonergic levels in brain regions including the cortex and hippocampus during sleep deprivation, again illustrating the complexity of the serotonin system in sleep regulation [87, 88].

Infusion of 8-hydroxy-2-dipropylaminotetralin hydrobromide (8-OH-DPAT), a largely selective 5-hydroxytryptamine (5HT)-1A receptor agonist, into the dorsal raphe nucleus promoted REM sleep, by means of activation of the 5HT-1A autoreceptor on these serotonergic neurons [89, 90]. Similar to these findings, 8-OH-DPAT activation of the 5HT-1A autoreceptor in the median raphe nucleus promoted hippocampal theta activity [91, 92], providing a mechanism by which the serotonergic median raphe may suppress theta activity indicative of REM sleep. Neonatal treatment of mice with the selective serotonin reuptake inhibitor escitalopram induced depression and anxiety-like behavior, as well as increased REM sleep [93]. The serotonin transporter knockout mouse expressed depression-like behavior, and levels of both REM sleep and serotonin were elevated [94–97]. Although these findings seem to contradict the proposed role of serotonin as a wake-promoting neurotransmitter, REM sleep promotion in the knockout mouse may be due to a down regulation of 5HT-1A receptors on cholinergic neurons in response to the increase in serotonergic tone. Neonatal introduction of compounds that block the 5HT-1A receptor in the serotonin knockout mouse reversed both behavioral and cortical abnormalities, including REM sleep stabilization [98].

Noradrenaline

Noradrenergic brain regions, particularly the brainstem locus coeruleus (LC), also play a major role in promoting wakefulness. The LC sends projections to a number of ARAS-related nuclei, including the basal forebrain, midline thalamus, and cortex [72, 73, 99–101]. Noradrenaline may act as an excitatory or inhibitory neurotransmitter, depending on the type of postsynaptic noradrenergic receptor. The majority of ARAS-related noradrenergic projections are excitatory, acting on α1 receptors [45, 102–105]. Noradrenergic projections to the sleep-related preoptic hypothalamic region, some cholinergic tegmental neurons, and the LC itself act on α2 receptors [106, 107]. LC neurons are most active during wakefulness, and largely cease activity during NREM and REM sleep [108–110]. Non-specific lesions of LC do not drastically alter vigilance states, though [111–115], suggesting that the LC may not be sufficient to alone produce wake, but still influences cortical activation. Recent studies suggest that stress-induced noradrenergic activation may contribute to insomnia, further suggesting that noradrenaline acts to promote wakefulness [116, 117]. Recently, cell-specific optogenetic excitation of noradrenergic LC neurons promoted NREM sleep to wake transitions, overall amounts of wakefulness, and locomotion [118]. Furthermore, optogenetic inhibition of these same neurons decreased amounts of wake and promoted the slow wave activity indicative of NREM sleep. Pharmacogenetic excitation of noradrenergic LC neurons by means of Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) produced cortical activation during isoflurane general anesthesia, as slow wave activity was reduced [119], again implicating noradrenergic systems as a major player in arousal.

Dopamine

Dopaminergic neurons, located in specific brain nuclei including the substantia nigra (SN) and ventral tegmental area (VTA), project to the basal forebrain and the cortex, and returning projections from a number of ARAS-related nuclei have been described [120–122]. Midbrain dopaminergic neuronal burst firing is associated with locomotion, select cognitive functioning, and reward [123–127]. Although single unit recordings were not able to directly correlate SN or VTA unit firing with changes in vigilance state [128], dopaminergic neuronal activity fluctuated across vigilance states, as burst firing increased in frequency during wake [122, 129–131]. Another population of dopaminergic neurons in the ventral periaqueductal gray expressed c-Fos immediately following sleep deprivation, indicating neuronal activation during wake, and these activated neurons were found to project to a number of forebrain ARAS-related nuclei [132]. Of note, treatment of narcolepsy with dopamine-stimulating compounds has proven somewhat successful, allowing stabilization of the vigilance state profile [133, 134].

Histamine

Histaminergic neurons located in the bilateral tuberomammillary nuclei of the hypothalamus (TMN) also play a role in

promotion of wake. Notably, first-generation antihistamines have a sedating effect, acting as antagonists on H1 receptors located on a number of wake-promoting nuclei [135]. Histaminergic TMN neurons project to a number of ARAS-related nuclei, including direct projections to the cortex [136–139]. Histaminergic neurons demonstrate a discharge profile similar to noradrenergic neurons, highly increased activity during wake and significantly decreased activity during sleep [140–142]. Levels of histamine in the posterior hypothalamus were highest during wake and decreased during both sleep states [143]. Both non-specific and histamine-specific lesions of TMN, as well as chemical manipulations, suggest that TMN histamine neurons are indeed wake promoting [141, 144]. Additionally, brain mast cells, which produce approximately 50% of brain histamine, are also implicated in promoting wakefulness [145].

Orexin

Recent investigations within the last 2 decades have described a specific population of neurons that express the neuropeptide orexin (also called hypocretin) in the perifornical (near fornix) region of the posterior hypothalamus. Neuroanatomical investigations revealed strong orexinergic input to ARAS wake-promoting nuclei [146, 147]. Orexinergic neurons fire most during wake, decrease activity during NREM sleep, and are largely silent during REM sleep, except for activation during occasional muscle twitching [148]. Levels of orexin are highest during wake in the lateral hypothalamus [149], and c-Fos studies revealed activation of orexinergic LH neurons immediately following sleep deprivation [150].

Optogenetic cell-specific stimulation of orexinergic neurons produced an increase in NREM–wake and REM–wake transitions [151]. Furthermore, these neurons preferentially fired at frequencies of 5–30 Hz, resembling the firing pattern recorded in orexinergic neurons during cortical activation. Optogenetic stimulation of noradrenergic LC neurons produced NREM sleep to wake transitions of a very short latency ($\sim$5 s) compared to orexinergic stimulation ($\sim$10–30 s), leading to the proposal that LC may be a primary effector of arousal [152]. Pharmacogenetic excitation of orexinergic neurons by means of DREADDs produced neuronal activation, reflected by c-Fos protein labeling, as well as increased time in wake at the expense of both NREM and REM sleep amounts [153]. Also, inhibition of orexinergic neurons with DREADDs decreased wake and elevated total amounts of NREM sleep.

Symptoms of the sleep disorder narcolepsy include hypersomnia, hallucinations, cataplexy, sleep-onset REM sleep, and sleep paralysis. Investigations in the narcoleptic canine model described a deficit in the orexin type 2 receptor [154]. Also, wake was significantly decreased in orexin knockout mice in which the orexin precursor prepro-orexin was deleted [155]. In these animals, the number of transitions between vigilance states was significantly increased, similar to that seen in narcoleptic patients [155]. Orexin-specific lesioning and genetic disruption studies produced a number of symptoms in animals similar to that seen in the narcoleptic, including increased state transitions and intrusion of REM sleep-like characteristics into wake [156–159]. Analysis of postmortem brain tissue collected from narcoleptics demonstrated a significant loss of orexin neurons [160, 161], and low cerebrospinal fluid levels of orexin were reported in cataplectic and narcoleptic patients [162, 163]. Recent investigations have attempted to reverse the neurodegeneration of orexin neurons in LH by means of systemic administration, gene transfer, and cell transplantation of orexin [164–169]. Furthermore, treatment of human narcoleptics with orexin improves a number of symptoms, including sleep abnormalities [169, 170].

Investigations in the narcoleptic canine model suggest that noradrenergic and serotonergic cell populations may play more of a role in the maintenance of muscle tone during wake, and histamine in maintenance of cortical activation. Cataplexy, such as seen during narcolepsy, involves a sudden loss of muscle tone, although consciousness remains. During cataplectic attacks in the dog, noradrenergic and serotonergic cell populations largely ceased firing, but histaminergic neurons remained active [142]. Histamine may therefore play a unique role in promoting wake, particularly cortical activation. Abnormalities in histamine levels in the CSF of narcoleptic patients have been reported [171, 172]. Notably, postmortem analysis of human narcoleptic tissue revealed a significant increase in the number of TMN histamine neurons [173].

Treatment of narcolepsy includes stimulant-like compounds, including dopamine reuptake inhibitors, which improve the sleep profile of the narcoleptic patient, and adrenergic, dopaminergic, and serotonergic reuptake inhibitors are effective in the treatment of cataplexy symptoms [45, 133, 134, 174]. Sodium oxybate has been shown to improve the sleep/wake profile and some cataplectic symptoms in narcoleptic patients [175–177]. Also, orexinergic antagonists are being pursued as a treatment for insomnia [178–180].

Gamma-Aminobutyric Acid (GABA) and Glutamate

In addition to sleep promotion, GABAergic neurons in the cortex and select subcortical regions, such as the basal forebrain, also play a role in the promotion of wake. GABAergic PV neurons play a necessary role in the generation and maintenance of cortical GBO, by means of interaction with cortical pyramidal neurons (reviewed above). Select basal forebrain cortically projecting GABA neurons have been shown to fire in relation to cortical GBO activity [56], and caudal basal forebrain lesions with ibotenic acid, presumably targeting GABAergic neurons, reduced cortical activation and

GBO [65]. A number of wake-promoting neurotransmitters, including those reviewed here, excite basal forebrain GABA neurons, which in turn may activate arousal systems that generate both cortical GBO and hippocampal theta rhythms [56]. Optogenetic excitation of basal forebrain GABAergic/PV neurons entrained GBO in the mouse [181]. In particular, 40 Hz optical stimulation of basal forebrain PV neurons increased cortical GBO. Thus, the basal forebrain and particularly its PV neuronal projecting population play a role in both promoting cortical GBO, as well as fine tuning the pattern of cortical activity during wakefulness.

As previously mentioned, both the dorsal and ventral pathways of the ARAS include glutamatergic excitatory projections. The dorsal pathway includes glutamatergic input from the reticular formation to the thalamus, as well as glutamatergic thalamocortical projections. The ventral pathway of the ARAS includes glutamatergic input from the parabrachial nucleus and reticular formation to the basal forebrain, and basal forebrain projections to the cortex include cholinergic, GABAergic, and, to a lesser extent, glutamatergic input.

Subcortical Modulation of GBO

Although GBO are generated locally in the cortex, subcortical input to the cortex influences GBO, beyond basal forebrain PV influence. Electrical stimulation of the brainstem reticular formation, and its presumed glutamatergic input to the hypothalamus and thalamus, promoted GBO, demonstrating that central activation of ARAS provides a mechanism of synchronization of different cortical subregions [182, 183]. Cholinergic brain nuclei of the ARAS promote high-frequency cortical oscillatory activity including GBO during wake and REM sleep [184–189]. Electrical stimulation of cholinergic brainstem tegmental neurons enhanced thalamocortical cell firing at gamma frequency, as well as the cortical GBO itself [190]. Lesions of basal forebrain cholinergic neurons attenuated high-frequency EEG activity, including GBO, particularly when lesions included the caudal basal forebrain cholinergic cell population [65, 68, 191–194]. Serotonin acts to inhibit cholinergic neurons in both the basal forebrain and tegmental zones [187, 195, 196], attenuating high-frequency beta and gamma activities [188].

NREM Sleep

EEG Profile of NREM Sleep

The cortical EEG profile of NREM sleep includes higher-voltage (amplitude) field oscillations, compared to wake, as well as a slowing of oscillatory activity frequency (Fig. 5.1). Human NREM sleep has been traditionally scored as four stages based on the Rechtschaffen and Kales (R and K) criteria [197]. More recently, the American Academy of Sleep Medicine suggested that NREM sleep may be classified in three stages [198]. N1, NREM sleep stage 1, includes a predominance of theta (4 < 8 Hz) and alpha (8–13 Hz) activity. N2, NREM sleep stage 2, includes both sleep spindles (described below) and K-complexes. K-complexes are brief high-voltage spikes of around 110 μV, and last approximately 0.5 s. They are unique to NREM stage 2 and are a combination of neocortical slow oscillations and spindles [44]. N3 includes that previously described by R and K criteria as stages 3 and 4. This stage is "deeper" NREM sleep, characterized by a predominance of slow delta frequency (1 < 4 Hz) oscillations, and therefore also called "slow wave activity" (SWA). Furthermore, throughout NREM sleep a neocortical slow oscillation (0.5–1 Hz) occurs, which plays a role in thalamic and intracortical synchronization, particularly synchronizing sleep spindles [44, 199–201]. During NREM sleep, EMG recordings exhibit lower muscle tone and little movement, and eye movement is usually absent. In rodent studies, stages of NREM sleep are usually not differentiated.

Sleep Spindles

Sleep spindles are most prominent in human NREM stage 2 [44, 45]. These spindles in humans are of the frequency of 11–16 Hz, lasting around 1 s, and are generated by interplay between the thalamic reticular nucleus (TRN) and thalamocortical neurons. Cortical EEG recordings in the mouse revealed an increase in cortical oscillatory activity of ~11 Hz during early NREM sleep, and also prominent during NREM–REM sleep transitions [202–204]. Sleep spindles promote the deafferentation of thalamocortical input to the cortex that is seen during NREM sleep, and GABAergic TRN neuronal activity particularly paces these oscillations [205, 206]. Optogenetic excitation of TRN GABAergic neurons induced burst firing in thalamocortical neurons, as well as produced cortical spindle activity [204] and increased the duration of NREM sleep [207]. LDT/PPT cholinergic input acts, in part, to inhibit TRN activity, thereby desynchronizing the TRN-thalamocortical oscillatory network and promoting wake and cortical activation [45, 206]. Moreover, basal forebrain neurons project to the TRN, particularly its rostral aspect [208], and chemical lesions in the basal forebrain attenuated spindle activity [209].

Sleep spindles are of current interest since they are markedly reduced in schizophrenia [210, 211]. Therefore, spindle activity is probably the most reliable biological marker for this disorder in sleep. Treatment with eszopiclone, a hypnotic with GABA-α2 receptor agonistic activity,

lessened the sleep spindle deficit seen in schizophrenics, as well as improved memory consolidation [212]. During NREM sleep, cortical slow wave activity coordinates the timing of hippocampal ripples as well as prefrontal spindle activity. In a rat model of schizophrenia, fragmented NREM sleep and impaired slow wave propagation was noted, as well as attenuated prefrontal spindle activity, suggesting that NREM sleep abnormalities such as seen in schizophrenia may produce a decoupling of hippocampal and neocortical activity [213].

Delta Slow Wave Activity (1 < 4 Hz)

As previously mentioned, NREM deep stage activity is indicated by cortical EEG oscillations predominantly in the delta frequency of 1 < 4 Hz, referred to as slow wave activity (SWA). Delta activity occurs as thalamocortical neurons are hyperpolarized. Phasic input to these hyperpolarized thalamocortical neurons produces a low-threshold calcium spike, on which sodium-mediated spikes occur (low-threshold burst). Another subsequent hyperpolarization then occurs, generating the delta frequency oscillation. Blocking thalamic input to the neocortex decreased sleep spindle activity and the frequency of NREM sleep SWA [214]. SWA is also blocked by cholinergic, serotonergic, and noradrenergic excitatory input to either thalamocortical or cortical neurons [45]. Recent investigations indicate that SWA originates locally in individual cortices during sleep [201, 215–217]. For example, individual cortical regions exhibit SWA during sleep deprivation/forced wakefulness, although other cortical subregions exhibited cortical EEG activity indicative of wake [216]. As sleep deprivation progressed, more cortical subregions exhibited sleep-like SWA, indicating an increased homeostatic response to extended wakefulness.

GBO During NREM Sleep

Slow oscillations seen during NREM sleep, including the slow 0.5 Hz wave and delta activity, may underlie limited GBO activity in NREM, activity that is much less than in wakefulness and REM sleep. Recent investigations have investigated high-frequency changes in the human cortical EEG during both NREM and REM sleep [218–221]. The up state of SWA is caused, in part, by prolonged cortical pyramidal depolarizations, and associated GBO were recorded in association with these up states, localized largely in the frontal cortex [200, 218, 219, 222]. This up state is followed by a down state, produced by extended hyperpolarization of pyramidal neurons due to GABAergic interneuronal inhibition. In one investigation, GBO were reported to be associated with this down state, specifically seen in temporal cortical regions [218].

NREM Sleep-Active Neurotransmitters: GABA and Galanin

Sleep-active GABAergic neuronal subpopulations are located in the preoptic nuclei of the hypothalamus. Lesioning and electrophysiological studies suggest that a proportion of neurons in the basal forebrain and the neighboring preoptic region promote NREM sleep [45, 223, 224]. c-Fos protein was expressed in preoptic GABAergic neurons, including the ventrolateral (VLPO) and median preoptic (MnPN) nuclei, during natural sleep and after recovery from sleep deprivation, when sleep was particularly enhanced [225, 226]. The VLPO is uniquely positioned to affect ARAS-related nuclei, for it receives input from a number of excitatory wake-related nuclei [227], and reciprocally projects to many of these same nuclei using GABA and galanin as inhibitory neurotransmitters [228]. Specific lesions to the core of VLPO produce largely NREM sleep disturbances [229]. Select basal forebrain/preoptic neurons increased firing during NREM sleep, and juxtacellular labeling and single unit recording techniques revealed that many of these neurons were GABAergic [54]. MnPN neurons fired immediately preceding entrance into NREM sleep, and continued throughout NREM sleep, and VLPO neurons were active largely during NREM sleep [223, 224, 230].

Evidence indicates that cortical neuronal nitric oxide synthase (nNOS) neurons modulate SWA. nNOS knockout mice exhibited disrupted NREM sleep and decreased amounts of SWA after sleep deprivation [231]. In addition, mice injected centrally with the nNOS antagonist 3-bromo-7-nitroindazole have reduced SWA compared to vehicle injections [232]. Recently, cortical GABAergic neurons that co-express nNOS and the neurokinin 1 receptor (i.e., the primary receptor for the pro-inflammatory molecule substance P) were activated during recovery sleep after sleep deprivation, assessed with c-Fos immunoreactivity [231, 233–236]. The activation of these cortical neurons is associated with changes in SWA and likely play a role in regulating SWA.

As mentioned, the VLPO is reciprocally connected with a number of ARAS-related nuclei [237]. Saper and colleagues proposed that this circuitry was reminiscent of a “flip-flop” switch as described in electrical engineering [238], depicted in Fig. 5.4. One exception of this mutual inhibition between wake and sleep-active nuclei is that histamine does not directly affect VLPO activity [239]. TMN histamine may inhibit VLPO indirectly, though, considering TMN histamine neurons are largely GABAergic. As shown in Fig. 5.4, orexin acts to switch the “flip-flop” between wake and NREM sleep states. Abnormalities in orexinergic circuitry would lead to abnormal vigilance state regulation,

which is similar to that seen in narcolepsy. Of note, orexin knockout mice exhibit excessive vigilance state changes [158]. Orexin therefore is an essential player in vigilance state regulation, promoting transitions between wake and sleep in the "flip-flop" model. Recent optogenetic investigations suggest that LC noradrenergic neurons may be a primary effector of arousal, transferring orexinergic LH activity [152].

The Circadian Drive to Sleep

The two-process model of sleep regulation was first proposed by Borbély and colleagues [240], involving both a homeostatic (process S, reviewed later) and circadian (process C) component. Circadian rhythms of behavior follow an approximate 24-h periodicity, and both endogenous internal and exogenous environmental oscillators influence vigilance state regulation. Such environmental cues are termed "zeitgebers" and include light and food. The interactions of both process S and C produce a distinct pattern of daily wakefulness and nocturnal sleep in humans [241–243].

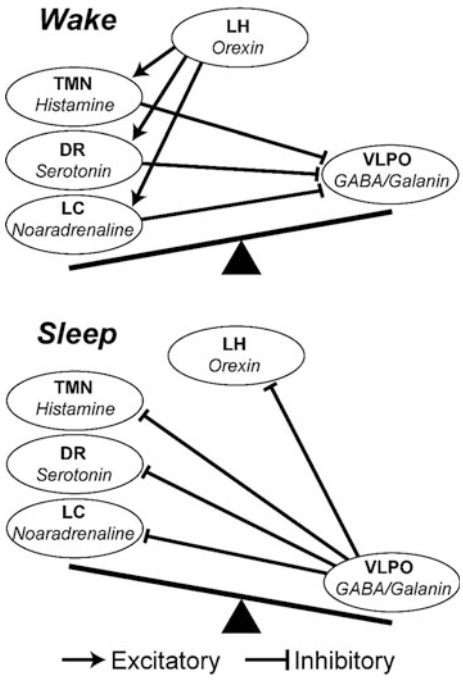

Fig. 5.4 "Flip-flop" switch model of sleep/wake transitions [238]. Histaminergic neurons of the tuberomammillary nucleus (*TMN*), serotonergic neurons of the dorsal raphe nucleus (*DR*), and noradrenergic neurons of the locus coeruleus (*LC*) promote wakefulness and inhibit ventrolateral preoptic (*VLPO*) sleep-active neurons. Lateral hypothalamus (*LH*) orexinergic neurons excite wake-active neurons, stabilizing the wake state. During sleep, GABAergic/galaninergic VLPO GABAergic/galaninergic neurons inhibit the wake-promoting nuclei, including LH. Mutual inhibition between these wake- and sleep-promoting nuclei produces vigilance state transitions

Overviews of circadian rhythmicity and its influence on behavior are beyond the scope of this chapter and available elsewhere [242–244].

A major internal oscillator of circadian rhythmicity is the suprachiasmatic nucleus of the hypothalamus (SCN). The SCN is the primary internal biological clock that influences sleep/wake regulation [243–245]. c-Fos neuronal activation studies and electrophysiological recordings indicate that SCN activity is highest during the inactive period of animals [243, 246]. Lesion studies of SCN produced disrupted rhythmicity of behavior, including vigilance states, as well as hormonal secretions. Notably, although vigilance state regulation was disrupted in SCN-lesioned animals, total amounts of sleep/wake over 24 h remained unchanged.

NREM Sleep Homeostasis

As posited in the two-process model of sleep regulation, sleep is influenced by both process S, the homeostatic drive to sleep based on SWA, and process C, the circadian drive to sleep [240]. Process S is an increase in the propensity to sleep due to the previous time spent awake. That is, the longer an animal (or person) stays awake, neural mechanisms act to increase the drive for sleep. Numerous studies have demonstrated that, as wake is extended with techniques such as acute sleep deprivation/fragmentation, the homeostat is pushed, and the intensity of NREM sleep, measured as SWA, is significantly increased, evident in the recovery period following sleep disturbance. Recent investigations suggest that SWA and sleep are regulated independently [247]. Some experimental sleep disruption protocols model the sleep restriction experienced by many individuals, in which only short amounts of sleep per day are allowed. SWA in the recovery period following multiple days of sleep restriction did not lead to enhancement of SWA in the rat [233, 248–250], yet functional detriments such as impaired cognition persisted [251]. Therefore, chronic sleep loss conditions appear to exhibit a compensatory allostatic response not applicable to the two-process model [249, 250].

Metabolic Homeostasis

Adenosine Triphosphate. One proposed hypothesis of sleep regulation is that sleep allows the replenishment of energy stores diminished during wake [252, 253]. Evidence indicates that adenosine triphosphate (ATP) is released into the extracellular space with increased waking activity and functions to enhance sleep [254]. The purine adenosine is the product of ATP degradation by enzymes including 5′-ectonucleotidase, which occurs as energy stores are used in cellular metabolism [255, 256]. Mice lacking 5′-ectonucleotidase have an attenuated NREM sleep response to sleep deprivation [257]. ATP levels were shown to increase in the

first few hours of NREM sleep, further supporting the relevance of the energy hypothesis; moreover, the increased ATP was associated with a reduction in phosphorylated adenosine monophosphate kinase and hence a favoring of anabolic processes [258].

Adenosine. Adenosine acts as a somnogenic neurotransmitter, promoting sleep by means of interaction with adenosine-specific receptors located in various brain regions [255, 256, 259, 260]. As an organism stays awake, adenosine levels increase, acting on adenosine receptors to inhibit wake-active nuclei of the ARAS, namely the basal forebrain and the cortex. Levels of extracellular adenosine increased selectively in the basal forebrain and the cortex as the sleep homeostat is pushed by means of either sleep deprivation or fragmentation [61, 261–264]. Adenosine diurnally fluctuates, as level rise during the dark (active) period in the rodent, and decrease as the light (inactive) period progresses [263–265]. In epileptic human subjects, indwelling microdialysis sampling in the cortex, hippocampus, and amygdala demonstrated a diurnal fluctuation, as extracellular adenosine levels were elevated during the active day [266].

Administration of adenosine or adenosine agonists into the basal forebrain diminished wake and promoted sleep, and adenosine antagonists increased amounts of wake [255, 256]. Of note, both caffeine and theophylline are adenosine receptor antagonists, explaining the wake-promoting effect of these compounds. Adenosine acts as a somnogen by means of adenosine 1 receptor activation in the basal forebrain [45, 255, 256, 262]. Mice lacking the adenosine 1 receptor gene have a decreased SWA response during the sleep recovery after sleep deprivation, as well as cognitive dysfunction in a working memory task, suggesting that adenosine 1 receptor activation is necessary for sleep homeostasis [267]. Both astrocytes and neurons of the basal forebrain release adenosine and modulate the homeostatic drive for sleep [45, 255, 268]. Recently, NREM sleep has been shown to play a role in metabolic homeostasis by means of a “glymphatic” mechanism [269]. In this study, as natural spontaneous sleep progressed, interstitial space expanded, allowing an increased exchange of cerebrospinal and interstitial fluids. The travel clearance of administered beta amyloid was increased during sleep, suggesting that sleep serves the purpose of removing toxic waste products that accumulate in the brain during wake.

Adenosine also acts as a somnogen in the subarachnoid space just ventral to the basal forebrain and the neighboring preoptic area, including the VLPO, largely by means of adenosine 2A receptor activation that disinhibits VLPO GABAergic/galaninergic sleep-promoting neurons [270]. Prostaglandin 2, another proposed somnogen, was intracerebrally injected into this region, and c-Fos neuronal activation was evident in VLPO neurons [271]. Additionally, NREM sleep amounts were significantly increased after prostaglandin VLPO injections [272], which promoted adenosine release [273].

Nitric oxide. Nitric oxide (NO) production promotes adenosine release during wake, such as seen during sleep deprivation [274, 275]. In vitro administration of NO or NO donors increased adenosine production in the basal forebrain and hippocampus [276, 277], and in vivo intracerebral injection of NO donors into the basal forebrain increased NREM sleep and basal forebrain adenosine release [278]. Therefore, as the sleep homeostat is elevated, levels of inducible NO are enhanced, leading to a release of adenosine in both the basal forebrain and the frontal cortex, in turn inhibiting basal forebrain and cortical wake-active neurons [279, 280.]

Cytokines. Cytokines are humoral factors that regulate both pathologic and normal functions including immune responses and sleep regulation [281–284]. The most well-studied cytokines are the pro-inflammatory molecules interleukin-1 beta (IL-1β) and tumor necrosis factor α (TNF-α), although many cytokines have been implicated in modulating sleep. Pro-inflammatory molecules typically enhance NREM sleep and SWA, while anti-inflammatory molecules attenuate these responses, demonstrated after enhanced waking activity or exposure to pathogens or other related molecules that enhance cytokines. Cytokines are present throughout the body including the brain and are produced by many brain cells types including neurons, microglia, perivascular macrophages, and astrocytes. Plasma and brain mRNA levels of IL-1β and TNF-α are elevated as the homeostatic drive for sleep is increased, such as occurs with sleep deprivation or spontaneous wake progression [285–287]. Administration of either of these cytokines enhances NREM sleep amounts and SWA in animal studies, and IL-1 systemic administration also induced sleep in humans [282–284, 288, 289]. Inhibition of cytokine production or knockout of either the IL-1 type 1 or TNF 55-kDa receptor in mice attenuated NREM sleep responses [290–295]. Extracellular ATP released by either immune cells, neurons or glia acts on the purine type 2 receptor, promoting glial release of both cytokines. In turn, these cytokines alter cell membrane properties allowing increased sensitivity to modulation by adenosine and neurotransmitters [282, 284].

Synaptic Homeostasis

Tononi and colleagues recently suggested that SWA provides a mechanism by which cortical synaptic homeostasis occurs, theorized in their **S**ynaptic **H**omeostasis H**y**pothesis (SHY) [296–298]. As proposed, wakefulness involves strengthening of many synapses as the animal navigates and learns from its environment. These brain mechanisms demand increased metabolism, as energy stores are used. During SWA, synaptic downscaling occurs, as synaptic strength is downregulated and energy reserves restored,

re-normalizing previously active synapses. Upregulation of the mRNA of a number of genes implicated in synaptic strengthening, including brain-derived neurotrophic factor (*bdnf*), neuronal activity-regulated pentraxin (*narp*), and activity-regulated cytoskeleton-associated protein (*arc*), was reported in animals killed immediately following wake, when compared to sleep mRNA profiles [299]. Ex vivo investigations analyzing the prefrontal cortex slice following sleep deprivation showed an increase in miniature excitatory postsynaptic currents (mEPSCs) in pyramidal neurons [300]. Investigations in drosophila demonstrated an increase in synaptic size and strength as flies were kept awake, and downscaling of synapses as sleep was allowed to proceed [301]. Cortical recordings in animals, as well as high-density EEG recordings in humans, demonstrate that the slope and amplitude of SWA diminishes as sleep progresses, which may also reflect synaptic downscaling [302–304].

Although SHY is an intriguing and valuable organizing hypothesis, there are many exceptions [45, 305]. For example, an increase in mEPSCs does not necessarily reflect synaptic strengthening due to neuronal firing. Many studies have shown an increase in synaptic strengthening mechanisms such as long-term potentiation during sleep, evident during NREM sleep spindles and REM sleep theta frequency oscillatory activity [306–312]. Recently, disrupted sleep was found to attenuate NREM branch-specific dendritic spine formation in the motor cortex of mice following motor learning, providing direct evidence that sleep promotes learning-dependent synapse formation [313]. Learning may demand both synaptic strengthening and weakening by such mechanisms as long-term depression, to allow extinction of non-critical forms of information [314, 315]. Also, most of all SHY-related investigations have evaluated synaptic strengthening in cortical regions, but not subcortical circuitry, such as that of the ARAS. Lastly, alternative mechanisms that may produce synaptic strengthening across the sleep/wake cycle, such as circadian fluctuation of temperature and glucocorticoids, need to be investigated [305].

Rem Sleep

EEG Profile of REM Sleep

REM sleep was first documented by Aserinsky and Kleitman in the 1950s [316, 317]. As shown in Fig. 5.1, the EEG profile of REM sleep is strikingly similar to that of wake, exhibiting cortical activation. Because of this similarity, this sleep state is also called "paradoxical sleep." EMG recordings reveal a lack of postural control and little muscle tone compared to wake. EOG recordings capture the rapid lateralized eye movements that define this stage. Also evident during REM sleep are two EEG phenomena: pontine-geniculo-occipital waves, and theta rhythmicity, particularly in the hippocampus. During REM sleep and wake, bursts of GBO are often associated with theta activity in the hippocampus. Parvalbumin neurons in the hippocampus fire at gamma frequencies, and this activity may provide a mechanism for phase locking of GBO in the cortex to theta rhythms [12, 17].

Pontine-Geniculate-Occipital Cortex (PGO) Waves

PGO waves consist of field potential activity in the dorsal pons, lateral geniculate nucleus, and occipital cortex. These waves are recorded in animals immediately preceding transitions into REM sleep, as well as during REM sleep, and the source of activation appears to be in the reticular formation [45]. The dorsolateral pons, brachium conjunctivum, and subcoeruleus/sublaterodorsal tegmental nuclei all appear to be involved in PGO wave generation [318–320]. PET scans and field potential recordings in humans have noted increased activity in the right geniculate and occipital cortex during REM sleep [321, 322], and simultaneous fMRI and EEG recordings revealed REM-related activation in the pontine tegmentum, thalamus, and visual cortex [323].

Theta Rhythmicity During REM Sleep

The hippocampal theta rhythm consists of field oscillatory activity in the frequency range of 5–8 Hz and is seen throughout REM sleep, as well as during select tasks during wake, including attention, spatial navigation, and movement [47, 48, 324]. Theta generation originates in reticular formation sites, particularly the RPO, nucleus gigantocellularis, and pontis caudalis. These neurons fire tonically during theta and project to such regions as the supramammillary nucleus of the hypothalamus (SUM), where the incoming tonic barrage of activity is translated into phasic output that then impinges on such forebrain regions as MS/DBv in the basal forebrain. SUM projections also directly terminate on hippocampal regions [325]. MS/DBv then sends GABAergic and cholinergic projections to the hippocampus, where the field oscillatory theta rhythm is recorded.

REM Sleep-Related Neurotransmitters

Acetylcholine

Transection studies revealed that brain regions anterior to the midbrain and posterior to the medulla were not necessary for REM-related brainstem activity [326, 327], and later lesioning studies determined that in this loci, largely the dorsolateral pons, were nuclei necessary for REM sleep generation including the serotonergic dorsal and median raphe nuclei, noradrenergic LC, and cholinergic LDT/PPT [45, 328]. Unlike the majority of wake-related neurotransmitters, cholinergic neurons are uniquely active during both

wake and REM sleep states. Levels of acetylcholine in the cortex, as well as choline acetyltransferase mRNA in the basal forebrain, are highest during REM sleep, compared to both wake and NREM sleep [52, 329].

Direct reticular formation injections of compounds that enhance cholinergic transmission such as carbachol, muscarinic agonists, or acetylcholinesterase inhibitors induce REM sleep [45]. Early studies using the cholinergic agonist carbachol in the cat demonstrated that reticular formation injections produced a REM-like sleep state [45, 330]. A similar induction of REM sleep can be induced in rats and mice, although the effect is not as robust, possibly due to species differences, difficulty of localization of the agent to the pontine reticular formation in smaller rodent brains, as well as differences in delivery methods [331–333]. Furthermore, non-specific lesioning of LDT/PPT attenuated REM sleep, and the amount of cholinergic cell loss in these tegmental regions strongly correlated with the amount of subsequent REM sleep loss [334]. c-Fos studies also indicate that LDT/PPT neurons are active during REM sleep [335, 336], although some investigators were unable to replicate these findings [114, 337]. Unit recordings reveal that a subpopulation of LDT/PPT neurons fire selectively during wake and/or REM sleep [69, 70, 196], and recent studies employing juxtacellular labeling and recordings demonstrated that many tegmental wake/REM-on cells were indeed cholinergic [71]. Also, cholinergic neurons of the basal forebrain fired in bursts in relation to hippocampal theta activity during both wake and REM sleep, and juxtacellularly identified cholinergic basal forebrain neurons were found to fire maximally during wake and REM sleep [53–56]. Cholinergic-specific lesioning in the basal forebrain produced a reduction in REM sleep individual bout duration, as the amplitude of theta activity was reduced [338]. It is likely that optogenetic and pharmacogenetic studies will greatly enhance our understanding of tegmental cholinergic neurons in REM sleep promotion.

GABA and Glutamate

Select GABAergic/galaninergic neurons in an extended cluster around the VLPO expressed c-Fos specifically during REM sleep, indicating that these neurons are active during REM sleep, and specific lesions to this region also produced REM sleep disturbance [114, 229]. Single unit recordings in the preoptic area revealed that select neurons fire preferentially during REM sleep, further confirming that a subpopulation of neurons in the preoptic region are REM sleep active [223, 224].

An area located near the cholinergic tegmental zone, the sublaterodorsal nucleus (SLD located ventral to the LC), also plays a role in promoting a major characteristic of REM sleep, muscle atonia. This area is called the perilocus coeruleus alpha in the cat, and either SLD or subcoeruleus nucleus in the rodent. Early investigations found that lesions in this region suppressed REM-related muscle atonia. In particular, larger lesions that included SLD, the amygdala and colliculus produced "oneric" dream-like behavior in the cat during REM sleep, including locomotion and head movement [339, 340]. GABAergic neurons in the pontine reticular formation most likely inhibit SLD activity during wake, and these neurons are themselves inhibited during REM sleep by means of tegmental cholinergic input [341–343]. Early work by Magoun and Rhines determined that a region in the ventral medulla in the vicinity of SLD played a role in muscle atonia during REM sleep, and later investigations described projections from SLD to a glycinergic cell population in the ventral medulla, which in turn projects to spinal cord motor neurons involved in postural muscle tone [344, 345]. More recently, Lu and colleagues proposed an alternative pathway, based on c-Fos and neuroanatomical tracer investigations, in which SLD sends a glutamatergic projection directly to GABAergic/glycinergic spinal cord interneurons, which in turn inhibit spinal cord motor neurons [114]. Recently, simultaneous blockade of both GABA-B and glycinergic/GABA-A receptors prevented REM sleep muscle atonia involving the trigeminal motor pool neurons [346, 347]. Therefore, brainstem GABAergic/glycinergic neurons promote atonia by inhibition of these motor neurons, as REM-active glutamatergic neurons excite these same GABAergic/glycinergic cell populations. It remains to be determined if similar mechanisms are at play involving other muscle atonia-related cell populations, such as hypoglossal motoneurons that innervate the genioglossal muscle or spinal cord motor neurons.

Melanin Concentrating Hormone

Interspersed among orexinergic neurons in the lateral hypothalamus are GABAergic neurons that secrete melanin concentrating hormone (MCH), and recent studies suggest that these neurons play a role in sleep regulation [348–351]. MCH acts to inhibit wake-active neuronal cell populations throughout the ARAS, including orexinergic neurons, allowing sleep to be expressed [350, 352, 353]. In turn, a number of wake-related brain nuclei may inhibit MCH activity. MCH neurons are largely inactive during wake, increase firing during NREM sleep, and fire maximally during REM sleep [354]. c-Fos assessed neuronal activation was also elevated in MCH neurons during sleep [355]. Intracerebroventricular injections of MCH significantly increased both NREM and REM sleep, and direct injections of MCH into wake-active nuclei such as RPO, dorsal raphe nucleus, or the basal forebrain promoted REM sleep [350]. MCH neurons act largely on the MCH1 receptor, localized on a number of ARAS-related nuclei. MCH1 receptor suppression by antagonists or genetic knockout produced decreased NREM and REM sleep amounts [349, 356–359].

Additionally, optogenetic stimulation of MCH neurons produced a significant decrease in wake, and excitation applied at the beginning of REM sleep extend REM sleep bout length [360]. Furthermore, optogenetic inhibition decreased REM sleep theta activity, although overall REM sleep amounts and bout lengths were largely unaffected [361].

The Reciprocal Interaction Model of REM Sleep Regulation

McCarley and Hobson introduced the reciprocal interaction model to explain the neural circuitry and neurotransmission involved in transitions to the REM sleep state, as well as the REM oscillator, which is about 90 min in humans and shorter in smaller animals [362]. A further goal was to have the model be mathematically correct in terms of describing these oscillations. Initially the model was purely based on Lotka-Volterra equations, originally proposed to describe predator/prey interactions. An update to the model included a more realistic limit cycle set of equations to account for circadian variation [363]. Other updates have included the growing neurophysiological knowledge of REM sleep control factors, including GABAergic influences on REM sleep regulation [45, 362, 363].

As proposed (Fig. 5.5), cholinergic LDT/PPT neuronal firing increases immediately preceding and during REM sleep. This cholinergic excitation promotes glutamatergic activity in reticular formation regions including the SLD, parabrachial nucleus, and RPO. Cholinergic activation, and excitatory effects on these glutamatergic populations, are responsible for many of the featured REM sleep characteristics reviewed here, including PGO waves, hippocampal theta activity, and muscle atonia. Cholinergic LDT/PPT neurons also inhibit select reticular formation GABAergic cell populations, whose role is to act as REM-off neurons, further promoting REM sleep. Both serotonergic and noradrenergic cell populations are REM-off and wake-on. Their activity during wake decreases significantly as REM sleep approaches due to autoinhibition, and they remain silent until the REM-wake transition [45]. The serotonergic dorsal raphe and noradrenergic LC both project to and inhibit LDT/PPT REM sleep-promoting activity. LDT/PPT cholinergic neurons excite GABAergic reticular formation populations which in turn inhibit both serotonergic and noradrenergic REM-off cell populations.

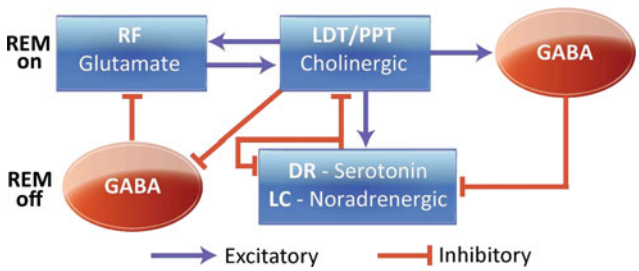

Fig. 5.5 Modified reciprocal interaction model of REM sleep control [362, 363] *Blue nuclei* and *arrows* are excitatory, and *red* inhibitory. Laterodorsal (*LDT*) and pedunculopontine (*PPT*) tegmental REM-on cholinergic activity excites reticular formation (*RF*) glutamatergic REM-on neurons. LDT/PPT REM-on neurons also excite GABAergic REM-on interneurons that act to inhibit dorsal raphe (*DR*) and locus coeruleus (*LC*) REM-off neuronal activity. LDT/PPT REM-on neurons also inhibit GABAergic REM-off interneuronal activity, in turn promoting REM-on RF neurons. As REM sleep progresses, REM-on cells begin to excite REM-off cells, leading to REM sleep cessation

It is important to note that LDT/PPT activity is comprised of both REM-on and wake–REM-on neurons (about 2/3) [69, 70, 364]. To test the hypothesis of differential inhibition of tegmental REM-on populations by aminergic neurons, Thakkar and collaborators developed a novel methodology in freely behaving animals allowing both extracellular single cell recording in PPT and local perfusion of neuropharmacological agents by way of an adjacent microdialysis probe [196]. Discharge activity of REM-on neurons was almost completely suppressed by local microdialysis perfusion of the selective 5-HT1A agonist 8-OH-DPAT, while this agonist had minimal or no effect on the wake/REM-on neurons. These findings suggest that REM sleep ends as the excitatory effects of REM-on neurons cause serotonergic and noradrenergic neurons to resume activity; this in turn, suppresses REM-on neuronal activity. In terms of further evaluation of the cholinergic influences on REM sleep using optogenetic or DREADD technology, it is important to note the presence of both REM-on and wake–REM-on neurons—important in EEG activation in both REM sleep and wake—in the cholinergic population. Activation of the entire population by optogenetic or DREADD experiments may thus fail to produce a clear-cut REM episode. We think early experiments that implicated the brainstem endogenous production of acetylcholine in REM sleep promotion by use of neostigmine are a helpful guide as to cholinergic influences on REM sleep, as microinjection of neostigmine into the pontine reticular formation of cats enhanced desynchronized sleep signs [365].

Summary

This chapter provides an overview of the neurobiology of vigilance state regulation. Over the last 50 years, both clinical and basic investigations have begun to elucidate the neural mechanisms regulating sleep, in part due to the development of exciting new experimental techniques. Increased understanding of these neural mechanisms will aid

the development of pharmacological and behavioral treatment of sleep pathology.

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Basic Circadian Timing and Sleep-Wake Regulation

6

Marc Cuesta, Philippe Boudreau, and Diane B. Boivin

Abbreviations

5-HT	5-hydroxytryptamine or serotonin
A1	Adenosine type 1 receptor
A2a	Adenosine type 2a receptor
AA-NAT	Arylalkylamine *N*-acetyltransferase
ACh	Acetylcholine
ACTH	Adrenocorticotropic hormone
AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ARC	Arcuate nucleus
BDNF	Brain-derived neurotropic factor
BNST	Bed nucleus of the stria terminalis
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CBT	Core body temperature
ccgs	Clock-controlled genes
CR	Constant routine
CRE	Calcium/cAMP response element
CREB	CAMP response element binding
CRH	Corticotropin-releasing hormone
DMH	Dorsomedial nucleus of the hypothalamus
DMV	Dorsal motor nucleus of the vagus
DRN	Dorsal raphe nuclei
EEG	Electroencephalography
EGF	Epidermal growth factor
EMG	Electromyography
ERKs	Extracellular signal-regulated kinases
EOG	Electrooculography
GABA	Gamma-aminobutyric acid
GCs	Glucocorticoids
GHT	Geniculohypothalamic tract
GLU	Glutamate
HB	Habenula
IL-1β	Interleukin-1 beta
IML	Intermediolateral column
IGL	Intergeniculate leaflet
LC	Locus coeruleus
LS	Lateral septum
LDT	Laterodorsal tegmental nucleus
LHA	Lateral hypothalamus area
LPT	Lateral pontine tegmentum
MPO	Medial preoptic area
MRN	Medial raphe nuclei
MT2	Melatonin type 2 receptor
NMDA	*N*-Methyl-D-aspartate
NO	Nitric oxide
NPY	Neuropeptide Y
NREM	Non-rapid eye movement
ORX	Orexin
PACAP	Pituitary adenylate cyclase-activating peptide
PC	Precoeruleus
PPT	Pedunculopontine tegmental nucleus
Process C	Circadian process of sleep-wake regulation
Process S	Homeostatic process of sleep-wake regulation
PSG	Polysomnography
PVN	Paraventricular nucleus of the hypothalamus
PVT	Paraventricular nucleus of the thalamus
RGT	Retinogeniculate tract
RORE	ROR-specific response elements
REM	Rapid eye movement
RHT	Retinohypothalamic tract
SCG	Superior cervical ganglion
SCN	Suprachiasmatic nucleus
SE	Sleep efficiency
SL	Sleep latency
SLD	Sublaterodorsal nucleus
SPZ	Subparaventricular zone
SWA	Slow-wave activity
TMN	Tuberomammillary nucleus
TNF-α	Tumor necrosis factor alpha
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone

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TST	Total sleep time
USW	Ultradian sleep-wake cycle
VIP	Vasoactive intestinal polypeptide
VLPO	Ventrolateral preoptic area
vPAG	Ventral periaqueductal gray matter
WASO	Wake after sleep onset
WMZ	Wake maintenance zone
ZT	Zeitgeber

The Circadian Timing System

Origin and Definition of Circadian Rhythms

On Earth, life has evolved under the influence of the cyclic exposure to sunlight and darkness due to the planet's revolution around its axis. As one rotation is achieved in 24 h, most living organisms display rhythmic variations with a similar period for numerous biologic parameters, such as gene and protein production, physiological functions, behaviors, and cognitive processes. It is thought that evolution has led to the development of species that could integrate this rhythmic variation in their functioning allowing them to anticipate environmental changes in order to increase their chances of survival. While the first written description of biologic rhythms was made during the fourth century B.C. by Androsthenes, it is only in 1729 that the French astronomer Jean-Jacques Dortous de Mairan demonstrated that these rhythms are not passive responses to variations of the outside world. By reporting the persistence of daily leaf movements of the sensitive plant *Mimosa pudica* in constant conditions (i.e., constant darkness), he was one of the first to demonstrate their endogenous origin [1].

Today, these intrinsic oscillations, found in humans and in almost all organisms among animals, plants, fungi, and cyanobacteria [2], are known to be driven by the circadian system (from the Latin *circa* and *dies*, meaning "about" and "one day," respectively). In mammals, this system comprises a multitude of oscillatory structures called "clocks" that are found throughout the body and are able to generate circadian rhythms through a hierarchical organization. For a biologic rhythm to be considered as circadian, it has to fulfill the following properties: The rhythm has to be endogenous, meaning that it persists under constant conditions; the rhythm has to be synchronized or entrained by external and internal cues (called *zeitgebers* or ZT from the German, meaning "time-giver"), the most potent being the light/dark cycle; the rhythm has to be temperature-compensated, meaning that a given rhythm remains constant when temperature increases or decreases across a physiological range [3, 4].

Neurolocalization of Circadian Rhythms: The Mammalian Central Clock

In mammals, circadian rhythms are driven by a central or "master" clock enclosed in a well-defined bilateral region of the anterior hypothalamus, namely the suprachiasmatic nuclei (SCN). The first demonstration establishing that the SCNs are essential for the production of circadian rhythms was published in 1972 in two independent studies, in which a bilateral lesion of the SCNs led to the loss of the cortisol secretion rhythm [5], as well as the rest-activity and drinking behavior rhythms [6]. A later study showed that a transplantation of fetal SCN was able to restore behavioral rhythmicity in hamsters bearing SCN lesions [7]. Notably, the period of the restored rhythm was the period expressed by the SCN of the donor. With this elegant demonstration, Ralph and collaborator demonstrated that the SCNs are the primary structures that generate internal circadian rhythmicity.

Anatomically, the SCNs are two nuclei located in the anterior hypothalamus, on top of the optic chiasm, bilateral to the third ventricle [8]. In humans, each SCN contains around 50,000 neurons for an approximate volume of 0.25 mm^3 [9–11] and can be subdivided roughly into "core" and "shell" regions, also described in most mammalian species [8, 12]. While the ventrolateral "core" neurons largely express vasoactive intestinal polypeptide (VIP), the dorsomedial "shell" neurons are rich in arginine vasopressin (AVP), and both neuropeptides co-localize with γ-aminobutyric acid (GABA) and sometimes with glutamate [12]. "Core" neurons primarily receive photic information from the retinohypothalamic tract (RHT) and densely project to the shell. "Core" neurons appear to be essential in the maintenance of internal coupling and the production of a coherent output signal from the SCNs [13]. Both "core" and "shell" regions [14] project mainly to local structures surrounding the SCNs [14, 15] (Fig. 6.1). Numerous other neurotransmitters and neuropeptides have been detected in the SCNs, but their presence and exact localization are species-specific, suggesting that the SCNs organization is more complex than the core-shell subdivision model [16, 17]. Of note, in humans, neurotensin-containing neurons are present in a larger population than that described in monkeys and all other species [17]. Whereas their role is still poorly defined, a loss of neurotensin-containing neurons has been reported in patients suffering from dementia [18, 19] and correlated with dampening in circadian amplitude such that of the core body temperature rhythm (or CBT) [19].

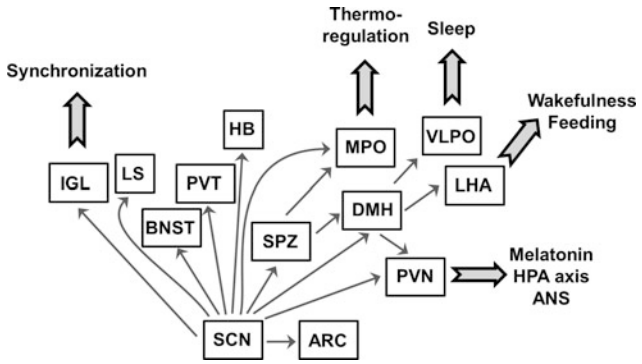

Fig. 6.1 Efferent neural projections from the SCN to different brains regions and their involvement in the regulation of physiological functions. *ARC* arcuate nucleus; *BNST* bed nucleus of the stria terminalis; *DMH* dorsomedial hypothalamus; *HB* habenula; *IGL* intergeniculate leaflet; *LS* lateral septum; *LHA* lateral hypothalamus area; *MPO* medial preoptic area; *PVN* paraventricular nucleus of the hypothalamus; *PVT* paraventricular nucleus of the thalamus; *SCN* suprachiasmatic nuclei; *SPZ* subparaventricular zone; *VLPO* ventrolateral preoptic area

Genesis of Circadian Rhythms: The Mammalian Molecular Clockwork

The molecular mechanisms responsible for the genesis of endogenous circadian rhythms have started to be unfolded in the 1990s. To our knowledge, the first mammalian circadian molecular oscillator model was proposed in 2000 [20], in which the self-sustained rhythmicity is generated by positive and negative components that form feedback core loops with a period of about 24 h (Fig. 6.2; see Table 6.1 for full official/alternative names of the different clock components). Initially, the model was based on reports of behavioral rhythms changes observed in transgenic mice for different "clock" genes. Since 2000, it has been progressively refined with the addition of new components and the development of new transgenic mouse models [3, 21]. Notably, the basic autoregulated feedback core loops have been preserved through evolution and their timing is similar in nocturnal and diurnal species, including humans (for review, see [3]). CLOCK and BMAL1 (two PAS domain helix-loop-helix proteins) represent the positive limb of the loop. In the cytoplasm, CLOCK and BMAL1 translocate to the nucleus where they act as transcription factors on genes containing an E-box (5′-CACGTG-3′) or an E′-box (5′-CACGTT-3′) on their promoter. The genes constituting the negative limb of the loop, namely *Per1/2/3* and *Cry1/2*, contain E-boxes, and their transcription is thus activated by CLOCK/BMAL1. Their protein products, PER and CRY, heterodimerize and bind to CK1ε/δ forming a complex that allows the phosphorylation of PER and CRY. This leads to the translocation of the complex to the nucleus where it accumulates to eventually repress the transcription of several genes, including *Per* and *Cry*. This inhibitory mechanism would be the result of the deacetylation of histones 3/4 following the recruitment of a PTB-associated splicing factor/SIN3-histone deacetylase complex (PSF/Sin3-HDAC complex) by PER/CRY [22].

In addition to this main feedback core loop, interconnected secondary loops and transcription factors have been described, which add supplementary layers of control allowing to fine-tune regulations of the circadian rhythmicity. One of these loops involves the CLOCK/BMAL1 complex, which controls its own production by a regulation of the transcription of other genes containing an E-box, namely *Rev-Erbα/β* and *Rorα/β/γ* (Fig. 6.2). Through a competitive binding on ROR-specific response elements (RORE) present on the *Bmal1* promoter, REV-ERB and ROR proteins can inhibit and activate *Bmal1* transcription, respectively, leading to their cyclic production. Despite this important role, REV-ERB and ROR are not essential to sustain oscillations within the SCN [23]. E-boxes can also be targeted by other transcription factors, such as DEC1/2, which both act to reduce E-box-mediated transcription [24]. Some other second accessory feedback loops involve transcription factors from the proline and acidic amino acid-rich basic leucine zipper family, which can bind to D-boxes (5′-TTATG[T/C]AA-3′) (e.g., DBP and TEF; see Table 6.1) [3].

Transcription factors and transcriptional regulation play a crucial role in the generation of circadian rhythms, but other mechanisms and molecules such as posttranslational modifications, microRNAs, and RNA-binding proteins are also considered important regulatory elements [25, 26]. For instance, the process of elimination of PER and CRY follows a precise timing that is required to end the repression phase and start a new cycle of transcription. Once PER and CRY are targeted by CK1ε/δ and AMPK, respectively, they are polyubiquitylated by β-TRCP1 and FBXL3 (nucleus) or FBXL21 (cytoplasm and nucleus), respectively (proteins that are part of an ubiquitin protein ligase complex, named SKP1-cullin-F-box or SCF ubiquitin ligase complex), which are then degraded by the 26S proteasome (Fig. 6.2). These posttranslational mechanisms allow a control of the stability/degradation rate of the PER and CRY proteins which is crucial to precisely set the period of the central clock [3, 27, 28].

While half of all mammalian genes are expressed rhythmically in at least one tissue [29], it appears that only a small number of genes are truly essential in the genesis of circadian rhythms. All the other rhythmic genes are called clock-controlled genes (ccgs) because they are not involved in the different loops but are regulated by them [30]. Ccgs are considered as the molecular output of the circadian clock. They represent the connection between the feedback core loop and a multitude of cellular and physiological functions, including SCN functions. For example, in the SCN, some of the ccgs, such as the *Avp* gene, are directly under the rhythmic control of CLOCK/BMAL1 via E-boxes [31] and *Avp* is known to be implicated in the circadian regulation of drinking behavior [32]. The rhythmic firing rate of SCN neurons is achieved via the

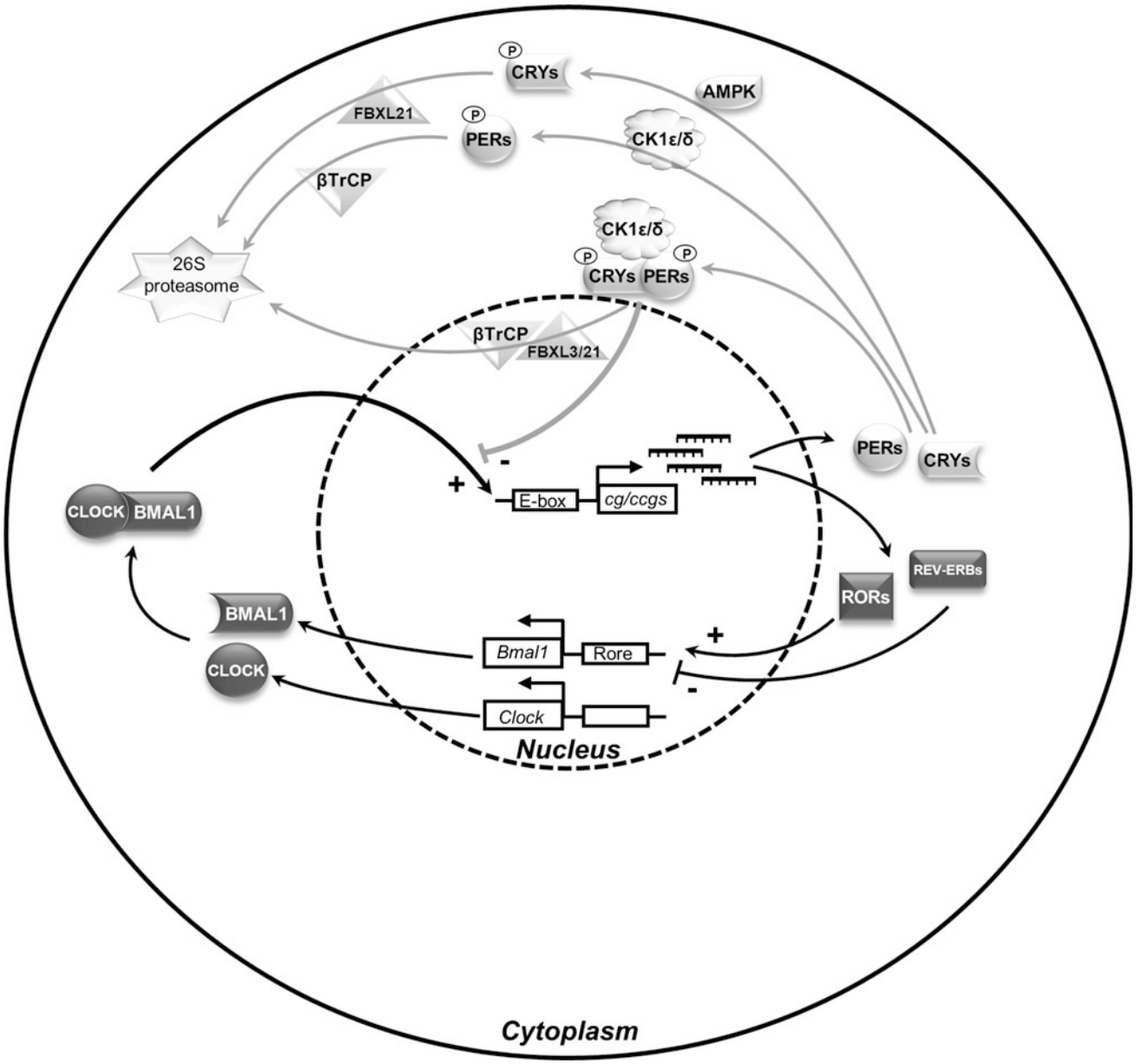

Fig. 6.2 Molecular model of the mammalian cell autonomous oscillator within a SCN cell as described in the text. Genes are represented in *italic* and proteins in CAPITAL. Nomenclature for each element is given in Table 6.1. CLOCK/BMAL1 activates transcription of genes containing an E-Box, including *Per* and *Cry*. PER/CRY, once translated into proteins, inhibit their own transcription. The other actors allow to fine-tune regulations of circadian rhythmicity. *CG* clock gene; *CCGs* clock-controlled genes; *P* phosphate

cyclic regulation of membrane potassium channels, and it is considered as an output of the central clock probably implicating ccgs [33, 34].

Organization of the Circadian System: A Hierarchical Multioscillatory System

For decades, SCN neurons were thought to be the only cells capable of generating self-sustained circadian oscillations explaining why the SCN has been considered as the "master" clock for so long. Today, we know that almost every cell of the body can express the main clock genes in a rhythmic fashion [35], and thus, many brain regions [36–38] and non-neuronal tissues [35, 39–41] can be considered as autonomous clocks, known as peripheral clocks. However, without environmental cues (e.g., in vitro), the oscillations seen in peripheral clocks usually dampen after few days due to a weak coupling between the cells constituting those clocks [42, 43], whereas the SCN can self-sustain

Table 6.1 Non-exhaustive list of core clock genes and associated circadian genes mentioned in the chapter

Gene	Alternative name	Full name
PER1	*PERIOD1*	Period circadian protein homolog 1
PER2	*PERIOD2*	Period circadian protein homolog 2
PER3	*PERIOD3*	Period circadian protein homolog 3
CRY1	–	Cryptochrome 1
CRY2	–	Cryptochrome 2
BMAL1	*ARNTL*; *MOP3*	Brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1
CLOCK	–	Circadian locomotor output cycle kaput
NPAS2	*MOP4*	Neuronal PAS domain-containing protein 2
RORα	*RORa*, *NR1F1*	Retinoic acid-related orphan receptor alpha
RORβ	*RORb*, *NR1F2*	Retinoic acid-related orphan receptor beta
RORγ	*RORc*, *NR1F2*	Retinoic acid-related orphan receptor gamma
REV-ERBα	*NR1D1*	Reverse viral erythroblastosis oncogene product alpha
REV-ERBβ	*NR1D2*	Reverse viral erythroblastosis oncogene product beta
CK1δ	*CSNK1d*	Casein kinase I delta
CK1ε	*CSNK1e*	Casein kinase I epsilon
AMPK	–	AMP-activated protein kinase
DBP	–	D-box binding protein
TEF	–	Thyrotroph embryonic factor
B-TRCP1	*BTRC*	Beta-transducin repeat containing protein 1
FBXL3	–	F-box and leucine-rich repeat protein 3
FBXL21	–	F-box and leucine-rich repeat protein 21
DEC1	*BHLHE40*	Differentiated embryo chondrocyte protein 1
DEC2	*BHLHE41*	Differentiated embryo chondrocyte protein 2
AVP	*ADH*	Arginine vasopressin

synchronized rhythms for weeks due to their specific neuronal network. The unique properties of SCN cells are due to their tight coupling elicited through synaptic connections and gap junctions that allow them to remain synchronized with each other even in the absence of a ZT [12].

In peripheral clocks, the molecular mechanisms responsible for the generation of circadian rhythms are similar to those described for the central clock despite the fact that some distinct genetic factors have been described [44, 45]. For instance, in some brain regions including the striatum and the hippocampus, CLOCK is substituted by its analogue NPAS2, while in the liver, both CLOCK and NPAS2 are expressed, but NPAS2 cannot maintain circadian oscillation when CLOCK is missing. Another example defines RORγ as being expressed specifically in peripheral tissues, but with a similar role to this attributed to RORα/β.

In a physiological point of view, these brain- and non-brain tissue-specific clocks, and ultimately, brain and organ functions are likely to be coordinated by the local circadian molecular machinery associated with the integration of systemic synchronizing factors. This dual control leads to the expression of robust circadian oscillations in peripheral clocks. It appears that most of these synchronizing factors primarily originate from the SCNs, although feeding-fasting cycles and temperature variations are known to entrain peripheral clocks [46, 47]. Based on this dual control, the current model of circadian organization in mammals postulates a hierarchical system in which the central clock in the SCNs controls a network of subordinate peripheral clocks throughout the brain and periphery [48]. Despite this apparent organization, it has been demonstrated that some peripheral structures can drive local physiological rhythms independently of the SCNs, such as the retina [41], the olfactory bulb [49], and the adrenal gland [50]. In addition, a line of evidence has shown the existence of two SCN-independent oscillators, namely the food-entrainable oscillator and the methamphetamine-sensitive circadian oscillator [51–57]. These two oscillators are known to control behavioral and hormonal rhythms even in SCN-lesioned animals or in the absence of clock genes, but neither the site nor the mechanisms underlying their functioning have been yet elucidated.

Communication Within the Circadian System: The Neural and Endocrine Pathways

We previously mentioned that neurons from the SCN project mainly to brain regions restricted to hypothalamic nuclei, with the main outputs directed to the subparaventricular zone (SPZ) and the dorsomedial nucleus of the hypothalamus (DMH) (Fig. 6.1) [58]. By projecting to other brain structures, the SPZ and DMH, and the other nuclei can control the rhythmicity of peripheral clocks and their outputs. One of these pathways connects the SCN to the ventrolateral preoptic area (VLPO) via the dorsal SPZ, which is known to control the circadian sleep-wake cycle [59]. Another pathway links the SCN to the medial preoptic area (MPO) through the ventral SPZ regulating the CBT rhythm [59]. In addition, other neuronal pathways areas of particular importance convey information outside of the brain to peripheral tissues. Indeed, using transneuronal retrograde tracers, distinct polysynaptic sympathetic and parasympathetic routes have been identified emerging from the SCN to end up in the liver, kidney, pancreas, bladder, heart, adrenal cortex, spleen, and brown adipose tissues [60–63]. For instance, connections emerging from the SCN reach the adrenal gland via the paraventricular nucleus of the hypothalamus (PVN) and the intermediolateral column (IML) (i.e., sympathetic pathway) and control the rhythm of sensitivity to adrenocorticotropic hormone (ACTH) [64, 65]. Sympathetic projections also control the rhythmicity of melatonin synthesis, a fundamental circadian endocrine factor. To do so, neurons from the IML project to the pineal gland via the superior cervical ganglia (SCG) and regulate in a rhythmic fashion the production of the rate-limiting enzyme arylalkylamine *N*-acetyltransferase (AA-NAT), implicated in melatonin synthesis [66, 67]. The parasympathetic nervous system also conveys rhythmic information via fibers originating in the SCN, which then reach the PVN and the dorsal motor nucleus of the vagus (DMV) allowing for instance a regulation of peripheral clocks found in white adipose tissue and the liver [68, 69]. It seems that through all these innervations, the SCN has the potential to orchestrate the circadian rhythmicity of peripheral oscillators and their metabolic and physiological functions throughout the entire body.

The SCN can also synchronize peripheral oscillators through a rhythmic control of numerous actors of the endocrine system. Among them, few hormones have been well described as regulators of the circadian system. As we previously mentioned, melatonin secretion is regulated by the SCN, and the resulting rhythm of melatonin is known to upregulate some actors of the immune system and to control several seasonal functions [70, 71]. In addition, melatonin would specifically facilitate sleep in humans [70]. Glucocorticoids or GCs (i.e., corticosterone in rats and mice; cortisol in humans) represent another class of hormones that seems essential for the regulation of peripheral clocks. Rhythmic GCs synthesis and secretion are under control of the central clock through direct and indirect projections reaching the PVN. In the PVN, parvocellular neurosecretory cells release corticotropin-releasing hormone (CRH) that controls the release of ACTH from the pituitary gland, itself controlling GCs release by the adrenal glands [50, 72]. The rhythm of GCs is known to regulate the synchronization of many peripheral clocks at both behavioral and molecular levels [45, 72]. The SCN also controls, through the PVN, the release of AVP and thyrotropin-releasing hormone (TRH), the latter stimulating the release of thyroid-stimulating hormone (TSH) and prolactin. Other hormones such as epinephrine and norepinephrine [73], leptin, glucose, and insulin [74] express a circadian rhythm and could constitute endocrine signals by which the central clock synchronizes peripheral oscillators, but further studies are needed to clarify their respective roles.

Synchronization of the Circadian System: External and Internal Factors

In animals, including humans, the endogenous period (or internal day length) of most circadian rhythms is close to, but not exactly, 24 h [75, 76]. To be in phase with the external world, the circadian system is continuously resynchronized to the 24-h terrestrial day through a mechanism called "synchronization" or "entrainment." As a relay between the external environment and the internal functions of the body, the SCN represents the primary structure implicated in this mechanism. Among external factors that influence the circadian system, the 24-h light/dark cycle is the most powerful and the most studied, but it has been demonstrated that variations in environmental temperature or food availability can act as synchronizing factors for the central clock [46, 77, 78]. Notably, a wide range of internal factors that convey physiological information to the central clock are integrated by the SCN in conjunction with light cues and thus participate in the synchronization of the SCN. Some of those internal factors will be described later in this chapter. Of note, in constant conditions, the period of time when nocturnal species are awake is considered as the "subjective" night, while it is named "subjective" day when they are asleep and vice versa for diurnal species.

The Photic Factor: Molecular and Behavioral Effect

In mammals, it has been known for decades that light information is received by image-forming rods and cones' photoreceptors located in the retina, which is then transmitted to the cerebral regions involved in visual processing. While rods and cones are also implicated in the detection of light information that is conveyed to the SCN, a subset of retinal ganglion cells expressing the photopigment

melanopsin (Fig. 6.3) has been described as fundamental for the SCN to be synchronized to the light/dark cycle [79]. Melanopsin cells are present in 0.2–2.5 % of the total number of retinal ganglion cells [79–81] and their maximal photosensitivity occurs in the blue-green light spectrum (~470 nm) [82]. Along with rods and cones, melanopsin cells convey photic information using a direct pathway, the RHT (Fig. 6.3) that has been described in mammals including humans [83–86]. The RHT innervates the ventrolateral "core" region of the SCN and releases glutamate and pituitary adenylate cyclase-activating peptide (PACAP). Moreover, an indirect pathway has been described that connects melanopsin cells to the ventral part of the SCN via the intergeniculate leaflet (IGL), which releases GABA and neuropeptide Y (NPY, Fig. 6.3) [87, 88]. Of note, the IGL is a thalamic structure implicated in the integration of photic and non-photic signals [87–89].

Glutamate released by RHT neuron terminals leads to the activation of multiple signaling pathways in the SCN following activation of *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [90]. This activation leads to a calcium influx into SCN neurons, which stimulates the synthesis of nitric oxide (NO) [91] known to act differentially depending on the time of day. During the early night, NO induces an activation of ryanodine receptors, which is followed by Ca^{2+} release from the endoplasmic reticulum [92]. During the late night, NO activates guanylate cyclase that stimulates the synthesis of cyclic guanosine monophosphate (cGMP) [92]. A third pathway, implicating cyclic adenosine monophosphate (cAMP) is effective throughout the night [93] and together these three pathways lead to the activation of the protein kinase A and extracellular signal-regulated kinases (ERKs), which phosphorylate cAMP response element binding (CREB) protein [94–96]. In turn, CREB activates *Per1* and *Per2* transcription in the SCN in response to its binding to the cAMP response element (CRE) present on *Per* gene promoters [12, 95–97]. Using alteration of *Per1/2* transcription [98, 99] and *Per1/2* mutant mice [100], these two genes have been attributed a causal role in the mediation of light-induced synchronization of the SCN. Both genes present temporal and spatial differences in their response to the photic factor [101–104]: *Per1* transcription is quickly induced throughout the night in ventral SCN cells; *Per2* expression is induced in the whole SCN, quickly in the early night and slowly or not at all in the late night. Of note, the expression of several other genes and clock genes (i.e., *Bmal1*, *Cry2*, *Rev-erbα*, *Rorβ*, and *c-fos*) is also regulated by light, but their role is less clear [101, 105–110].

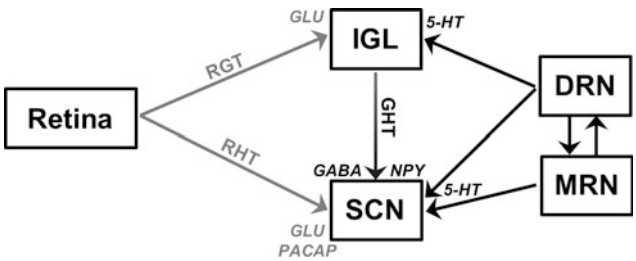

Fig. 6.3 Main afferent neural projections to the SCN, RHT and RGT convey photic cues from the retina to the SCN and the IGL, respectively (*gray arrows*). Non-photic information is conveyed from raphe nuclei (DRN and MRN) to the SCN and the IGL (*black arrows*). The IGL conveys both photic and non-photic cues to the SCN (*black/gray arrow*). Neuropeptides and neurotransmitters are indicated in *italic*. *5-HT* serotonin; *DRN* dorsal raphe nucleus; *IGL* intergeniculate leaflet; *GABA* γ-aminobutyric acid; *GHT* geniculohypothalamic tract; *GLU* glutamate; *MRN* median raphe nucleus; *NPY* neuropeptide Y; *PACAP* pituitary adenylate cyclase-activating peptide; *RGT* retinogeniculate tract; *RHT* retinohypothalamic tract; *SCN* suprachiasmatic nuclei

Thus, from the retina, photic information induces a daily resetting of the central clock by a modulation of the molecular clock leading to changes of the circadian phase of SCN neurons. As SCN neurons form a tightly coupled network, the entire SCN quickly adjusts to a shift of the light/dark cycle. The phase of the SCN can be delayed or advanced by several hours each day in most mammalian species, according to the time of day when the retina receives light [89, 111]. The central clock can then relay photic information to peripheral oscillators through neuronal connections or endocrine signals as previously described, leading to phase adjustments of the circadian rhythms of these oscillators as well as those of their outputs (e.g., locomotor activity, feeding timing, and CBT). For instance, to assess the effects of light on the rhythm of locomotor activity, it is possible to apply discrete light pulses at different time points in animals or humans studied in constant conditions (e.g., constant darkness in rodents and constant routine or CR in humans). Using this method, a phase response curve to light can be defined, which expresses the magnitude of the induced phase shift as a function of the time of light exposure (Fig. 6.4). In both nocturnal and diurnal species, including humans, the phase response curve to light displays a similar pattern with the larger light-induced phase shifts occurring mainly during or close to the subjective night (i.e., active and resting period in nocturnal and diurnal species, respectively) [89, 101, 112–116].

In humans, light exposure in early morning (i.e., after CBT reached its minimal value) is known to phase advance the circadian system [114], while light exposure at night (i.e., before the CBT minimum) results in phase delay of the circadian system. Light intensity [117–119], wavelength [120, 121], and prior light exposure [122] were shown to be important determinants of light-induced phase shifts of the circadian system.

Using a simulated night shift experiment, we recently demonstrated the ability of light to entrain peripheral clocks in humans, through synchronization of the central clock [123].

The Non-photic Factors: Focus on Melatonin, Activity, Sleep and the Serotonergic System

Besides light, many factors can modify the rhythmicity of the circadian system at both molecular and behavioral levels. The most studied non-photic factors cited in this chapter and their effects on clock gene expression in the SCN and the rest-activity cycle are summarized in Table 6.2. This chapter will focus on two categories of non-photic factors, melatonin and factors related to activity, sleep, and the serotonergic system. In animals, food intake represents another well-studied non-photic factor known to synchronize the circadian system. As there have been excellent reviews describing them [55–57], it will not be further discussed here. Many other factors that influence the central clock and/or peripheral clocks have been described (e.g., dark pulses, temperature, GCs, and drug of abuse). Most of these studies have been conducted in nocturnal species and the few results obtained with diurnal species highlight differences between these two types of species that could be relevant to human chronobiology, considering the diurnal nature of human life.

To date, melatonin has been the most studied non-photic synchronizer in humans (for a review, see [124]), and its phase-shifting effects have also been described in several nocturnal and diurnal mammals (Table 6.2). In humans, exogenous melatonin induces phase advances when administered in the late afternoon/evening and phase delays when given in the morning [125, 126]. Similar results have been reported in the evening in nocturnal and diurnal rodents [127, 128]. These effects would be dependent on the

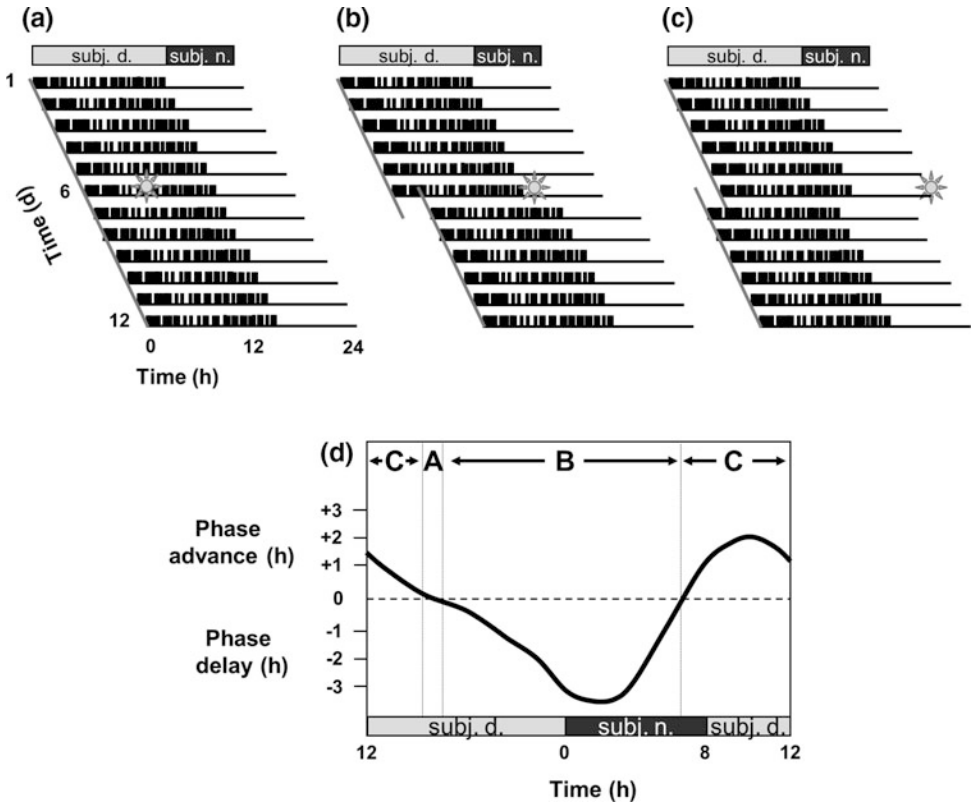

Fig. 6.4 Schematic illustration of light-induced phase shifts of the rest-activity cycle in diurnal humans. Schematic actograms (A, B, C) illustrate the rest-activity rhythm of diurnal humans kept under constant conditions (e.g., constant routine). An actogram is a graph that plots activity levels. In each actogram, twelve successive days are represented from top to bottom, one row corresponding to one day (24-h period). The subjective days (16 h long) and nights (8 h long) are indicated by the *gray* and *black bars*, respectively, at the top of each actogram. In constant conditions, humans express their endogenous period (usually longer than 24 h) explaining why, for a given day, the onset of activity occurs later than the previous day. On the 6th day of recording, a light pulse, represented on the actograms by a *gray* "*sun*," is applied in the middle of the subjective day (*A*), the beginning of the subjective night (*B*), or the end of the subjective night (*C*). In response, the rest-activity rhythm is either not significantly shifted (*A*), phase delayed (*B*), or phase advanced (*C*). Thus, each discrete pulse of light, given at a specific time, leads to various magnitude and direction of shifts. (*D*) represents the phase response curve of the resetting effect of light with by convention phase advance and delays expressed as positive and negative phase shifts, respectively. *subj. n.* subjective night; *subj. d.* subjective day

activation of melatonin type 2 receptor (MT2), which have been found in the SCN of mammals including humans [129–131]. However, *Per* expression is not modified in response to melatonin injections in nocturnal rats [101].

Another well-studied category of non-photic factor comprises behavioral and pharmacological stimuli that are related to levels of activity, sleep deprivation, and the serotonergic system through direct (implicating serotonin or 5-hydroxytryptamine (5-HT) and 5-HT agonists) and indirect (via the IGL and implicating GABA and NPY) connections between the dorsal and median raphe nuclei (DRN and MRN) and the SCN (Fig. 6.3) [132–136]. In nocturnal species, these factors are mainly effective when applied during the middle of the subjective day and they lead to a phase advance of locomotor activity rhythm and a decrease in the expression of *Per1* and/or *Per2* in the SCN [137–142]. Results obtained from diurnal species are limited and provide different results (Table 6.2) [143–148] from those observed in nocturnal species, underlying the differences between these species in terms of sensitivity and responses to non-photic factors. For instance, sustained physical exercise in humans results in a phase delay of the human circadian system when performed at night or in the morning, and a phase advance when exercise is performed in the evening [146, 149–151]. Despite these resetting effects, exercise has been shown to have no effect on the endogenous circadian period of rhythmic parameters in humans [151, 152]. These observations raise an important issue for the development of pharmacological and therapeutic tools that act on the circadian system because they are usually developed and tested in nocturnal species for possible applications to humans.

Of note, this category of activity/serotonin factors highlights the tight connections between the sleep-wake cycle and the circadian system. First, the sleep-wake cycle is closely linked to the activity of 5-HT neurons. For instance, the activity of 5-HT neurons in the cat dorsal raphe is regular and slow during waking episodes [153]. This activity decreases and loses its rhythmicity at the beginning of a sleep episode, until the complete disappearance at the onset of rapid eye movement (REM) sleep episode. Second, 5-HT release in the SCN region occurs during the waking period of nocturnal and diurnal animals and is correlated with the electrical activity of 5-HT neurons [110, 143, 154, 155]. In addition, hyperactivity is known to induce a release of 5-HT into the SCN through fibers originating from the MRN [155], and lesions of 5-HT fibers can block the behavioral phase advances normally present in response to hyperactivity [156]. Third, an induced transient 5-HT deficiency in rats leads to a temporary loss of the circadian rhythms in

Table 6.2 Main behavioral and molecular effects of non-photic factors

Type of factor	Nocturnal species			Diurnal species		
	Timing	Rest-activity rhythm	*Per1/2* expression	Timing	Rest-activity rhythm	*Per1/2* expression
Melatonin	Evening	Phase advance [127]	No effect [101]	*Rodents*: Evening	Phase advance [128]	?
				Humans: Late afternoon/Evening	Phase advance [125, 126]	?
				Humans: Morning	Phase delay [125, 126]	?
Hyperactivity or sustained activity	Midday	Phase advance [137]	Decrease [138]	*Rodents*: Early night	Phase advance [144]	?
				Humans: Evening	Phase advance [146, 149–151]	?
				Humans: Night/morning	Phase delay [146, 149–151]	?
5-HT	Midday	Phase advance [110, 139]	Decrease [139]	*Rodents*: Night	Phase advance [143]	No effect [143]
NPY	Midday	Phase advance [140]	Decrease [141]	?	?	?
GABA	Midday	Phase advance [142, 287]	Decrease [147]	*Rodents*: Midday	Phase delay [147]	Decrease *Per2* [148]

locomotor activity and sleep-wake cycle [157]. Taken together, these results suggest that 5-HT not only promotes wake and inhibits REM sleep [158], but also participates in the circadian regulation of sleep and wake behaviors [157].

The Circadian System in Humans: Specificities and Methods of Investigation

Most of the cellular and molecular data presented in this chapter have been obtained using animal models rather than human subjects, mostly due to the lack of available techniques to measure the intrinsic molecular or electrical activity of the human SCN in vivo and the obvious limited possibilities of human sampling. Nevertheless, laboratories working on human chronobiology typically use robust peripheral output signals primarily regulated by the SCN, thus reflecting the circadian functioning of the central clock. These so-called central circadian markers are derived from physiological measures such as CBT, sleep propensity, or hormone levels such as melatonin and cortisol. Their rhythms are usually defined by their phase, amplitude, and period. The phase represents the time of day when a rhythmic parameter reaches its maximal value (i.e., acrophase or crest time; used for melatonin and cortisol) or its minimal value (i.e., bathyphase or nadir time; used for CBT). The amplitude and period of circadian signals are less commonly reported, though they also provide important information on the state of synchrony/desynchrony between the SCN, peripheral oscillators, and the 24-h environment. In individuals living on regular conditions (entrained to a day-oriented schedule), CBT rhythm typically peaks before habitual bedtime and reaches its minimum values in the second half of the night [159]. Sleep propensity is inversely related to CBT [160]. Melatonin levels start increasing in the evening, reach a peak in the middle of the night, and decrease in the morning with undetectable values occurring during the day [123, 159]. Cortisol secretion peaks just after awakening and slowly decreases through the day to reach its nadir early at night [123]. With the relatively recent discovery of peripheral clocks, markers of those clocks such as clock gene expression (i.e., peripheral markers) have started to be measured in humans as an accessible alternative to central markers. Moreover, they represent a valuable tool to assess the relative synchronization of the different parts of the circadian system. To date, clock gene expression in peripheral oscillators has been measured in different human tissues, including peripheral blood mononuclear cells [159, 161, 162], skin cells [163–165], adipose tissue [166, 167], oral mucosa [163], bone marrow [168], hair follicles [169], and more recently *postmortem* brain regions [38, 170, 171]. Results from these studies indicate that the molecular mechanisms underlying the generation of circadian rhythms are similar in humans and other mammalian species.

In humans, circadian markers can be measured in ambulatory conditions, but they are likely to be masked by behaviors and external stimuli. Negative masking is a process reducing the expression of a circadian pattern [172]. For instance, light exposure at night inhibits the release of melatonin [173]. In contrast, positive masking reflects the expression of a variable in addition to its circadian pattern. In diurnal species, light exposure at night induces a bout of locomotor activity at a time when animals are supposed to sleep [173]. Transient fluctuations in cortisol induced by stress are often high enough to mask the cortisol rhythm [174, 175]. Exercise and feeding have also been described as masking factors that increase the CBT [175, 176]. To precisely describe the circadian profile of a given circadian marker in humans, rigorous protocols need to be used to "unmask" it. Specifically to measure the circadian phase and amplitude, physiological signals have to be measured for at least one complete cycle ($\geq$ 24 h) under constant conditions, such that the influence of the external and internal masking factors (e.g., the sleep-wake cycle, light, food intake, and activity levels) is minimized and/or distributed throughout the day. The most commonly used protocol in human chronobiology, namely the CR (constant routine) [175, 177, 178], is based on this idea and takes place in a laboratory environment of constant dim lighting and ambient temperature. In addition, subjects are requested to stay awake for at least 24 h (up to 72 h), usually in a semirecumbent position to control the level of activity, and meals are replaced by hourly snacks that provide all the essential nutriments needed in a non-circadian rhythmic fashion. Many variations of the CR are in use, with the goal to minimize these masking effects [175]. One of the main issues of the CR is the absence of sleep, especially with protocol >24 h that are known to induce sleep deprivation and negatively affect alertness and performance. As an alternative, a CR protocol with sleep (i.e., constant posture protocol) has been proposed, but by introducing periodic changes in the sleep-wake cycle, parameters such as CBT are affected. Thus, the choice of one or another variant of the CR needs to be based on the type of parameters of interest for a given study. While the CR and its alternatives are very useful to assess the phase and amplitude of central and peripheral circadian markers, other protocols have been developed that focus on other properties of the circadian system. The forced desynchrony protocol induces an internal desynchronization, which is forced by scheduling subjects on sleep-wake regimens that are very different from the classical 24-h rhythm, thus being outside of the range of entrainment of the circadian system (e.g., 28-h day, 20-h day, and 11-h day) [179]. This means that the circadian system cannot be synchronized by the sleep schedule and

instead expresses its own endogenous period. Thus, the phase relationship between the imposed sleep-wake cycle and the circadian system is lost, meaning that the sleep-wake cycle occurs at a variety of circadian phases. This protocol has been very useful to establish the endogenous circadian period of the human central clock and has been used primarily to evaluate circadian and homeostatic influences on observable processes such as sleep, sleep structure, electroencephalographic (EEG) power density in different sleep stages, cognitive performances, mood, and hormonal rhythms (see [179] for references). Other protocols, called multiple naps or ultradian sleep-wake cycle (USW) procedures, have been developed [180–183]. They can be considered as extreme examples of the forced desynchrony protocol. Indeed, in those protocols, the duration of one cycle is usually very short (90 or 120 min) with a wake-sleep ratio that can be of 60/30 min or 60/60 min (the later minimizing the observable sleep restriction). In some extreme cases, the ratio can drop to 15/5 min [184, 185] or 13/7 min [186]. While those protocols do not allow the study of the homeostatic contribution on observable processes, they have the advantage to make possible the examination of the sleep propensity at multiple circadian phases due to the numerous transitions between lights on and lights out.

Circadian Regulation of the Sleep-Wake Cycle

The Sleep-Wake Cycle

As opposed to wakefulness during which functions for survival such as feeding and breeding activities are possible, sleep is a reversible vigilance state characterized by a reduction in voluntary motor functions, sensory perception, and responsiveness and is associated with immobility in a species-specific position. Of note, submitted to the same 24-h light/dark environment, a variety of sleep-wake schedules and sleep durations are observed across species. While some species adopt a diurnal or nocturnal behavior, others are essentially active around dawn and dusk and thus adopt a bimodal behavior [187]. Some species sleep for more than 20 h daily (e.g., cat), while others sleep only for 3 h (e.g., horse) [188]. In humans, sleep is consolidated in a period of approximately 8 h at night, making it one of the most evident behaviors under circadian regulation. It is also interesting to recognize that the sleep-wake cycle can indirectly regulate the circadian system through cyclic exposure to light and darkness. This is especially important in modern society since the development of artificial lighting provides accessible brighter light at night, facilitating nocturnal activities.

Sleep has been historically viewed as a passive behavioral state until the identification of paradoxical sleep by Jouvet et al. [189], also known as REM sleep. With the development of EEG techniques in humans, sleep was subsequently described using standardized terminology and criteria developed by Rechtschaffen and Kales [190], recently updated and simplified by the American Academy of Sleep Medicine [191]. Sleep is generally assessed by polysomnography (PSG), which comprises EEG to measure frontal, central, and occipital cortical activity, electromyography (EMG) to measure muscle activity, and electrooculography (EOG) to measure eye movements. PSG recording is used to classify sleep into two main categories: REM sleep and non-REM (NREM) sleep. NREM sleep can be subsequently subdivided into 3 stages (i.e., stage N1 to N3) marked by progressive slowing and synchronization of electrical cortical activity, as observed on the EEG channels [191]. In healthy individuals, NREM and REM sleep alternate in cycles of approximately 90–110 min and are measured from the end of a REM sleep episode to the end of the subsequent one. The respective proportion of NREM and REM sleep during a sleep period differs between cycles. More N3 sleep (also known as slow-wave sleep) is typically observed in the early night and decreases with time spent asleep. On the other hand, the length of REM sleep bouts during each sleep cycle increases with the amount of time spent asleep. More precisely, the greatest amount of REM sleep is observed in the early morning hours.

The Two-Process Model

Initially proposed by Borbely [192], the two-process model of sleep regulation provides a theoretical framework describing the temporal organization and timing of sleep (Fig. 6.5). The homeostatic process, or Process S, reflects the increased sleep pressure as a function of the amount of time spent awake and its decline as a function of time asleep, similar to an hourglass effect. The circadian process, or Process C, regulates sleep as a function of time of day and depends on the action and timing of the SCN. As a result of the balance between the circadian and homeostatic processes, only a narrow set of sleep-onset times permits a continuous sleep period of about 8 h (i.e., sleep onset ~6 h before CBT minimum) [193–195]. Since its introduction in 1982, other components, such as sleep inertia and a NREM/REM sleep oscillator, have been added to the original two-process model, but the simple conceptual model developed by Alexander Borbely remains the most influential. It has been recently extended to predict alertness and vigilance around the clock [196].

The Homeostatic Process

For a long time, the sleep-wake cycle was considered to be regulated by the accumulation and elimination of a sleep-promoting substance in the organism. To date, many researchers have confirmed the existence of a homeostatic process regulating sleep, but have yet failed to identify a single sleep-related factor. The homeostatic process regulates sleep propensity as a function of the sleep-wake cycle length, independently of the time of day. Specifically, the homeostatic sleep drive or Process S increases when sleep is absent or restricted and conversely declines in response to sleep. Within a sleep period, the EEG slow-wave activity (SWA, 0.5–4.5 Hz) power measured during NREM sleep has been used to quantify Process S. It has been shown to be correlated with the duration of the prior wake period and to decline across the sleep period [197]. In contrast to Process S, the Process C only has a small influence on SWA [195]. The influence of waking on Process S has been estimated by quantifying the level of SWA during naps after various durations of waking [198]. Process S has been modeled by a saturating exponential function throughout the wake period, followed by an exponential decline during sleep [196]. Of note, sleep pressure dissipation during the sleep period is faster than sleep pressure accumulation during the wake period. Furthermore, the decline in Process S following sleep initiation is steeper in the first hours of sleep compared to the last ones. Based on the exponential decline of SWA throughout the sleep period, it has been estimated that after ~4.3 h of sleep, 75 % of the SWA needs would be fulfilled [195].

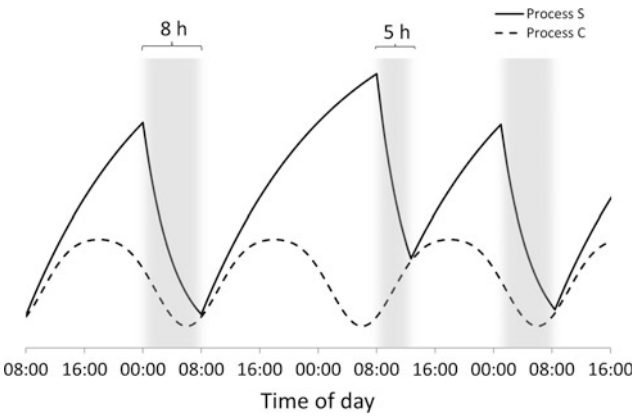

Fig. 6.5 The two-process model of sleep regulation. This model illustrates the interaction between the homeostatic (S) and circadian (C) processes in the control of sleep and waking [288]. Here, Process C represents the circadian variation in the strength of the wake signal, whereas Process S represents the dynamic changes in sleep pressure. During a standard day (e.g., 1st cycle; wakefulness: 08:00–00:00, sleep: 00:00–08:00), Process S (*continuous line*) increases exponentially during the wake period. During that time, Process C sends a wake signal that reaches its peak at the end of the evening. This allows the subject to remain awake for 16 consecutive hours. Sleep (*shaded bars*) is then initiated a few hours after the evening circadian peak of wakefulness. This time also corresponds to the start of the declining limb of the CBT cycle. Process S is at its peak at bedtime and then decreases exponentially throughout the night. At the end of the night, the circadian drive for waking is at its nadir, whereas the circadian drive for sleeping is at its peak. This allows the subject to remain asleep for 8 consecutive hours. When wakefulness is sustained during 24 h and sleep is initiated in the morning (as it is often the case for the first shift of a night shift worker), individuals usually wake up after a reduced amount of sleep. In this case, the present model predicts that about 5 h of consecutive sleep would occur (modified from Daan et al. [288])

Theta power (5–7 Hz) can also be used as an estimate of Process S and parallels sleep propensity during quiet wakefulness [199, 200]. As for SWA, the time course of theta power with time spent awake follows a saturating exponential function [201]. The rise rate of theta power measured during 40 h of sleep deprivation in humans and during enforced wakefulness in rats has been correlated with the SWA power increase observed in the beginning of a recovery sleep period [199, 200].

In the last decade, the synaptic homeostasis hypothesis has been proposed, in which Process S corresponds to the varying synaptic strength or neuroplasticity observed during the sleep-wake cycle [202]. More specifically, this hypothesis states that wakefulness is associated with synaptic potentiation and thus increased energy requirements in several cortical circuits caused by the acquisition of new information during waking. During sleep, the decrease in SWA observed during sleep is presumed to be caused by the progressive downscaling in synaptic strength during the sleep period. In this model, each synapse of a given network would undergo the downscaling process, but the relative weight of each synapse would be conserved, thus resulting in a decrease of energy and space requirement leading to a subsequent increased benefit for memory and learning capacity. Consistent with this hypothesis, it is now admitted that topographical differences exist between EEG derivations when measuring SWA and theta power during sleep and wakefulness, respectively. Indeed, frontal compared to occipital EEG derivations show increased SWA and theta power, especially in response to sleep recovery [203–205]. In addition, the regulation of SWA can be local, restricted to the specific learning cortex regions [203, 204, 206–209]. Brief local sleep can even be identified in local cortical region when rats are submitted to prolonged wakefulness even though the animal remains awake [210].

Some biochemical markers have been found to correlate with Process S and could represent chemical mediators of the homeostatic sleep drive. Such mediators are expected to accumulate during wakefulness and decline with sleep. Among others, adenosine [211], prostaglandin [212], interleukin-1β (IL-1β), tumor necrosis factor alpha (TNF-α), brain-derived neurotropic factor (BDNF), and epidermal growth factor (EGF) [213] have been described, but to date

adenosine represents the most studied candidate in the possible mediation of the homeostatic sleep drive [214]. First, extracellular adenosine accumulation is site specific. With time spent awake, adenosine starts to accumulate in the basal forebrain [211], followed by an increase in the frontal cortex [215]. Then, during sleep recovery, these levels decrease in the cortex and in the basal forebrain. Second, it was shown that sleep is induced by injections of adenosine or adenosine type 1 (A1) receptor agonists in the basal forebrain of cats [211] and by adenosine type 2a (A2a) receptor agonist injections near the VLPO area in rats [216]. This could be due to the fact that adenosine inhibits the release of acetylcholine (ACh) by cortical [217] and basal forebrain [218] neurons via a presynaptic mechanism. Third, caffeine is known to be an adenosine antagonist [219] inducing a reduction of sleepiness and EEG theta activity during wakefulness and a decrease of SWA during subsequent sleep [220]. Finally, in addition to the direct modulation of the frontal cortex activity, inhibition of the basal forebrain by the accumulation of adenosine can in turn promote sleepiness via its projection throughout the cortex. As described in the next section of this chapter, the basal forebrain is indeed part of the ascending arousal pathway regulating sleep.

The Circadian Process

One of the first indications that sleep and sleep propensity are regulated by the circadian system aroused from the work of Nathaniel Kleitman who noticed that staying awake for more than 24 h is usually associated with higher levels of alertness, the next morning in comparison with the levels observed at night [221, 222]. Following that simple but important observation, the circadian rhythmicity of sleep has been extensively studied by placing humans and animals in time-free conditions for several days [89, 223]. As we previously mentioned, without time cues, the circadian endogenous system free-runs with a period close to, but not exactly, 24 h [75, 224, 225]. Under these conditions, sleep propensity is modulated by the slowly shifting (i.e., free-running) rhythm of CBT [223].

The relative contribution of Processes C and S can be better appreciated when participants are studied under a forced desynchrony protocol described earlier in this chapter. Using this experimental paradigm, the main sleep period successively occurs at different circadian phases. Both Processes S and C can thus be mathematically separated and their specific contributions to the various sleep parameters can be observed. With such an approach, it was possible to determine that sleep latency (SL), total sleep time (TST), sleep efficiency (SE), and wake after sleep onset (WASO) have a strong circadian rhythm with increased sleep propensity around the time of CBT minimum [181, 193–195, 226, 227]. In addition, these measurements are influenced by the homeostatic process since sleep consolidation decreases with time spent asleep [194, 195]. The amount of REM sleep and REM sleep latency also follow a strong circadian rhythm with respective maximum and minimum in the morning, approximately 1–2 h following the bathyphase of CBT [181, 194, 195, 226, 227]. Process S can also influence the proportion of REM sleep which increases with time spent asleep. NREM sleep is controlled by the circadian and homeostatic system [195, 226]. The overall proportion of NREM sleep follows a circadian rhythm different from that of REM sleep, with the maximum values observed in the evening and early night [181, 195, 227]. With deeper sleep (i.e., N3 vs N1), there is a shift from an equivalent contribution of Processes S and C in N1, to an almost exclusive contribution of Process S in stage N3 [181, 194, 195, 226].

Subsequently, the introduction of the forced desynchrony protocol confirmed the existence of the circadian regulation of sleep in humans, independently of the homeostatic process. When scheduled to live on a 28- or 20-h rest-activity cycle, most sleep parameters present a circadian rhythm independent of their homeostatic regulation. Thus, this paradigm confirmed that a consolidated 8 h of sleep can only be obtained when sleep is scheduled approximately 6 h before CBT minimum, even though the time spent awake before each sleep period remains about the same [193–195].

The structure responsible for the circadian regulation of sleep was first evidenced following SCN lesions in rodents. In these nocturnal animals, the total duration of sleep over 24 h is similar to wild-type animals, but sleep is randomly distributed in small bouts throughout the 24-h day rather than consolidated bouts mainly during the day [228–231]. SCN-lesioned animals no longer present consolidated rhythms of NREM and REM sleep and display frequent sleep stages transitions and arousals [229, 231, 232]. The sleep recovery process (i.e., increased sleep duration and SWA) is not affected in SCN-lesioned [230] or arrhythmic [233] animals and confirms that Processes C and S arise from different neural substrates.

Although they are independent processes, evidence obtained from the manipulation of the sleep-wake cycle suggests that a higher homeostatic drive can reduce the circadian regulation of sleep. The circadian amplitude of sleep propensity was shown to be reduced in response to chronic sleep deprivation (i.e., 4-h vs. 8-h sleep opportunity per 24 h) in humans [234]. During 6 h of sleep deprivation, the SCN firing activity was reduced to 87 % compared to the baseline levels in rats [235]. During the following 7 h of

recovery sleep after sleep deprivation, the SCN neuronal firing activity during NREM and REM sleep was significantly reduced by about 40 and 30 %, respectively, compared to baseline levels [235]. During NREM sleep, the increase in SWA paralleled the decrease in SCN firing rate, both during normal sleep [236] and during recovery sleep after sleep deprivation [235]. Taken together, these studies suggest that the relative weight of Process C can change with the sleep-wake history, or at least with acute sleep deprivation.

The literature suggests that the SCN has both a sleep- and wake-promoting action depending on circadian phase. First, the majority of SCN-lesioned studies does not show changes in the total amount of sleep or sleep stages throughout 24 h [228–231], although some contradictory evidence has been reported [237, 238]. Furthermore, the proportion of sleep stages throughout the circadian day in SCN-lesioned animals is equivalent to the average 24-h rhythm observed in wild-type animals [228–230], although some evidence suggests that it might be different for REM sleep [231]. It is notable that, even when the homeostatic process is challenged, similar results can be obtained. For example, in the study of Mistlberger et al. [230], wild-type rats were sleep deprived for 24 h. Following this sleep deprivation, the authors analyzed the variation in the amount of sleep and sleep stages over 24 h. Surprisingly, they showed that during the first 12 h following sleep deprivation (corresponding to the habitual active period), the amount of sleep was lower than during the second 12 h (i.e., from 12 to 24 h after sleep deprivation, corresponding to the habitual rest period). In SCN-lesioned rats, when recovery sleep is compared to baseline levels, the proportion of sleep over wakefulness is increased to a constant level during the 24 h following sleep deprivation, with values in between the maximum and minimum levels observed in wild-type rats. This suggests that the SCN restrains sleep propensity during the habitual active period and promotes sleep during the habitual rest period.

Wake Maintenance Zones and Sleep Propensity Zones (The Interaction)

In entrained condition, humans sleep at night and are active during the day. However, when sleep timing was studied in time isolation environments, a bimodal distribution of sleep propensity was observed throughout the 24-h day, with two high sleep propensity and two high alertness zones [239, 240]. A first zone of high sleep propensity is observed at the end of the night, near the CBT minimum. A second peak in sleep propensity is observed in the early afternoon. Of note, in certain countries, naps are commonly taken after lunch and thus during this zone of high sleep propensity. Important, increased drowsiness, errors, and risk of accident have been reported to follow a bimodal patterns with increased levels late at night and in the afternoon [241–243]. Conversely, "wake maintenance zones" (WMZs) are also observed and are characterized by high levels of alertness and difficulty to fall asleep. The first WMZ occurs in the morning, approximately 3–4 h after waking up in the morning [239]. It is usually associated with increased productivity at work and thus represents a profitable timing to plan intellectually demanding tasks. A WMZ is also observed in the evening, approximately 1–2 h before the habitual bedtime. It was indeed shown that in a well-rested individual, advancing bedtime by 1 or 2 h could lead to longer sleep-onset latencies. This is especially important in sleep-onset insomnia patients who often try to advance their bedtime to lengthen their main sleep period, resulting in longer sleep-onset latencies and increased anxiety due to insomnia [244, 245]. These zones are important to consider in our daily schedule to more efficiently plan naps, activities, or when periods of sleep or wakefulness need to be acutely and temporarily displaced. Shifting the sleep-wake schedule, as observed in shift workers or after transmeridian travels, disrupt the normal temporal harmony between Processes C and S, a situation that can lead to reduced sleep duration and quality and lower levels of alertness.

In humans, the interaction between Processes S and C leads to the consolidation of an ~8-h sleep period at night and an ~16-h wake period during the day. In entrained conditions, sleep is initiated in the evening on the decreasing limb of the CBT rhythm, 1–2 h after the evening WMZ. The circadian regulation of distal heat loss, helped by the vasodilation effect of melatonin, is thought to facilitate sleep initiation at the usual bedtime [246]. The following exponential decline in Process S suggests that most of the deep-sleep needs are fulfilled within the first half of the night. Despite the reduced homeostatic need for sleep, the sleep period lasts approximately 8 h because Process C maximally promotes sleep in the second half of the night. Then, after awakening in the morning, sleep propensity is low as a result of the previous time spent asleep.

A phenomenon known as sleep inertia is responsible for the reduced alertness that can be observed in the time period following awakening [247]. Sleep inertia appears to depend on several factors such as sleep stages, time of day and amount of prior sleep deprivation, although its precise duration and severity requires further research [247, 248]. In the late morning, Process S is still low, sleep inertia has dissipated, and Process C starts to promote wakefulness, thus explaining the WMZ observed in the morning. In the afternoon, a zone of higher sleep propensity is observed as a

result of the time spent awake. In the evening, Process C keeps us awake until bedtime by promoting wakefulness maximally during the evening WMZ, even if Process S is elevated (Fig. 6.5).

Brain Regions Implicated in Sleep Regulation

During wakefulness, a series of ascending arousal pathways activate the thalamus and cortex. Two major arousal pathways have been defined. In the first one, cholinergic neurons from the pedunculopontine tegmental nucleus (PPT) and the laterodorsal tegmental nucleus (LDT) activate reticular and relay nuclei of the thalamus to facilitate thalamocortical transmissions. In the second pathway, monoaminergic neurons originating primarily from the locus coeruleus (LC), the ventral periaqueductal gray matter (vPAG), the DRN and MRN, the tuberomammillary nucleus (TMN), the lateral hypothalamus, and the basal forebrain contribute to diffusely activate the cerebral cortex. Sleep occurs when the arousal pathways are directly inhibited by the VLPO via GABAergic and galaninergic neurotransmitters [249]. The VLPO is innervated by inhibitory afferent fibers from nuclei of the arousal ascending pathways. This mutual inhibition between ascending arousal pathways and the sleep-promoting system (i.e., VLPO) can be viewed as a "flip-flop switch" that facilitates sharp transitions between wakefulness and sleep [58]. Orexin (ORX) neurons of the lateral hypothalamus area (LHA) reinforce the wake-promoting system by projecting to the cerebral cortex and to nuclei of both major arousal pathways. The VLPO also projects to ORX neurons and inhibits their action during sleep. Through its massive input to the DMH, the SCN modulates the activity of the VLPO, median preoptic nucleus, and ORX neurons [250]. Therefore, the central circadian clock directly acts as a time-keeping device for the sleep-wake cycle.

Transitions between NREM and REM sleep can be explained in a similar way by mutual inhibition of REM-on and REM-off centers [249, 251]. This switch is composed of the precoeruleus (PC) and sublaterodorsal nucleus (SLD, REM-on) mutually inhibiting the vPAG and lateral pontine tegmentum (LPT, REM-off). Other regulatory areas strengthen this mutual inhibition to facilitate NREM/REM transitions but are not necessarily inhibited by the opposite side of the NREM/REM switch. During REM sleep compared to NREM sleep activity, centers of the ACh arousal pathway including the LDT and PPT (REM-on) increase their activity, while the firing rate in most regions of the monoaminergic pathway completely ceases or decreases. These REM-off regions include the LC, DR/MR, vPAG, and ORX neurons. During both NREM and REM sleep, the VLPO remains active and maintains its inhibition over the monoaminergic arousal pathway.

Intriguingly, sleep centers can also influence the activity of the SCN. Compared to wake and REM sleep, NREM sleep was shown to reduce SCN neuronal activity in rats [236]. Specifically, SCN neuronal firing rate was negatively correlated with the amount of SWA (1–4 Hz) and sigma activity (11–14 Hz), both indicators of sleep homeostasis. This inhibition of SCN activity by SWA was confirmed by selective SWA and REM sleep deprivation experiments. The SCN receives afferent cholinergic projections from the PPT and LDT, serotonergic projections from the DR, and, to a lesser extent, noradrenergic projections from the LC, all implicated in arousal ascending pathways and in the generation of NREM/REM sleep cycling [236, 249, 252]. The presence of afferent neuronal connections to the SCN suggests that the sleep-wake cycle per se could modulate the circadian pacemaker [151].

Chronotype

Although humans are diurnal, individual preferences in the sleep-wake cycle and daytime activity timing are reported and are referred to as chronotype, or morningness-eveningness. Questionnaires have been developed to assess these differences and aim to identify the times of day at which the individual feels better to perform more demanding tasks and to sleep [253, 254]. The chronotype was reported to vary with age [255–257] and gender [258]. Teenager between the ages of 11–18 years tends to progressively delay their bedtime by ~2.5 h [255], a phenomenon that parallels pubertal development [256]. Of note, a progressive change from early to late chronotype has been observed starting at childhood, accelerating during puberty and peaking around the age of 20, with women (~19.5 years) reaching a maximum "eveningness" approximately 1.5 years before men (~21 years) and slowly declining thereafter. Nevertheless, from the age of 20–50 years, men generally present a later chronotype than women, with this sex difference disappearing after the age of 50 [257]. These changes during puberty are associated with a >60 % decrease in SWA and theta power from 9 to 18 years of age [259]. Thus, the homeostatic process is highly affected during adolescence. At that age, adolescents also tend to go to bed and wake up later, reflecting changes in chronotype throughout adolescence [260]. Moreover, later bedtimes could also enhance exposure to light at night and reduce light exposure in the morning and thus entrain the circadian system to a later phase.

Earlier circadian phases of melatonin and CBT have been reported in morning compared to evening chronotypes [261–265]. This difference was also recently reported in peripheral genetic markers, namely in the circadian oscillation of *Per1*, *Per2*, and *Rev-erbα* expression in samples of oral mucosa

[266]. Thus, it suggests that circadian entrainment differs between morning and evening types and influences the timing of their sleep-wake cycle. Of note, a variable-number tandem repeat in the human clock gene *Per3* has been correlated with chronotype, as well as with circadian rhythm sleep disorders [267–269], though not all studies report significant results [270, 271]. The shorter allele of *Per3* ($Per3^{4/4}$ vs. $Per3^{5/5}$) was associated with eveningness, but the acrophase of melatonin, cortisol, and *Per3* mRNA peripheral expression did not differ between carriers of the shorter and longer alleles [272]. Nevertheless, markers of sleep homeostasis were considerably different between *Per3* genotypes: The $Per3^{5/5}$ group was more affected by sleep deprivation, presented more theta and alpha EEG activity during wakefulness, and showed elevated SWA during NREM sleep compared to the $Per3^{4/4}$ group. These results suggest that the homeostatic drive for sleep also influences the timing of the sleep-wake cycle, which underlines the interaction between Processes C and S.

Most of the population is classified as neither morning nor evening type, but a significant proportion can be classified as moderate-to-severe morning or evening type [257, 273]. Patients suffering from delayed or advanced sleep-wake phase disorders can be considered as extreme morning or evening types, although chronotype questionnaires are not sufficient to make a diagnostic [274]. Delayed sleep-wake phase disorder has been associated with circadian gene polymorphism, including *PER3*, *CLOCK*, and *AA-NAT*, a limiting enzyme in melatonin synthesis. An association was also found between the c.3111T/C allele of the *CLOCK* gene and a latter bedtime as well as daytime sleepiness [275]. As for the advanced sleep-wake phase disorder, it has been associated with mutations in the *PER2* and *CK1*δ genes [276, 277] and which highlights the contribution of the circadian system to extreme chronotypes.

Conclusion

Most of us are unaware of the impact of the circadian system in our daily life until our sleep-wake cycle is displaced out of synchrony with this system. Unlike other species, humans can voluntarily and abruptly change their sleep-wake behavior or sustain wakefulness throughout the night, mainly because of social and professional incentives. Abrupt circadian misalignment, as observed in shift workers or in transmeridional travelers, leads to important acute performance and alertness impairments, as well as sleep disturbances [278–281]. Moreover, only a slight delay or advance of the endogenous circadian system relative to the scheduled sleep periods is sufficient to result in clinically relevant sleep-onset and sleep maintenance difficulties. This can lead to chronic sleep disturbances as it has been reported in patients suffering from insomnia, delayed sleep-wake phase disorder, advanced sleep-wake phase disorder, or non-24-h sleep-wake disorder [245]. Long-term exposure to circadian misalignment has been associated with increased risk of several medical conditions, including obesity, metabolic syndrome, diabetes, hypertension, gastrointestinal disorders, endometriosis, adverse pregnancy outcomes, cardiovascular disease, and cancer [282–285]. There is a high prevalence of comorbidity between psychiatric conditions and sleep-wake and circadian rhythm disorders. Interconnections between the circadian, sleep, and mood systems are such that deregulation of one system can lead to deregulation of the others [286]. Different pharmaceutical and non-pharmaceutical interventions have been proposed to treat circadian rhythm disorders including chronotherapy, light therapy, and melatonin and are usually planned based on the phase of the circadian system [245]. Further research is needed to increase the efficiency of these therapies and to develop a better way to assess human circadian rhythms in clinical populations.

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Neurotransmitters, Neurochemistry, and the Clinical Pharmacology of Sleep

7

Max Hirshkowitz and Hanul Bhandari

Overview

Physicians practicing sleep medicine use a wide assortment of medications and other substances. Some pharmacologic agents induce sleep; some enhance wakefulness, while others alter the endogenous sleep–wake rhythm. These chemically induced actions may represent a substances' principle therapeutic effect but often the soporific or alerting property occurs as a side effect.

With western societies' ever growing pace and complexity, an individual's alertness or drowsiness level increasingly impacts productivity and safety. Consequently, sleep's mental and physically restorative properties loom ever more important. However, competing daily for time allocation, scheduled sleep time often loses out to work and recreation. Today's pharmacopeia is enormous and continues growing. Attempting to memorize by rote every drug's sleep–wake alterations would be quite a challenge. To facilitate better recall and improve an overall understanding of how medications (and other substances) affect sleep, we organized this chapter according to neurotransmitter systems. Knowing how particular neurotransmitter systems alter sleep and familiarity with the substance's mechanism of action can help the clinician predict the sleep–wake effects. In this chapter, we endeavor to develop *rules of thumb* concerning sleep-related drug effects. Generic medication names are used throughout this chapter; however, because we know many medications by their brand names Table 7.1 is included for cross-reference.

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Stimulating Transmitter Systems

Dopamine and Norepinephrine

Pharmacology

Dopamine (DA) and norepinephrine (NE) are monoaminergic neurotransmitters collectively known as catecholamines [1]. In DA neurons, synthesis begins with tyrosine from the blood that is first hydroxylated to dihydroxyphenylalanine (DOPA) and then decarboxylated to DA. The DA is bound into vesicles and if the vesicle fuses with the cell membrane it is released to the synapse [2]. DA can be catabolized intracellularly by monoamine oxidase (MAO) to 3,4-dihydroxy-phenylacetic acid (DOPAC) or extracellularly by catechol-*O*-methyltransferase (COMT) into homovanillic acid (see Fig. 7.1). DA neurons project to many brain areas via several tracts. The largest amount of DA projects via the nigrostriatal tract (from the substantia nigra to the striatum). The tuberoinfundibular tract runs from the hypothalamus's arcuate nucleus to the pituitary stalk. The mesolimbic tract and the mesocortical tract connect ventral tegmentum to limbic areas and to prefrontal area, respectively. Many structures are involved, including hippocampus, amygdala, arcuate nucleus, periventricular hypothalamus, septum, thalamus, and frontal cortex [3]. In noradrenergic neurons, synthesis follows the same course as for dopamine but then in an extra reaction, dopamine beta hydroxylase converts DA to NE. Like DA, the NE is bound into vesicles that will release if fused with the cell membrane (see Fig. 7.2). MAO will catabolize NE to normetanephrine and COMT catabolism will result in homovanillic acid or 3-methoxy-4-hydromandelic acid [4]. NE synthesis occurs in several areas including the locus coeruleus (LC) which projects to the cerebral cortex, hypothalamus, thalamus, and hippocampus. There is a stepwise reduction in LC activity with the highest levels during wakefulness, reduced during NREM sleep, and nearly silent during REM sleep [5].

Pharmacological probes can be used to manipulate dopaminergic neurons to help elucidate the underlying mechanism. The precursor L-DOPA can increase chemical

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Table 7.1 Medication classifications and names

Classification	Pharmacological agent (brand name(s))
Amphetamine derivatives	Amphetamine mixed salt (Adderall), dextroamphetamine (Dexedrine, Dextroamphet, Dextrostat, ProCentra), methamphetamine (Desoxyn), lisdexamfetamine (Vyvanse), benzphetamine (Didrex), methylphenidate (Ritalin, Concerta, Metadate, Methylin, Quillivant)
DA precursor	Levodopa (Parcopa, Sinemet, Dopar, Larodopar)
DA agonist	Apomorphine (Apokyn), pramipexole (Mirapex), ropinirole (Requip), rotigotine (Neupro)
Traditional antipsychotics (D_2/D_3 antagonist)	Haloperidol (Haldol), chlorpromazine (Thorazine, Largactil), thioridazine (Mellaril)
Atypical antipsychotics	Amisulpride (Solian), olanzapine (Zyprexa), aripiprazole (Abilify), carpipramine (Pranzinil), asenapine (Saphris), clotiapine (Entumine), clocapramine (Clofekton), iloperidone (Fanapt), clozapine (Clozaril), lurasidone (Latuda), paliperidone (Invega), mosapramine (Cremin), perospirone (Lullan), quetiapine (Seroquel), remoxipride (Roxiam), sertindole (Serdolect), resperidone (Resperdal), sulpiride (Eglonyl, Sulpirid), zotepine (Nipolept), ziprasidone (Geodon, Zeldox)
Adrenergic α_1 agonist	Phenylephrine (AK-Dilate, AK-Nefrin, Efrin)
Adrenergic α_2 agonist	Clonidine (Catapres), guanfacine (Intuniv, Tenex)
Adrenergic α_1 antagonist	Prazosin (Minipress)
Adrenergic α_2 antagonist	Yohimbine (Aphrodyne, Yocon)
Adrenergic β agonist	Albuterol (Proventil, Ventolin, ProAir), terbutaline (Brethine, Bricanyl, Brethaire), isoproterenol (Medihaler-Iso, Isuprel)
NE β antagonist	Propranolol (Inderal)
Tricyclic antidepressant (TCA)	Amitriptyline (Elavil, Tryptanol, Endep, Vanatrip), doxepin (Aponal Adapine, Sinquan, Sinequan), imipramine, clomipramine
SNRIs	Duloxetine (Cymbalta), venlafaxine (Effexor), desvenlafaxine (Pristiq), milnacipran (Savella), atomoxetine (Strattera), reboxetine (Edronax, Prolift)
Atypical antidepressants	Bupropion (Wellbutrin, Zyban), trazodone (Desyrel, Trazorel, Trialodine, Thombran, Trittico, Molipaxin), mirtazapine (Remeron, Zispin), nefazodone (Serzone)
MAO inhibitors	Phenelzine (Nardil), isocarboxazid (Marplan), tranylcypromine (Parnate)
H_1 antagonist	Diphenhydramine (Benadryl), triprolidine (Actidil, Mydil), brompheniramine (Bromfed, Dimetapp, Dimentane, Bromfenex)
H_2 antagonist	Cimetidine (Tagamet), ranitidine (Zantac, Zinetac), astemizole (Hismanal), terfenadine (Seldane, Triuldan, Teldane)
Barbiturates	Barbital (Veronal), phenobarbital (Luminal), pentobarbital (Nembutal)
BZDs	Chlordiazepoxide (Librium), clorazepate (Tranxene), diazepam (Valium), flurazepam (Dalmane), lorazepam (Ativan), oxazepam (Serax), temazepam (Restoril), clonazepam (Klonopin), alprazolam (Xanax), estazolam (ProSom), quezepam (Doral), midazolam (Versed)
BZRAs	Zolpidem (Ambien), zaleplon (Sonata), eszopiclone (Lunesta), zopilcone (Immovane)
Chloral hydrate	Chloral hydrate (Aquachloral, Novo-Chlorhydrate, Somnos, Novtec, Somnote)
Alcohol	Alcohol
AChE inhibitors	Physostigmine (Antilirium, Eserine, Isotopo Ersine), donepezil (Aricept), rivastigmine (Exelon), galantamine (Razadyne)
ACh agonists	Arecholine, nicotine, carbachol (Carbastat, Carboptic, Isotopo Carbachol, Miostat)
Ach antagonists	Scopolamine, atropine
5-HT precursor	L-tryptophan
5-HT_2 antagonist	LSD_{25}
5-HT_{1A} partial agonist	Buspirone (Ansial, Ansiced, Anxiron, Axoren, Bespar, BuSpar, Buspimen, Buspinol, Buspisal, Narol, Spitomin, Sorbon)
5-HT antagonist	Cyproheptadine (Periactin), methysergide (Sansert, Deseril)
SSRIs	Fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa), escitalopram (Lexapro), fluvoxamine (Luvox), dapoxetine (Priligy)
Melatonin	Circadin
Melatonin agonists	Ramelteon (Rozerem), agomelatine (Valdoxan, Melitor, Thymanax)
Orexin antagonist[a]	Almorexant, suvorexant
Unknown	Modafinil (Provigil), armodafinil (Nuvigil), sodium oxybate (Xyrem)

[a]Currently not in the market

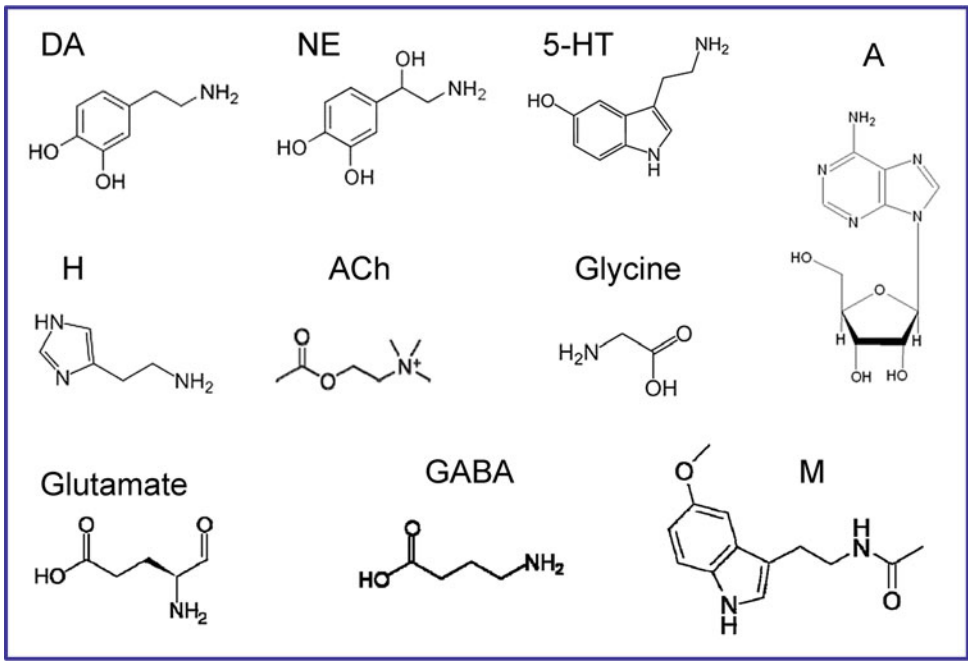

Fig. 7.1 Neurotransmitter diagrams

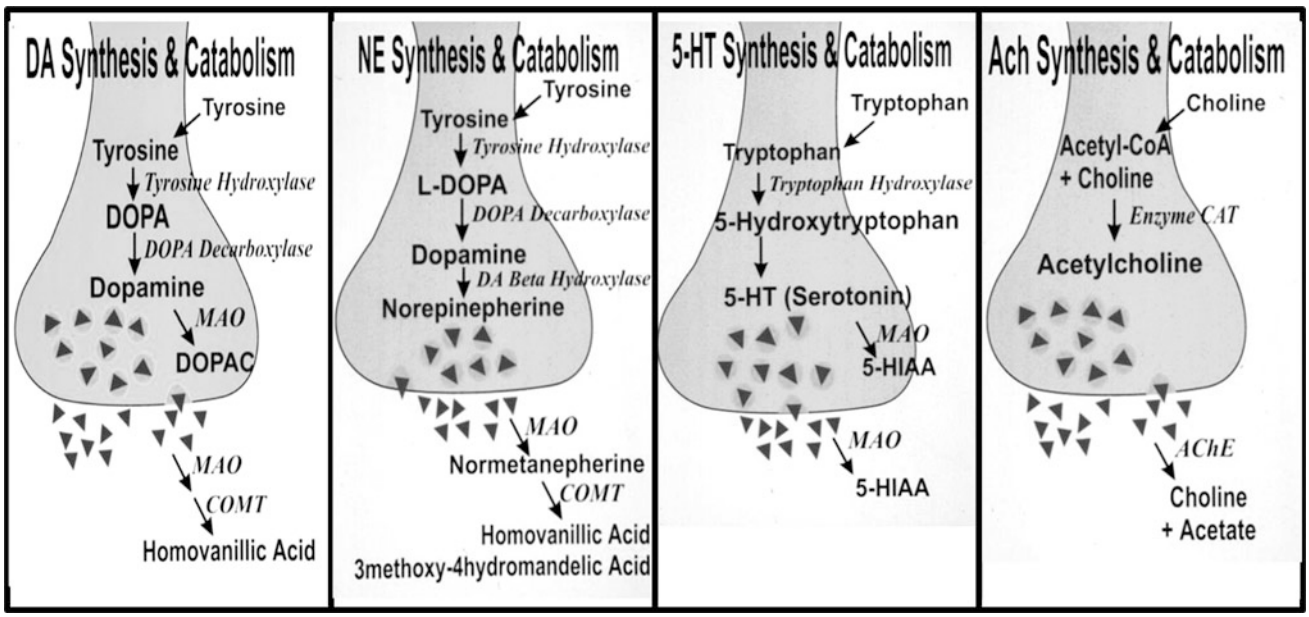

Fig. 7.2 Monoamine and acetylcholine synthesis and catabolism

needed to synthesize DA. By contrast, reuptake into the presynaptic neuron can be inhibited by traditional stimulants (e.g., amphetamines) and cocaine. Postsynaptic receptors can be agonized by apomorphine, pergolide, bromocriptine, pramipexole, rotigotine, and ropinirole. These are G-bound receptors and agonist action differs between drugs. Receptor antagonism can be accomplished with pimozide and any of the traditional neuroleptics (e.g., chlorpromazine, haloperidol, or thioridazine). Intra- and intercellular catabolism can be diminished by monoamine oxidase inhibitors (e.g., phenelzine and tranylcypromine) [6].

NE containing neurons can be chemically probed with a wide variety of compounds. Alpha-methyl-p-tyrosine (AMPT) can retard the synthesis of DA and NE by blocking

the conversion of tyrosine to DOPA. Disulfiram also inhibits NE synthesis by blocking the final step in which DA is converted to NE. Traditional stimulants (e.g., amphetamine) cause vesicles to rupture producing large-scale synaptic release in addition to blocking presynaptic reuptake, thereby greatly increasing synaptic catecholaminergic concentration. This produces excitation and diminishes sleep. Ultimately, the NE or DA that is trapped synaptically gets catabolized resulting in a net depletion of available DA and NE. This "crash" as it is dubbed by stimulant abusers is associated with very profound hypersomnolence. NE reuptake inhibition is also characteristic of tricyclic antidepressants (e.g., imipramine, protriptyline, nortriptyline, and amitriptyline) [7]. However, this property varies widely between compounds. More recently, more specific NE reuptake inhibitors have been developed (e.g., atomoxetine, reboxetine) [8].

Postsynaptically, the central nervous system includes α_1, α_2, and β NE receptors. These receptors can be agonized or antagonized by different pharmacological agents, including phenylephrine (α_1 agonist), prazosin (α_1 antagonist), clonidine (α_2 agonist), yohimbine (α_2 antagonist), and propranolol (β blocker) [9]. More agents are listed in Table 7.1.

Sleep Effects

Dopamine plays an important role in maintaining wakefulness. Consequently, it is not surprising that patients with Parkinson's disease (and related DA deficits) commonly suffer from sleepiness. Some pharmacological agents that increase synaptic availability of NE and DA tend to raise arousal level and decrease REM sleep. This is markedly true of the traditional psychostimulants. These central nervous system stimulants increase arousal level by means of autonomic sympathetic activation (and thereby decrease drowsiness). For many years, these drugs were the mainstay of therapeutics for treating disorders of excessive sleepiness. The older amphetamines formulations of benzedrine, dexedrine, and desoxyn have largely been replaced by mixtures of amphetamine salts (e.g., Adderall®), lysine bound lisdexamfetamine (e.g., Vyvanse®), and the amphetamine congener, methylphenidate. Lisdexamfetamine is a prodrug and was developed in an attempt to decrease abuse potential [10]. Other, dopaminergics with stimulant properties have also been used to treat the sleepiness associated with narcolepsy and idiopathic hypersomnia, including selegiline, pemoline, and mazindol [11]. Pemoline is seldom used today because it was "black boxed" for provoking hepatic failure and jaundice and mazindol was never very popular due to its limited efficacy. Polysomnographic evaluation indicates that compounds in this class generally increase time spent awake and the number of awakenings. They also typically prolong both latency to sleep onset and latency to the first occurrence of REM sleep. In addition to decreasing total sleep time, traditional psychostimulants also suppress REM and slow wave sleep (see Table 7.2). Individuals seeking to extend the duration of their wakefulness period (whether for recreational or vocational purposes) are known to abuse these medications. Trismus (lockjaw), bruxism, and both sleep-related and awake teeth clenching are associated with amphetamine and amphetamine-like stimulants. Thus, teenagers and young adults abusing such substances during all-night dance parties (sometimes called raves) may accessorize their fashion statement with athletic mouth pieces designed to protect the teeth. Most of the formulations also produce significant euphoria, increasing further their potential for abuse. Abused substances include both pharmaceutical and black market products such as homemade methylamphetamine (speed), cocaine, and MDMA (3,4-methylenedioxy-*N*-methylamphetamine, commonly known as Ecstasy, X, or XTC). Methylamphetamine abuse is epidemic. In 2003, more than 10,000 small scale and 130 "superlabs" (capable of producing 10 lb per production cycle) were seized by law enforcement. Moreover, the Drug Enforcement Administration (DEA) has reported that in 2012, 11,210 laboratories producing methylamphetamine were seized.

Dopamine precursors and various DA receptor agonists (D2, D3, and D4), originally designed mainly for treating Parkinson's Disease, are used to treat Restless Legs Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD). This class of drugs includes pramipexole, ropinirole, apomorphine, rotigotine, and bromocriptine. Currently, pramipexole and ropinirole appear to be the medications of choice for treating RLS [12] and both have been approved for this use by the U.S. Food and Drug Administration. At the doses prescribed, these medications are not stimulants. In fact, there have been reports of the opposite, that is, occurrence of sleep attacks. These drugs are also implicated in compulsive disorders (e.g., triggering excessive gambling, eating, and sexual urges). Recently, rotigotine has come into the market for treating RLS transdermally. With a side effect profile much like pramipexole and ropinirole, it provides an alternate route of administration [13]. With respect to RLS and PLMD, medications having the opposite effect, that is, worsening these conditions, include tricyclic antidepressants, selective serotonin reuptake inhibitors, some antiemetics (prochlorperazine and metoclopramide, lithium, some calcium channel blockers (verapamil, nifedipine, and diltiazem), antihistamines, and traditional neuroleptics [14].

Dopamine (D2 and D3) receptor antagonists in the form of traditional neuroleptics reliably produce sedation, increase sleep efficiency, increase slow wave sleep, and usually suppress REM sleep to some degree. This holds true for chlorpromazine, haloperidol, and thioridazine. The newer, non-D2, and non-D3 neuroleptics (clozapine, olanzapine, risperidone, ziprasidone) have variable effects on slow wave sleep with some producing decrease while other (e.g.,

risperidone, olanzapine, and ziprasidone) associated with an increase (perhaps related to its higher affinity 5-HT_2 receptors). These newer atypical antipsychotics do not universally produce sedation [15]. The amount of sedation produced appears to be determined by the combination of the drug's relative potency and its affinity for the histamine-1 (H_1) receptor. For example, clozapine is very sedating and it has high H_1 affinity (32) and low potency (and consequently a need for large doses 50 mg), while olanzapine is less sedating even with an H_1 affinity of 1149 because with its high potency there is need for only a low dose (4 mg). Quetiapine also falls into the low potency (80 mg dose needed) and moderate H_1 affinity (5.2) category and thus is moderately sedating. Like traditional neuroleptics, these newer drugs can increase restless legs and periodic leg movement activity during sleep.

The tricyclic antidepressants (TCAs) comprise a wide range of compounds that share a similar three-ring chemical structure. This group of agents includes imipramine, desipramine, amitriptyline, nortriptyline, clomipramine, trimipramine, doxepin, and protriptyline. Across the board, TCAs increase slow wave sleep (mildly to moderately) and suppress REM sleep (mildly to markedly). This can be seen in Table 7.2. TCAs are generally sedating (with a few exceptions, e.g., protriptyline). The range of sedation varies greatly and is most likely a function of antihistaminergic activity (see section on histamine). Imipramine, the prototypical compound in this class, is regarded as a non-selective NE reuptake inhibitor. In vitro acute biochemical activity studies reveal that it also produces serotonin reuptake inhibition, has high α_1 and muscarinic acetylcholinergic receptor affinity, and binds somewhat to histamine receptors. In sleep medicine, imipramine is best known for its REM suppressing properties and for decades was widely used as an anticataplectic agent for treating patients with narcolepsy. Imipramine's slow wave sleep enhancing and REM sleep suppressing properties are illustrated in Fig. 7.3. In this patient, latency to the first REM sleep episode was almost 3 h, twice as long as normal. No REM sleep episode occurred at the usual 90–120 mins latency from sleep onset (the missing REM sleep episode). Additionally, REM sleep continued to be suppressed later in the night while slow wave sleep appeared to be above normal. The other popular TCA used in this manner is protriptyline. Protriptyline also has the advantage of being non-sedating; however, it can exacerbate erectile problems in men (that in turn can render therapeutic adherence problematic). The REM suppressing properties of TCAs appear to stem from a combination of aminergic (norepinephrine and serotonin) and anti-acetylcholinergic properties. The aminergic properties theoretically provide activation of REM-off systems, while the anticholinergic properties would inhibit REM-on systems. For example, clomipramine, the most REM suppressing TCA, strongly agonizes 5-HT by inhibiting reuptake of serotonin and also has moderate antimuscarinic properties. By contrast, the TCA amitriptyline, another strong REM suppressor, blocks acetylcholine with its very high muscarinic binding affinity but is a weaker serotonin reuptake inhibitor.

Monoamine oxidase inhibitors (MAOIs), as a class, are the strongest suppressors of REM sleep. They, of course, alter catabolism of all biogenic amine neurotransmitters (DA, NE, and serotonin) and like the TCAs; they can be used as antidepressants. It did not go unnoticed that until the atypical antidepressant bupropion was developed, all known antidepressant medications suppressed REM sleep. Furthermore, even instrumentally suppressing REM sleep by awakening sleepers in the laboratory whenever they entered REM sleep improved mood in patients diagnosed with depression [16]. Thus, it was posited that REM sleep promoted depression in some individuals and that REM sleep suppression was necessary and sufficient to achieve an antidepressant effect. The atypical antidepressants (e.g., venlafaxine and trazodone) suppress REM sleep (especially early in the night with some rebound toward morning). However, with the synthesis of bupropion (and afterward nefazodone), the axiom that REM suppression was necessary to achieve an antidepressant property was disproved; neither of these antidepressants suppress REM sleep. Nonetheless, while it may not be necessary to suppress REM sleep, REM suppression remains sufficient to produced antidepressant effects. Also noteworthy is that unlike the TCAs, the atypical antidepressants venlafaxine, nefazodone, bupropion, and trazodone do not increase slow wave sleep.

Histamine

Histamine (H) is an important excitatory neurotransmitter in the central nervous system. Posterior hypothalamus histaminergic neurons are thought to generate wakefulness. In particular, the tuberomammillary nucleus (TMN) is a histamine rich structure thought to play a crucial role in maintaining alertness. TMN may also represent the brain's main source of H. The TMN appears to generate physiologic "normal wakefulness" not associated with over-activation of motor and reward systems. H neuron activity follows a similar stepwise pattern to that of NE, that is, high activity during wakefulness, decreased during NREM sleep, and very low levels during REM sleep. This may help explain why the patients described by von Economo with posterior hypothalamic encephalitic damage were extremely sleepy but those with anterior lesions were not.

Central histaminergic effects are most well recognized for the drowsiness produced by central H_1 antagonists (that are actually inverse agonists) exemplified by action of

Table 7.2 Medication effects on sleep

Classification	Pharmacologic agent	SWS	REM	Wakefulness	Other sleep effects
DA agonists (traditional psychostimulants)	Cocaine, amphetamine	↓↓	↓↓	↑↑↑	Severe hypersomnia and prominent REM sleep rebound after discontinuing it after chronic use, bruxism may occur
DA precursor	Levodopa	↔	↑ (low doses) ↓ (high doses)	↑	Insomnia may be seen at higher doses
DA agonists	Apomorphine, rotigotine, pramipexole, ropinirole	↔	↔	↑	–
Traditional and atypical antipsychotics	Haloperidol, chlorpromazine, thioridazine, risperidal, olanzapine	↑	↑	↓↓↓	Increase PLMs and RLS-like symptoms
Adrenergic α_1 agonist	Phenylephrine	↓	↓	↑	–
Adrenergic α_2 agonist	Clonidine	↑	↓	↓↓	–
Adrenergic α_1 antagonist	Prazosin	↔	↑?	↓	Decreases nightmare distress
Adrenergic α_2 antagonist	Mirtazapine	↔	↔	↓↓	–
Adrenergic β agonist	Isoproterenol, albuterol, terbutaline	↔	↔	↔	–
Adrenergic β antagonist	Propanolol	↓	↓	↑	Can provoke nightmares
SNRIs	Duloxetine	↑	↓	↑	May exacerbate PLMs
	Venlafaxine, desvenlafaxine, milnacipran	↑	↓↓	↑	May exacerbate PLMs
SSRIs	Fluoxetine, citalopram, escitalopram, fluvoxamine, dapoxetine	↓	↓	↑	–
	Paroxetine	↓	↓↓	↑↑	–
	Sertraline	↔	↓↓	↔	–
TCAs	Amitryptiline, nortryptiline, clomipramine	↑	↓↓↓	↓↓↓↓	Increases PLMs and sleep-related movements, may cause RLS-like symptoms
	Doxepin	↑↑	↓↓	↓↓↓↓	
	Clomipramine	↑	↓↓↓↓	↔	
MAO inhibitors	Phenelzine	↓	↓↓↓↓	↑↑	Strong REM sleep suppressors, increase PLMs, prominent REM sleep rebound on discontinuation
	Tranylcypromine	↓	↓↓↓	↑↑↑	
H_1 antagonists	Diphenhydramine, triprolidine, brompheniramine	↑	↓	↓	Upon discontinuation, dream intensity increases
H_2 antagonists	Cimetidine	↑	↑	↓	Interacts with many other medications' metabolisms by cytochrome P_{450} pathway
	Ranitidine	↔	↔	↔	
Barbiturates	Pentobartbital, phenobarbital	↓	↓↓↓	↓↓↓	Severe AEs on withdrawal, overdose leads to respiratory drive suppression
BZDs	Triazolam, diazepam, lorazepam, midazolam	↓↓	↓	↓↓↓	Tolerance and rebound on discontinuation
BZRAs	Zopiclone, zolpidem, eszopoclone, zaleplon	↔	↔	↓↓↓	Low overdose liability, minor AE on withdrawal

(continued)

Table 7.2 (continued)

Classification	Pharmacologic agent	SWS	REM	Wakefulness	Other sleep effects
Chloral hydrate	Chloral hydrate	↔	↔	↓↓↓	–
Alcohol	Ethanol	↔	↓	↓	Increases arousals
AChE inhibitors	Physostigmine, rivastigmine, galantamine, donepezil	↔	↑	↓	Shortens REM sleep latency
Ach agonists	Arecholine	↑	↑	↓	Shortens REM sleep latency, insomnia at higher doses
	Nicotine	↑	↑	↓	Increases SL and WASO
Ach antagonists	Scopolamine, atropine	↓	↓	↑	Increases REM sleep latency
5-HT precursor	L-tryptophan	↑	↓	↔	Increases REM density, decreases SL
5-HT_2 antagonist	LSD_{25}	↔	↑	↑	Increased arousals, decreased REM sleep latency, provoked REMs in SWS
5-HT_{1A} partial agonist	Buspirone	↔	↓	↔	Reportedly a treatment for SSRI-induced bruxism
5-HT antagonist	Cyproheptadine	↑	↑	↔	–

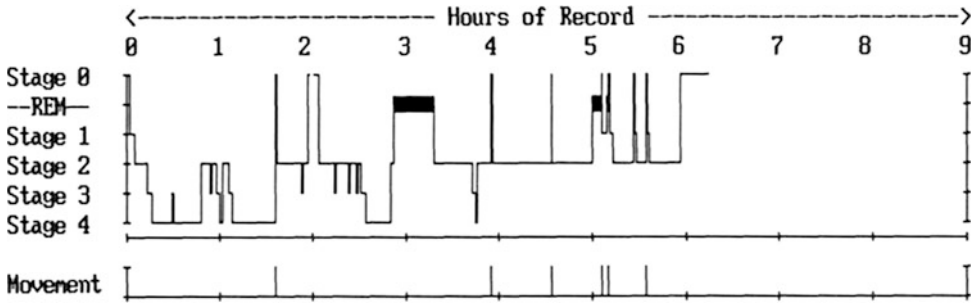

Fig. 7.3 Imipramine and sleep macroarchitecture

diphenhydramine [17]. H_1 antagonists also can decrease REM sleep or REM density. H_2 antagonists have little effect on sleep; however, cimetidine may increase slow wave sleep. Table 7.2 tabulates the main effects of antihistamines on sleep. Sedation that occurs as a side effect of other compounds often has its roots in an antihistaminergic property. Examination of in vitro acute biochemical activity reveals that the sedating TCAs—amitriptyline, trimipramine, and doxepin all have $+++H_1$ receptor affinity [18]. Other sedating medications with known antihistaminergic activity include trazodone, mirtazapine, and quetiapine. Other properties of H_1 receptor blockade are weight gain, hypotension, and potentiating other CNS depressants.

Although not fully understood, the mechanism of action for the wake-promoting medication modafinil is thought to act, in part, via a histaminergic mechanism [19]. However, modafinil also activates glutamatergic circuits and appears to inhibit GABA transmission. Cats administered modafinil show immediate gene product c-fos activation in TMN [20]. Modafinil extends wakefulness and improves performance in normal subjects undergoing sleep deprivation; increases sleep latencies on the multiple sleep latency test (MSLT) in patients with narcolepsy [21] and shift work sleep disorder [22]; increases sleep latency on the maintenance of wakefulness test (MWT) in patients with narcolepsy and sleep apnea (with residual sleepiness) [23–25], but does not alter nocturnal sleep when administered in the morning [26]. The American Academy of Sleep Medicine currently recommends modafinil as the first line treatment for sleepiness associated with narcolepsy [27]. In addition to having an indication for use in narcolepsy, the U.S. Food and Drug Administration (FDA) has also approved modafinil for treating (1) residual sleepiness in patients with sleep apnea who are otherwise well treated with positive airway pressure and (2) sleepiness associated with shift work sleep disorder [28]. In 2007, the dextroenantiomer of modafinil (armodafinil) was also approved for conditions that can be treated with modafinil.

Orexin

Orexins are a pair of excitatory neuropeptide hormones (orexin-A and orexin-B) discovered in 1998 [29, 30]. Produced by a small hypothalamic cell group with widespread projections throughout the brain, orexins appear to promote

wakefulness. Some researchers refer to orexin as hypocretin, because of the locus of origin. These neurons activate structures with other stimulating neurotransmitter systems, including DA, NE, ACh, and H [31].

The discovery of orexin was a major breakthrough for our understanding of narcolepsy. Mutations in genes producing orexin or their receptors were found in narcoleptic mice and dogs. Humans with narcolepsy appear to have an orexin deficit produced by an autoimmune mechanism. Orexin can be detected in cerebrospinal fluid of approximately 90 % of patients with the "narcolepsy-cataplexy syndrome," as it is called in the UK [32]. Direct brain injection of orexin produces wakefulness and can reverse some of the effects of sleep deprivation [33]. A number of orexin agonists (stimulants) and antagonists (sedatives) are being developed. At this point, however, we have little data concerning the effects of orexigenic substances on human sleep. Suvorexant and almorexant are dual orexin receptor antagonists developed to promote sleepiness by reducing wakeful drive [34, 35]. Figure 7.4 illustrates their structure compared to orexin-A and orexin-B. Currently, suvorexant has been approved for medical use.

Glutamate

The brain's most common neurotransmitter is glutamate. The *N*-Methyl-D-Aspartate (NMDA) glutamate receptor is regulated both electrically and chemically. It has binding sites for glutamate, magnesium, glycine, zinc, and phencyclidine. NMDA antagonists include amantadine, dextromethorphan, ketamine, tiletamine, riluzole, memantine, kynurenic acid, and phencyclidine (PCP). PCP (referred to as "angel dust" on the street) can produce hallucinations and psychosis. NMDA receptor agonists include: Aminocyclopropanecarboxylic acid, D-Cycloserine, D-serine, L-alanine, L-aspartate, and Quinolinate. NMDA receptors are concentrated in hippocampus, amygdale, basal ganglia, and cerebral cortex.

Inhibitory Transmitter Systems

GABA

GABA is the main inhibitory neurotransmitter in mammalian central nervous system. It begins as glutamic acid that is catalyzed by GAD to form GABA. $GABA_A$ agonism promotes flux in the chlorine channel. GABA, benzodiazepines, or barbiturates can increase dilation of the ionophore and thereby promote transmission in this inhibitory pathway. Barbiturates, benzodiazepines, benzodiazepine receptor agonists, alcohol, chloral hydrate, steroids, and picotoxins can all affect this system. While there are direct and partial GABA agonists, in sleep medicine practice, the drugs traditionally used to manage the symptoms of insomnia are mainly benzodiazepines (BZDs) and benzodiazepine receptor agonists (BZRAs). GABA neurons are widely distributed in the brain with high concentration in the thalamus.

Chloral hydrate was the first pharmaceutical sleeping pill, developed circa 1860. Chloral hydrate shortens sleep latency and initially increases sleep time. It has been described as

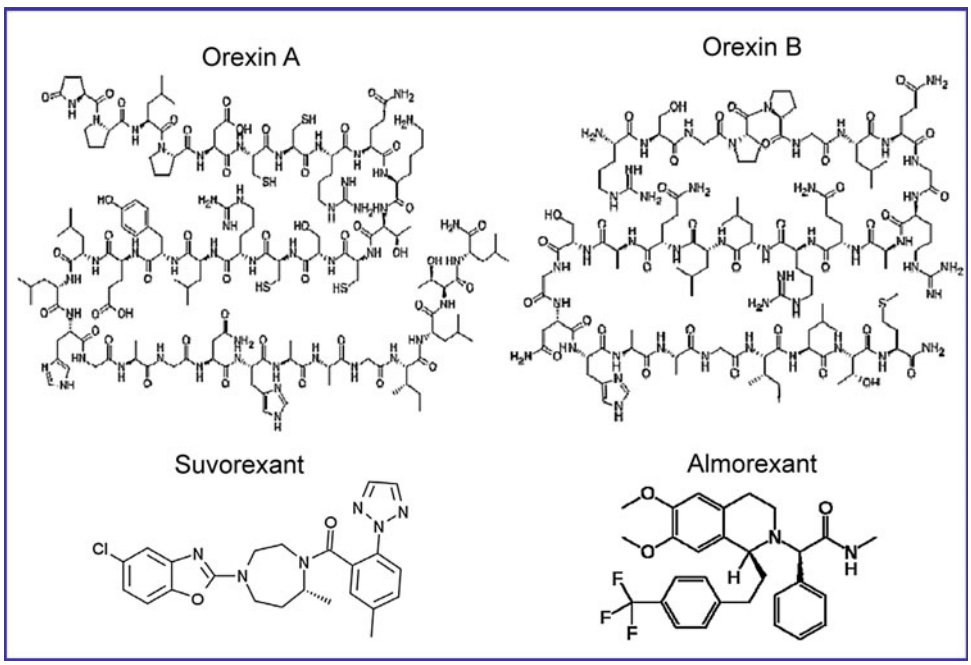

Fig. 7.4 Orexins and dual orexin receptor antagonists

"alcohol in pill form" because after it passes through the gut it forms an alcohol-like compound. Probably best known for its popularization in detective mystery stories by Dashiell Hammett and Raymond Chandler where when mixed with alcohol becomes a "Mickey Finn" and is used to stupefy the gangsters' adversary. Bromides and paraldehydes followed but did not enjoy much success. At the turn of the twentieth century, barbiturates were first synthesized by Adolf von Baeyer and found to be extremely sedating [36]. Polysomnographic studies show that most barbiturates shorten the latency to sleep onset, increase total sleep time and sleep efficiency, decrease wakefulness after sleep onset and the number of awakenings in patients with insomnia. They also tend to decrease REM sleep, perhaps by impairing the muscles that move the eyes and mildly decrease slow wave sleep [37, 38]. Micro-architectural sleep changes included increased β EEG, increased δ spindles, and decreased arousals [39]. Barbiturates, however, are extremely toxic. One popular index for describing toxicity is the ratio of the effective dose found for 50 % of animals tested (ED_{50}) to the lethal dose for 50 % of animals tested (LD_{50}). This ratio provides a safety index with smaller numbers (larger ranges) being less dangerous. For barbiturates, the ratio is only approximately 10:1 (depending of type) meaning that ingesting 10 times the effective dose confers a significant risk of death [40]. Thus, if a prescription provides the patient with 30 pills, it becomes a potential vehicle for committing suicide. 90 % of patients with major depressive disorder have insomnia and 17 % (or more) of patients coming to sleep disorders centers complaining of insomnia have a mood disorder. This circumstance sets the stage for potential tragedy. In the first three-quarters of the twentieth century, many suicides involved barbiturate sleeping pills.

In the 1960s, benzodiazepines (BZD) sleep aids were developed. Compared to barbiturates, BZDs were amazingly safe. In most cases, it was not even possible to determine a lethal dose. Thus, it was joked at the time that the only way a BZD would kill you was if you were run over by the truck delivering them to the pharmacy. However, it soon became apparent that when BZDs were combined with alcohol, this safety was compromised. BZDs have four major characteristics; they are (1) sedating, (2) anxiolytics, (3) myorelaxant, and (4) anticonvulsant [41]. Secondary properties include ataxia, amnesia, and potentiating of alcohol. BZDs proved very effective for treating insomnia: shortening latency to sleep onset, increasing total sleep time, and improving sleep efficiency. They did not suppress REM sleep as much as barbiturates but on average decrease slow wave sleep more than barbiturates. δ spindle activity is increased in a dose–response manner but without dramatic β wave enhancement on the EEG. Figure 7.5 shows polysomnographic tracings from a patient taking temazepam nightly for more than a year. Awakenings and brief arousals are reduced by most BZDs tested [42–44]. Early BZDs tended to be long acting, the champion being flurazepam with its 72–100 h half-life (without counting its active metabolite). In second place, quazepam weighs in with a 27–43 h half-life followed by estazolam with a 10–24 h half-life and temazepam with a 4–18 h half-life [45]. Triazolam was the first short acting BZD for promoting sleep but fell out of favor after high profile reports of amnesia [46] (but all BZDs potentially produce amnesia). Half-life is important for two reasons. First, in combination with the drug's minimal effective dose and the dose administered, it dictates the duration of action (or therapeutic window). If the duration of action extends beyond the individual's sleep episode, there will likely be residual sedation, commonly referred to as "hangover." Secondly, pharmacokinetic *rule-of-thumb* estimates elimination time as 5–6 times the half-life of a compound. It should be realized that the vast majority of medications used in clinical practice are administered according to principles of the infectious disease model. This involves dosing a drug until it reaches therapeutic level and then maintaining it at that level until the bacteria, germ, or microorganism is eradicated. Usually, drug level is maintained for a while longer just to be certain and prevent re-infection. Most psychiatric medication is administered this way but kept at therapeutic level indefinitely (because there was no infection to kill to begin with). By contrast, we desire sleeping pills to work like a switch. One wants to (1) administer the drug, (2) have it rapidly get to therapeutic level, (3) hover there for precisely 7.5 h, and then

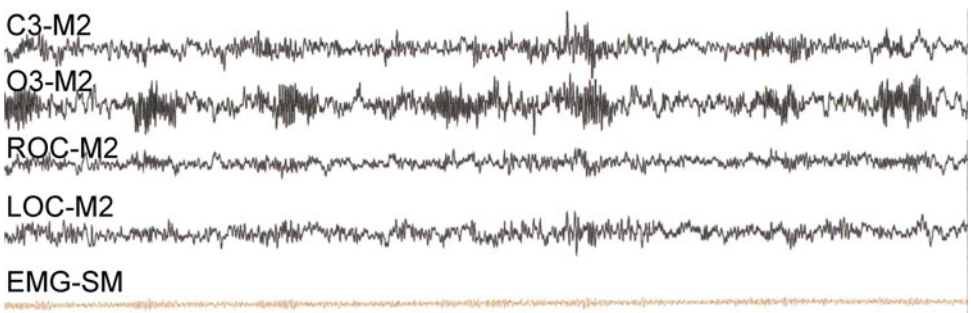

Fig. 7.5 Temazepam and sleep microarchitecture

(4) instantly disappear without a trace. Having drug eliminated fast and completely helps assure there is no hangover, receptors have the maximal time to re-regulate, and there is no cascading drug level produced by adding drug into a system that already has residual drug on board. Of course, pharmacokinetics are not so well behaved. Also, we do not dose patients the way we do laboratory animals; that is, we use fixed doses rather than equivalents in milligrams per kilogram weights. Chances are that there will be undershoot and overshoot with respect to a medication's duration of action compared to the desired therapeutic window. If receptor systems down regulate, adapt, or habituate, then tolerance will more likely to develop in longer acting substances, notwithstanding their potency.

In the 1980s, benzodiazepine receptor agonists (BZRAs), lacking the characteristic benzene ring structure, were developed. These medications boasted generally shorter half-life, little or no alteration of sleep macro-architecture, and greater propensity for increasing sedation than producing anxiolytics, myorelaxant, or anticonvulsant effects [47–49]. At the time, it was speculated that the different characteristics associated with BZD receptor agonism were mediated by subtype receptors. The data from knockout genetic studies in mice and rats confirmed this hunch almost 15 years later [50]. The different BZRAs boast varying degrees of greater affinity to the receptor subtype thought to mediate sedation (α_1) than other receptor subtypes (typically α2). The receptor affinity ratio for currently marketed BZRAs with indication for treating is 2:1 for zopiclone, 10:1 for zolpidem, and 13:1 for zaleplon [51]. Other BZRAs for treating insomnia include variants of these compounds; that is, eszopiclone, the left handed entimer of zopiclone (which turns out to be the active isomer) and zolpidem MR, a multiple release version of zolpidem designed to extend its therapeutic window by 1–2 h. Table 7.2 summarizes characteristics of and differences between barbiturates, BZD, and BZRA sleep-promoting substances.

Adenosine

Kleitman, the dean of American sleep research, postulated that the basic rest activity cycle was governed by the buildup of a "hypnotoxin" during wakefulness that was eliminated during sleep [52]. This general characterization lives on today in our conceptualization of the homeostatic drive for sleep accumulating as "sleep pressure" (or "sleep debt" when unpaid and overdue). There are many possible candidates for a modern-day "hypnotoxins." Perhaps the most obvious candidate is adenosine. Adenosine delivered to the preoptic area and anterior hypothalamus induces NREM sleep. As an animal experiences prolonged wakefulness, basal forebrain adenosine levels rise and they subsequently decline during recovery sleep [53, 54]. Although benzodiazepines ($GABA_A$ receptor agonists) decrease adenosine uptake; caffeine (adenosine antagonist) does not alter benzodiazepine receptor action [55].

Adenosine receptors can be antagonized by the methylxanthines caffeine (found in coffee) and theobromine (found in chocolate). Figure 7.6 shows the chemical structure for adenosine, caffeine, and theobromine. When an individual does not get enough sleep at night to rid the basal forebrain of its adenosine load, morning awakening is usually accompanied by residual sleepiness. Drinking a morning cup (or two) of coffee, or better yet coffee with chocolate in it (mocha java), provides an effective, albeit temporary, antidote. Overall, polysomnographic studies of methylxanthines show decreases in total sleep time, slow wave sleep, and REM sleep [56]. Latency to sleep onset is increased but more important, wake after sleep onset can rise dramatically (see Fig. 7.7).

According to legend, the effect of coffee beans was first noticed by a goat herder from Caffa Ethiopia named Kaldi. He noticed that his goats became hyperactive after eating the red "cherries" from a certain plant when they changed pastures. He tried a few berries himself and became as "hyper" as his herd [57]. The storied origins of chocolate remain even more fanciful; however, chocolate was thought to first be extracted from cocoa in the Amazon circa 2000 BCE. Chocolate became an important part of Mayan culture in the sixth century CE. Subsequently, some 600 years later, the Aztecs attributed creation of the cocoa plant to Quetzalcoatl who smuggled it to earth from paradise when he descended from heaven on a beam of light [58]. It was truly considered the food of the gods.

Glycine

Glycine is the simplest amino acid and can be produced by protein hydrolysis. This sweet tasting compound was first isolated from gelatin in 1820. This central nervous system inhibitory neurotransmitter is particularly important for its role in mediating atonia occurring during REM sleep. Activation of glycine receptors produces inhibitory postsynaptic potentials (IPSP) that decreases spinal alpha and gamma motor neuron activity. Strychnine blocks glycine receptors. Along with glutamate, glycine's co-agonist, it can activate NMDA receptors. Ingesting 3 g glycine before bedtime reportedly improves alertness and subjective feelings after awakening from sleep [59].

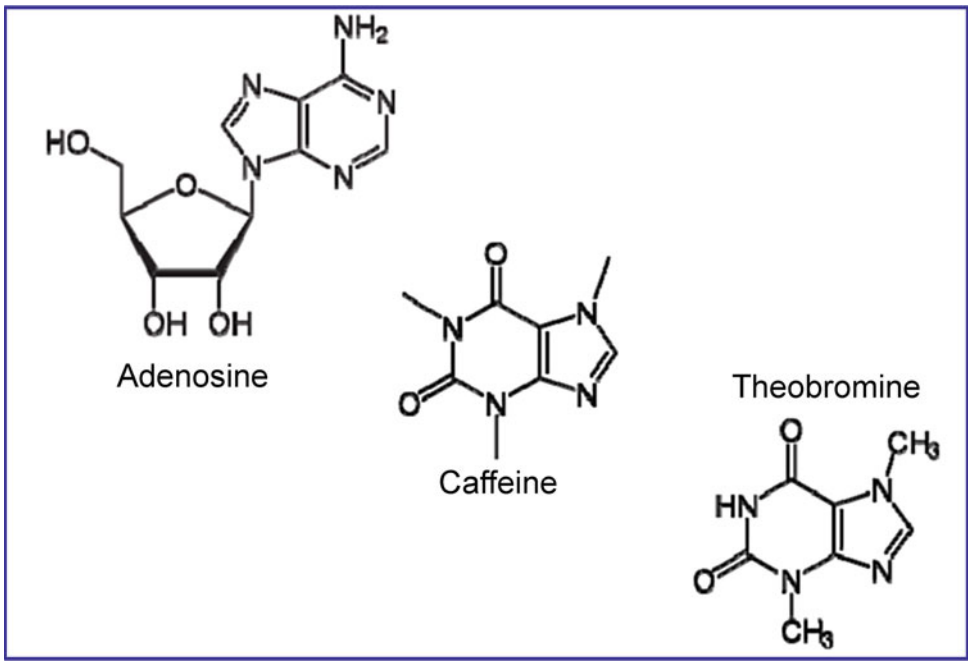

Fig. 7.6 Adenosine, caffeine, and theobromine

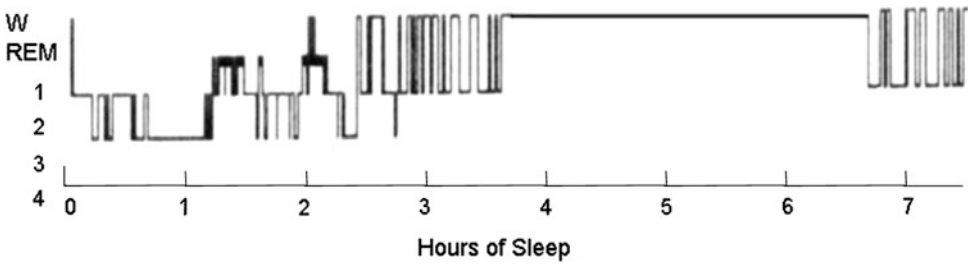

Fig. 7.7 Caffeine and sleep macroarchitecture

Regulating Transmitter Systems

Acetylcholine

Acetylcholine (ACh) begins as circulating choline in the blood. It is taken into presynaptic neurons and is combined with acetyl-CoA to form acetylcholine (reaction catalyzed by CAT). The ACh is then bound into vesicles that are released synaptically upon fusing with the cell wall. Synaptic ACh can be catabolized by acetylcholinesterase (AChE), rendering choline and acetate.

ACh plays a major role in regulating REM sleep [60]. There is a large concentration of ACh in the gigantocellular nucleus of the reticular formation. During the waking state, aminergic neurons are highly active and ACh is implicated in memory processes, as noted in the loss of ACh neurons in the nucleus of Meynert causing Alzheimer's disease. By contrast, during slow wave sleep, cortical activity is greatly reduced. Then, during REM sleep, cortical acetylcholinergic activity returns to high levels [61]. REM sleep "on" neurons are plentiful in the laterodorsal tegmentum and the pedunculopontine tegmentum (LDT/PPT) [62]. Basal forebrain cholinergic neurons project to the hippocampus, amygdala, and cortex. Opposing these cells are the REM sleep "off" cells in the dorsal raphe (a serotonin reservoir) and the locus coeruleus (where most of the brain's NE is synthesized).

Chemical probes of ACh include the agonists–arecholine, nicotine, carbachol, and pilocarpine. Antagonists include scopolamine, atropine, hyoscine, and curare. Agonism can also be achieved by using AChE inhibitors (e.g., physostigmine and donepezil). Table 7.2 shows some of the sleep changes produced by these system probes. In general, AChE inhibitors can increase REM sleep duration, hasten its appearance, or both [63, 64]. ACh agonists enhance REM sleep [65] and antagonists suppress REM sleep and its activity [66]. Administering arecholine or physostigmine intravenously can provoke REM sleep occurrence whereas scopolamine dramatically delays REM sleep onset.

Serotonin

In opposition to acetylcholine, the indoleamine serotonin serves as an inhibitor of REM sleep (see Fig. 7.8). Activation of brainstem raphe nuclei suppresses REM sleep (as does locus coeruleus activation). These biogenic amines are considered REM "off" cells responsible for reciprocal interaction with the LDT/PPT REM "on" cholinergic generators [67]. Nonetheless, serotonin raphe neurons project widely through the brain, including the hippocampus, hypothalamus, thalamus, septum, and cerebral cortex [68]. Brainstem raphe activity is highest during wakefulness, less active during NREM sleep, and nearly silent during REM sleep.

Serotonin begins with tryptophan that is hydroxylated to 5-hydroxytryptophan which is later reduced to 5-hydroxytryptamine (5-HT) which is serotonin. The 5-HT is bound in vesicles and can be released synaptically. Its main catabolite is monamine oxidase that reduces it to 5-hydroxyindolacetic acid. The synthesis of 5-HT can be stimulated by L-tryptophan or inhibited with parachloralphenylalenine (PCPA) [69].

Functional agonism can be achieved by inhibiting the reuptake of synaptic 5-HT into the presynaptic terminal to be rebound in vesicles and ultimately re-used. Many tricyclic antidepressants non-selectively inhibit serotonin reuptake along with having anticholinergic properties that produced undesirable side effects (e.g., dry mouth, ataxia, diplopia, tachycardia, constipation, memory loss, and confusion). The newer selective serotonin reuptake inhibitors (SSRIs) antidepressants quickly became preferred because they required fewer dose adjustments and were less complicated by adverse events. By contrast, serotonin can be antagonized with methysergide and cyproheptadine (which also has antihistaminergic properties). Type-2 receptor antagonism is produced by the hallucinogen lysergic acid diethylamide (LSD_{25}) and presynaptic autoreceptor partial agonism can be achieved with buspirone. Postsynaptic receptors are G-bound proteins, and there is a wide array of them. Table 7.2 describes some of the change in sleep produced by chemically probing the 5-HT system. In addition to a general REM suppressing action of 5-HT agonists [70], these drugs sometimes unhinge the choreography of physiologic changes and activities that make up REM sleep. For example, rapid eye movements characteristically accompany wakefulness and REM sleep. However, it was noted that patients treated with SSRIs would often have rapid eye movements in sleep stages N1, N2, and N3 [71]. The phenomenon was so common it developed the moniker "Prozac Eyes" after the brand name of fluoxetine, the prototypical SSRI (see Fig. 7.9). SSRIs are also reported to decrease the frequency of dream recall but increase the intensity of the dreams that are remembered [72]. The breakdown in coordination of gating mechanism produced by 5-HT alteration extends beyond mere eye movement activity. 5-HT agonists are noted for provoking an iatrogenic form of REM sleep behavior disorder [73], presumably by failing to provoke or sustain striate muscle atonia when dreaming commences. Additionally, SSRIs and TCAs generally increase muscle activity and movements during sleep [74, 75].

Melatonin

Although melatonin (MT) is an endocrine secreted largely by the pineal gland, it is synthesized from 5-HT by pinealocytes. The catalyst NAT (5-HT *N*-acetyl transferase) transforms 5-HT first to *N*-acetyl-5-HT and then to HIOMT (hydroxyindole-O-methyltransferase) and finally to melatonin [76]. MT is released in response to decreasing environmental light and thus synchronizes our physiology with the light–dark cycle. In a sense, it is the "signal of darkness to the brain" [77]. Therefore, if we are rats, our response to rising melatonin would be to become more alert. By

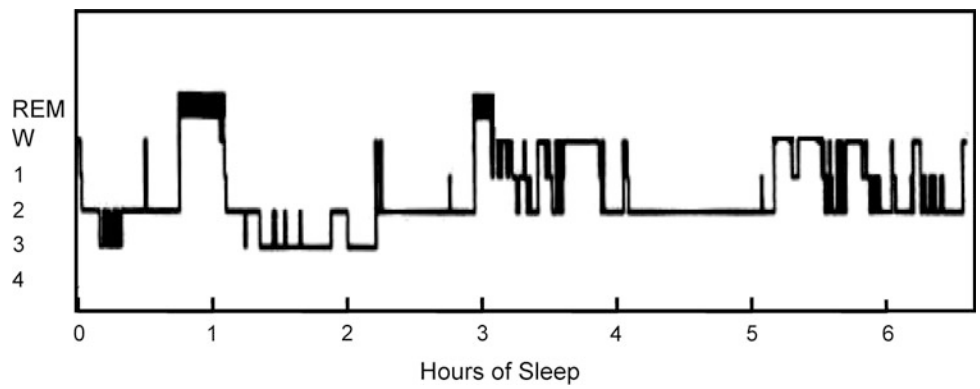

Fig. 7.8 Fluoxetine and sleep macroarchitecture. Note the short REM sleep latency early in the night and SWS dominating the 2nd NREM–REM cycle (typical in depression). As drug becomes active later in night, REM sleep is suppressed and sleep becomes fragmented

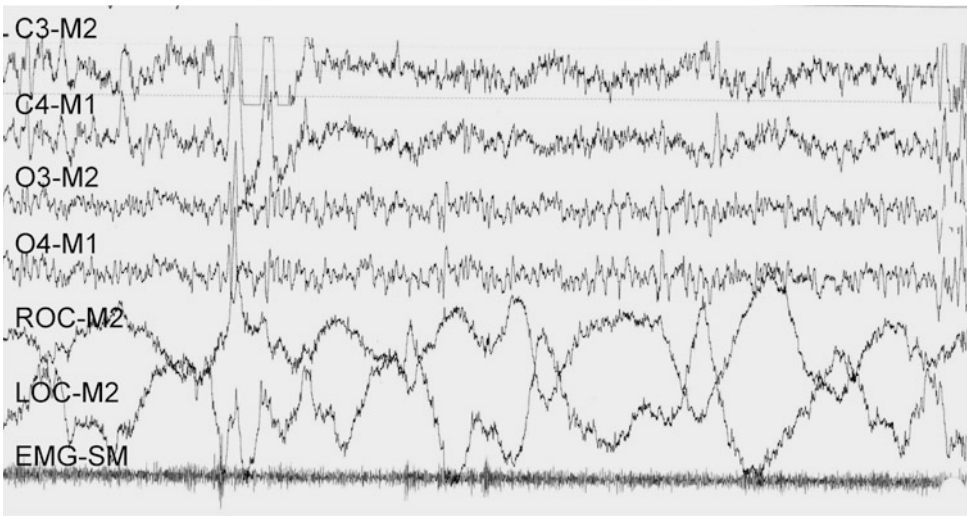

Fig. 7.9 Fluoxetine and sleep microarchitecture

Table 7.3 Clinical pharmacology for sleep disorders

Sleep disorder	Class or disorder	Treatment medication
Insomnia	BZDs	Temazepam, chlordiazepoxide, quazepam, clonazepam, flurazepam, estazolam, triazolam
	BZRAs	Zolpidem, zaleplon, eszopiclone, zopiclone
	Chronobiotics	Ramelteon, agomelatine, melatonin
	Antidepressants	Trazodone, doxepin, amitryptiline, nortryptiline, mirtazapine
	Antipsychotics	Quetiapine, olanzapine
	Orexin antagonists[a]	Suvorexant, almorexant
Narcolepsy	Excessive daytime sleepiness	Modanafil, armodafinil, amphetamine-like agents, SNRIs
	Cataplexy	Sodium oxybate, SSRIs, TCAs
Sleep-disordered breathing	REM sleep suppressants and/or agents to increase airway tone	TCAs, medroxyprogesterone acetate, SSRIs, mirtazapine, theophylline, modafinil, armodafinil, donepezil
PLMD and RLS	Assorted	Iron, pramipexole, rotigotine, ropinirole, levodopa, opiates, BZDs
Parasomnias	Nightmares	Prazosin, quetiapine, olanzapine, gabapentin, mirtazapine
	Terrifying hypnagogia	SSRIs, TCAs, modafinil, armodafinil
	REM sleep behavior disorder	Clonazepam, melatonin, pramipexole
	Sleep-related painful erections	Propanolol, clozapine
	Nocturnal leg cramps	Magnesium citrate
	Sleep-related bruxism	Amitryptiline
	Enuresis	Desmopressin
	Nocturnal paroxysmal dystonia	Anticonvulsants

[a]Amorexant is currently not in the market

contrast, if we are humans (or at least more human than rat), our response to MT would be to become sleepy and get ready to retire for our major sleep period. Presumably, the MT is occupying central MT_1 and MT_2 receptors sites in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN is a bilaterally represented structure containing several thousand cells just above the optic chiasm and to either side of the third ventricle. Melatonin decreases the

SCN activating properties that hold homeostatic sleep drive (sleep debt) at bay and thereby result in sleep onset. Thus, melatonin plays a pivotal role in the 2-process model of sleep regulation (sleep drive and circadian rhythm) as described by Borbély [78].

Melatonin can act as a chronobiotic and provide time cues (zeitgabers) [79]. The studies by Sack and colleagues clearly demonstrated this property in blind from birth children [80]. These patients have a chaotic circadian sleep–wake rhythm due to lesions in both visual and retino-hypothalamic tracts. Administering melatonin daily at a set time entrains the sleep–wake cycle remarkably well. Melatonin has also been studied as a potential sleep-promoting substance [81]. It appears to decrease latency to sleep in several published studies. Whether these findings reflect hypnotic or chronobiotic properties is difficult to determine. Melatonin, however, has a very short half-life (approximately 20 min). This may be problematic for exogenously administered melatonin, whereas pineal's continual release renders the short half-life unimportant for naturally occurring endogenous melatonin. Several pharmaceutical companies make or are developing melatonin and melatonin agonists for the treatment of insomnia. Circadin® is a prolonged-release melatonin formulation approved in Europe for treating primary insomnia in patients 55 years and older with poor quality sleep. Ramelteon is a selective melatonin MT_1 and MT_2 agonist with a 2.6 h half-life (and active metabolites) approved in the USA for treating insomnia [82]. In clinical pivotal trials, an 8 mg oral dose of ramelteon taken 30 min before bedtime shortened both objective and self-reported latency to sleep onset in adults with primary insomnia [83]. Similar results were found for individuals age 65 years and older who were diagnosed with insomnia. Agomelatine is a potent melatonin receptor agonist and 5-HT_{2C} antagonist with a 1–2 h half-life. It appears to have antidepressant, anxiolytics, and sleep-promoting properties but has yet to be approved for use to treat insomnia in the American market.

Clinical Pharmacology and Summary

Overall, there appear to be several general observations we can make about drug-related changes in sleep, wakefulness, and sleep architecture. These should not be taken as hard-and-fast rules because there are exceptions. Nonetheless, these general principles may be helpful for predicting how sleep will respond to a substance, given its effects on neurotransmission. The basic 8 rules of thumb are:

1. Catecholamine agonists promote wakefulness and most suppress REM sleep
2. Centrally acting H1 antihistamines are sedating
3. Orexin deficit underlies sleepiness in narcolepsy
4. GABAA agonists and BZD receptor agonists are somnogenic
5. Adenosine antagonists are somnolytic
6. Cholinergic enhancing agents promote REM sleep while anticholinergic agents suppress REM sleep
7. NE and 5-HT agonists suppress REM sleep
8. Melatonin is the signal of darkness in the environment to the brain

Clinically, we capitalize on substance-induced sleep alterations. For example, we use wake-promoting substances to bolster alertness in patients suffering from disorders of excessive somnolence. By contrast, sedating agents are used to treat insomnia. REM sleep suppression represents an approach to treating cataplexy, and chronobiotics may be helpful for individuals with circadian rhythm disorders. Additionally, a variety of medications have therapeutic application that was determined empirically. Table 7.3 shows some of the current therapeutics in sleep medicine clinical practice.

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Neurobiology of NREM Sleep and Thermoregulation in Sleep

8

Ronald Szymusiak

Introduction

The regulation of body temperature and sleep interacts in multiple ways. The biological clock in the suprachiasmatic nucleus (SCN) of the hypothalamus determines circadian variations in both core body temperature (CBT) and sleep-wakefulness, and these rhythms are normally coupled [1]. Across mammalian species, whether diurnal or nocturnal, the major sleep period occurs during the circadian phase of lowered CBT and waking behaviors predominate during the elevated phase of the CBT rhythm [2]. The sleep-related fall in the CBT is achieved through organized thermoregulatory adjustments that include reductions in metabolic heat production and increased heat loss to the environment. Homeostatic responses of the thermoregulatory system to heat or cold challenge can be diminished during non-REM sleep compared to waking, and in some species, thermal homeostasis is severely compromised during REM sleep [3, 4].

In addition to sleep-related changes in thermoregulation, manipulation of environmental temperature or body temperatures can alter sleep. Sleep is suppressed in heat or the cold and can be maximized in a thermoneutral or mildly warm environment [4]. Passive whole-body warming and localized increases in brain temperature or peripheral skin temperature (Tsk) have been shown to promote sleep [5–8].

An important concept that has emerged from neurobiological studies is that brain mechanisms that control sleep are anatomically and functionally coupled to thermoregulatory circuits in the brain. Thermoregulatory adjustments occurring around the time of sleep onset in humans, particularly dynamic changes in CBT and distal Tsk, are important determinants of sleep latency, sleep composition, and sleep quality. Therapies that target thermosensitive control of arousal states may have therapeutic potential in treating disorders of initiating and maintaining sleep [2, 9].

Sleep-Related Changes in Body Temperature Regulation

The onset of sleep is associated with a fall in CBT and a readjustment of thermoregulatory control. This coupling between sleep and lowered CBT is most striking in animals like primates (Fig. 8.1), with highly consolidated daily sleep periods [10]. It is also evident in rodents that display both circadian and ultradian rhythms in sleep/wake, with some episodes of sleep normally occurring during the active (nocturnal) phase (Fig. 8.2a).

The sleep-related fall in CBT is an integrated thermoregulatory response, not a passive consequence of behavioral quiescence associated with sleep. The decline in CBT at the transition from waking to sleep persists in humans on a modified constant routine protocol (Fig. 8.3b), in which the level of behavioral activity during the 8-h prior to lights out is kept minimal and constant (Kräuchi et al. 2004) [2].

At the transition from waking to sleep, the thermoregulatory system responds as if the thresholds for inhibition of heat production and for activation of heat loss responses have shifted to lower levels of CBT and/or Tsk. Wake-to-sleep transitions are accompanied by an integrated series of thermoregulatory adjustments, including a reduction in metabolic rate, increased heat loss to the environment through peripheral vasodilation (Fig. 8.3a, b) and, in warm environments, increased evaporative cooling. Body temperature falls to a lower regulated level which is maintained throughout the consolidated sleep period (Fig. 8.1). A simplified way of thinking about these changes is that the body's thermostat has been reset to a lower level during sleep, i.e., a sleep-related lowering of an internal thermal "set point."

With respect to thermoregulatory control, the body can be compartmentalized into a heat producing core and a heat loss regulating shell (Fig. 8.3a). The size of the shell can vary

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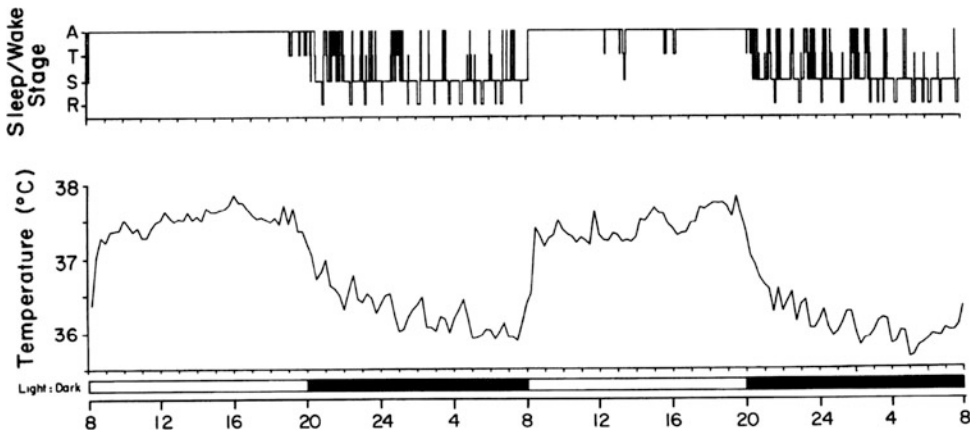

Fig. 8.1 Diurnal rhythms of sleep and waking states (*top*) and body temperature (*bottom*) in a squirrel monkey entrained to a 12/12-hr *light/dark* cycle. *A* awake; *T* transitional sleep; *S* non-REM sleep; *R* REM sleep. From Wexler and Moore-Ede [10], with permission

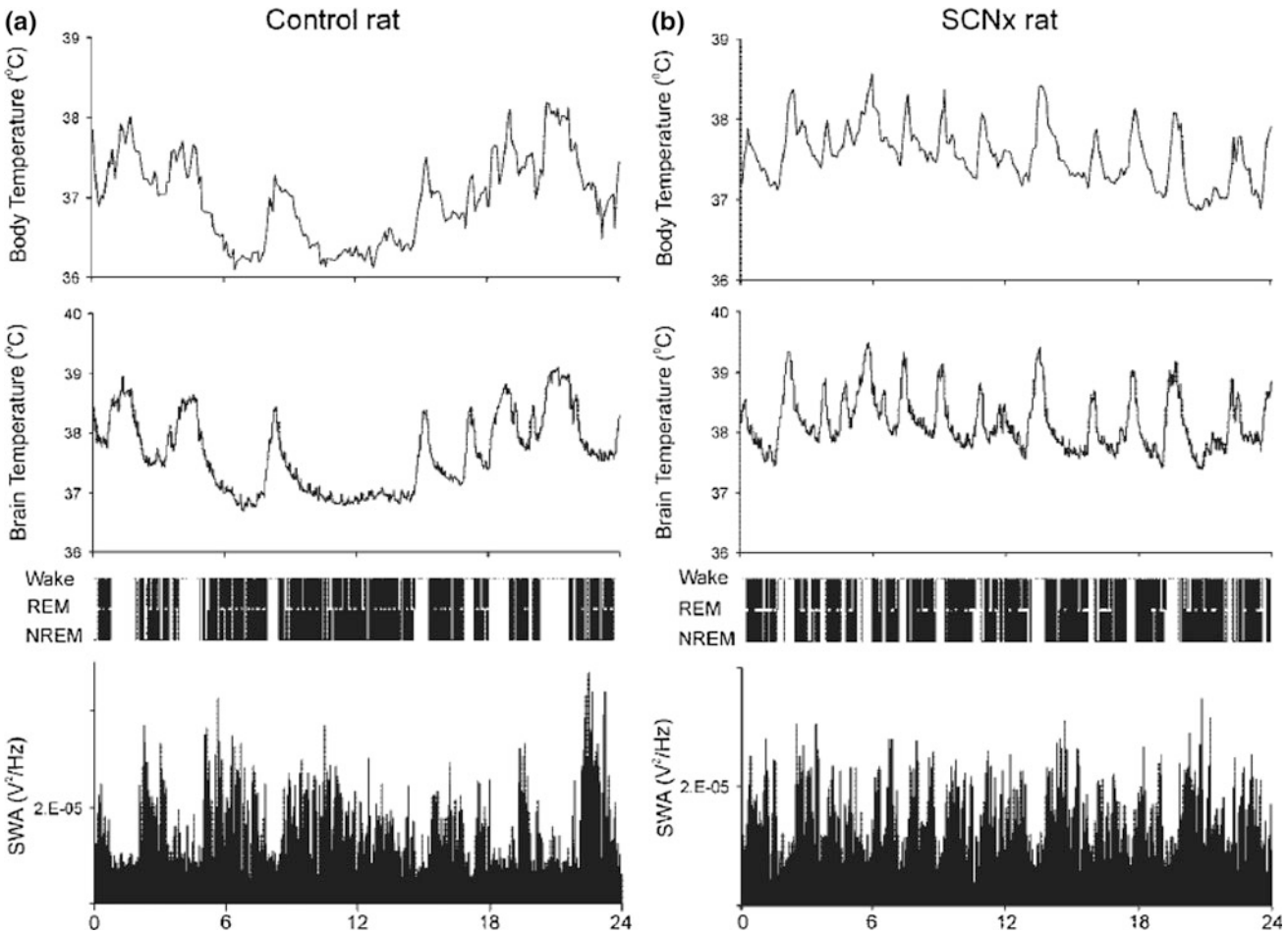

Fig. 8.2 **a** From *bottom* to *top*, plots of diurnal rhythms in core body temperature, brain temperature, sleep-waking states, and cortical EEG slow-wave activity (SWA) in a normal rat. **b** Plots of diurnal rhythms of the same variable in **a**, in a rat with bilateral lesions of the suprachiasmatic nucleus (SCN). From Baker et al. [16]

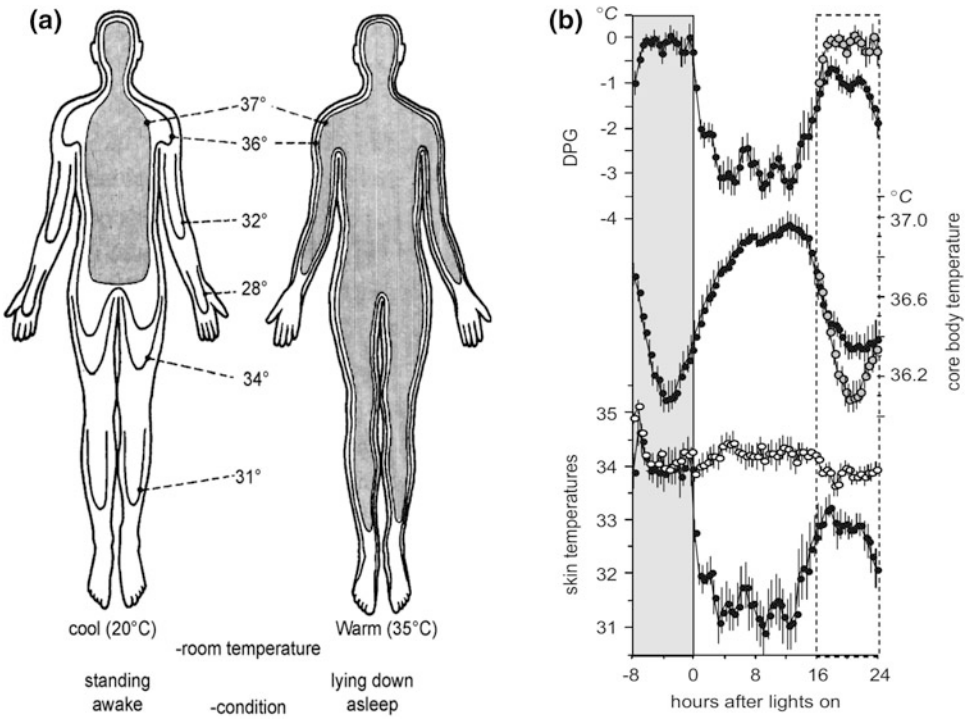

Fig. 8.3 **a** Schematic diagram of a human body indicating the small size of the heat producing core (shown in *gray*) relative to the large size of the heat loss regulating shell (shown in *white*) in a cool (20 °C) environment. During exposure to a warm ambient temperature (35 °C), the core expands significantly as blood flow to the periphery increase to promote facilitate heat loss to the environment. A similar expansion of the core relative to the shell occurs around the time of sleep onset and during the initial non-REM sleep episodes in humans, with the permission from Kräuchi [2]. **b** Dynamics of changes in CBT and Tsk during human sleep. Effects of an 8-h nocturnal sleep period (*shaded area*) on CBT, proximal and distal Tsk and DPG under constant routine conditions. Note the increases in distal Tsk and DPG that coincides with the steep decline in CBT early in the sleep period. The dashed line indicate a 8-h sleep deprivation period when the subjects usually sleep. Data from the 8-h sleep episode are double-plotted on the 8-h sleep deprivation period (gray dots). Modified from Kräuchi [2], with permission

considerably depending on ambient thermal conditions. The shell is large in cool/cold environments when blood flow is diverted away from the limbs to the core to conserve heat (Fig. 8.3a). The shell contracts in warm/hot environment when blood flow to the limbs increases to promote heat loss. The thermoregulatory changes that occur at the wake-to-sleep transition redistribute heat from the core to the shell (Fig. 8.3a), increasing distal Tsk, facilitating heat loss to the environment, and augmenting the decrease in CBT (Fig. 8.3b).

The sleep-related reduction in metabolic heat production and consequent energy savings can be taken as evidence of an energy conservation function of sleep. The sustained lowering of CBT during the sleep episode also has a net energy conserving effect by reducing the CBT-to-ambient temperature gradient which reduces the rate of heat loss to the environment. This latter factor can be important in small mammals with a high surface to volume ratio that have inherently higher rates of environmental heat exchange. Behavioral aspects of sleep onset such as seeking a thermally comfortable nest and adoption of curled heat-conserving postures can also contribute to energy savings by minimizing heat exchange with the environment across an extended period of sleep.

Highly specialized energy conserving adaptations in mammals, such as hibernation and shallow torpor, can be viewed as extreme readjustments in thermoeffector thresholds [11]. Hibernation and torpor are characterized by prolonged and reductions in metabolic activity and body temperature. These events occur seasonally, when thermoregulatory demands are greatest and food availability is low. Bouts of hibernation and torpor are initiated as extensions of sleep episodes, and the dramatic fall in CBT is accompanied by integrated thermoregulatory adjustments similar to those observed during normal sleep [11]. Thermoregulation is not suspended during hibernation or torpor, but the thermoregulatory system behaves as if the thermal set point has been lowered, albeit dramatically so. This is most obvious in shallow torpor, where CBT is maintained well below normal sleeping levels, but significantly above ambient temperature.

Homeostatic responses to thermoregulatory challenges are modulated by arousal state. While CBT is maintained at reduced levels compared to waking during consolidated

sleep episodes, thermoregulatory effector responses persist during non-REM sleep at normal or diminished levels, i.e., the magnitude of effector response to a thermal stimulus may be somewhat reduced compared to waking [12]. During non-REM sleep, there is a reduction in the thresholds and/or gains of autonomic heat and cold defense responses, with an effective expansion of the inter-threshold zone, which is the ambient temperature range between activation of heat production and heat loss responses.

Compared to non-REM sleep, thermoregulatory responses during REM sleep can be severely compromised [4]. This is particularly evident for cold defense responses, where the muscle atonia of REM sleep is incompatible with maintaining heat production via shivering or elevated muscle tone. Partial suppression of heat loss effector responses (e.g., panting) has also been described in REM sleep [13]. As a result of these thermoregulatory changes, animals are more vulnerable to thermal challenges during REM sleep compared to either waking or NREM sleep.

Exposure to hot or cold environments disrupt sleep (see below). This response may be adaptive in minimizing exposure to thermal stress during sleep when homeostatic compensation is weak. Thermal factors have undoubtedly played a role in the evolution of behavioral strategies for species-specific selection of sleeping environments, e.g., nests, sheltered locations, adoption of heat-conserving postures.

The seeming paradox of a sleep-related fall in CBT, combined with the selection of a relatively warm, insulated environment prior to sleep onset can be understood by considering the competing thermoregulatory requirements at work. Lowering metabolic rate and CBT during sleep can yield significant energy conservation benefits. However, diminished thermoregulatory adjustments to heat and cold challenge during sleep dictates that thermal homeostasis can be best achieved over the course of a several hour sleep period by selection of a sleeping environment that poses minimal thermal stress and ultimately maximizes energy conservation.

Interactions Between Circadian Rhythms in Sleep and Body Temperature

In healthy, entrained primates, including humans, habitual sleep onset occurs on the falling phase of the body temperature rhythm, 4–6 h before the CBT minimum (Fig. 8.1 and Fig. 8.3b). The onset of sleep is accompanied by an acceleration in the rate of the decline in CBT. In contrast, morning awakenings occur on the rising phase of the temperature rhythm, 1–3 h after the temperature minimum [2, 14]. The CBT rhythm is dictated by circadian rhythms in heat production and heat loss, with the rhythm in heat production phase advanced with respect to the heat loss rhythm [2]. A CBT rhythm persists during sleep deprivation or during constant routine protocols [15]. Nevertheless, behavioral changes associated with waking and sleep do exert positive and negative masking effects on the circadian temperature rhythms, and the magnitude of the 24 h peak-to-trough difference in body temperature is reduced during sleep deprivation or constant routine.

Circadian rhythms in body temperature and sleep are regulated by the biological clock located in the SCN of the hypothalamus. In experimental animals, lesions of the SCN abolish the 24 h rhythm in both sleep and body temperature [1]. In SCN-damaged rodents, circadian rhythms in sleep and body temperature are eliminated, yet daily total sleep amounts are unchanged. This indicates that the homeostatic regulation of sleep is largely undisturbed by SCN damage. However, the sleep-related fall in CBT persists in rodents with SCN lesions [16]. These animals exhibit ultradian rhythms in body temperature and sleep, and the two variables remain strongly coupled following SCN ablation, i.e., sleep episodes are reliably accompanied by falls in CBT (Fig. 8.2b).

The phase relationship between sleep and body temperature rhythms at sleep onset is an important determinant of subsequent sleep latency, sleep amount, and sleep quality. This has been most convincingly demonstrated in human subjects undergoing internal or forced desynchronization in environments without time cues. During internal desynchronization, sleep and body temperature rhythms free-run with different periods, and eventually, the two rhythms temporally dissociate [15, 17]. In forced desynchrony protocols, subjects adhere to a sleep-wake schedule significantly longer or shorter than 24 h (e.g., 28 or 20 h) and when this is done in the absence of time cues, body temperature and sleep rhythms dissociate as in internal desynchronization [15]. With both methods, over the course of several days the onset of the major sleep period will occur at all phases of the body temperature rhythm. Sleep episodes that are initiated on the falling phase of the temperature rhythm are associated with shorter sleep latencies, longer sleep episode durations, and maximal amounts of Stage N3 [15]. In contrast, sleep episodes initiated on the rising phase of the temperature rhythm are associated with longer sleep latencies, short sleep episode durations, more REM sleep but less Stage N3 sleep [15]. The functional importance of these phase relationships is demonstrated by the fact that, during internal and forced desynchronization, the phase of the CBT rhythm at sleep onset is a better predictor of sleep bout length than is prior time awake.

Collectively, findings indicate that thermoregulatory changes manifested at different phases of the CBT rhythm determine the expression of sleep. Activation of heat loss and suppression of heat production occurring during the falling phase of the temperature rhythm promotes sleep onset, sleep maintenance, and EEG slow-wave activity during sleep. Increased heat

production and heat conservation accompanying the rising phase of the temperature promote waking.

Effects of Environmental and Body Temperature on Sleep

Human and animal studies demonstrate that the temperature of the sleeping environment is an important determinant of sleep amount and sleep quality. In all mammals studied, exposure to moderate hot or cold environments will suppress sleep and/or cause sleep fragmentation [4, 18]. In some species, REM sleep is more easily disrupted by thermal stress than non-REM sleep. In rats, where thermoregulatory responses during REM sleep are absent or weak, REM sleep suppression can occur under conditions of minimal thermal stress and in the absence of any significant change in non-REM sleep amounts [18, 19]. From a thermoregulatory perspective, the REM sleep suppressing effects of heat and cold exposure in these species are adaptive. Increased time spent awake or in non-REM sleep means that a lower threshold and stronger thermoregulatory responses will be evoked to maintain thermal homeostasis.

In contrast to the sleep suppressing effects of moderate-to-severe thermal stress, mild increases in ambient temperature or mild warming of the body can promote sleep. An animal's thermoneutral zone is defined as the range of environmental temperatures at which resting metabolic rate is minimal and constant. Within the thermoneutral zone, minimal effort is required to maintain thermal homeostasis and thermal homeostasis is achieved largely through peripheral vasomotor adjustments that control heat exchange with the environment. Chronic exposure of rats to an environmental temperature that is at the upper end of the thermoneutral zone increases in daily total sleep time over baseline levels [20].

Whole-body warming, achieved by immersion in a hot bath a few hours prior to normal bedtime, promotes sleep in humans [5]. Hot baths prior to bedtime can reduce sleep latency and increase amounts of slow-wave sleep in the first half of the night. The timing of body warming is a critical factor. Optimum sleep-promoting effects of hot bath immersion are achieved 1–2 h prior to bedtime. Hot baths taken early in the day are ineffective. The critical variable in achieving sleep promotion appears to be that CBT remains slightly elevated above normal levels at bedtime, helping to promote a stronger heat loss response at sleep onset.

In rats, similar increases in non-REM sleep and in EEG slow-wave activity are observed following whole-body warming achieved by exposure to an elevated ambient temperature. Sleep is suppressed during initial heat exposure as body temperature increases. The elevations in non-REM sleep time and EEG slow-wave activity are observed during the 2 h after the end of heating as body temperature falls [21]. Collectively, these findings are consistent with the idea that mild activation of thermoregulatory heat defense mechanisms promotes sleep.

Hypothalamic Regulation of Sleep and Body Temperature

Neurons in the preoptic and anterior hypothalamus (POA) are critically involved in thermoregulation [22]. Experimental damage to the POA in animals causes persistent deficits in thermoregulatory defense against heat and cold exposure. Direct infusion of various neurotransmitters or neuromodulators into the POA can alter body temperature and thermoregulatory function.

Specialized temperature-sensing neurons localized in the POA play an important role in body temperature control [22, 23] Warm-sensing neurons (WSNs) are excited by local increases in temperature and inhibited by cooling. Cold-sensing neurons (CSNs) are excited by local decreases in temperature and inhibited by local warming. The functional importance of these temperature-sensing neurons for thermoregulatory control is evidenced by experimental findings that localized warming or cooling of the POA can evoke fully integrated heat defense or cold defense responses that are similar to those evoked by exposing the whole animal to hot or cold environments [22, 23].

POAH temperature-sensing neurons receive inputs from corresponding thermoreceptors in the skin [24]. Inputs from warm sensors in the skin excite POA WSNs (Fig. 8.4). Afferents from peripheral cold sensors activate POA CSNs. Peripheral-to-central thermoreceptor connection is a mechanism by which changes in skin temperature caused by increasing or decreasing ambient temperature can initiate thermoregulatory responses in advance of any alteration in the temperature of the brain or the body core [22, 24].

The level of activation of POA WSNs versus CSNs is an important determinant of the regulated level of body temperature [24]. Preferential excitation of WSNs and inhibition of CSNs will result in reduced metabolic heat production, increased heat loss from the periphery, and the lowering of body temperature to a stable, lower level. Activation of CSNs will have the opposite effect: increased metabolism, heat conservation, and an increase in CBT. Adjustments of thermoregulatory thresholds can arise from changes in thermosensitive neuronal activity evoked by factors such as immune system activation or changes in neurotransmitter/neuromodulator release in the POA. Fever is the prototypical example of an increase in the thermal set point, in which the elevation in CBT is accompanied by an increase in metabolic heat production and reduced heat loss [24, 25]. Exogenous or endogenous substances that evoke fever (e.g.,

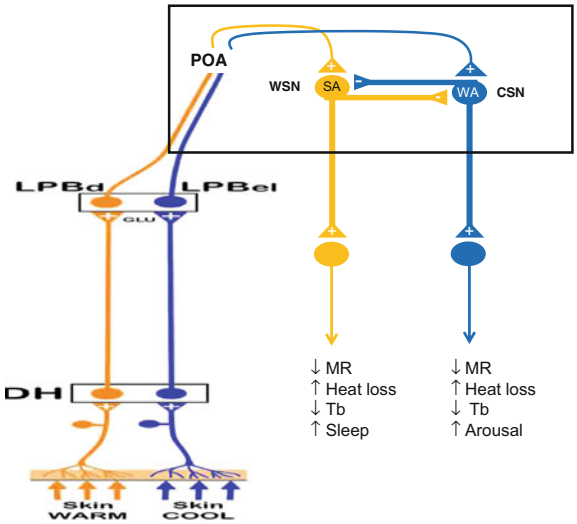

Fig. 8.4 Schematic diagram of the afferent pathways originating in the skin relayed through the dorsal horn of the spinal cord (DH) and lateral parabrachial nucleus in the brainstem (LPB) and converging upon temperature sensitive neurons in the preoptic/anterior hypothalamus (POA). Inputs from peripheral warm receptors excite warm-sensitive neurons (WSN; *orange*) in the POA, a significant subset of which are also sleep-active (SA). Inputs from peripheral cold receptors excite cold sensitive neurons (CSN; *blue*), a majority of which are wake-active (WA). Reciprocal inhibitory connections are thought to exist between WSNs and CSNs. When the population of WSNs in the POA are activated, metabolic rate (MR) decreases, heat loss increases, body temperature (Tb) falls, and sleep propensity is increased. When CSN activity predominates, MR increases, heat is conserved, Tb increases, and EEG and behavioral arousal are enhanced. Activation of sleep-active WSNs through mild–moderate increases in Tb, Tsk, or local POA temperature can all have sleep-promoting effects. In healthy entrained humans, behavioral adjustments (lying down, adjustments of microclimate with bedcovers and/or bed clothing) and physiological changes (melatonin release, decreased sympathetic tone, spontaneous activation of sleep-active WSNs) that occur around habitual bedtime augment the flow of blood to the periphery and increase Tsk and the DPG. This has a feed-forward effect of further activating the central sleep-active WSN population, promoting rapid transitions to stable, deep sleep

lipopolysaccharide, prostaglandin E1) have been shown to excite POA CSNs and to inhibit WSNs. It can be hypothesized that the circadian rhythm in body temperature is driven by changes in the relative activation of warm- versus cold-sensing neurons regulated by output of the SCN, with WSN activity predominating on the descending phase of the rhythm and CSN predominating on the rising phase.

The neural control of sleep and thermoregulation is co-localized in the POA and adjacent brain structures and hypothalamic temperature-sensing neurons participate in sleep regulation [26]. Experimental POA damage that disrupts thermoregulation also causes persistent insomnia, suggesting that thermo- and sleep-regulatory neuronal systems are anatomically related [26, 27]. They appear to be functionally related as well. As summarized in the previous section, local warming or cooling of the POA can evoke robust whole-body heat and cold defense responses. Milder increases in POA temperature, in addition to suppressing metabolic rate and augmenting peripheral vasodilation, reduce sleep latency, promote non-REM sleep, and increase EEG slow-wave activity during non-REM sleep [27]. Local POA cooling has the opposite effects, causing sleep suppression and reduced EEG slow-wave activity during sleep. At the systems level, in can be shown that activation of POA WSNs promotes sleep via inhibition of ascending arousal systems located in the hypothalamus and brainstem. POA warming suppresses waking-related activity of neurons in the basal forebrain, the lateral posterior hypothalamus, the midbrain reticular formation, and the dorsal raphe nucleus [28, 29].

As documented by single neuronal recordings in cats and rats, the majority of POA WSNs exhibit elevation of spontaneous discharge rate during sleep onset and non-REM sleep, compared to waking [30, 31]. The majority of CSNs are maximally activated during waking and exhibit reduced discharge during sleep onset and non-REM sleep. Thus, the changes in POA thermosensitive neuronal activity at sleep onset mimic the pattern expected to accompany a lowering of the thermal set point. This pattern of thermoreceptor activity is consistent with the thermoregulatory responses that normally accompany sleep onset, i.e., reduced metabolic rate and increased heat loss at the periphery (Fig. 8.4).

The ability of local POA warming to evoke non-REM sleep and EEG synchrony indicates that activation of POA WSNs is sufficient for sleep promotion. The sleep- and EEG slow-wave-promoting effects of evening hot bath immersion in humans depend on the residual mild elevation in body

temperature at bedtime, which enhances the activation of WSNs during sleep onset and sleep. Just as changes in Tsk can evoke thermoregulatory responses in anticipation of changes in brain/body temperature, increases in Tsk through application of warming stimuli or increases in peripheral blood flow would excite sleep-active WSN in the POA promoting sleep onset and sleep stability (Fig. 8.4).

Thermoregulatory Control of Human Sleep

Neurobiological studies in experimental animals reveal close anatomical and functional interrelationships between sleep and body temperature control mechanisms in the brain and indicate that activation of hypothalamic neuronal circuits that promote heat loss normally occurs at sleep onset and during non-REM sleep. In humans, the magnitude of the heat loss response around the time of sleep onset is an important determinant of sleep latency, sleep amount, and sleep quality [32–34]. The magnitude of heat loss response in humans can be reliably assessed by quantifying the temperature gradient from distal skin sites (hand and feet) to proximal skin sites (e.g., forehead, stomach, thigh, or some weighted average of several proximal skin sites. A high distal-to-proximal skin temperature gradient (DPG) occurs when Tsk of the feet and hands are warm with respect to proximal sites, indicative of elevated blood flow to distal skin and elevated heat exchange at these sites Fig. 8.3. A low DPG reflects peripheral vasoconstriction and diminished peripheral heat loss. A high DPG is associated with reduced sleep latency, increased Stage N3 sleep, and reduced number of arousals from sleep [2, 34]. The distal-to proximal gradient is also positively correlated with subjective sleepiness after morning awakenings and after awakenings from daytime naps.

It can be hypothesized that thermoregulatory responses that normally accompany sleep onset in humans play a role in reinforcing and consolidating circadian and homeostatic aspects of sleep regulation. In an entrained individual, habitual sleep onset times will occur on the descending phase of the CBT rhythm. Homeostatic sleep drive is also high at this time, because of sustained prior waking. As CBT falls following the nadir of the 24 h rhythm, activation of heat loss mechanisms results in elevated Tsk. Elevations of endogenous melatonin that normally coincide with habitual bedtime in entrained individuals may also promote lowering of the thermal set point and augment peripheral vasodilation [35]. Collectively, these events would result in activation of peripheral warm sensors and excitation of hypothalamic warm-sensing neurons via peripheral-to-central thermosensory pathways (Fig. 8.4). Activation of central warm sensors will increase sleep propensity via suppression of arousal systems and hasten sleep onset, resulting in further increases in peripheral Tsk and heat loss [27]. Thus, thermoregulatory changes have the potential to exert feed-forward excitatory effects on brain mechanisms that control sleep onset and sleep maintenance, leading to more rapid and seamless transitions from waking to consolidated sleep.

Insomnia is the most common sleep complaint, and sleep disturbance is a prominent symptom in several psychiatric and neurological disorders. In many instances, insomnia complaints are accompanied by abnormalities in circadian rhythms, including abnormalities in the CBT rhythm [36]. Sleep onset insomniacs may exhibit a phase delay in the CBT rhythm of >2 h, indicating disturbance of circadian timing or entrainment. This phase delay means that attempts to fall asleep would often be occurring in closer than normal proximity to the CBT peak, and thermoregulatory adjustments that promote sleep might not be as readily evoked. In the elderly, phase delays in the CBT may also be a contributing factor to the increased incidence of insomnia [36, 37]. Although CBT abnormalities in disorders associated with insomnia may be secondary to other underlying pathologies, manipulation of thermoregulatory control, either pharmacologically or behaviorally, in ways that promote heat loss at sleep onset may help to improve sleep amount and sleep quality. Findings confirm the ability of skin warming to facilitate sleep in normal sleepers and in individuals with insomnia and disturbed nocturnal sleep [9, 37, 38].

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Phylogeny of Sleep

9

Kristyna M. Hartse

Sleep is a mysterious, intricate biological symphony which is composed and conducted by the genetics, anatomy, physiology, neurochemistry, environment, and psychology of living organisms. The phenomenon of sleep is not a uniquely human experience, and with many variations on a theme, it is ubiquitous throughout the animal kingdom. In order to understand why we sleep and why there are perturbations which result in sleep disorders, it is of importance to study sleep in many different living organisms, including those with a long phylogenetic history, which may shed light on the origins of sleep. However, one might reasonably ask how can the study of sleep in diverse creatures such as insects, reptiles, birds, and dolphins—organisms so unlike ourselves—contribute to our knowledge about human sleep? At first glance the immediate answer would appear to be "not much." However, to entertain the possibility that the study of animal sleep is inconsequential or even irrelevant in understanding human sleep and its disorders would be shortsighted. The identification and study of model organisms such as the fruit fly (*Drosophila melanogaster*), for example, have produced a dramatic explosion in our molecular and genetic knowledge about the mechanisms controlling the expression of sleep. These findings reverberate with new insights across the entire spectrum of sleep disorders medicine. Although the exact functions and purposes of sleep still remain unknown, many pieces of the sleep puzzle derived from phylogenetic studies have laid the foundation for unraveling these mysteries.

Most animal sleep studies have been performed in familiar mammals, and a recent review [1] underlines the fact that primarily mice, rats, cats, and dogs have been used experimentally to construct animal models of human sleep disorders. However, the literature is rich with studies of unusual mammalian and nonmammalian species which, although displaying remarkable variations in environment, evolutionary history, behavior, life span, anatomy, and physiology, exhibit the behavioral characteristics of sleep and provide clues to the origins of sleep. At least from a behavioral standpoint, sleep appears to be a universally conserved phenomenon, and as we shall see, genetic and molecular aspects of sleep have also been conserved. Insects, fish, amphibians, reptiles, and invertebrates as well as mammals including egg laying monotremes (platypus and echidna), marine-dwelling cetaceans (whales, dolphins, porpoises) and pinnipeds (seals), marsupials (kangaroo, possum), and placental mammals all display behavioral sleep. Documentation of distinctive electrophysiology, which can be different from that of mammals, may also accompany behavioral sleep in nonmammals. By studying living organisms with a long history in the fossil record, clues to the role of sleep in species survival as well to the function of sleep might be obtained. There are several recent detailed reviews on behavioral and electrophysiological characteristics of mammalian and nonmammalian sleep [2–6]. Here, we will not recapitulate these details, but rather draw upon relevant studies from the animal literature to explore how clues from phylogenetic studies have contributed to the understanding of human sleep and human sleep disorders.

The Definition of Sleep

The first task in understanding sleep mechanisms is to define sleep. There are two different approaches to this definition, behavioral and electrophysiological. The behavioral definition of sleep is well established, and behavioral criteria have been used to identify sleep in diverse insects, invertebrates, mammalian, and nonmammalian organisms. These criteria include (1) a species specific posture; (2) behavioral quiescence; (3) increased arousal thresholds; (4) state reversibility to distinguish sleep from coma or torpor; and (5) a homeostatic response to sleep deprivation, i.e., an increase in sleep amount following sleep deprivation. In mammals, there are distinctive electrophysiological events which accompany behavioral sleep and which distinguish sleep

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from wakefulness. During nonrapid eye movement (NREM) sleep, the EEG is characterized by high amplitude slow waves as well as by other distinctive wave forms such as sleep spindles and K complexes. In humans, NREM sleep has been subdivided into three or four separate sleep stages with specific EEG waveform criteria detailed for each stage [7, 8]. Rapid eye movement (REM) sleep alternates in a cyclical fashion with NREM sleep. REM sleep is characterized by a low amplitude EEG similar to that of waking, skeletal muscle atonia, and rapid eye movements. REM sleep is a period of intense physiological activity in a sleeping organism and other distinctive events during REM sleep include vivid dreaming in humans, increased single neuron firing in the brain, increases in brain temperature, and penile erections. REM sleep is also referred to as paradoxical sleep (PS) recognizing the incongruity of this active physiology in a sleeping organism.

Since there is a close correspondence between the distinctive electrophysiological markers of mammalian sleep and behavior, electrophysiology is generally a more efficient means, rather than continuous visual observation of behavior, in defining mammalian sleep. However, as we shall see, although the behavioral criteria for sleep may be met, the electrophysiological expression of sleep is often different in nonmammalian species.

In comparison with mammals, there are relatively few electrophysiological studies which have been performed during behavioral sleep in nonmammalian organisms. Furthermore, there is controversy as to whether the "true" indicators of electrophysiological sleep are present since nonmammalian electrophysiology is quite different from that of mammals. The high amplitude slow waves defining mammalian NREM sleep have not been reliably observed during nonmammalian behavioral sleep with the exception of birds [9]. Similarly, REM sleep has not been rigorously documented in nonmammals, again with the exception of brief bouts of avian REM sleep usually lasting less than 10 s. In mammals, the thick neocortical layer responsible for generating slow wave activity, is absent in nonmammals, making it unlikely that slow waves can be generated without this anatomical substrate. There are some scattered observational reports of REM sleep in nonmammals, but most studies have not presented rigorous or convincing evidence for REM sleep.

There is, however, a variety of other electrophysiological correlates associated with behavioral sleep in invertebrates and nonmammalian vertebrates. A sampling reveals a decline in local field potentials during behavioral sleep in fruit flies [10, 11], spindle-like activity during quiescence in the frog [12], isolated spikes and spike trains during behavioral quiescence in the octopus [13], spikes during behavioral wakefulness and waves of 15–20 Hz during behavioral sleep in the crayfish [14], and high amplitude spikes during behavioral sleep which disappear with behavioral waking in turtles, tortoises, lizards, and caiman [15–18].

These findings, which are dissimilar to the electrophysiology of mammalian sleep, have prompted debate as to whether the sleep of nonmammalian organisms is the same state as mammalian sleep and whether it is logical or scientifically reasonable to impose the mammalian criteria for sleep on nonmammalian species [19–21]. Other electrophysiological findings which further complicate the picture include reports of high amplitude slow waves characteristic of mammalian NREM sleep occurring during behavioral sleep in young caimans [22], REM sleep in lizards [23], high amplitude slow waves during waking in lizards [24], and high amplitude spikes during reptilian behavioral sleep which appear to be analogous to ventral hippocampus spikes recorded during NREM sleep in mammals [25]. Libourel and Herrel [4] have recently suggested that explanations for these varied findings in reptiles may be the result of differences between natural or seminatural recording conditions and laboratory conditions, differences in habituation to the recording environment, differences in electrophysiological recording techniques, methodological differences in evaluating arousal responses, and differences in electrode placements since no stereotaxic atlases of reptilian brains are available to ensure consistency of electrode placement. This debate surrounding sleep in reptiles is central to the question of whether nonmammalian organisms sleep if they do not exhibit mammalian electrophysiology. Rather than attempt to resolve this issue, examples from phylogenetic sleep studies will be used to evaluate the contribution of phylogeny to human sleep.

Model Organisms in the Study of Sleep

The revolution in our current knowledge about the neurochemical, molecular, and genetic bases for sleep has been propelled forward at an extraordinary rate by the introduction of model organisms, primarily the fruit fly (*Drosophila melanogaster*), and round wormas (*Caenorhabditis elegans*) as well as the zebrafish (*Danio rerio*) (Figs. 9.1, 9.2, 9.3). Compared to mammals, there are a number of features which make these organisms both practical and scientifically desirable for study. There is economic and logistical ease in maintaining large colonies, and a short life span as well as short reproductive cycles allow for the rapid evaluation of experimental manipulations. Increased statistical power can be achieved as the result of a large number of available subjects, and there is the potential for rapid replication of results in genetically identical organisms under similar

conditions. Furthermore, the presence of drosophila appendages such as wings and legs allow for observations of complex behaviors. The most significant scientific advantage is the relatively small number of neurons (approximately 100,000) in the adult drosophila brain as compared to the staggeringly large number of neurons (approximately 86 billion) in the adult human brain [26, 27]. The drosophila genome has been mapped with shared homologues identified in humans [28–31]. In addition, the neurotransmitters which have been demonstrated to play a role in the control of human sleep, including serotonin, dopamine, acetylcholine, GABA, and epinephrine (the equivalent of octopamine in drosophila), and in the case of zebrafish, orexin, are present [32, 33].

A model organism is a model only if, despite strong genetic similarities to humans, there is evidence that behavior meets the criteria for sleep. *Drosophila* quiescence does fulfill the criteria established for behavioral sleep [34, 35]. Behavioral quiescence, a stereotypic posture, elevated arousal thresholds, state reversibility with stimulation, and a homeostatic response to deprivation of rest, i.e., rest increased following the period of rest deprivation are present. This homeostatic response to deprivation is independent of at least one central clock gene, indicating that the homeostatic response is not simply a circadian response rather than a response to rest deprivation. Additional evidence for the similarity between *drosophila* quiescence and human sleep includes a similar response to drugs including caffeine, modafinil, and methamphetamine [36–38]. Antihistamines increase quiescent periods in *drosophila* similar to drowsiness in humans [35]. Finally, there are age-related changes in sleep similar to the changes in sleep amounts across the human life span [35, 39].

Drosophila is the organism which has arguably received the most attention as a model system for the genetic and molecular study of sleep. However, zebrafish (*D. rerio*) also offer similar biological and behavioral properties with respect to sleep for consideration as a model organism [40, 41]. Another proposed model organism is the round worm (*C. elegans*). During lethargus, a quiescent behavioral state which occurs after each of four molts, the behavioral criteria for sleep, including a homeostatic response to rest deprivation and elevated arousal thresholds, are present [42, 43]. There is genetic and molecular conservation between *drosophila* and *C. elegans* [44, 45]. A recent study also provides evidence that quiescence during molts in another worm, the tobacco hornworm (*Manduca sexta*), meets the behavioral criteria for sleep [46]. Thus, these model organisms with their practical and experimental advantages may have the potential to observe, and perhaps unlock, the underlying mechanisms controlling the expression of sleep.

Optimal Sleep and Mortality

> The ill effects of insufficient sleep may be witnessed on some of the principal organic functions, but it is the brain and nervous system that suffer chiefly in the first instance. The consequences of a too protracted vigil are too well known to be mistaken, and many a person is suffering, unconscious of the cause, from the habit of irregular and insufficient sleep.
>
> William A. Hammond, 1866 [47].

The consequences of insufficient sleep have long been a subject of debate and discussion. Still today, some of the most common questions asked of sleep clinicians revolve around sleep quality and sleep amounts: How many hours of sleep per night are necessary for good health, is a lack of

Fig. 9.1 The Fruit Fly (*drosophila melanogaster*)

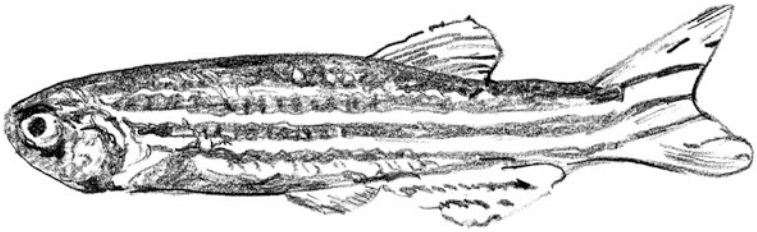

Fig. 9.2 The Zebra Fish (*danio reiro*)

sleep harmful, and will inadequate amounts of sleep or poor quality sleep affect longevity? As we shall see, there are data to suggest that too little or too much sleep may impact health and life span in humans. For example, persistent, but not intermittent, self-reported insomnia is associated with an increased risk of all-cause mortality over a 20-year follow-up period, suggesting that decreased sleep amounts negatively impact life span [48]. In contrast, prolonged sleep amounts have been associated with an increased risk of fatal and nonfatal stroke [49], conversely suggesting that increased sleep amounts negatively impact health. Although studies of sleep in nonhuman organisms reveal significant variations in sleep amounts, there are no data available which shed light on the impact of these variations in promoting species survival and longevity. As we shall see, however, there are examples of "natural" sleeplessness in the animal world, and most importantly the genetic manipulation of model organisms has advanced our knowledge about the mechanisms controlling sleeplessness.

One approach to addressing the question of whether there are optimum amounts of sleep associated with a long life span would be to examine the relationship between sleep amounts and mortality in large populations. A systematic relationship between human sleep and mortality was first described over 30 years ago [50], and since that time a body of epidemiological literature has accumulated which suggests fairly consistently that short and, somewhat inconsistently, that long sleep amounts are associated with increased mortality as well as with diseases such as obesity, diabetes, hypertension, and cardiovascular disease [51–55]. Typically, the best survival curves are associated with about 7 h of sleep per night. Shorter sleep times are variably defined in these studies as 4–6 h per night and long sleep times as more than 8–9 h per night, raising the question of whether the common recommendation of a minimum of 8 h of sleep per night is appropriate [56]. Of note is that in virtually all epidemiological studies, sleep duration was assessed by subjective estimates and not overnight sleep studies utilizing polysomnography, suggesting the possibility of subjective over- and underestimates of sleep duration which could bias results. Also, it cannot be determined in these epidemiological studies whether short and long sleep durations are the direct cause of increased mortality or whether short and long sleep durations are the product of an underlying intervening condition which in turn is responsible for these associations with mortality.

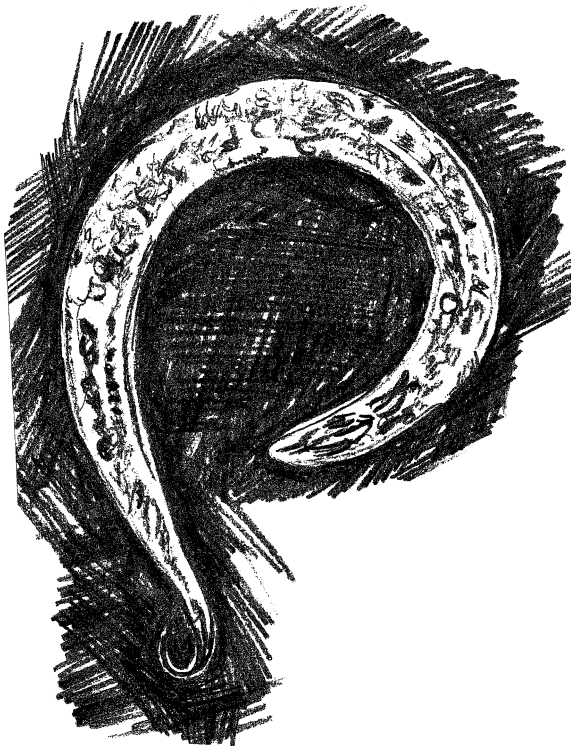

Fig. 9.3 The Round Worm (*caenorhabditis elegans*)

The most extensive and rigorous review of the literature addressing the question of optimal sleep time was recently performed by a panel of sleep experts assembled by the American Academy of Sleep Medicine and the Sleep Research Society [57]. The consensus of the panel was that less than 6 h of sleep is inadequate to support optimal health, but no consensus could be reached about the effects of 9 h or more on optimal health. The final consensus was that 7 h was the minimum amount of daily sleep necessary to support optimal health. However, no consensus could be reached about an upper maximum threshold of sleep for optimal health. This is not surprising. A careful review of the epidemiological studies supporting a relationship between sleep duration and mortality raises the issue of, for example, how

variable methodologies for determining total sleep time may weaken the conclusions which can be drawn from the U-shaped curve characteristic of the relationship between sleep duration and mortality [58]. Also of interest in these considerations of mortality and sleep duration is the demonstration of a dose–response relationship between hypnotic sleep medications typically used to treat short sleep and an increased mortality risk as well as an increased cancer risk for the most frequent users of hypnotics [59]. These findings suggest that intervening variables, inconsistently assessed in epidemiological studies, may contribute substantially to the association between sleep duration and mortality.

Human epidemiological studies, although inviting speculation about the predictive value of sleep amounts in determining life span, do not reveal the biological mechanisms responsible for this relationship. There are age-related changes in *drosophila* sleep similar to the sleep fragmentation and decreased sleep amounts observed in aging humans, suggesting that *drosophila* may shed light on the mechanisms mediating sleep and longevity in humans [39]. Several genetically engineered *drosophila* mutants, including *Minisleep* (*mns*), *Hyperkinetic* (*Hk*), *Sleepless* (*sss*), *and Insomniac* (*inc*), have been developed which have markedly reduced sleep amounts in comparison with wild-type flies [60–62]. Life span in these short sleeping flies is reduced, suggesting that sleep duration has a direct relationship to longevity. Of note is that waking behavior was not impaired in mutant strains. These mutations are mediated by *Shaker*, a gene which encodes for the voltage dependent potassium channel. Another short sleeping mutant, *fumin* (*fmn*), which has a mutation in the dopamine transporter gene (DAT), does not show a reduced life span nor do these flies exhibit a homeostatic response to sleep deprivation [63]. There is substantial evidence from a number of studies to indicate that dopaminergic systems have a major role in the expression of arousal and sleep [36, 64]. Mutations of the *amnesiac* (*amn*) gene, which has a role in the adenylate cyclase/cAMP signaling pathway, are associated with fragmented sleep and, similar to *fmn*, are not associated with a rebound in quiescence following deprivation [65]. Of note is that a high-calorie diet in *fmn* mutants results in further reductions in sleep amounts and reduced longevity, suggesting that accelerated aging and shortened sleep are impacted by increased caloric intake [66]. Also time-restricted feeding with food access limited to 12 h per day in wild-type flies, although not changing caloric intake, is associated with improvements in sleep and ameliorates an age-related cardiac decline [67]. These studies indicate that there are a number of different factors which affect the expression of sleep. Also of interest are mutations in genes which would not seem to play a role in sleep expression such as the fragile X mental retardation gene (*Fmr1*). Overexpression of drosophila *Fmr1* results in shortened sleep, whereas the loss of *Fmr1* is associated with significantly longer sleep amounts as compared to control flies. In neither mutant was there a homeostatic response to sleep deprivation, and of particular interest relevant to the human epidemiological studies is that life span is reduced in both the short and long sleeping *Fmr1* mutants [68]. Finally, it is most likely that there is not a single dedicated "sleep gene," but that other genes more broadly controlling cellular and neuronal functions also control the expression of sleep. An example is the demonstration that decreasing cyclin A, a protein which regulates the progression of cells through the cell cycle, results in decreased total sleep and a decrease in the homeostatic response to sleep deprivation [69]. More recently, a sleep regulating protein *redeye* (*rye*) which interacts with *sss* has been identified in short sleeping mutants and after sleep deprivation in wild-type *drosophila* [70].

The cellular mechanisms controlling sleep in humans are virtually unknown. The complaint of insomnia, difficulty falling and staying asleep typically with resulting daytime fatigue, affects approximately 30 % of the population in varying degrees of severity [71]. Not only physiological factors, but the contribution of psychological factors to this disorder, make it a daunting task to untangle the mechanisms which are involved in the expression of human sleeplessness. There are two disorders characterized by shortened sleep which have been identified in this category of sleep difficulties and which have a known genetic basis. The first is advanced sleep phase syndrome in which affected family members have a mutation of the hPER2 clock gene involved in controlling the timing of sleep. Although the sleep cycle is regular in affected family members, there is a four hour advance of sleep, temperature, and melatonin rhythms in affected as compared to unaffected family members [72]. A second disorder of sleeplessness with a known genetic basis is fatal familial insomnia. This disorder is a rare, inherited, progressive neurodegenerative disease in which there is a progressive inability to sleep eventually culminating in total sleeplessness and death [73]. Autopsy findings reveal selective bilateral neuronal loss and reactive gliosis of the anterior and dorsomedial thalamic nuclei with an accumulation of prion protein. In affected individuals, there is a single mutation on the prion protein gene PRNP at position 178 combined with a mutation at position 129 [74]. Although these are two very specific instances of sleep difficulty, there is, however, evidence to suggest that short sleepers do carry a gene with a specific DEC2 (also known as BhLHE41) mutation. This mutation was identified in a family with two individuals who had lifelong short sleep averaging 6.25 h per day as compared to noncarrier family members who averaged 8.06 h per day [75]. Subsequent work has identified other mutations of BHLHE41 associated with decreased total sleep time and with fewer average

lapses in performance on a psychomotor vigilance task, suggesting resistance to the effects of sleep deprivation [76].

Despite this large body of literature which suggests that sleep and longevity are related, there continues to be no clear answer to the question of whether there is an optimal amount of sleep which can promote maximum longevity in humans. Additionally, understanding the genetic and cellular mechanisms responsible for human sleeplessness is clearly in its infancy. There are, of course, no formulas to translate the equivalency of *drosophila* sleep minutes which can be manipulated by these mechanisms into human sleep hours. As previously noted, at least some of the ambiguity in human studies may be related to subtle differences in survey questioning about sleep amounts which result in subjective under- or overestimation of sleep time [58].

There are also variables identified from *drosophila* studies which may interact with genetics to potentially affect sleep with respect to longevity including social enrichment or isolation, environmental conditions, diet, methods of evaluating quiescence, and climates and altitudes [77–82]. There is also recent evidence that variations in population density during normal *drosophila* larval development affect sleep duration in adults, but not in *amn* mutants, suggesting lifelong cellular changes in sleep controlling mechanisms dating from infancy as the result of environmental exposures [83]. Although not as intensively studied as *drosophila*, other mammals and non-mammals also demonstrate that environment and social experience may affect the expression of sleep. For instance, sleep in honey bees is increased by exposure to the bee colony environment in comparison with isolated bees [84]. Electrophysiological recordings of unrestrained sloths in the rain forest reveal that total sleep time is substantially less than under laboratory conditions [85]. The threat of predation and social status may also play a significant role in determining sleep amounts in mammals [86–88]. In reptiles, young caimans recorded in a colony exhibited differing electrophysiology from caiman recorded in isolation, suggesting that these differences in environment and socialization may have affected the expression of sleep [17, 22].

The most striking example of the evolutionary effects of habitat upon sleeplessness is illustrated by studies in the Mexican cavefish (*Astyanax mexicanus*) [89, 90]. Surface- and cave-dwelling populations of these fish differ remarkably in daily sleep amounts with surface fish averaging over 800 min and three different cave-dwelling populations averaging 110–250 min per day. Blockade of B-adrenergic receptors with propranolol produced dose-dependent increases in cave fish sleep without any effect at any dose on sleep of surface-dwelling fish. Adrenergic antagonists did not affect sleep in surface dwellers, but cavefish sleep increased significantly in response to the B1 antagonist atenolol. The number of catecholamine neurons is conserved in cavefish as opposed to surface-dwelling fish, suggesting that an increase in the adrenergic arousal system in cavefish as compared to surface dwellers has occurred during evolution. Other recent fish studies have examined circadian rhythmicity in aging killifish (*Nothobranchius*) as well as the induction of quiescence by melatonin in the three spot wrasse (*Halichoeres trimaculatus*) [91, 92].

In summary, much of the appeal of the findings from human epidemiological studies resides in the simplicity of the U-shaped curve which suggests that the relationship between longevity and sleep is straightforward. Both short sleep and long sleep are associated with increased mortality. However, as we have seen from the animal literature, these data are fraught with many potentially uncontrolled and confounding genetic, environmental, and ecological factors which have the potential to alter this relationship. An unambiguous answer to the question of how much sleep and under what conditions are necessary for optimal longevity remains unanswered.

Pharmacological Development

A significant advantage of utilizing model organisms to explore the molecular basis of sleep lies in their well-studied genome which is amenable to precise manipulation. Another potentially productive area in which these model organisms may be of substantial benefit is in the area of developing new and focused pharmacological treatments for human diseases, including sleep disorders [30]. For example, approximately 70 % of human genes have at least one zebrafish orthologue, and as a result, zebrafish have been extensively used to develop human disease models [28, 93]. The correspondences between the human genome and the genomes of model systems suggest that model organisms could be instrumental in developing in vivo drug treatments at a molecular level for modifying or treating human sleep disorders. Zebrafish are sensitive to major classes of drugs including anxiolytics, hypnotics, and stimulant among others which could potentially be used to treat disordered sleep [33, 40]. In addition, the cost of screening pharmacologically active compounds is substantially less expensive in an organism such as the zebrafish so that an increased number of compounds can be economically evaluated. New effects and mechanisms of drug action on waking and quiescence produced by similar major neurotransmitter pathways in both zebrafish and mammals, and identification of poorly understood compounds can be rapidly assessed.

Cross-translational studies between model organisms and humans also open new avenues for the discovery of waking and sleep biomarkers which may have practical application. One example is the discovery of salivary amylase as a biomarker for sleepiness and sleep drive in both *drosophila* and humans utilizing cross-translational studies [38, 94]. The

potential applications of such a "sleepiness marker" are far reaching. For example, multiple sleep latency testing (MSLT), a series of daytime nap tests spaced throughout the day according to a standard protocol, is currently the standard electrophysiological assessment tool for objectively evaluating a patient's subjective complaint of sleepiness. The maintenance of wakefulness test (MWT) is used in a similar protocol to evaluate daytime alertness [95]. With further elaboration of the salivary amylase findings, convenient, rapid, cost-effective alternatives to the MSLT and MWT could potentially be developed for objective assessment of sleepiness and alertness in settings where polysomnography is unavailable. Another practical application of these findings may be the assessment of drowsy drivers similar to breathalyzer assessments of alcohol consumption or the assessment of persons such as air traffic controllers, bus drivers, or train conductors whose occupations require a high degree of alertness to ensure public safety.

The utilization of model organisms for development of effective pharmacological treatments and sleep-related biomarkers is still in development. However, as knowledge about sleep mechanisms continues on a rapid, steep trajectory, it is not unreasonable to anticipate that the practical application of this knowledge will also follow.

Sleep Disorders

Narcolepsy

The mechanisms underlying the expression of narcolepsy were virtually completely unknown until the serendipitous discovery by Dr. William Dement of a dog with what appeared to be cataplectic attacks similar to the cataplectic attacks demonstrated by human narcoleptic subjects [96]. Since that time, understanding the etiology of narcolepsy has arguably been primarily the result of discoveries in animal research [97, 98]. The cardinal symptoms of narcolepsy include excessive daytime sleepiness, hypnagogic hallucinations, sleep paralysis, and cataplexy, a sudden loss of muscle tone with strong emotions. Electrophysiologically, narcolepsy is diagnosed by the rapid onset of REM sleep, typically with a latency of less than 15 min as compared to the 60- to approximately 90-min latency to the onset of REM sleep in normal subjects. Narcolepsy, in conjunction with a history of clinical symptoms, is diagnosed by the rapid onset of REM sleep during a protocol of daytime nap testing [95]. Based on epidemiological studies in several countries, the prevalence of narcolepsy has been estimated at between 25 and 50 per 100,000 persons [99]. Of all the sleep disorders, the genetics, neuropharmacology, and molecular mechanisms of narcolepsy appear to be the best understood [100]. The discovery of orexin (hypocretin) deficiency resulting from the loss of orexigenic neurons in narcoleptic dogs, mice, and humans and the close association of the human leukocyte antigen DQB1*0602 and DQA1*0102 in almost all narcoleptics has led to the conclusion that narcolepsy is an autoimmune disease [101]. However, the mechanisms by which orexin is depleted are unknown. Potential environmental triggers for the development of narcolepsy which have been identified include upper airway infections and the H1N1 flu vaccine in genetically susceptible individuals [102, 103].

Gene therapy clinical trials are now being performed for a variety of human diseases including cancer, cardiovascular disease, Parkinson's disease, and cystic fibrosis [104]. Hypothalamic gene replacement therapy in orexin-deficient mice improves sleep quality and the timing of REM sleep, but does not improve cataplexy [105]. Conversely, gene transfer into the zona incerta in orexin-deficient mice improves cataplexy, but not sleep fragmentation [106]. There are no data on gene replacement in narcoleptic humans, but the findings in mice suggest that this approach may be a promising one. As the result of this research in narcolepsy, a new sleeping medication, suvorexant, has been developed as a treatment for insomnia. Suvorexant is a dual orexin 1 and orexin 2 receptor antagonist which dose dependently enhances sleep in humans [107, 108]. Suvorexant was approved for human use by the Food and Drug Administration in August, 2014. Of interest is a detailed account of suvorexant's approval process which appeared in the popular press [109].

A major stumbling block in the use of model organisms to study narcolepsy is the absence of REM sleep. Birds are the only nonmammalian organism to display convincingly behavioral and electrophysiological signs of REM, but avian REM sleep bouts are brief, lasting only a few seconds. Could it be possible that REM sleep is present in *drosophila* or zebrafish and that it has simply been missed? This seems unlikely particularly in light of a recent detailed video analysis of zebrafish eye movements and respiration during sleep which did not uncover any credible evidence for the presence of REM [110]. Additionally, the limited behavioral repertoire of model organisms precludes their usefulness in evaluating, for example, cataplexy or sleep paralysis which are major signs of narcolepsy. The *drosophila* brain does not contain orexin. However, zebrafish have a distribution of orexin expressed in the brain in a fashion similar to that of mammals [111]. Overexpression of orexin in zebrafish results in elevated motor activity, decreases in arousal thresholds, and shortened, disturbed sleep in the dark [111, 112]. During the course of evaluating zebrafish hypocretin receptor mutants, Yokogawa et al. [112] made several interesting observations with respect to sleep. Normal adult zebrafish maintained under constant light conditions have an almost complete suppression of sleep. A homeostatic

rebound response to this sleep deprivation was not observed, and a progressive return to sleep occurred over the course of one to two weeks. Following sleep deprivation in response to electrical stimulation, there was no homeostatic response when animals were released into light, but a homeostatic rebound occurred with release into darkness. Additionally, exposure to light during the last 6 h of the biological night produced a marked suppression of sleep without a homeostatic rebound with release into darkness.

Although the orexigenic substrate of the zebrafish brain parallels that of the mammalian brain, the zebrafish is not a particularly enlightening model organism to elaborate upon mechanisms controlling narcolepsy. None of the model organisms studied to date would appear to serve as a model for narcolepsy. Furthermore, the unusual response of zebrafish sleep to light with sleep suppression and to the absence of a homeostatic response following sleep deprivation suggests that there are components of zebrafish sleep which should not be considered as a model substrate for sleep disorders.

Sleep Apnea

The cardinal symptoms of obstructive sleep apnea (OSA) are well known and unmistakable in their presentation: loud snoring and pauses in respiration terminated by explosive snores, breath holding episodes witnessed by a bed partner, and excessive daytime sleepiness resulting from the arousals terminating often hundreds of respiratory pauses during sleep. Severe OSA is a risk factor for arterial hypertension, heart failure, stroke, pulmonary hypertension, and maternal morbidity [113, 114]. A familial component has been described in several studies [115–117]. There are two reports of a naturally occurring model of sleep apnea in the English bulldog which has a crowded upper airway anatomy similar to sleep apnea patients [118] and in obese miniature pigs [119]. Nonmammalian species have not been observed to have sleep apnea, and model organisms have not been developed for experimental evaluation of this disorder.

The experimental research on sleep apnea has been focused on the induction of sleep apnea in dogs, rats, and mice by artificially occluding the airway and exposure to repetitive hypoxemia [120–123]. The cardiovascular and neurochemical consequences of sleep apnea have been described in these experimental models, but the genetic and cellular components of sleep apnea are not well understood. OSA is a complex disease process with multiple interactive factors including age, weight, gender, arterial and pulmonary hypertension, cardiovascular disease, and metabolic disorders. It is almost certainly the case that there are multiple cellular and genetic components contributing to the expression of OSA. A gene encoding the allele APOEe4 which is essential for cholesterol metabolism and transport has been associated with OSA in adults and children. However, a meta-analysis of studies reporting an association between APOE and sleep apnea concluded that the association is weak [124]. Another meta-analysis of OSA genetic association studies revealed that TNFA rs1800629, which may also be associated with heart disease and heart failure as well as chronic obstructive pulmonary disease, was significantly associated with OSA [125]. These authors concluded that studies examining OSA genetics did not typically provide robust evidence. Thus, the complexity of OSA presents significant challenges in understanding the genetics of this order, and at least at the present time, a model organism with a well-known genome combined with the symptoms of OSA does not appear to be on the horizon.

Restless Legs Syndrome (RLS)

Clinical symptoms of RLS include restless, creeping, crawling, uncomfortable sensations in the legs during sedentary activities with a worsening of these sensations beginning in the evening. They are accompanied by an irresistible urge to move the legs for temporary relief. Typically, there is a worsening of the sensations at sleep onset which results in substantial difficulty falling asleep. Key factors in the expression of RLS are iron deficiency and the involvement of the dopaminergic system in regulating iron metabolism, although the mechanism of this relationship is not clearly understood. Currently, dopamine agonists, such as ropinirole and pramipexole, which enhance brain dopamine, are the treatments of choice for RLS [126]. Prevalence, depending upon the complexity of survey questions, ranges between 9.4 and 15 % querying RLS as a single symptom. This range changes somewhat to 3.9–14.3 % utilizing the criteria of the International Restless Legs Syndrome Study Group [127, 128]. Inclusion of stricter diagnostic criteria such as the frequency and severity of symptoms results in decreased estimates of prevalence.

Genome-wide association studies (GWAS) have opened a new window onto the genetic underpinnings of human RLS. GWAS studies in both European and US populations have identified genomic loci which are associated with restless legs syndrome including *MEIS1, BTBD9*, and *MAP2K5/LBXCOR1* on chromosomes 2p, 6p, and 15q [129–131]. Animal models have been proposed for the study of restless legs syndrome. Mice and rats with lesions of the A-11 dopaminergic nucleus which projects to the spinal cord have demonstrated an increase in locomotor activity [132, 133]. Spontaneously hypertensive rats exhibit increased motor activity, suggesting a possible model for the study of RLS [134]. One study in *C. elegans* demonstrated that the MEIS1 worm orthologue increased ferritin expression and human

cells cultured in iron-deficient conditions revealed decreased MEIS1 expression, lending further support to the role of these genes in iron metabolism [135].

Animal studies are typically the catalyst for human research. However, the discovery of these potential RLS loci via human GWAS provided a reverse "human to animal" stimulus for the development of a *drosophila* RLS model [136]. As described above, the diagnosis of RLS in humans is accompanied by reports of an irresistible urge to move the legs for relief of discomfort. Of course, these sensations cannot be communicated by *drosophila*, but movement can be operationally used to infer the presence of RLS. Genetic alteration of the fly homologue *dBTBD9* which corresponds to human *BTBD9* resulted in fragmented sleep characterized by a decrease in the duration of sleep bouts and an increase in the number of sleep bouts and waking after sleep onset, suggesting the sleep fragmentation of RLS patients. However, sleep duration in flies per 24-h period was not different between mutants and controls. Although flight and negative geotaxis were normal in mutants, when confined to a restricted space flies were hyperlocomotive, reminiscent of the movements experienced by RLS patients during the forced immobility test (FIT) [137]. Uninterrupted bouts of walking were also longer in mutants. Comparing dopamine levels in mutants and controls, mutants revealed a 50 % reduction in dopamine, suggesting a relationship between alterations between *BTBD9* and maintenance of normal dopamine levels. Also of note is that treatment with pramipexole, a dopamine agonist, restored sleep consolidation in mutants to control levels, again suggesting a significant role for dopamine in the expression of RLS. dBTBD9 is also implicated in the regulation of iron metabolism and ferritin homeostasis.

These genetic explorations into the expression of RLS in a model system provide evidence of the complex relationship between specific genes and the role of dopamine in regulating ferritin levels. Ideally, with further studies more effective treatments for RLS will be discovered.

Unusual Sleep Disorders

There is a group of unusual sleep disorders, the parasomnias, in which the distinction between waking and sleep becomes blurred and waking behavior appears to intrude into sleep. Included in this group of disorders are confusional arousals, REM behavior disorder (RBD), sleep walking, and sleep-related eating disorders [138]. Complex vigorous motor activity which can become violent in the case of RBD and loud vocalizations may accompany these disorders. Not a great deal is known about the prevalence of parasomnias, but sleep walking, for example, is relatively common with a lifetime prevalence estimated at 29.2 % [139]. RBD is rarer with a prevalence of 2.01 % and subclinical RBD estimated at 4.95 % in a Korean elderly population [140]. Due to the complexity of behavior in parasomnias, no animal models have been developed to study these disorders, and not surprisingly no naturally occurring animal models of parasomnias have been identified. However, early studies in cats revealed "dream enacting" behavior following pontine tegmental brainstem lesions, reminiscent of the vocalizations and motor movements in RBD [141, 142].

Can sleep and wakefulness be present in the same brain at the same time? This possibility seems counterintuitive to our normal experience since we typically dichotomize states of alertness as being either waking or sleep and the transition between them as drowsiness, often euphemistically described as being half awake or half asleep. The parasomnias suggest that the comingling of sleep and waking in the same neural substrate is possible, and insights from animal studies are of benefit in shedding light on this issue.

There are a number of examples in the animal literature in which "nonquiescent" or literally "motorically active" sleep is present, suggesting that sleep can be compatible with behavior typically present during waking. For example, nocturnal "sleep swimming" fish inhabiting coral reefs in the Red Sea vigorously move the dorsal, pectoral, and caudal fins in fixed body positions at a frequency of strokes approximately twice the rate with daytime swimming outside the coral reef [143]. This behavior may function to aerate the reef and assure healthy corals. Captive dolphin and killer whale neonates and their mothers remain continuously active and do not exhibit signs of behavioral sleep for several months postpartum with gradually increasing periods of behavioral quiescence which eventually return to normal amounts, but do not exceed normal amounts, of behavioral sleep [144, 145]. Dolphins are able to maintain continuous vigilance with accurate echolocation for a testing period of up to 15 days [146]. In the laboratory birds demonstrate marked decreases in EEG defined sleep during the migration season, and data from freely moving swifts equipped with data loggers during a 200-day nonstop flight suggest that sleep occurs during periods of decreased activity during flight [147–149].

There is the possibility that these animals are unique and simply do not sleep. However, this would be contrary to findings from virtually all other living organisms. Alternatively, a variant of sleep may be present which coexists with waking and which allows for sustained vigilance in the presence of physiological sleep. In fact, there is a unique form of sleep, unihemispheric sleep, a state in which one hemisphere of the brain exhibits waking EEG activity simultaneously with sleeping EEG activity in the other hemisphere. Unihemispheric sleep has been recorded in dolphins [150], whales [151], fur seals [152], and birds [9]. Only NREM sleep has been observed in whales and dolphins, whereas in birds and seals REM sleep is present. Of interest is a recent demonstration of decreased orexin bouton density in the cerebral cortex of a porpoise and a whale compared to ten mammalian species [153]. The presence of

unihemispheric sleep offers the significant advantages of an ability for part of the brain to sleep during long-distance migration while maintaining sentinel functions in monitoring the environment [148, 154].

Unihemispheric sleep is clearly an unusual form of physiological sleep. However, there are recent human electrophysiological studies utilizing scalp, intracerebral EEG, and unit recordings which suggest the possibility that there are also coexisting regional differences in human sleep and waking. For example, detailed sleep electrophysiological studies have demonstrated that 85 and 75.8 % of sleep spindles and slow waves, respectively, have been detected in less than half of brain recording sites [155]. This regionality of sleep waveforms, along with the demonstration of unihemispheric sleep in animals, suggests that parasomnias such as sleep walking or RBD may be a manifestation of simultaneously occurring waking and sleep processes. There is also further evidence from intracerebral recordings that motor cortex activation lasting from 5 to more than 60 s can occur simultaneously with an increase in slow wave activity in the dorsolateral prefrontal cortex [156]. Also relevant in this regard is the finding that human sleep spindles recorded in the hippocampus precede the sleep spindles and K complexes characteristic of Stage 2 sleep recorded from neocortical scalp electrodes [157]. Similarly in cats, increases in ventral hippocampus spikes precede the onset of NREM sleep, also suggesting that sleep processes may begin in different brain regions at different times in both animals and humans, strengthening the similarities between these electrophysiological processes [25]. Studies in both the echidna, a primitive egg laying mammal considered the basal stock of living mammals, and the ostrich, a basal bird, demonstrate that elements of both NREM and REM sleep may be simultaneously present during behavioral sleep [158, 159]. Further illustrating the simultaneous presence of different physiological states in humans are data from a single subject with stereotaxically implanted electrodes who experienced confusional nocturnal arousals [160]. During these episodes, there was localized activation of the motor, cingulate, insular, temporopolar, and amygdalar cortices in the presence of slow waves recorded from the frontal and parietal dorsolateral cortices and in the presence of spindles recorded from the hippocampal cortex.

Parasomnias are very poorly understood, and the triggers which initiate waking-like behaviors during sleep are completely unknown. There are no readily available animal preparations in which to study these unusual behaviors. Unihemispheric sleep in marine-dwelling mammals and birds hints that there is a capacity for simultaneous expression of both waking and sleeping electrophysiology in the same brain. However, the mechanisms controlling the expression of unihemispheric sleep may be controlled by different, more orderly processes than the processes which result in the often explosive behavior and vocalizations which accompany many of the human parasomnias. Nonetheless, the parasomnias suggest that sleep and waking may be the manifestation of simultaneous waking and sleep.

Conclusions

Although the behavioral and electrophysiological parameters of sleep have been described in great detail in many living organisms, the cellular origins of sleep are still elusive. Studying living organisms is unlikely to provide a definitive answer to the question of how sleep originated, and the behavioral or cellular origins of sleep cannot be preserved in the fossil record. There is one speculative observation that a dinosaur fossil from the Cretaceous era (between 145 and 65.5 million years ago) has been preserved in an avian-like sleeping posture [161]. Sleep is undoubtedly an ancient behavior which has been conserved through evolution, but the crucial life sustaining functions it serves to maintain its presence in many different species is unclear.

Knowledge about sleep mechanisms has rapidly evolved by utilizing model organisms as the genetic and molecular substrates for the study of mechanisms controlling sleep. Even though there are tremendous benefits to the utilization of these organisms, there are also a number of issues which are raised.

Considerations in the Use of Model Organisms

A major question is whether model organisms can truly serve as models for the exploration of human sleep mechanisms and sleep disorders. As we have seen, there is a remarkable correspondence among the genetic, neurochemical, and cellular operations of model organisms and humans. However, it is obvious that the complexity of human behavior and the unexplored cellular effects of human emotions and psychology upon sleep cannot be unraveled by model organisms. The clinical understanding of human sleep disorders relies not only upon the patient's descriptions and environment, but also on observations of witnesses to the patient's symptoms. For example, can it be assumed that frequent movements of the fruit fly's legs are a model for the uncomfortable sensations described by patients in restless legs syndrome? Thus, even though a model may produce a wealth of information about the "technical" aspects of sleep, this does not ensure that this model is necessarily the model for human discovery. Is human NREM sleep the homologue of behavioral sleep in model organisms? There have been no convincing data which have demonstrated the presence of REM sleep in model organisms, and electrophysiological correlates of human NREM sleep have not been described. This absence of some electrophysiological sleep correlate of behavior is a

significant drawback for an organism modeling human sleep. Also, there have been a large number of studies, particularly in *drosophila*, to suggest that short sleep has adverse effects upon life span. What is the translation factor between old age in "drosophila days" and "human years?" What is the translation factor between short or long drosophila "sleep minutes" and short or long human "sleep hours?" These questions are probably unanswerable. Finally, there are some aspects of sleep in model organisms which are different from human sleep characteristics such as the absence of a homeostatic rebound in sleep following deprivation of quiescence in some mutant flies or the suppression of sleep upon exposure to light and the lack of a subsequent homeostatic response in zebrafish.

These questions should not, of course, discourage the use of model organisms in discovering clues to the cellular and genetic mechanisms of human sleep. There has been a massive increase in understanding the cellular basis of sleep, almost completely unknown just a few years ago, as the result of complex cellular manipulations performed in these organisms. It seems unlikely that model organisms will provide us with a "true" model of sleep disorders such as sleep apnea or narcolepsy, and their major utility may lie in being model organisms for understanding the cellular and genetic basis of sleep.

Besides enlightening our understanding of the cellular mechanisms controlling sleep, another area of interest with respect to the use of model organisms is the demonstration of positive and negative effects of social isolation or enrichment upon sleep. These findings suggest that greater attention should be devoted to exploring the impact of environmental factors in assessing human sleep problems. Furthermore, it would be of interest in these studies to determine in model organisms the effects of, for example, predation or threat on sleep in a controlled environment.

Treatments for Human Sleep Disorders Resulting from the Use of Model Organisms

Ideally, understanding the genetic and cellular mechanisms controlling human sleep would be fruitful in yielding more effective treatments for human sleep problems. There has been one recent addition to the armamentarium of sleeping medications, suvorexant, which was developed directly as the result of research in narcolepsy and the identification of orexigenic neurons in the expression of waking and sleep. The identification of salivary amylase as a marker for sleepiness which arose from cross-translational studies in drosophila and humans may also potentially find a practical use in the more widespread identification of sleepiness. With continued research into the details of sleep mechanisms revealed by the use of model organisms, it is anticipated that these findings will translate into practical applications.

Phylogenetic Studies and Human Sleep

The remarkable diversity in sleep behavior and electrophysiology in nonmammalian organisms has provided an array of clues which sheds light upon the understanding of normal and disturbed human sleep. One of the most interesting examples of diversity in animal sleep is the unihemispheric sleep of cetaceans which challenges the notion that sleep is a global state affecting all areas of the brain in the same manner and at the same time. Organisms which display unusual sleep-related behavior such as sleep swimming fish, cetaceans, and their offspring which do not exhibit behavioral sleep for several continuous months after birth, and the demonstration of prolonged, continuous flight in birds offer hints that there may be clues in nature for at least some human sleep complaints of short sleep. New monitoring techniques such as high-resolution video monitoring, in vivo calcium imaging, and multielectrode recording probes hold promise for more refined analyses of behavior and electrophysiology in nonmammalian species [110, 162, 163]. Additionally, behavioral and electrophysiological studies of animals in their own habitats utilizing new technologies will expand our understanding of the diversity of sleep.

Sleep studies in animals have unquestionably enhanced our appreciation of the behavioral, molecular, and environmental factors which govern the expression of sleep, and, in turn, these studies have provided insight into the factors influencing human sleep and its disorders. The biological symphony of sleep continues to be performed throughout nature, and ongoing scientific exploration on a variety of fronts will only continue to enlighten our understanding of this intricate, universal composition.

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Sleep and Anesthesia: Different States with Shared Pathophysiological Traits

10

David Hillman, Roop Kaw, and Ralph Lydic

Introduction

Although sleep and anesthesia are different states of consciousness, data from many laboratories now indicate that examining physiological traits in one state and elucidating the mechanisms that generate them can provide clinically useful insights into traits and underlying mechanisms in the other [1–6]. Breathing disorders are cases in point. Patients prone to upper airway obstruction or hypoventilation during sleep also have these tendencies during anesthesia, and the reverse is also true [7]. In this chapter, we consider similarities and differences between sleep and anesthesia, their neurophysiological bases and the implications for enhancing clinical care.

Sleep is a behavioral state of unconsciousness which is actively generated by the brain. It is an inhomogeneous state occurring in a variety of postures and comprising distinct stages, both of which influence breathing and other physiological functions. The states can be broadly divided into rapid eye movement (REM) sleep (named for the presence of rapid eye movements) and non-rapid eye movement (NREM) sleep. While, relative to wakefulness, muscle activation is diminished during NREM sleep, the changes are profound in REM sleep. A key feature of REM sleep is that spinal alpha motoneurons are hyperpolarized resulting in atonia of antigravity muscles and hypotonia of upper airway and respiratory pump muscles. These changes are fundamental to the vulnerability to upper airway obstruction and hypoventilation that occurs during sleep, particularly REM sleep, in predisposed individuals.

Reconciliation of fossil evidence with molecular clock analyses indicates that mammals first appeared about 60 million years ago [8]. It is notable that all placental, terrestrial mammals exhibit two distinct states of sleep, an evolutionary perspective suggesting that mammalian brains evolved neural networks for generating states of sleep from their earliest origins. In contrast, the history of anesthesia is brief, with the first successful human anesthesia occurring approximately 170 years ago. Anesthetic molecules, therefore, have existed for about three ten thousanths of one percent of mammalian history. The absence of any evolutionary pressure to evolve an anesthesia center in the brain favors the shared circuits hypothesis that anesthetic molecules cause loss of wakefulness by acting on sleep-generating neuronal systems [6, 9, 10].

This is a relatively recent notion as it was believed for much of the twentieth century that anesthetic drugs exerted their action through effects on neuronal cell membranes. This more recent ligand-based theory postulates anesthetic activation of pathways involved in the production of sleep and wakefulness [2, 11–13]. Particular attention has been given to GABA-a-mediated pathways [6]. A parallel advance has come from evidence provided from many sources, suggesting that no single brain region generates states of sleep and wakefulness [3, 14, 15]. Studies of the role of signal transduction pathways in causing states of sleep and anesthesia show that proteins referred to as regulators of G protein signaling (RGS proteins) modulate sleep disruption caused by isoflurane and sevoflurane anesthesia [16].

Human brain imaging data (Fig. 10.1) illustrate the regions and neuronal networks that are altered during states of sleep and wakefulness, as well as during states of anesthesia [17]. While postulation of a sleep center has simplifying appeal, the changes illustrated by Fig. 10.1 and an extensive literature fail to support the primacy of any particular brain center-generating states of anesthesia or sleep [3]. Thus, the notion of sleep centers has been supplanted by a view that future advances will come from a deeper

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understanding of network dynamics. This consideration is not limited to sleep neurobiology. For example, efforts to understand respiratory rhythm generation also incorporate network analyses [18].

The construction of mathematical and conceptual models that attempt to describe the generation of sleep or respiratory rhythms also must confront the difficulty in phase switching from sleep to wakefulness or from inspiration to expiration. One promising advance that may help understand phase switching is the discovery of an evolutionarily conserved feature of the central nervous system that functions to resist changes in states of behavioral arousal [4]. Data from fruit fly demonstrate a genetic basis underlying the neural inertia that resists phase switching from one bistable state (wakefulness) to another (anesthesia) [5].

Among vertebrate mammals facets of the shared neurophysiology underlying the generation of sleep and anesthesia may help explain the similar effects that sleep and anesthesia have on other physiological traits, including muscle activation and ventilatory control. The elimination of wakeful cortical influences reduced reflex gain and decreased ventilatory drive seen in both states predisposes to upper airway obstruction and/or hypoventilation, with individuals vulnerable to these problems in one state being at high risk of them in the other. The shared neurophysiology may also help explain other similarities between the states including the suggestion that anesthesia (unmodified by surgery and pain) may have some sleep-like restorative powers, as has been demonstrated in rodents (although not in Drosophila) [19, 20]. Furthermore, better understanding of this shared neurophysiology informs efforts to devise sedative drugs that induce a more sleep-like restorative state, particularly for use in sleep-challenging environments such as ICU. Sleep loss in such circumstances appears to be a significant factor in the production of postoperative delirium, and dexmedetomidine is an example of a drug with sleep-like sedative actions that exhibits promise in managing this difficult syndrome [21].

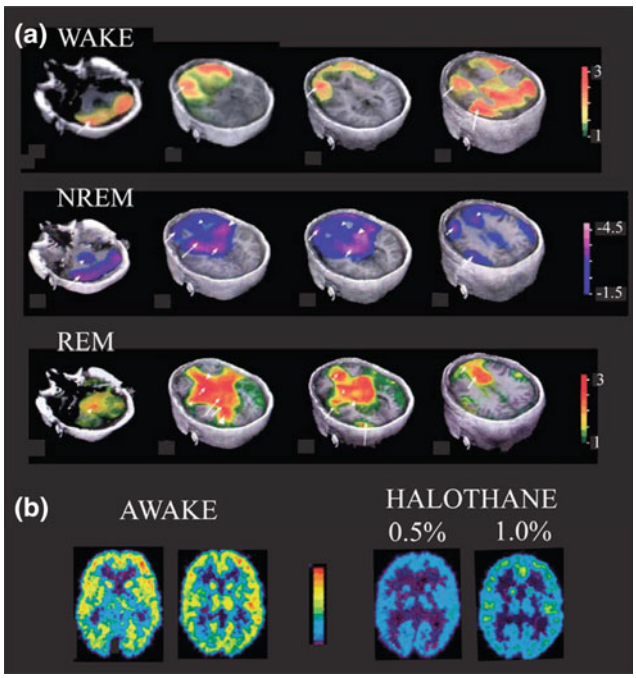

Fig. 10.1 Human brain imaging with positron emission tomography (*PET*) reveals anatomically distributed changes in brain function across states of arousal**. a** PET imaging of cerebral blood flow (*CBF*) in 37 humans during states of wakefulness, NREM sleep and REM sleep. *Yellow* and *red colors* indicate increases in CBF, whereas *blue* and *purple* indicate decreases in CBF. Modified from Braun [65]. **b** PET measures using F-18 fluorodeoxyglucose illustrate widespread changes in brain metabolism caused by halothane anesthesia. Modified from Alkire [66]. These pioneering studies have been supported over the years by additional brain imaging data that demonstrate anatomically distributed changes in brain function across states of arousal rather than selective change in specific brain regions posited as centers for particular states of arousal

While sleep and anesthesia have these shared characteristics, based on activation of shared pathways, their most fundamental differences relate to mode of offset of these effects. Sleep is readily disrupted by environmental stimuli, physiological disturbance or psychological disequilibrium and reverses spontaneously when the need for it has been requited. The capacity to arouse protects the sleeping patient. In contrast, suppression of arousal is a basic aim of general anesthesia. This makes the anesthetized patient highly vulnerable and critically dependent on observation and, where indicated, intervention by others until rousability is reliably restored. As a drug-induced state of unconsciousness anesthesia requires drug elimination for its reversal. The drug-induced stability of the state precludes spontaneous arousal or awakening, or disturbance by psychological factors or environmental stimuli. Unlike sleep, with its variable stages and postures, anesthesia is a relatively homogenous state, although depth varies with anesthetic dose.

Furthermore, while the propensity for sleep increases with increased time awake and is subject to diurnal variation, increasing late at night, anesthesia is largely independent of these homeostatic and circadian influences. Not completely, though, there is some animal evidence for recovery from sleep deprivation during anesthesia and for lower anesthetic drug requirement during circadian periods of high sleep propensity than at less sleep conducive times of the day [19, 22] (Fig. 10.2).

Clinical Correlates: Anesthesia, Sleep and Breathing

(a) Upper Airway Collapsibility

Upper airway obstruction—partial and complete—during anesthesia and sleep is a consequence of the combination of

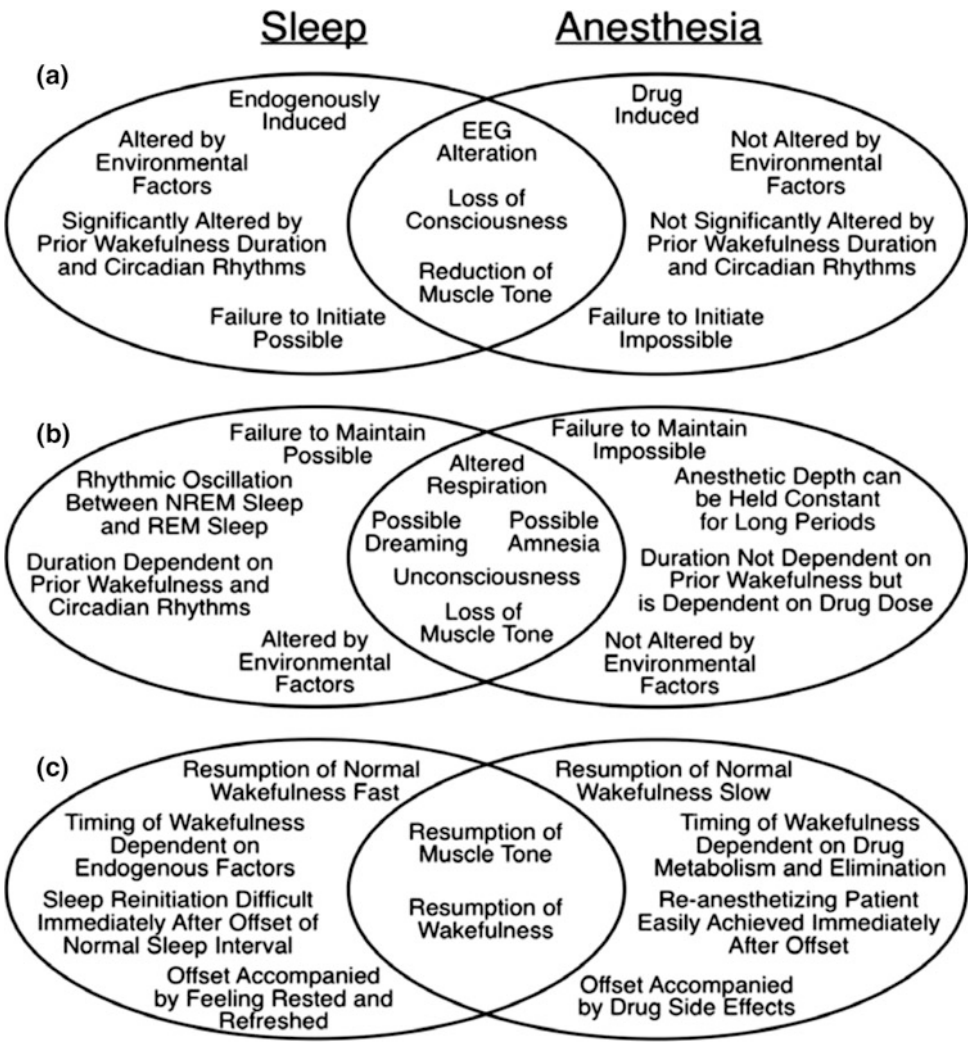

Fig. 10.2 Sleep and anesthesia: similarities and differences. Reproduced from Watson et al. [67], with permission

a narrow, anatomically predisposed airway and the permissive effect of state-related upper airway muscle relaxation, the degree of which varies with anesthetic depth or sleep stage (being most profound in REM sleep). Predisposing features acting to narrow the airway include: skeletal factors that constrict the skeletal confines, such as retrognathia; increased soft tissue around the pharynx, as in obesity and macroglossia; pharyngeal muscle weakness, as seen in many neuromuscular disorders; and as tonsillar and adenoidal hypertrophy. Familial issues also play a part: Some have inherently narrow pharynges. Further, it appears that upper airway neuromotor responses are impaired in OSA patients relative to controls; variability in collapsibility of the upper airway between individuals cannot be explained by structural loads alone [23, 24]. Certain postures also predispose to upper airway obstruction including recumbency, supine position and neck flexion. Alcohol, sedatives and opioids also exacerbate narrowing of the pharyngeal airway through their effects on pharyngeal muscle tone.

There are two main sites for obstruction in the pharynx: the velopharynx (that portion behind the soft palate) and the retrolingual hypopharynx. Indeed, the velopharynx—usually the narrowest segment of the pharynx—appears to be the primary site of obstruction in 80 % of events in both sleep and anesthesia. Increased collapsibility of the upper airway occurs quite abruptly with the encephalographic alpha–theta transition at sleep onset and with loss of consciousness/rousability during anesthetic induction [25, 26]. This emphasizes the importance of conscious state as a determinant of muscle activation.

Predicting those with narrow "difficult" upper airways is a time honored pursuit in anesthesia, mainly in relation to predicting difficult tracheal intubation. "Can't intubate, can't ventilate," where the patient cannot be tracheally intubated or ventilated by bag and mask after induction of anesthesia is a dreaded scenario and identifying patients at risk allows such problems to be circumvented (e.g., by awake intubation) or avoided (e.g., by use of regional anesthetic techniques rather than general anesthesia). Clinical predictors of

difficult intubation include oropharyngeal crowding (the Mallampati score) and a short thyromental distance (signifying micro- or retrognathia) [27]. These have also been found to be of value in predicting those with obstructive sleep apnea (OSA). Indeed, there is a close relationship between difficult intubation and the presence of OSA [28]. Furthermore, the tendencies to upper airway obstruction during anesthesia and during sleep are related [7]. Pharyngeal collapsibility under anesthesia is substantially higher among OSA patients than those without OSA [29]. An airway that proves "difficult" in one state tends to also be difficult during the other.

It follows that where such problems are noted in sleep or anesthesia, then implications for behavior in the other must be considered. For example, difficulty with intubation should prompt the anesthesiologist to consider whether the patient has OSA, as should increased propensity to upper airway obstruction during anesthesia or recovery. Similarly a history of OSA should alert the anesthesiologist of increased difficulty with airway management during anesthesia and increased risk of obstruction in the postoperative period. This risk is compounded by compromise of protective arousal responses by anesthetic, analgesic and sedative drugs during this time.

(b) OSA and Anesthesia

These issues emphasize the importance of identifying at-risk patients preoperatively. There is a growing literature documenting increased risk of perioperative cardiorespiratory complications in patients with OSA [30–32]. Particular risk appears to attend major surgery where there is a need for postoperative opioids and sedatives, presumably because of the depressant effects these can have on protective arousal responses. There is significant variability between individuals in their sensitivity to these depressant effects. Recently, it has been shown that in volunteers at high risk of OSA, nocturnal hypoxemia is associated with greater sensitivity to opioids, suggesting that increased potency of opioid analgesia could be a marker of its propensity to depress respiration during sleep [33].

Identifying OSA and predicting patients those most at risk of perioperative complications ("risk stratification") is a challenge for anesthesiologists. Important factors determining risk are likely to include degree of collapsibility of the relaxed upper airway, susceptibility to the depressant effects of analgesic and sedative drugs, and sensitivity of arousal responses in the case of an obstructive event. There is a general relationship between degree of airway collapsibility and apnea–hypopnea index (AHI), making this (as in sleep medicine) an important metric of severity [34]. However, the safety issues center on capacity to arouse from an obstructive event. The propensity to arousal failure might be better reflected by other metrics such as length of apneas and hypopneas and the degree of associated hypoxemia. Those individuals with lengthy apneas accompanied by deep desaturations on preoperative sleep study are of concern, as these characteristics suggest little tolerance for further depression of arousal [35]. It is notable that (in contrast to multiday surgery) outpatient surgery does not appear to be associated with demonstrable increased risk of postoperative adverse events in OSA patients [36]. This may reflect the fact that such patients, having emerged from anesthesia, are not exposed to the risk of re-suppression of arousal responses through postoperative administration of opioids and sedatives [37].

Obesity is an important OSA consideration in several ways. Besides being a risk factor for OSA, it predisposes to hypoventilation and to disordered gas exchange during sleep and anesthesia. Obesity-related reduction in functional residual capacity (FRC) when recumbent and asleep or anesthetized promotes atelectasis in the dependent regions of the lungs with consequent shunt. The reduction in FRC reduces oxygen stores in the lungs. Both these effects magnify the degree of desaturation observed during an obstructive event of a given duration [38].

Upper airway surgery presents additional risk for patients with OSA, as postoperative edema can temporarily further narrow the airway. Somewhat paradoxically, such problems can be seen in the early postoperative course following palatal surgery to treat snoring and OSA [39]. Children undergoing upper airway surgery for OSA present particular risks based on their small airway dimensions and low lung volumes relative to body size [40].

Because of its potential for perioperative problems and because its presence helps alert the anesthesiologist to the possibility of difficulties with airway maintenance intraoperatively, identifying OSA preoperatively is an important task. A popular tool is the acronymic Stop-BANG questionnaire, which asks 8 questions relating to OSA risk: the presence of loud **S**noring, daytime **T**iredness and lethargy, **O**bserved apneas, history of elevated blood **P**ressure, a **B**ody mass index of greater than 35 kg/m^2, **A**ge greater than 50 years, a **N**eck circumference more than 40 cm and male **G**ender [41, 42]. A positive response to 5 or more of these questions indicates high risk of OSA, while a score of 3–4 indicates intermediate risk. A problem with the questionnaire is that while highly sensitive for the presence of OSA, it is relatively non-specific. This together with a high community prevalence of OSA means that it designates many patients as at risk, with a high rate of false positives. This leaves anesthesiologists with a dilemma: which patients justify extra resources perioperatively? How do they risk stratify? The answers are not yet clear, but factors such as severity of

OSA, inherent arousal thresholds, postoperative opioid and sedative requirements, sensitivity to the depressant effects of these, and presence of comorbidities including obesity and vascular disease are all likely to be influential.

Current guidelines for the perioperative management of OSA are understandably cautious [43]. Some general principles apply (Table 10.1). Circumventing the difficulties associated with general anesthesia and postoperative sedative and analgesic by use of regional anesthetic/analgesic techniques is an attractive option if appropriate for the surgical procedure [44]. Where general anesthesia is required, then use of anesthetic drugs that readily reverse at the end of the procedure and, where possible, use of non-opioid analgesics following it are likely to help. Close observation is required until the patient is sentient and not likely to be exposed to further treatments which have potential to compromise arousal. Availability and use of positive airway pressure (PAP) therapies postoperatively are further tenet. These treatments are much more easily implemented if the patient already has some familiarity with them. This provides a strong rationale for preoperative diagnosis and initiation of treatment where practicable.

(c) Sleep Hypoventilation and Type 2 Respiratory Failure

Besides OSA, another major category of sleep-disordered breathing is (non-obstructive) sleep hypoventilation. The sleep-associated decrease in ventilatory drive, a consequence of the combination of loss of the stimulatory effects of wakefulness and a specific state-related down-regulation of hypercapnic and hypoxic ventilatory responses, ensures that any disorder with the potential for hypoventilation is exacerbated by sleep, particularly REM sleep where ventilatory drive is at its nadir. Such disorders have in common an imbalance between the load on respiratory muscles and their capacity to cope with these loads. Common examples of conditions that increase the load on muscles include obesity and advanced lung diseases such as chronic obstructive pulmonary disease. Conditions that decrease their capacity to cope include a wide variety of neuromuscular disorders affecting the respiratory (and upper airway) muscles, high spinal injuries, diaphragmatic palsy and the inefficiencies associated with the low flat diaphragm of emphysema and use of respiratory depressant drugs. Emphysema is an example of a condition that both loads the muscles (by increasing airway resistance) and decreases their capacity to cope (through the hyperinflation-associated decrease in inspiratory muscle mechanical advantage). Often hypoventilation coexists with upper airway obstruction, as is the case in obesity hypoventilation syndrome and in neuromuscular disorders that involve both upper airway and respiratory pump muscles. Obesity hypoventilation is common in obese patients with OSA: a recent meta-analysis of more than 4000 such patients demonstrated that 19 % of them had daytime hypercapnia, fulfilling the criteria for obesity hypoventilation syndrome [45].

Where there is a gross imbalance between load on respiratory muscles and their capacity to cope, a state of type 2 (hypercapnic) ventilatory failure exists and continuous mechanical ventilatory support is required. In conditions associated with a slow evolution in this imbalance (such as progressive neuromuscular problems or obesity), sleep hypoventilation may precede daytime respiratory failure by months or years [46]. Indeed sleep hypoventilation is both a harbinger of wakeful type 2 respiratory failure and a contributor to its evolution. The hypercapnia and hypoxemia that occur with significant sleep hypoventilation cause a loss of sensitivity to these ventilatory stimulants, through buffering of hypercapnia-associated decreases in extracellular pH levels

Table 10.1 Principles for perioperative management of patients with OSA

Principles for perioperative management of patients with OSA
• Assess risk of OSA preoperatively by systematic enquiry
• When probability of previously undiagnosed OSA is high, refer patients for preoperative sleep evaluation if surgery is elective and there is a likely need for postoperative opioids or sedation
• Where OSA has been previously diagnosed and the patient is compliant with CPAP, ensure it is available for perioperative use
• Where previously diagnosed but not compliant with CPAP, reinstruct in its use
• Avoid sedative premedication
• Use regional anesthesia and analgesia where practicable
• When general anesthesia is used, be prepared for difficult intubation and other difficulties in airway maintenance. Use techniques that allow early return of consciousness
• Minimize postoperative sedation
• Ensure CPAP is available for early postoperative use
• Observe in a high-dependency unit with continuous monitoring of respiratory parameters (oximetry, oro-nasal airflow) until the patient is sentient and able to self-administer CPAP. Patients requiring ongoing opioids or sedation should remain in a high-dependency area until this need abates
• Use lateral positioning, a nasopharyngeal airway, and oxygen therapy where CPAP is refused and upper airway obstruction is problematic
• Consider OSA in patients who encounter difficulties with airway management perioperatively. Inform the patient and refer for investigation for the possibility where clinically indicated

and roll-off of hypoxic responsiveness. Intervention along this evolutionary pathway with bi-level ventilatory assistance, delivered noninvasively during sleep, can prevent or reverse daytime respiratory failure where the imbalance between load and capacity on muscles is of moderate degree [46].

Not surprisingly, given their similar effects on ventilatory drive, the same problems predispose to hypoventilation during anesthesia where spontaneous ventilation is preserved. Despite this, sleep hypoventilation has not yet been seriously examined as a risk factor for postoperative respiratory complications, including respiratory failure. However, a recent retrospective study has shown that most patients with obesity hypoventilation syndrome are unrecognized at the time of elective surgery and that they are at substantially greater risk of respiratory failure after elective surgery than patients with OSA alone (44.4 vs. 2.6 %) [30]. Where postoperative respiratory failure occurs, the possibility of sleep-related hypoventilation should be considered, particularly where predispositions exist and where there is not an acute event (such a pneumonia or pulmonary edema) to explain it. Such patients often require bi-level ventilatory assistance rather than CPAP. An empiric inspiratory PAP of 16–18 cm H_2O and expiratory PAP of 9–10 cm H_2O can be used to initiate therapy to overcome upper airway obstruction and improve ventilation with subsequent titration conducted according to therapeutic response [42].

(d) Periodic Breathing

Besides OSA and sleep hypoventilation, a further form of sleep-disordered breathing is periodic breathing. While this can also be present during wakefulness, it is always worse during, and often confined to, sleep because wakefulness provides its own stimulatory, dampening effect on periodicity [47]. It can take the form of Cheyne–Stokes respiration where there is regular waxing and waning of ventilation, as seen in heart failure and cerebrovascular disease, or ataxic (Biot's) breathing where the waxing/waning pattern is irregular, as seen with chronic opioid use. The combination of periodic breathing and OSA is a form of "complex" sleep apnea. It is notable that untreated OSA aggravates heart failure and so the problems of OSA and periodic breathing may not only coexist, but also be inter-dependent.

At a fundamental level, irregular breathing occurs because of: increased ventilatory responsiveness to hypercapnia or hypoxia (as may occur, for example, following a cerebrovascular accident); loss of dampening effects on changes in blood gas tensions with small changes in ventilation (as may occur in the presence of low lung volume associated with reduced O_2 and CO_2 stores or at altitude); or prolonged delays in feedback between the effects of changes in ventilation and the chemoreceptor responsible for modulating them (as may occur with the increased circulation times of cardiac failure).

This instability in ventilatory drive affects the upper airway muscles as well as the respiratory pump muscles. Hence, periodic breathing and upper airway obstruction frequently coexist. These problems are of relevance to anesthesiology, both as this instability represents a potential for postoperative ventilatory instability and because it alerts to the possibility of an underlying disorder requiring independent evaluation. For example, breathing periodicity during sleep is frequently seen in low cardiac output states with approximately 50 % of those with an ejection fraction of <45 % having this problem [48].

Irregular breathing patterns are also frequently seen with chronic opioid use [49]. While the mechanism for this remains to be fully elucidated, one possibility is that while hypercapnic ventilatory responsiveness is depressed (as it is with acute opioid use), the depression of hypoxic ventilatory responses seen acutely gives way to a long-term increase in hypoxic responsiveness. This has a destabilizing effect on ventilation. The influence of these changes on ventilation during and after anesthesia, particularly if additional opioids are required, remains to be defined, but the underlying instability in breathing pattern generation suggests a potential for postoperative ventilatory problems [50]. Ongoing efforts to understand the mechanisms by which opioids depress breathing aim to localize brain sites and cellular substrates of opiate action. Respiratory depression caused by opiates can be caused, in part, by G protein-gated inwardly rectifying potassium channels (GIRK channels) [51].

Periodic breathing can be addressed using a PAP therapy known as adaptive servo ventilation. This applies increased pressure support during the waning hypoventilatory phase of the periodic breathing, decreasing it during the waxing hyperventilatory phase. Combined with positive end expiratory pressure, this therapy can pneumatically splint the upper airway, provide pressure support and act to dampen the periodicity.

(e) Disordered Gas Exchange

In addition to the problems discussed to this point, which have substantial obstructive and/or hypoventilatory components, gas exchange is also compromised during sleep and anesthesia as a result of recumbency and a state-related decrease in inspiratory muscle activation. These changes lead to a decrease in FRC at sleep onset and with induction of anesthesia [52, 53]. The magnitude of the reduction is variable between individuals, but generally of the order of 20 %. It can be much greater with obesity. In the morbidly obese, FRC can be well below closing volume, the lung volume at and below which airway closure occurs in the

dependent parts of the lung. In the most severe cases, FRC is close to residual volume [54]. Where FRC is less than closing volume, then airway closure (in the dependent parts of the lung) is present for at least part of the breathing cycle. The effect is to cause atelectasis and shunt with hypoxemia a prominent feature. In many cases of morbid obesity, this derangement is present in addition to hypercapnia consequent upon alveolar hypoventilation.

(f) Postoperative Delirium and Cognitive Decline

Sleep and sedative hypnosis have overlapping neuroimaging and EEG signatures. In activating the VLPO and inducing sleep through its alpha-adrenergic inhibition of the locus coeruleus, dexmedetomidine produces an EEG pattern akin to slow wave sleep wave NREM sleep. In contrast, sedatives such as benzodiazepines and low-dose propofol activate GABA receptors with little effect on noradrenergic activity [55]. An accompaniment of this appears to be that these agents create the potential for some persisting connectedness with the environment at low levels of consciousness, predisposing to an acute confusional state akin to delirium. Furthermore, disrupted sleep reduces cognitive reserve, and it appears that sleep disruption or restriction in the immediate perioperative period may precipitate delirium, particularly where cognitive reserves are low [56–58]. Longer-term sleep disruption, as with OSA, could also contribute to such a decline in cognitive reserves, and recent evidence suggests that it is a significant predictor of postoperative delirium [59, 60]. Apart from its capacity to disrupt sleep, OSA could also contribute to postoperative delirium indirectly through its pro-inflammatory tendencies and its relationship to metabolic syndrome. Recent literature points to a higher propensity for decline in cognitive function after non-cardiac surgery among patients with metabolic syndrome [61]. This has also been observed in a rat model of metabolic syndrome and attributed to dysregulation of the inflammatory response to surgery [62]. Data from in vitro studies support the interpretation that brain inflammation can up-regulate $GABA_A$ receptors and increase the sensitivity of some neurons to general anesthetics [63].

The notion that sleep could be an antidote to postoperative delirium is driving the quest for sedative drugs that induce natural or near-natural sleep particularly in sleep-challenging environments (such as critical care units) or circumstances (such as the first few days postoperatively). The concept of curtailing the noradrenergic stimulation has been recently proposed as an important aim in sedation to reduce the connectedness to the environment as in natural sleep. Dexmedetomidine is a promising agent in this respect, although there is evidence that dexmedetomidine-induced sedation differs significantly from sleep [21, 64]. Irrespective of this, sedative interventions cannot be at the cost of impairing arousal responses in those vulnerable to upper airway obstruction where the airway is unprotected.

Conclusions

Sleep and anesthesia are related states. Their shared influences on respiratory and upper airway function suggest that information from one state can be applied to the other and at-risk patients identified. These considerations extend beyond OSA to include sleep hypoventilation, periodic breathing and disordered gas exchange. Sleep disruption can also affect postoperative cognitive function, providing a further reason for identifying and dealing with sleep disorders preoperatively where the opportunity exists. Arousal suppression is a critical difference between the states. Patients with sleep-disordered breathing require close observation and, often, PAP therapies until sentient and no longer at risk of further periods of unconscious sedation.

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Physiological Changes of Sleep

11

Sudhansu Chokroverty

In 1958 when sleep medicine was in its infancy without fundamental understanding of the physiology and functions of sleep, Robin [1] stated that "there are a number of physiological differences between the sleeping and the waking state" and he concluded that "the interrelations between sleep and the pathologic physiology of disease constitute a fruitful field for a more complete understanding of many diseases." How right he was as reflected by fruitful research in sleep medicine decades later. A constellation of physiological changes are observed in humans which are distinctly different in three states of our existence (e.g., wakefulness, non-rapid eye movement [NREM] and rapid eye movement [REM] sleep) [2]. These sleep-related changes play an important role in energy conservation, memory consolidation and thermoregulation besides other functions, and are important to understand the pathophysiology of many primary sleep and medical disorders including critically ill patients in the intensive-care units with unstable hemodynamic, respiratory and immune mechanisms. A case in point is the implication of reduced upper airway dilator muscle tone in sleep causing upper airway collapse and obstructive sleep apnea (OSA) in susceptible individuals. In a similar manner stroke, myocardial infarction, cardiac arrhythmias and even sudden cardiac death may be related to profound changes occurring during REM sleep in late night and early morning hours.

Physiological changes are known to occur in both the somatic nervous system and the autonomic nervous system (ANS) during sleep. Important changes in the endocrine system and temperature regulation are also associated with sleep. This chapter provides a review of the physiological changes in the central somatic nervous system and the ANS, including changes in the respiratory, cardiovascular, and neuromuscular systems, and in the gastrointestinal tract during sleep contrasting these changes with the conditions in the waking state. Some attention is also given to thermal and endocrine regulation. For a discussion about cytokines, immune function and sleep factors as they relate to the physiological changes in sleep, the readers are referred to Chaps. 2 and 12. Tables 11.1, 11.2 and 11.3 summarize the physiological changes during wakefulness, NREM and REM) sleep. For a more detailed discussion, readers are referred to excellent reviews by Orem and Barnes [3] and Lydic and Biebuyck [4].

Changes in the Central Somatic Nervous System During Sleep

Sleep is not just a state of rest and repose; many areas of central nervous system (CNS) show excitation during sleep as demonstrated by intracellular electrophysiological studies, C-fos activation shown by immunohistochemical observations and positron emission tomographic (PET) scans of the brain. NREM sleep is characterized by enhanced activity of ventrolateral preoptic and median preoptic neurons in the anterior hypothalamic nuclei and to a certain extent also lower brainstem nucleus tractus solitarius (NTS); in contrast, the wake-promoting neurons in the ascending reticular activating system (ARAS), histaminergic, aminergic and orexinergic neurons as well as most of the cerebral cortical regions are deactivated. During REM sleep, much of the cortical regions are activated along with pontine areas controlling REM sleep coupled with a paralyzed body caused by excitation of motor atonia pathways in the brain stem and spinal cord. The combined alterations in the somatic CNS and the ANS (see further on) are responsible for vast physiological changes in the body systems and organs during sleep.

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Table 11.1 Summary of physiological changes in breathing during sleep

Parameters	Wakefulness	NREM sleep	REM sleep
Respiratory rate	Normal	Decreases	Variable, apnea may occur
Minute ventilation	Normal	Decreases	Decreases further
Alveolar ventilation	Normal	Decreases	Decreases further
$PaCO_2$	Normal	Increases slightly	Increases further slightly
PaO_2	Normal	Decreases slightly	Decreases further slightly
SaO_2	Normal	Decreases slightly	Decreases further
Hypoxic ventilatory response	Normal	Decreases	Decreases further
Hypercapnic ventilatory response	Normal	Decreases	Decreases further
Upper airway muscle tone	Normal	Decreases slightly	Decreases markedly or is absent
Upper airway resistance	Normal	Increases	Increases further

Table 11.2 Summary of physiological changes in heart and circulation

Physiological characteristics	NREM	REM
Heart rate	↓	↑↓
• Cardiac output	↓	↓↓
• Systematic arterial BP	↓	↓↑
– Dippers		
– Extreme dippers		
– Non-dippers		
– Reverse dippers		
• Pulmonary arterial BP	↑	↑
• Peripheral vascular resistance	—↓	↓
• Systematic blood flow		
– Cutaneous	—	↓
– Muscular	—	↓
– Mesenteric	—	↑
– Renal	—	↑
• Cerebral blood flow	↓	↑

↓ = Decreased; ↑ = Increased; ↓↑ = Uncertain; — = Unchanged

There are also changes in certain neural reflexes and cortical evoked potentials during sleep. The H-reflex, the electrical counterpart of monosynaptic muscle stretch reflex is decreased in amplitude because of motor neuron hyperpolarization, presynaptic inhibition and disfacilitation of brain stem aminergic and lateral hypothalamic orexinergic neurons projecting to brain stem motor and aminergic neurons as well as ventral horn cells of the spinal cord.

Polysynaptic reflexes which are useful in clinical studies include blink reflex and spinal flexor reflex. Certain components of these reflexes (R2) also decrease or are unobtainable during sleep. Babinski response (extensor plantar-response) which is absent in wakefulness in normal individuals may be elicited in sleep as a result of cerebral cortical inhibition and release of lower centers.

Somatosensory cortical evoked potentials (SEPs) attenuate during sleep, particularly during slow-wave sleep (SWS). Motor evoked potential (MEP) amplitude following magnetic brain stimulation also shows attenuation in all stages of sleep. There is an increased intracortical inhibition of interneurons in NREM sleep and decreased intracortical facilitation in REM sleep as determined by paired brain magnetic stimulation technique [5].

Neuroimaging studies have clearly shown areas of activation and deactivation of various regions of the brain during NREM and REM sleep, emphasizing that sleep is a variable and dynamic state and not simply a passive period in our life (see Chap. 21).

Clinical Relevance: In narcolepsy-cataplexy syndrome during cataplectic episodes, there is marked inhibition of

Table 11.3 Physiological changes during normal wakefulness and sleep in the gastrointestinal system

Physiological characteristics	Wakefulness	Sleep
Swallowing frequency	Normal	Decreased
Salivary flow	Normal	Decreased
Esophageal acid clearance time	Normal	Prolonged
Lower and upper esophageal sphincter pressure	Normal	Decreased
Esophageal peristaltic contractions	Normal	Decreased
Gastric motility	Normal	Decreased
Gastric acid secretion	Depends on food ingestion	Peak Secretion between 10 P.M. and 2 A.M.
Migrating motor complex (MMC) recurs every 90 min)	Normal velocity	Reduced velocity
Colonic motility	Normal	Decreased
Rectal motor activity and anal canal pressure	Normal	Increased periodic activity with retrograde propagation and higher anal canal pressure

monosynaptic reflexes including H-reflex. Blink reflex excitability study during cataplectic episodes may show facilitation of R2 component and impaired habituation suggesting involvement of brain stem interneurons in the pathogenesis of cataplectic motor phenomenon [6]. MEP amplitude during a cataplectic spell showed inconsistent results. One study documented persistence of MEP indicating enhanced cortical excitability [7], but another study [8] showed MEP amplitude attenuation. In RLS patients, spinal flexor reflex study during sleep disclosed hyperexcitability suggesting release of spinal motor centers from supraspinal inhibition [9].

Autonomic Nervous System and Sleep

Central Autonomic Network

The existence of a central autonomic network (CAN) in the brain stem with ascending and descending projections that are often reciprocally connected has been clearly shown by work done in the 1980s and 1990s (Figs. 11.1 and 11.2) [10 –11]. The NTS may be considered a central station in the CAN. The NTS, which is located in the dorsal region of the medulla ventral to the dorsal vagal nucleus, is the single most important structure of the autonomic network and is influenced by higher brain stem, diencephalon, forebrain, and neocortical regions (Fig. 11.3; see also Figs. 11.1 and 11.2). The NTS receives afferent fibers—from the cardiovascular system and the respiratory and gastrointestinal tracts—important for influencing autonomic control of cardiac rhythm and rate, circulation, respiration, and gastrointestinal motility and secretion (Fig. 11.4). Efferent projections arise from the NTS and are sent to the supramedullary structures, including hypothalamic and limbic regions, and to the ventral medulla, which exerts significant control over cardiovascular regulation [12–14]. The ventral medulla sends efferent projections to the intermediolateral neurons of the spinal cord (see Figs. 11.1 and 11.2). Box 11.1 lists afferent and efferent connections of NTS, considered a major central station of the CAN. The final common pathways from the NTS are the vagus nerve and sympathetic fibers, which send projections to the intermediolateral neurons of the spinal cord to orchestrate the CAN for integrating various autonomic functions that maintain internal homeostasis. The NTS also contains the lower brain stem hypnogenic and central respiratory neurons. Dysfunction of the ANS, therefore, may have a serious impact on human sleep and respiration.

Box 11.1. Afferent and Efferent Connections of Central Autonomic Network (CAN)

Nucleus tractus solitarius (NTS), the major central station of the CAN

- Afferents
  - Cardiovascular
  - Respiratory
  - Taste
  - Gastrointestinal
  - Descending projections from cerebrum and upper brain stem
- Efferents
  - Ventral medulla
  - Intermediolateral neurons
  - Inspiratory neurons

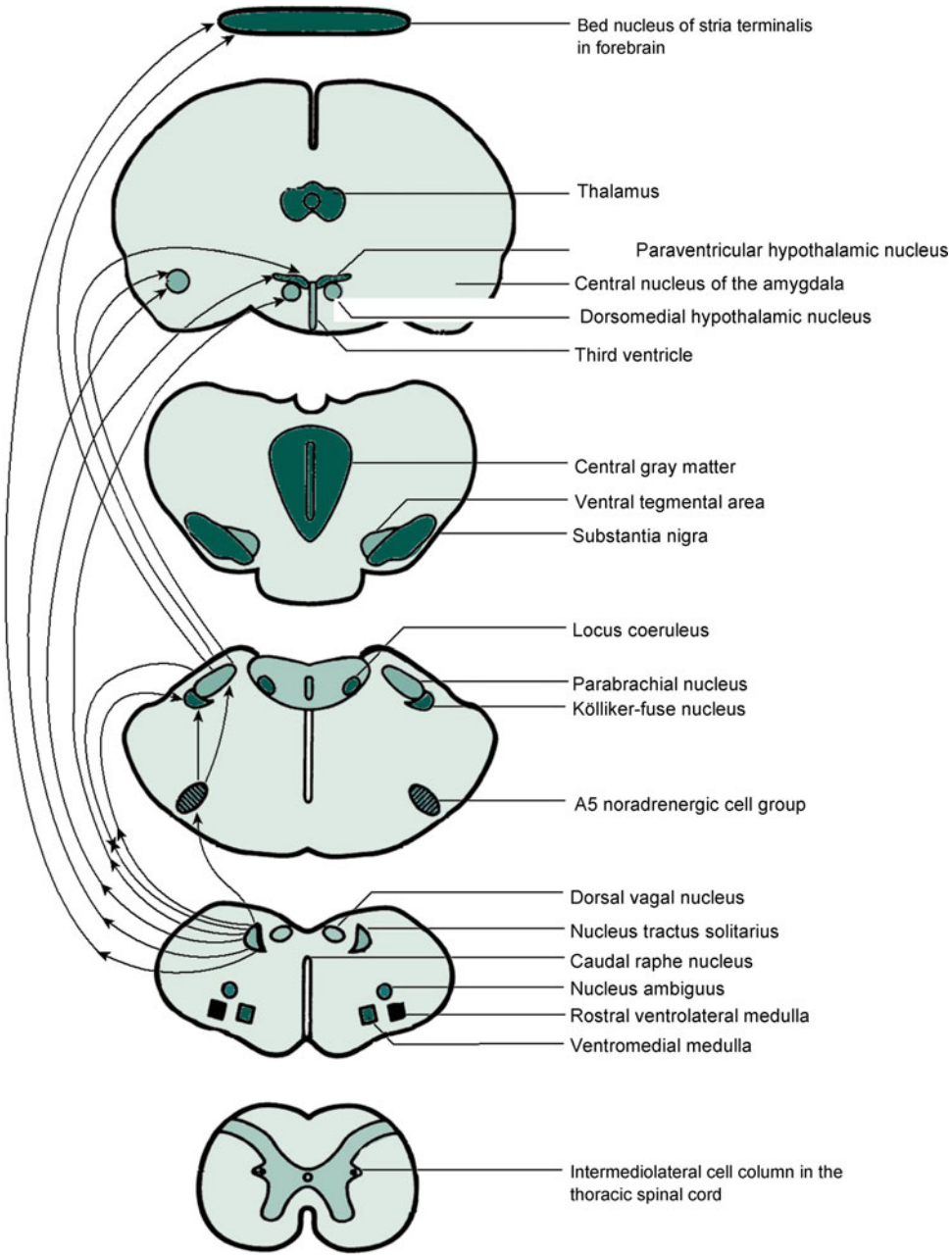

Fig. 11.1 The ascending projections from the central autonomic network (Reprinted with permission from Chokroverty [15])

- Vagal efferents to cardiovascular, respiratory and gastrointestinal systems
- Ascending projections to upper brain stem and cerebrum.

The cardiovascular system and respiration play significant roles in the maintenance of the internal homeostasis in human beings [13– 17]. Cardiovascular control in humans is maintained reflexively, involving peripheral receptors in the heart and blood vessels with afferents to the CNS and efferents to the heart and blood vessels. Sympathetic preganglionic neurons regulating the cardiovascular system are located predominantly (90 %) in the intermediolateral neurons of the thoracic spinal cord, with a small number (10 %) in the adjacent spinal structures. Parasympathetic preganglionic neurons controlling the heart and circulation are located in the nucleus ambiguus as well as in the dorsal

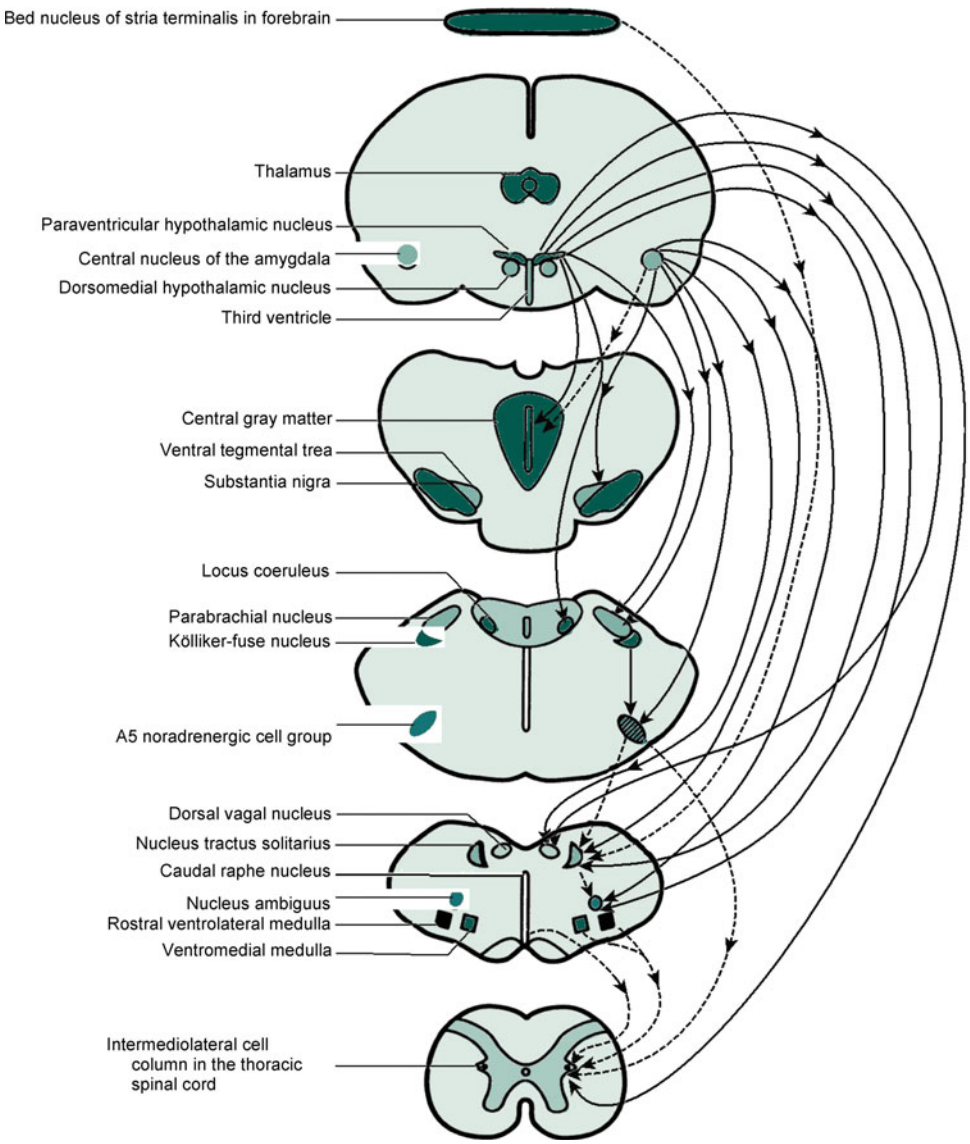

Fig. 11.2 The descending projections from the central autonomic network (Reprinted with permission from Chokroverty [15])

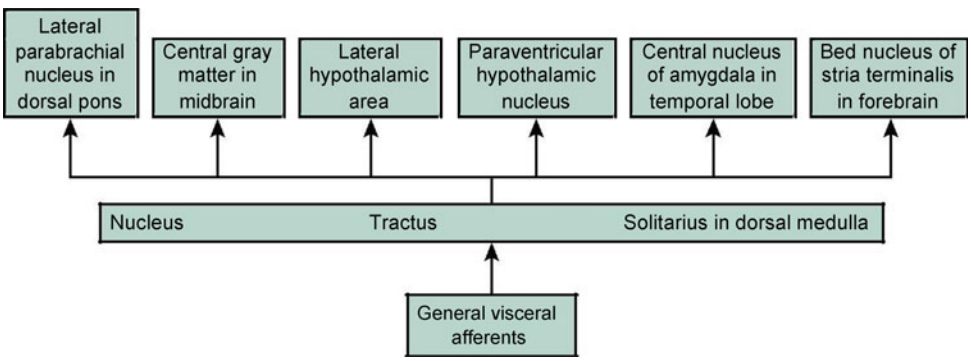

Fig. 11.3 Schematic diagram of central autonomic network: ascending projections from nucleus tractus solitarius (Reproduced with permission from Chokroverty [16])

motor nucleus of the vagus in the medulla. Sympathetic preganglionic neurons in the intermediolateral column of the spinal cord as well as parasympathetic preganglionic neurons in the nucleus ambiguus and dorsal motor nucleus of the vagus are the central determinants of cardiovascular regulation. Both the sympathetic and parasympathetic preganglionic neurons have extensive connections to the CAN, which in turn is influenced by peripheral afferents (Fig. 11.5;

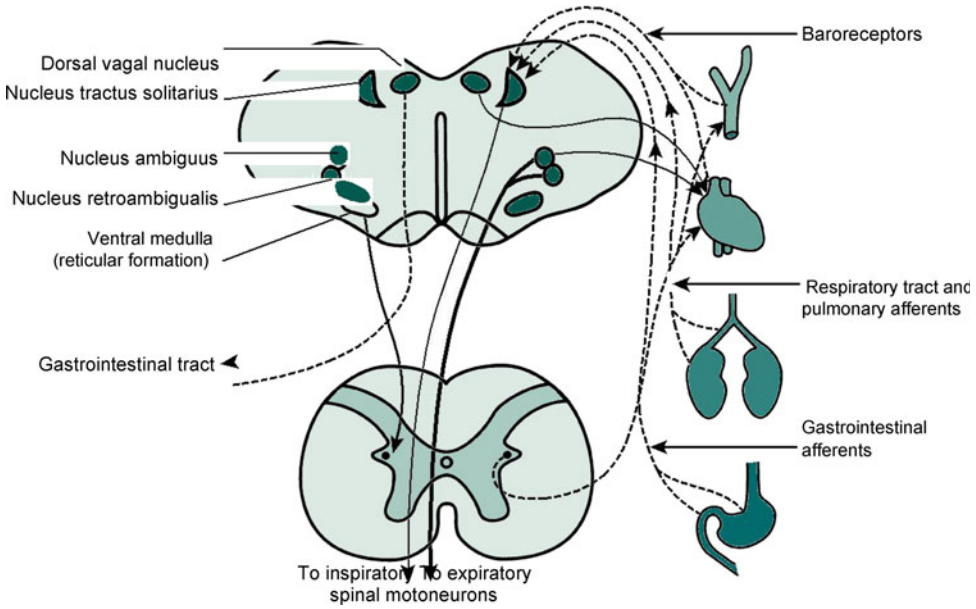

Fig. 11.4 The visceral afferents to and efferents from the nucleus tractus solitarius (Reprinted with permission from Chokroverty [15])

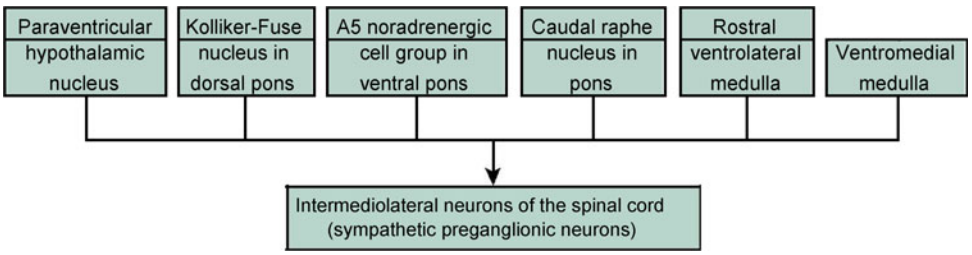

Fig. 11.5 Schematic diagram showing descending hypothalamic and brain stem inputs to intermediolateral neurons in the spinal cord (Reprinted with permission from Chokroverty [15])

see also Figs. 11.1, 11.2, 11.3, 11.4). There is direct projection from the hypothalamic paraventricular nucleus (PVN) to sympathetic preganglionic neurons in the spinal cord (see Figs. 11.2 and 11.5).

Autonomic Changes During Sleep

During sleep in normal individuals, there are profound changes in the functions of the ANS [10, 12, 18–25] (See Box 11.2). Most of the autonomic changes that occur during sleep involve the heart, circulation, respiration, and thermal regulation. There are also pupillary changes. Pupilloconstriction occurs during NREM sleep which persists after preganglionic sympathectomy and is maintained during REM sleep due to tonic parasympathetic drive. Phasic dilation during phasic REM sleep results from central inhibition of parasympathetic outflow to the iris.

Box 11.2. Functional Changes in the AUTONOMIC NERVOUS SYSTEM DURING SLEEP

- NREM Sleep
  - Increased parasympathetic activity
  - Decreased sympathetic activity
  - Decreased low-frequency (LF) components reflecting decreased sympathetic tone but increased high frequency (HF) components reflecting increased respiratory vagal tone
- REM Sleep
  - Further increase in parasympathetic activity

- More marked decrease in sympathetic activity
- Intermittent bursts of sympathetic activity in phasic rapid eye movements
- Profound increase in sympathetic activity in skin and muscle vessels (microneurographic recordings)
- Variable LF and HF with decreased HF and intermittent increment of LF components.

Autonomic functions during wakefulness must be compared to those during sleep to understand ANS changes in sleep [18]. The basic ANS changes during sleep include increased parasympathetic tone and decreased sympathetic activity during NREM sleep accompanied by a reduction of circulating levels of norepinephrine and epinephrine. During REM sleep, there is further increase in parasympathetic tone and further decrease of sympathetic activity; intermittently, however, there is an increase in sympathetic activity during phasic REM sleep resulting in swings in BP and HR causing tachy–brady arrhythmias. The ANS changes during sleep can be assessed by measuring heart rate variability (HRV) [26]. The indices of HRV can be documented by fast Fourier transform showing power in the following bands: HF, LF, very low frequency (VLF), and ultra low frequency (ULF). HF band power ranges from 0.15 to 0.4 Hz. The power in the LF band ranges between 0.04 and 0.15 Hz. The VLF band power ranges from 0.003 to 0.04 Hz, and the power in the ULF band is 0.003 Hz or less. The major contributor of the HF component is the efferent vagal activity. The LF component is thought to be a marker of sympathetic modulation by some authors [27, 28], whereas others [29, 30] considered this to contain both sympathetic and vagal influences. Therefore, the LF/HF ratio is thought to reflect sympathovagal balance [28, 29]. The significance of VLF and ULF components remains uncertain, but these may be markers of humoral and hormonal fluctuations. Both spectral components and direct nerve recordings (see below) show that the HF component predominates during NREM and the LF component predominates during REM sleep. During NREM sleep, the LF component decreases, whereas the HF component increases, reflecting increased vagal tone. In contrast, during REM sleep, extreme variation in LF and HF with increased LF and decreased HF components is noted. The heart rate (HR) changes precede electroencephalographic (EEG) changes during transition of sleep states. HRV is similar in presleep and intrasleep wake periods. It should be further noted that the HF component mainly reflects the respiration–vagal modulation of sinus rhythm, whereas the nonrespiratory LF component reflects the sympathetic modulation of the heart in addition to baroreflex responsiveness to beat-to-beat variations in blood pressure (BP) [31,32]. Power spectrum analysis of normal subjects at sleep onset by Shiner et al. [33] showed that the wake/sleep transition period represents a transitional process between two physiologically different states, with a decrement of LF power and unchanged HF power causing a decrement of the LF/HF ratio reflecting a shift toward parasympathetic predominance. Thus, NREM sleep can be considered as a state of relative cardiorespiratory stability, whereas REM sleep is a state of profound instability with an intense autonomic and respiratory dysregulation. In a recent study, Richard et al. [34] pointed to the effect of gender on autonomic and respiratory responses during sleep. They noted that, in women, there was a greater NREM-to-REM increment in LF, a greater decrement in HF, and a greater increment in LF/HF power. NREM-to-REM excitatory cardiorespiratory responses are, therefore, more marked among women compared to men.

There is also a profound change of sympathetic activity in muscle and skin blood vessels. Microneurographic technique measures peripheral sympathetic nerve activity in the muscle and skin vascular beds. The technique permits direct intraneural recording of efferent sympathetic nerve activity involving the muscle and skin blood vessels by using tungsten microelectrodes [35–39]. Muscle sympathetic nerve activity is reduced by 10–30 % in stages N1 and N2 sleep and by 30–50 % from wakefulness to SWS, but increases to levels above waking values during REM sleep [38]. Although sympathetic nerve activity increases in the skeletal muscle vessels (vasoconstriction) during REM sleep, the sympathetic drive decreases in the splanchnic and renal circulation (vasodilation) [38]. Sympathetic nerve activity is lower during NREM sleep than during wakefulness but increases above the waking level during REM sleep, particularly during phasic REM sleep (Fig. 11.6). During the arousal and appearance of K complexes in NREM sleep, the bursts of sympathetic activity transiently increase.

Clinical Relevance

The implications of changes in the ANS during sleep in humans are profound. Reduced HRV may be noted in patients with myocardial infarction, cardiac transplantation, and diabetic autonomic neuropathy [26, 27, 30, 40, 41]. There is a significant relationship between the ANS and cardiovascular mortality, including sudden cardiac death. Lethal arrhythmias are related to either increased sympathetic activity or decreased vagal activity. HRV (e.g., reduced HRV) is a strong and independent predictor of mortality after acute myocardial infarction. HRV study thus has potential for assessment of ANS fluctuations in patients

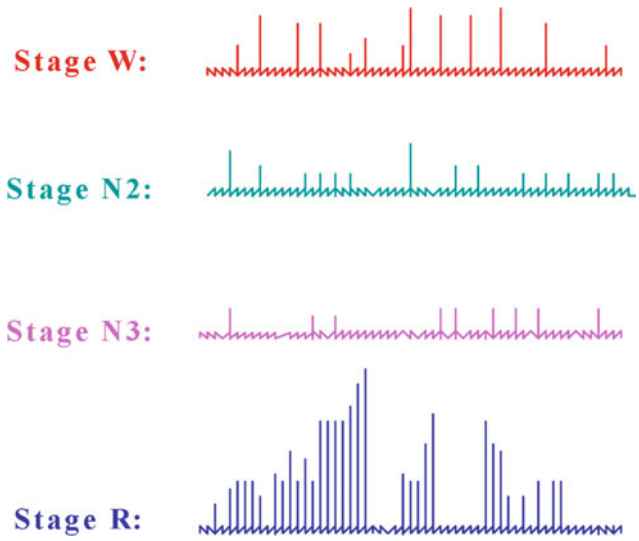

Fig. 11.6 Sympathetic nerve activity (SNA) during wakefulness (W), NREM sleep (Stages N1 an N2) and REM sleep (Stage R) in a normal subject shown schematically. Progressive decrement of SNA from W to Stage N2 and Stage N3 but marked increment in Stage R (Adapted from: Somers et al. [38])

with cardiovascular and noncardiovascular disorders and may help us understand physiological phenomena, disease mechanisms, and effects of medications. Furthermore, disorders of the ANS in humans, such as multiple systems atrophy, familial dysautonomia, and secondary autonomic failure (see Chap. 41), adversely affect respiratory and cardiovascular functions during sleep. A number of human sleep disorders may affect autonomic functions (e.g., obstructive sleep apnea syndrome (OSAS), cluster headache, sleep terrors, REM sleep behavior disorder and narcolepsy [25, 42, 43]). Thus, significant sleep-related changes in the ANS affecting the circulatory, respiratory, gastrointestinal, and urogenital systems have important clinical implications in patients with central or peripheral autonomic failure (e.g., sleep-related respiratory dysrhythmias, cardiac arrhythmias, gastrointestinal dysmotility and urogenital disorders). Thus, there is a bidirectional relationship between the ANS and sleep: autonomic changes can alter sleep regulation and in turn sleep disturbances can affect the ANS.

In patients with OSAS, chronic sympathetic hyperactivity is thought to play a major role in linking OSAS with hypertension, cardiac ischemia, congestive cardiac failure and stroke [41, 42]. A variety of cardiovascular reflex tests measuring HR and BP changes to special maneuvers (e.g., head-up tilt, valsalva maneuver, deep breathing, hand grip, cold face, cold pressor and mental arithmetic tests) can detect integrity of sympathetic and parasympathetic divisions of the ANS as well as baroreflex [23, 43]. Baroreflex is an important mechanism to maintain BP homeostasis [22–25]. Baroreflex function [44, 45] can be evaluated by an indirect technique of baroreflex sensitivity (BRS) which is defined as change in HR per unit change in arterial BP [23, 24]. The slope of the changes in RR interval (or HR) in relation to BP changes determines BRS which indirectly assesses baroreflex function. BRS is increased during NREM sleep as result of resetting of baroreflex function, and this results in slowing of the HR despite a decrement of BP [22, 23, 43, 45].

Other tests to evaluate ANS function included HR spectral analysis of HRV and recording of muscle and skin sympathetic nerve activity (MSNA and SSNA) using tungsten microelectrodes inserted into the peroneal and median nerves [38]. Additionally, imaging studies are available such as MIBG scintigraphy [46] to assess cardiac sympathetic innervation, which is impaired in post ganglionic cardiovascular autonomic disorders.

Respiration and Sleep

Functional Neuroanatomy of Respiration

In order to understand the control of breathing, it is essential to have a basic knowledge about the functions of breathing, the functional anatomy of breath, and control of respiration during wakefulness and asleep. The function of breathing is to maintain an adequate alveolar ventilation and diffusion across the alveolar capillary membranes (i.e., elimination of carbon dioxide [CO_2] to and supply of oxygen [O_2] from the atmospheric air containing 21 % O_2 78 % nitrogen, and 1 % other inert gases), and to maintain arteriolar homeostasis (i.e., normal partial pressure of oxygen [PO_2] and carbon dioxide [PCO_2]). An adequate pulmonary circulation is essential to complete the processes of alveolar ventilation and diffusion. The respiratory system consists of three interrelated and integrated components: central controllers located in the medulla aided by the supramedullary structures, including forebrain, peripheral chemoreceptors, and pulmonary and upper airway receptors; the thoracic bellows, consisting of respiratory and other thoracic muscles and their innervation and bones; and the lungs, including the airways.

In 1812, Legallois [47] discovered that breathing depends on a circumscribed region of the medulla. After an intensive period of research in the nineteenth century on the respiratory centers, in the twentieth century, Lumsden [48, 49], and later Pitts et al. [50], laid the foundation for modern concepts of the central respiratory neuronal networks. Based on

sectioning at different levels of the brain stem of cats, Lumsden [48, 49] proposed pneumotaxic and apneustic centers in the pons and expiratory and gasping centers in the medulla. Later, Pitts' group [50] concluded from experiments with cats that the inspiratory and expiratory centers were located in the medullary reticular formation.

Upper brain stem respiratory neurons are located in the rostral pons, in the region of the parabrachial and Kölliker-Fuse nuclei (pneumotaxic center), and in the dorsolateral region of the lower pons (apneustic center) [51]. These two centers influence the automatic medullary respiratory neurons, which comprise two principal groups [51–59]. The dorsal respiratory group (DRG) located in the NTS is responsible principally, but not exclusively, for inspiration, and the ventral respiratory group (VRG) located in the region of the nucleus ambiguus and retroambigualis is responsible for both inspiration and expiration (Fig. 11.7). The VRG contains the Botzinger complex in the rostral region and the pre-Botzinger region immediately below the Botzinger complex, responsible mainly for the automatic respiratory rhythmicity as these neurons have intrinsic pacemaker activity. These respiratory premotor neurons in the DRG and VRG send axons that decussate below the obex and descend in the reticulospinal tracts in the ventrolateral cervical spinal cord to form synapses with the spinal respiratory motor neurons innervating the various respiratory muscles (see Figs. 11.3 and 11.4). Respiratory central pattern generator (RPG) [60] includes neurons in the dorsolateral pons (e.g., parabrachial [PB], and Kolliker-Fuse [KF] nuclei in this region), NTS and ventrolateral medulla (Ventral respiratory group [VRG]). Box 11.3 summarizes functions of various respiratory neurons [60]. The site of central chemoreceptor zone is not definitely known but most likely located in the retrotrapezoid nucleus (RTN) in the rostral medulla (part of the parafacial nucleus) between the facial nucleus in the lower pons and the ventral surface of the medulla, and contains glutamatergic neurons [61, 62]. RTN neurons innervate also the brainstem area containing the RPG [61]. The neurons in the arcuate nucleus at the ventromedial aspect of the medullary pyramid may also have a role in central chemosensitivity and respiratory frequency [60].

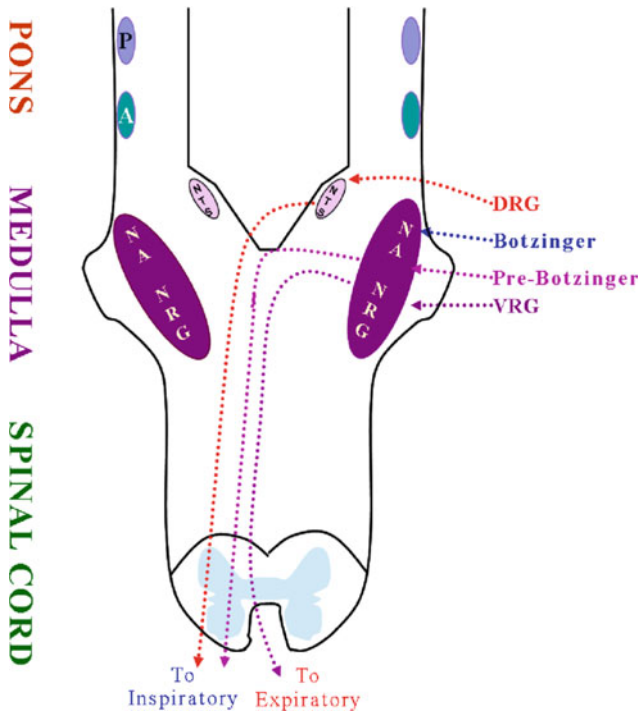

Fig. 11.7 Schematic representation of central respiratory neurons in Pons and Medulla. *DRG* Dorsal respiratory group with projections to contralateral predominantly inspiratory muscles. *VRG* Ventral respiratory group with projections to contralateral inspiratory and expiratory muscles. *P* Pneumotaxic center; *A* Apneustic center. See text for further details

Box 11.3. Functions of Respiratory neurons [60]

- PB and KF nuclei control the phase-switch between inspiration and expiration.
- The NTS is the primary relay station for medullary reflexes controlling respiration.
- The Botzinger complex (in the VRG) contains expiratory neurons.
- The pre-Botzinger complex is responsive for respiratory rhythm generation.
- The rostral VRG contains inspiratory neurons.
- The caudal VRG contains expiratory neurons.
- The DRG contains mainly, but not exclusively inspiratory neurons

PB: parabrachial; KF: Kölliker-Fuse
NTS: nucleus tractus solitarius
VRG: ventral respiratory group
DRG: dorsal respiratory group.

Control of breathing by the medullary respiratory neurons to regulate the rate, rhythm, amplitude, rhythmicity and pattern of breathing, and internal homeostasis depends on a variety of afferent inputs to respiratory neurons in the brainstem. These include the parasympathetic vagal afferents from the peripheral respiratory tracts and receptors, the carotid and aortic body peripheral chemoreceptors (sensing predominantly low O_2 but to an extent also increased CO_2 and H+),

the central chemoreceptors in the medulla sensing alteration in CO_2 or H(+) in the local circulation, the supramedullary structures (e.g., forebrain, midbrain, and pontine regions), and the reticular activating systems [51, 63–66].

Breathing is controlled during wakefulness and sleep by two separate and independent systems [52–57, 67]: the metabolic or automatic [53, 54], and the voluntary or behavioral [67]. Both metabolic and voluntary systems operate during wakefulness, but breathing during sleep is entirely dependent on the inherent rhythmicity of the autonomic (automatic) respiratory control system located in the medulla [55–57]. Voluntary control is mediated through the behavioral system that influences ventilation during wakefulness as well as nonrespiratory functions [68, 69] such as phonation and speech. In addition, the wakefulness stimulus, which is probably derived from the ARAS [70–72], exerts a tonic influence on the brain stem respiratory neurons during wakefulness.

The voluntary control system for breathing originating in the cerebral cortex (forebrain and limbic system) controls respiration during wakefulness and has some nonrespiratory functions [65, 67]. This system descends with the corticobulbar and corticospinal tracts partly to the automatic medullary controlling system and to some degree both terminates and integrates there. However, it primarily descends with the corticospinal tract to the spinal respiratory motor neurons, in the high cervical spinal cord, where the fibers finally integrate with the reticulospinal fibers originating from the automatic medullary respiratory neurons for smooth, coordinated functioning of respiration during wakefulness [53, 54, 57, 73, 74].

There is a close interrelationship between the respiratory [52–54] central autonomic [12, 75, 76], and lower brain stem hypnogenic neurons [77–83] in the pontomedullary region. The hypothalamic and lower brain stem hypnogenic neurons are also connected [84]. Reciprocal connections exist between the hypothalamus, the central nucleus of the amygdala, parabrachial and Kölliker-Fuse nuclei, and the NTS of the medulla (see Figs. 11.1 and 11.2) [75, 11, 73, 15]. In addition, the NTS connects with the nucleus ambiguus and retroambigualis (see Fig. 11.2) [75, 11, 73, 15]. Thus, their anatomic relationships suggest close functional interdependence among the CAN, the respiratory and hypnogenic neurons. In addition, peripheral respiratory receptors (arising from the pulmonary and tracheobronchial tree) and chemoreceptors (peripheral and central) interact with the CAN in the region of the NTS [51–54, 85].

The thoracic bellows component consists of thoracic bones, connective tissue, pleural membranes, the intercostal and other respiratory muscles, and the nerves and blood vessels. Respiratory muscle weakness plays a critical role in causing sleep dysfunction and sleep-disordered breathing in neuromuscular disorders. Box 11.4 lists the respiratory muscles. The main inspiratory muscle is the diaphragm (innervated by the phrenic nerve, formed by motor roots of C3, C4, and C5 anterior horn cells), assisted by the external intercostal muscles (innervated by the thoracic motor roots and nerves), which expand the core of the thoracic cavity and lungs during quiet normal breathing. Expiration is passive, resulting from elastic recoil of the lungs. During forced and effortful breathing (e.g., dyspnea and orthopnea), accessory muscles of respiration assist the breathing. Accessory inspiratory muscles include the sternocleidomastoideus, trapezius, and scalenus (anterior, middle, and posterior) as well as the pectoralis, serratus anterior, and latissimus dorsi. Accessory expiratory muscles consist of internal intercostal and abdominal muscles (e.g., rectus abdominis, external and internal oblique, and transversus abdominis) innervated by thoracic motor roots and nerves. Normally, these three respiratory components (central controllers, chest bellows, and lungs) function smoothly in an automatic manner to permit gas exchange (transfer of O_2 into the blood and elimination of CO_2 into the atmosphere) for ventilation, diffusion, and perfusion. Minute ventilation is defined as the amount of air breathed per minute, which equals about 6 L; about 2 L stay in the anatomic dead space, consisting of the upper airway and the mouth, and 4 L participate in gas exchange in the millions of alveoli constituting alveolar ventilation. Respiratory failure may occur as a result of dysfunction anywhere within these three major components of the respiratory control systems.

Box 11.4 The Respiratory Muscles

Inspiratory Muscles

- Diaphragm
- External intercostal

Accessory Inspiratory Muscles

- Sternocleidomastoideus
- Scalenus (anterior, middle, posterior)
- Pectoralis major
- Pectoralis minor
- Serratus anterior
- Serratus posterior superior
- Latissimus dorsi
- Alae nasi
- Trapezius.

Expiratory Muscles (*silent during quiet breathing but contract during moderately severe airway obstruction or during forceful and increased rate of breathing*)

- Internal intercostal
- Rectus abdominis
- External and internal oblique
- Transversus abdominis.

Control of Ventilation During Wakefulness

The function of ventilation is to maintain arterial homeostasis (i.e., normal partial pressure of oxygen [PO_2] and carbon dioxide [PCO_2]) [86]. The PCO_2 depends predominately on the central chemoreceptors with some influence from the peripheral chemoreceptors, whereas PO_2 depends entirely on the peripheral chemoreceptors. To maintain optimal PO_2 and PCO_2 levels, the metabolic or autonomic respiratory system uses primarily the peripheral and central chemoreceptors but also to some extent the body's metabolism and the intrapulmonary receptors [86]. It is well known that hypoxia and hypercapnia stimulate breathing [87, 88]. Hypoxic ventilatory response is mediated through the carotid body chemoreceptors [89, 90]. Normally, this response represents a hyperbolic curve that shows a sudden increase in ventilation when PO_2 falls below 60 mm Hg [51, 55–57, 86] (Fig. 11.8). Conversely, the hypercapnic [86, 88] ventilatory response is linear (see Fig. 11.8). It is mediated mainly through the medullary chemoreceptors [91] but also to some extent through the carotid body peripheral chemoreceptors [89]. The central respiratory chemosensitivity depends predominantly on an adequate response of chemosensory neurons of the RTN to sensing changes in CO_2 or H(+) in the local circulation [92]. When PCO_2 falls below a certain minimum level, which is called the apnea threshold, ventilation is inhibited [86]. The metabolic rate (e.g., carbon dioxide production [VCO_2] or oxygen consumption [VO_2], particularly VCO_2) affects ventilation in part [86]. During sleep, metabolism slows. The intrapulmonary receptors do not seem to play a major role in normal human ventilation [86]. The Hering-Breuer reflex, important to respiration, depends on pulmonary stretch receptors. Vagal afferent stimulation by increasing lung inflation terminates inspiration.

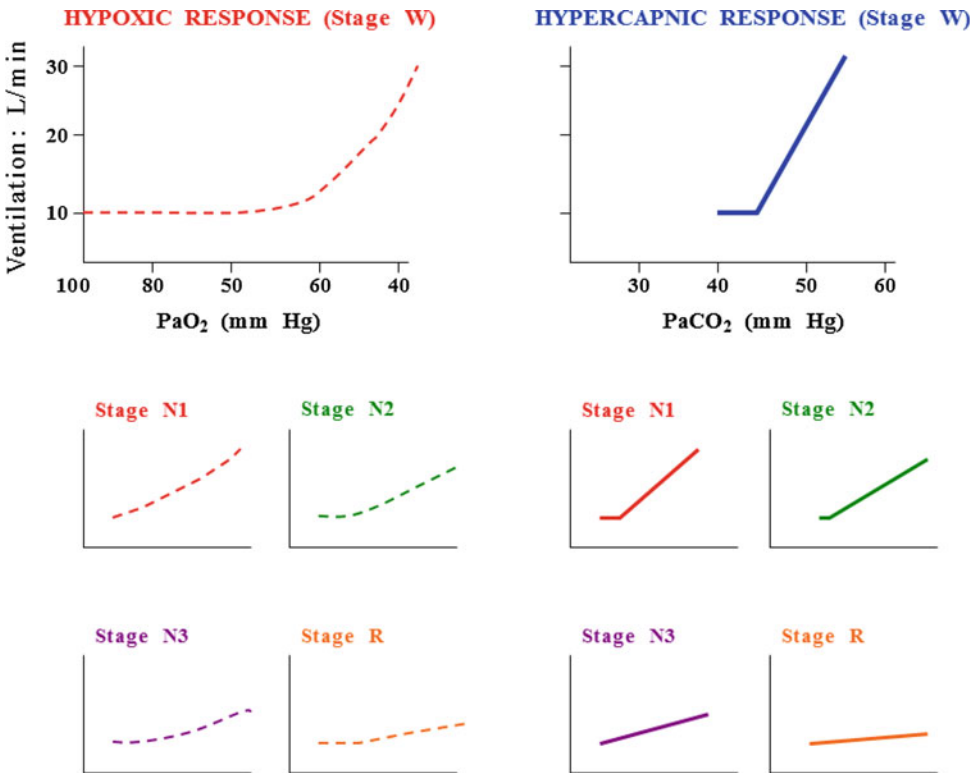

Fig. 11.8 Hypoxic and hypercapnic ventilatory responses during wakefulness, NREM (Stages N1, N2 and N3) and REM (Stage R) sleep in a normal man shown schematically. There is progressive decrement of responses with shift to the right from wakefulness to Stages N1, N2, N3 and REM state (Stage R). (Adapted from References [93, 94]

Control of Ventilation During Sleep

In normal persons, during both REM and NREM sleep, clear alterations are noted in tidal volume, alveolar ventilation, blood gases, respiratory rate and rhythm, chemosensitivity, respiratory muscle tone and upper airway reflexes and resistance [55–57, 65, 67, 95–100].

Changes in Ventilation

During NREM sleep, minute ventilation falls by approximately 0.5–1.5 L/min [86, 92, 96, 97, 101, 102, 103, 104] and this is secondary to reduction in the tidal volume. REM sleep shows a similar reduction of minute ventilation, up to approximately 1.6 L/min [86, 92, 98, 102, 104, 105]. Although there is a discrepancy in the literature regarding REM sleep-related ventilation in humans, it is generally accepted that most reduction occurs during phasic REM sleep.

The following factors, in combination, may be responsible for alveolar hypoventilation during sleep [86, 92]: reduction of VCO_2 and VO_2 during sleep, absence of the tonic influence of the brain stem reticular formation (i.e., absence of the wakefulness stimulus), reduced chemosensitivity (see *Chemosensitivity and Sleep* later), and increased upper airway resistance to airflow resulting from reduced activity of the pharyngeal dilator muscles during sleep [102, 106].

Changes in Blood Gases

As a result of the fall of alveolar ventilation, the PCO_2 rises by 2–8 mm Hg, PO_2 decreases by 3–10 mm Hg, and arterial oxygen saturation (s) decreases by less than 2 % during sleep [96, 98, 99, 107, 108]. These changes occur despite reductions of VO_2 and VCO_2 during sleep [109].

Respiratory Rate and Rhythm

In NREM sleep, the respiratory rate primarily shows a slight decrement, whereas in REM sleep the respiration becomes irregular, especially during phasic REM [86]. There is also waxing and waning of the tidal volume during sleep onset resembling Cheyne-Stokes breathing [95, 98, 109–111] which is related to several factors [86]: sudden loss of wakefulness stimulus, reduced chemosensitivity at sleep onset (see *Chemosensitivity and Sleep* later), and transient arousal. During the deepening stage of NREM sleep, respiration becomes stable and rhythmic and depends entirely on the metabolic controlling system [55–57, 65, 86, 98].

Chemosensitivity and Sleep

A rising arterial PCO_2 and falling arterial PO_2 stimulate ventilation. Hypoxia acts through peripheral chemoreceptors in the carotid bodies, whereas CO_2 acts mainly through the central chemoreceptor in the medulla and also to an extent through the carotid body chemoreceptor.

Hypoxic ventilatory response in humans is decreased in NREM sleep in adult men but not in women, whereas hypoxic ventilatory response during REM sleep is significantly decreased in both men and women (Fig. 11.8) [93, 95, 112–116]. The underlying mechanisms for this gender difference are not clear [117]. This reduction could result from two factors: (1) increased upper airway resistance to airflow during all stages of sleep [102, 106, 118] and (2) decreased chemosensitivity.

Hypercapnic ventilatory response also decreases by approximately 20–50 % during NREM sleep [96, 99, 103, 94, 119] and further during REM sleep (Fig. 11.8) [116, 94, 119]. This results from a combination of two factors: (1) a decreased number of functional medullary respiratory neurons during sleep and (2) increased upper airway resistance [102, 106, 118]. During sleep, the CO_2 response curve shifts to the right so that increasing amounts of PCO_2 are needed to stimulate ventilation [108]. These findings suggest decreased sensitivity of the central chemoreceptors subserving medullary respiratory neurons during sleep. The marked blunting of the hypercapnic ventilatory response during REM sleep could also be related to increasing brain blood flow during this sleep state [107].

Metabolism and Ventilation During Sleep

There is a definite decrease in VCO_2 and VO_2 during sleep [109, 120, 121]. Metabolism slows suddenly at sleep onset and accelerates slowly in the early morning at approximately 5:00 A.M. [109]. During sleep, ventilation falls parallel to metabolism. The rise of PCO_2 during sleep, however, is due to alveolar hypoventilation and is not related to reduced metabolism [86]. The role of the intrapulmonary receptors during normal sleep in humans is unknown [86].

Table 11.4 Upper airway dilator muscles (secondary respiratory muscles)

Muscles	Innervation
Nasal muscles	
• Compressor naris	VII
• Dilator naris	VII
• Alae nasi	VII
Palatal muscles	
• Palatoglossus	X
• Palatopharyngeus	X
• Levator veli palatini	X
• Tensor veli palatini	V
• Musculus uvulae	X
Tongue muscles	
• *Protruders*	XII
– Genioglossus	C1–C2 (carried by XII)
– Geniohyoid	XII
• *Retractors*	XII
– Hyoglossus	XII
– Styloglossus	
– Palatoglossus	
Pharyngeal muscle (constrictors)	
• Superior pharyngeal	X
• Middle pharyngeal	X
• Interior pharyngeal	X
• Stylopharyngeus	IX
Muscles of mastication (control position of the mandible and hyoid bone opening the pharyngeal airway)	
• Temporalis	V
• Masseter	V
• Lateral pterygoids	V
• Medial pterygoids	V
Hyoid muscles	
• **Suprahyoid**	V
– Mylohyoid	XII
– Hyoglossus	V
– Digastric (anterior belly)	VII
– Digastric (posterior belly)	VII
– Stylohyoid	C1–C2 (carried by XII)
– Geniohyoid	CI–C4
• **Infrahyoid**	C1–C4
– Sternohyoid	C1–C4
– Omohyoid	C1–C4
– Sternothyroid	X
– Thyrohyoid	X
• **Laryngeal muscles**	X
– Posterior cricoarytenoid	X
– Lateral cricoarytenoid	X
– Interarytenoid	X
– Thyroarytenoid	X
– Cricothyroid	
– Aryepiglottic	
– Thyroepiglottic	

V 5th cranial nerve; *VII* 7th cranial nerve; *IX* 9th cranial nerve; *X* 10th cranial nerve; *XII* 12th cranial nerve; *C1–C4* Ventral primary rami of the cervical spinal roots

Arousal Responses During Sleep

Hypercapnia is a stronger arousal stimulus than hypoxemia during sleep. An increase in PCO_2 of 6–15 mm Hg causes consistent arousal during sleep [113], whereas SaO_2 would have to decrease to 75 % before arousing a normal person [106, 122].

Laryngeal stimulation normally causes cough reflex response, but this is decreased during both states of sleep and is more markedly decreased during REM than NREM sleep [123]. Thus, clearance of aspirated gastric contents is impaired during sleep. In infants, laryngeal stimulation causes OSA, and this has been postulated as one mechanism for sudden infant death syndrome (SIDS) [124].

Upper Airway Reflexes, Receptors and Resistance

The upper airway reflexes are important in controlling the upper airway resistance and upper airway space. The activity of the upper airway inspiratory dilator muscles reflexively increases at the onset of inspiration due to the negative intrathoracic pressure. These respiratory-related increased pharyngeal muscle activations during inspiration are an attempt to enlarge the upper airway space to resist the sub-atmospheric inspiratory airway collapsing pressure. These upper airway muscles can be considered, in a way, respiratory muscles ("secondary" respiratory muscles) which modulate rather than generate airflow (see Table 11.4). Such reflex responses, however, are decreased during sleep, making the upper airway susceptible to suction collapse. This decreased upper airway reflex response probably results from decrement in the excitability of the upper airway motor neurons. The pressure sensitive upper airway muscle receptors send impulses via the glossopharyngeal (IXth cranial) and vagal (Xth cranial) nerves to respiratory centers in the medulla. The role of the upper airway reflexes in maintaining the upper airway resistance is strengthened by the observation of increased frequency of obstructive apneas and hypopneas in normal subjects during sleep following upper airway anesthesia [125] as well as increased apnea index after upper airway anesthesia in snorers [126]. Patients with OSA, however, do not show an increase in their apnea index after upper airway anesthesia which does not support a role for upper airway reflexes in the pathophysiology of OSAS [127, 128]. Alcohol, benzodiazepines, and age clearly cause a decrement in upper airway reflex response [129–131]. There are two other receptors important for control of ventilation: intrapulmonary stretch receptors sending afferent impulses via the vagus (Xth cranial) nerve to the inspiratory

neurons in the NTS in the medulla responsible for reflex termination of inspiration (Hering-Breuer reflex); and lung parenchymal irritant or J receptors causing increased ventilatory effort associated with pulmonary congestion.

Changes in the Upper Airway and in Intercostal Muscles and Diaphragm Tone

Upper airway resistance increases during sleep as a result of hypotonia of the upper airway dilator muscles [100, 102, 106, 118, 132, 133] (see *Physiologic Changes in the Neuromuscular System* later). There is also hypotonia of the intercostal muscles and atonia during REM sleep. The phasic activities in the diaphragm are maintained, but the tonic activity is reduced during REM sleep [57]. As a result of the supine position and hypotonia of intercostal muscles, the functional residual capacity (FRC) decreases [134, 135]. In most normal individuals, there are circadian changes in airway patency with mild bronchoconstriction during sleep at night [136].

Summary and Conclusions

During wakefulness, both metabolic and voluntary (behavioral) control systems are active. In NREM sleep, the voluntary system is inactive and respiration is entirely dependent on the metabolic controller—behavioral influences and wakefulness stimuli are not controlling respiration. The nature of ventilatory control during REM sleep has not been determined definitively, but most likely the behavioral mechanism is responsible for controlling breathing in REM sleep. Ventilation is unstable during stage N1, stage N2 and REM sleep, and apneas may occur, particularly at sleep onset and during REM sleep. Respiratory homeostasis is thus relatively unprotected during sleep. However, the breathing is more regular and stable during stage N3 (SWS). Following three mechanisms may be responsible for this singly or in combination:

1. Increased genioglossus muscle single motor unit (SMU) activity during SWS compared with stage N1 or stage N2 [137]. This may be related to three possible factors: (a) higher PCO_2 during SWS than stage N2 (this is unlikely but possible); (b) higher upper airway resistance during stage N3 than stages N1 and N2 triggering activation of local mechanoreceptors (variable results in prior studies); and (c) increased central respiratory drive (a theoretical possibility as no prior study is available to prove this).
2. Increased arousal threshold in SWS compared with stages N1 or N2, preventing arousal related instability of breathing [138].
3. Increased phasic upper airway muscle activity in SWS [139].

The major cause of hypoventilation and reduced ventilatory response to chemical stimuli during sleep is increased airway resistance [102, 106, 118, 140]. The increased resistance results from reduced activity of the pharyngeal dilator muscles as well as decreased output from the sleep-related medullary respiratory neurons [141]. The reduction of the medullary respiratory neuronal activity in sleep causes a loss of the tonic and phasic motor output to the upper airway muscles, resulting in an increase in airway resistance. Other factors that contribute to sleep-related hypoventilation include the following [55–57, 65, 86, 142]: reduction of metabolic rate by approximately 10–15 %; absence of wakefulness stimuli; reduced chemosensitivity; increased blood flow to the brain during REM sleep, which may depress central chemoreceptor activity; and functional alterations in the CNS during sleep, such as cerebral cortical suppression due to reticular inhibition and physiological cortical deafferentation (presynaptic and postsynaptic inhibition of the afferent neurons [143]) as well as postsynaptic inhibition of motor neurons during REM sleep (see *Physiologic Changes in the Neuromuscular System* later).

Physiological Changes in the Neuromuscular System

Physiological changes have been noted during sleep in both the somatic nervous system and the ANS that in turn produce changes in the somatic and smooth muscles of the body. This section presents a discussion of the physiological changes noted during sleep in the somatic muscles, including cranial, limb, and respiratory muscles.

Changes in Limb and Cranial Muscles

Alterations of limb and cranial muscle tone are noted during sleep. Muscle tone is maximal during wakefulness, slightly decreased in NREM sleep, and markedly decreased or absent in REM sleep. Electromyography (EMG), particularly of the mentalis or the submental muscles, is necessary to identify REM sleep and is thus important for scoring technique. In addition, transient phasic (myoclonic) bursts are noted during REM sleep. An important EMG characteristic is documentation of periodic limb movements in sleep, which are noted in the majority of patients with restless legs syndrome; patients with a variety of sleep disorders; and normal individuals, most commonly elderly ones.

Upper Airway Muscles and Sleep

Changes occur in the function of the upper airway dilator muscles (Table 11.4) during sleep that have important clinical implications, particularly for patients with sleep apnea syndrome. The upper airway dilator muscles can be considered secondary respiratory muscles which are responsible for modulating and maintaining airflow but not for generating airflow and controlling breathing [144]. These muscles are located in the nose, tongue, soft palate, pharynx, hyoid arch and larynx (Table 11.4). All these upper airway muscles show phasic bursts synchronous with inspiratory intercostal muscles (external intercostal and diaphragmatic activities). The coordinated activity of these upper airway dilator muscles by generating opposing forces to counter the collapse of upper airway (resulting from negative subatmospheric pharyngeal pressure induced by diaphragmatic contraction) maintains upper airway patency [130, 131, 144] for a smooth performance of normal breathing. The upper respiratory tract subserves both respiratory and nonrespiratory functions [145]. In experimental studies in cats, pharyngeal motor neurons in the vagus and glossopharyngeal nerves were found to be located in the medulla, overlapping the medullary respiratory neurons [146]. The experimental study by Bianchi et al. [147] demonstrated that, after changes induced by chemical stimuli (normocapnic hypoxia and normoxic hypercapnia), pharyngeal motor activities are more sensitive than phrenic nerve activation. The influence of sleep on respiratory muscle function has been reviewed by Gothe et al. [148] and Horner [130, 131].

Nasal Muscles

The compressor and dilator naris, and alae nasi muscles are the most rostral part of the upper airway secondary respiratory muscles. EMG recordings have been shown that the phasic inspiratory activation of the alae nasi muscles precedes the onset of airflow and diaphragmatic activation during wakefulness and sleep, and this interval is increased during NREM sleep [144]. This asynchrony in susceptible individuals may contribute to upper airway collapse during sleep [144]. The phasic alae nasi inspiratory activity is maintained, although decreased, during apneic episodes in OSA. Nasal CPAP is shown to reduce EMG muscle tone in the alae nasi suggesting that nasal CPAP may open the upper airway passively [127].

Genioglossus Muscle

This is the principal tongue muscle and has been studied best to show its role in OSA. The genioglossus and geniohyoid muscles are mainly responsible for forward displacement of the tongue (protrusion), whereas three other tongue muscles (Table 11.4) are responsible for backward displacement of the tongue (retrusion). EMG recordings can be obtained by intramuscular electrodes percutaneously via a submental or transoral approach or by submental surface electrodes which may record additional activation from the neighboring muscle (e.g., mylohyoid, anterior belly of the digastric, hyoglossus and geniohyoid) [144]. Genioglossal EMG activities consist of phasic inspiratory bursts and variable tonic discharges [137, 139, 144], which are mildly decreased during NREM sleep but markedly decreased during REM sleep [144–153]. In OSA patients, this sleep-dependent hypotonia of the tongue may be responsible for backward displacement of the tongue partially or completely against the posterior pharyngeal wall causing apnea or hypopnea in an anatomically compromised posterior airway. Thus, the genioglossus muscle plays an important role in upper airway OSAS. In OSA patients, genioglossal muscle tone is increased during wakefulness as a compensatory measure.

Selective reduction of genioglossal or hypoglossal nerve activity (i.e., disproportionately more reduction than the diaphragmatic or phrenic activities) has been noted with alcohol, diazepam, and many anesthetic agents [149]. Conversely, protriptyline and strychnine selectively increase such activity [150].

Palatal Muscles

Levator veli palatini and palatoglossus muscles in humans show phasic inspiratory and tonic expiratory activities [154, 155], but tensor veli palatini muscle shows tonic activity during both inspiration and expiration in wakefulness and sleep [156, 157]. During sleep in normal individuals, palatal muscles (palatoglossus, tensor veli palatini, and levator veli palatini) show decreased tone causing increased upper airway resistance and decreased airway space.

Masseter Muscle

Masseter contraction closes the jaw and elevates the mandible. In sleep apnea patients, masseter activation is present during eupneic episodes but decreased during apneic ones. Masseter EMG activity decreases immediately before the apnea, is absent during the early part of the episode, and increases at the end of the apneic period [158]. Based on experiments using chemical stimuli, Suratt and Hollowell [158] concluded that masseter activity can be increased by hyperoxic hypercapnia and inspiratory resistance loading. It appears that phasic EMG bursts start in the masseter at the same time as in the genioglossus and the diaphragm. Suratt and Hollowell [158] did not find phasic activity in masseter muscle in normal subjects during regular breathing, but

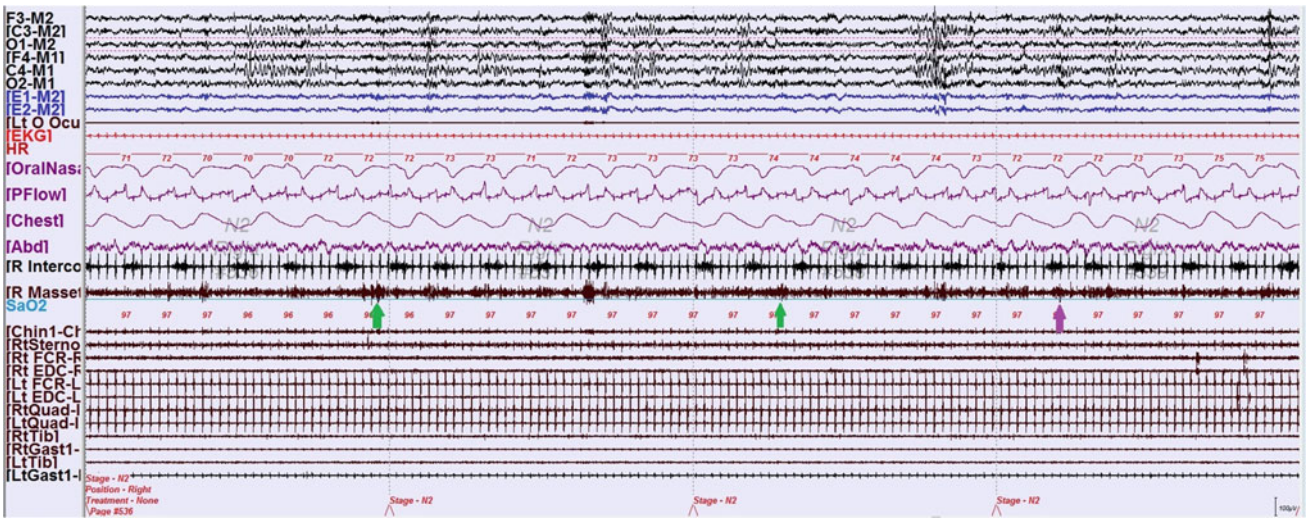

Fig. 11.9 A 120-s epoch from polysomnogram of a year-old healthy subject showing muscle bursts in the surface electromyographic (*EMG*) recording from right (R) masseter muscle during stage N2. EMG bursts are seen during both expiratory (*green arrows*) and inspiratory (*purple arrow*) phases but more frequently seen during expiration. *Top six channels* Electroencephalogram (international nomenclature); *E1-M2* and *E2-M2* Left and right electro-oculogram; *Lt O ocu* left orbicularis oculi; *EKG* Electrocardiogram; *Hr* Heart rate; *Oral Nas* Oronasal thermistor *PFlow* Nasal pressure transducer, *chest and Abd* Chest and abdominal respiratory effort channels; *R Interco* right external intercostal (inspiratory) EMG channel; *R masse* right masseter muscle; SaO_2 arterial oxygen saturation by finger oximetry; *Chin 1-Chin 2* submental EMG; *R sterno* right sternocleidomastoideus EMG; *Rt FCR* right flexor carpi radialis EMG; *Rt EDC* right extensor digitorum communis EMG; *Lt FCR* left flexor carpi radialis EMG; *Rt Quad* right quadriceps EMG; *Lt Quad* left quadriceps; *Rt Tib* right tibialis anterior EMG; *Rt Gast* right gastrocnemius EMG; *Lt Tib* Left tibialis anterior EMG; *Lt Gast* left gastrocnemius EMG

noted such activity during inspiratory stimulation such as inspiratory resistance loading or hypercapnia. In sleep apnea patients, spontaneous phasic masseter activity was noted during regular breathing. Using surface electrodes, the present author has documented phasic respiratory bursts in masseter muscle in normal subjects and those without sleep apnea (Fig. 11.9) [unpublished observation].

Intrinsic Laryngeal Muscle Activity

Intrinsic laryngeal muscles, controlled by the brain stem neuronal mechanism, play an important role in the regulation of breathing [159–161]. In addition, the larynx participates in phonation, deglutition, and airway protection [160]. The posterior cricoarytenoid (PCA) muscle is the main vocal cord abductor. Laryngeal EMG can be performed by placing hooked wire electrodes percutaneously through the cricothyroid membrane [161].

PCA demonstrates phasic inspiratory bursts in normal subjects during wakefulness and NREM sleep [159]. In addition, there is tonic expiratory activity in wakefulness that disappears with NREM sleep. In REM sleep, PCA EMG shows fragmented inspiratory bursts and variable expiratory activity. During isocapnic hypoxia and hyperoxic hypercapnia, normal subjects show increased phasic inspiratory PCA activity but minimal increase in tonic expiratory activity [159].

Hyoid Muscles

Suprahyoid muscles (those inserted superiorly on the hyoid bone) include the geniohyoid, mylohyoid, hyoglossus, stylohyoid, and digastric muscles [162]. Infrahyoid muscles (those that insert inferiorly) include the sternohyoid, omohyoid, sternothyroid and thyrohyoid muscles [162]. The size and shape of the upper airways can be altered by movements of the hyoid bone. Motor neurons supplying these muscles are located in the pons, the medulla, and the upper cervical spinal cord. The hyoid muscles show inspiratory bursts during wakefulness and NREM sleep that are increased by hypercapnia. The relative contribution of hyoid, genioglossus, and other tongue muscles in the maintenance of pharyngeal patency needs to be clarified [162].

It is important to understand central neuronal mechanisms and the contributions of neuromodulators and neurotransmitters involved in sleep-related suppression of pharyngeal muscle activity [130, 131]. This knowledge will help in designing treatment for upper airway OSAS.

Mechanism of Mild Muscle Hypotonia in NREM Sleep

Mild muscle hypotonia in NREM sleep appears to result from a combination of disfacilitation of brain stem motor

neurons controlling muscle tone (e.g., mild reduction of activity of locus ceruleus noradrenergic and midline raphe serotonergic neurons) and slight hyperpolarization of brain stem and spinal motor neurons [163]. In addition, there is a direct cerebral cortical mechanism to explain mild muscle hypotonia in NREM sleep, as evidenced by significant enhancement of intracortical inhibition during slow-wave sleep (SWS) after paired-pulse transcranial magnetic brain stimulation [164]. Intracellular microelectrode recording of motor neurons at the onset of NREM sleep by Chase and collaborators [163] clearly showed either no change in membrane potential or a slight hyperpolarization. It should be remembered that the resting membrane potential is determined by an unequal distribution of ions on the outside and the inside of the membrane and by differential permeabilities of the concentration of the sodium, potassium, and chloride ions.

Mechanism of Muscle Atonia or Hypotonia in REM Sleep (See also Chap. 39)

REM sleep is characterized by almost complete cessation of voluntary muscle tone in the presence of a highly active forebrain (paralyzed body with an activated brain) with inhibition of the mesencephalic locomotor region. This is nature's way of preventing abnormal movements during REM sleep in the presence of highly active cerebral cortex and forebrain regions. The dorsal pontine tegmentum appears to be an important central region responsible for limb muscle atonia in REM sleep [78, 165–167]. Muscle atonia during REM sleep is initiated during activation of a polysynaptic descending pathway from the peri–locus ceruleus alpha in the region of the nucleus pontis oralis to the lateral tegmentoreticular tract, the nucleus gigantocellularis and magnocellularis in the ventral region of the medial medullary reticular formation (the inhibitory region of Magoun and Rhines) [165, 166], and finally, the ventral tegmentoreticular and reticulospinal tracts to the alpha motor neurons causing hyperpolarization and muscle atonia (Fig. 11.3) [167–170]. During REM sleep, an increased number of c-Fos (a nuclear protein synthesized during neuronal activation) labeled cells were detected by immunocytochemical techniques in the inhibitory region of Magoun and Rhines. A key element in the REM sleep-generating mechanism in the pons is the activation of γ-aminobutyric acidergic (GABAergic) neurons located in a subgroup of the pontine reticular formation (sublaterodorsal nucleus [SLD]) as well as GABAergic neurons in the ventrolateral periaqueductal gray region in the mesencephalon [167, 170, 171]. An activation of GABAergic neurons causes excitation or disinhibition of cholinergic neurons, and inhibition of noradrenergic and serotonergic neurons, in the pons. The cholinergic neurons, in turn, excite pontine glutamatergic neurons projecting to the glycinergic premotor neurons in the medullary reticular formation, causing hyperpolarization of the motor neurons and muscle paralysis during REM sleep. This GABAergic mechanism also plays an important role in motor neuron hyperpolarization (see later). Based on more recent study Luppi et al. [171] concluded that REM-on SLD neurons are predominantly glutamatergic. Ventral SLD sends both direct and indirect projections via the ventromedial medulla to brain stem and spinal motoneurons causing hyperpolarization of these neurons using GABA and glycine inhibitory neurotransmitters. During REM sleep, there is also disfacilitation of motor neurons as a result of reduction of the release of midline raphe serotonin and locus ceruleus noradrenaline partially contributing to muscle atonia. Additional contribution to REM atonia comes from lateral hypothalamic hypocretinergic neurons (see further on). Finally, a cerebral cortical mechanism may also contribute to the inhibition of spinal motor neurons in REM sleep, as evidenced by decreased intracortical facilitation in the paired-pulse transcranial magnetic brain stimulation techniques [164].

In summary, there are four fundamental mechanisms responsible for muscle atonia in REM sleep: inhibitory postsynaptic potentials (IPSPs) causing postsynaptic inhibition of motor neurons (major mechanism); disfacilitation (i.e., a reduction of excitation) of presynaptic spinal excitatory neurons; disfacilitation of brain stem and spinal motor neurons controlling muscle tone; and decreased intracortical facilitation (e.g., paired-pulse brain magnetic stimulation technique). During wakefulness and NREM sleep, there are a few spontaneously occurring low-amplitude IPSPs, but during REM sleep, in addition to an increase in these low-amplitude IPSPs, high-amplitude REM sleep-specific IPSPs are noted. These are generated by sleep-specific inhibitory interneurons located mainly in the brain stem (immunocytochemical techniques are used to prove this observation) that send long-projecting axons to the spinal cord and short axons to the brain stem motor neurons [165–170]. As a result of these IPSPs, motor neurons are hyperpolarized by 2–10 mV during REM sleep. Intracellular recordings reveal increased number and appearance of REM sleep-specific IPSPs in the lumbar motor neurons of cats [163, 172–176]. Thus postsynaptic inhibition of motor neurons is responsible for the atonia of somatic muscles, as evidenced by intracellular recordings of spinal motor neurons in chronic spinal preparations of cats. These potentials are derived from inhibitory interneurons, possibly located either in the spinal cord or in the brain stem, from which long axons project to the spinal motor neurons [165, 174, 176]. In addition, there is also postsynaptic inhibition causing a decrease in the Ia monosynaptic excitatory postsynaptic potentials (EPSPs), resulting in motor neuron

hyperpolarization. Lesions of the dorsal pontine tegmentum abolish muscle atonia of REM sleep [173–179]. Similar episodes of REM sleep without muscle atonia have also been observed in cats with localized lesions in the ventromedial medulla [180].

Intermittently during REM sleep, there are excitatory drives causing motor neuron depolarization shifts as a result of EPSPs [163, 173–176]. Muscle movements caused by these excitatory drives during REM sleep are somewhat different from the movements noted during wakefulness. These movements are abrupt, jerky, and purposeless. EPSPs during REM sleep reflect increased rates of firing in the motor facilitatory pathways during REM sleep. Enhanced IPSPs during REM sleep check these facilitatory discharges, thus balancing the motor system during this activated brain state; otherwise the blind, unconscious subject will jump out of bed, as may happen in pathologic conditions such as REM sleep behavior disorders [163, 181]. Facilitatory reticulospinal fibers are responsible for transient EPSP phasic discharges causing muscle twitches in REM sleep. Corticospinal or rubrospinal tracts are not responsible for these twitches because Pompeiano showed in 1967 that destruction of these fibers in cats [182] did not affect these twitches.

What neurotransmitters drive these IPSPs? Glycine, a major inhibitory neurotransmitter, was originally thought to be the only driving force. The elegant work by Chase and Morales [163, 183] suggested that glycine is the main neurotransmitter responsible for motor neuron hyperpolarization and IPSPs. The REM sleep-specific IPSPs are reversed after strychnine (a glycine antagonist) administration by microiontophoretic application into the ventral spinal cord [163]. In contrast, picrotoxins and bicuculline (a GABA A antagonist) did not abolish these IPSPs. Recent evidence, however, suggests an important contribution by GABA in addition to glycine [184–189]. Brooks and Peever [188, 189] have shown in their experimental studies in rats that GABA A, GABA B and glycine receptors play a role in mediating REM muscle atonia. It is notable that, in the experiments by Chase and Morales, although the GABA antagonist picrotoxin did not reverse REM sleep-related IPSPs, it reduced the IPSP duration considerably. According to Nitz and Siegel [190, 191], there is a selective GABAergic inhibition of noradrenergic and serotonergic neurons during REM sleep accounting for cessation of discharge of these aminergic cells. As a result of this cessation, there is disfacilitation of motor neurons. GABA may also have a direct inhibitory effect on interneurons and motor neurons. Experimental studies in rats by Besnard et al. [192] and Kubin [193] also provided evidence of wakefulness-related serotonergic and noradrenergic excitatory drive to hypoglossal neurons and withdrawal (disfacilitation during REM sleep).

What is the role of hypocretin in REM motor atonia? Hypocretinergic neurons located in the lateral hypothalamus play a facilitatory role in the motor system by direct projections to the motor neurons and indirectly through projections to the monoaminergic, and cholinergic neurons [163, 194–197]. Hypocretinergic neurons also project to REM generating reticularis pontis oralis nucleus (REM-on) in the Pons and to REM-off neurons in the Pons to suppress REM sleep [198]. Hcrt neurons facilitate motor activity during wakefulness but enhance motor inhibition during REM sleep. There is withdrawal of Hcrt activation of the locus ceruleus noradrenergic and midline raphe serotonergic neurons during REM sleep, as well as withdrawal of Hcrt activation of the spinal motor neurons causing disfacilitation of these brain stem and spinal motor neurons contributing to muscle atonia.

REM Sleep-Related Alterations in Respiratory Muscle Activity

During REM sleep, activity of upper airway muscles and the diaphragm is reduced. Three types of REM sleep-related alterations in the respiratory muscles have been described [199]:

1. *Atonia* of EMG activity throughout the REM sleep period is found. Somatic muscles characteristically show this response, which is related to glycine as well as GABA-mediated postsynaptic inhibition of motor neurons [163, 173–176, 188, 189, 200].
2. Rhythmic activity of the diaphragm persists in REM sleep, but certain diaphragmatic motor units cease firing. Kline et al. [201] described *intermittent decrement of diaphragmatic activity* during single breaths. Upper airway muscles also show similar changes.
3. *Fractionations of diaphragmatic activity* refer to pauses lasting 40–80 ms and occur in clusters correlated with pontine-geniculate-occipital waves, which are phasic events of REM sleep [202].

What is the mechanism of muscle atonia in the upper airway muscles during REM sleep? Postsynaptic inhibition of motor neurons during REM sleep as described previously is a critical mechanism mediating suppression of hypoglossal motor neurons during REM sleep. Kodama et al. [184], Nitz and Siegel [190, 191] as well as Brooks and Peever [188, 189] suggested that both glycine and GABA play important roles in the regulation of upper airway and postural muscles. A combination of decreased monoamines (e.g., noradrenaline and serotonin) and increased GABA release in the motor neuron pools may be involved in the REM sleep muscle atonia. Fenik et al. [185, 186] as well as

several other authors [192, 193, 203–209] suggested that the suppression of upper airway motor tone, including the genioglossus muscle tone, during REM sleep is caused by withdrawal of excitation mediated by norepinephrine and serotonin. Fenik et al. [185, 186] concluded that suppression of motor activity or muscle atonia of the hypoglossus and other upper airway dilator muscles is caused by all or some of the following mechanisms: the withdrawal of motor neuronal excitation mediated by norepinephrine and serotonin, and increased inhibition mediated by GABA and glycine. In summary, the selective inhibition of monoaminergic and orexinergic (hypocretinergic) systems (disfacilitation) coupled with direct active inhibition of motor neurons by GABA and glycine produces a loss of postural muscle tone.

Summary and Clinical Relevance

There is considerable reduction of the activity of the upper airway dilator muscles during NREM sleep, with further reduction in REM sleep, causing increased upper airway resistance and narrowing of the upper airway space. Increased upper airway resistance, which is noted during sleep in normal individuals, may predispose to upper airway occlusion and OSA in susceptible individuals [100]. The site of the upper airway obstruction in OSA is usually at the level of the soft palate, but in approximately half the patients the obstruction extends caudally to the region of the tongue, with further caudal extension during REM sleep [210–218]. Therefore, decreased tone in the palatal, genioglossal, and other upper airway muscles causing increased upper airway resistance and decreased airway space plays an important contributing role in upper airway obstruction in OSA, particularly because many OSA patients have smaller upper airways than individuals without OSA [210, 219–222]. An understanding of these physiological changes in the genioglossus and other upper airway muscles stimulated successful development of hypoglossal nerve stimulation systems for treatment of OSA patients [223]. As a result of the complex effects of sleep on respiration, there is an overall reduction in ventilation during sleep compared to wakefulness [100]. This may not significantly affect a normal person, but may cause life-threatening hypoxemia and abnormal breathing patterns during sleep in patients with neuromuscular disorders, chronic obstructive pulmonary disease, and bronchial asthma, especially in those with daytime hypoxemia [100]. The chemoreflex control of breathing may vary across patients with OSAS. In patients with an apnea-hypopnea index of greater than 30, Mahmed et al. [224]. have shown a significant overnight increase in chemoreflex sensitivity of 30 %, which is another contributing factor toward destabilization of breathing during sleep in this condition. The circadian changes of mild bronchoconstriction during sleep in normal individuals may be accentuated in patients with asthma, causing a marked decrease in peak flow rate, which may in turn cause severe bronchospasm [100, 127].

In summary, during sleep there is a reduction of metabolism and sympathetic activity as a result of which there is depression of respiration, circulation and other vital functions [225]. Following suggested physiological factors may be responsible for breathing dysfunction in sleep [224, 225]:

1. Reduction of skeletal muscle or upper airway muscle tone;
2. Reduced hypoxic and hypercapnic ventilator response;
3. Loss of the wakefulness stimulus causing functional changes in the CNS and reduced respiratory neuronal drive;
4. Fluctuation of excitatory and inhibitory impulses on breathing during various stages of sleep and transition to sleep;
5. Reduced FRC;
6. Ventilation/perfusion (V/Q) mismatch related to body position.

These physiological mechanisms do not affect normal healthy individuals but may worsen breathing in compromised individuals (e.g., those with narrow upper airway space or altered central ventilator stability [i.e., those with high loop gain]).

Physiological Changes in the Heart and Circulation During Sleep

Physiological changes in the heart during sleep include alterations in HR and cardiac output. Changes in circulation during sleep include changes in BP, peripheral vascular resistance (PVR), and blood flow to various systems and regions [226, 227]. All these cardiovascular hemodynamic changes are controlled by the ANS. Briefly, sympathetic inhibition is associated with a decrease in BP and HR during NREM sleep, whereas in REM sleep, intermittent activation of the sympathetic system accounts for rapid fluctuations in BP and HR [38].

Heart Rate

The HR decreases by 5–8 % during NREM sleep and shows frequent upward and downward swings during REM sleep [18, 20, 227–236]. Bradycardia during NREM sleep results from a tonic increase in parasympathetic activity (sympathectomy has little effect) [18, 230, 231]. Bradycardia

persists during REM sleep and becomes intense owing to tonically reduced sympathetic discharge. Phasic HR changes (bradytachycardia) during REM sleep are due to transient changes in both the cardiac sympathetic and parasympathetic activities. [18, 228–231]. Thus parasympathetic activity predominates during sleep, and an additional decrease with intermittent increase in sympathetic activity is observed during REM sleep.

In several studies, the HRV during sleep stages has been documented after spectral analysis [20, 231–233, 235]. The documentation of the HF component of the electrocardiogram clearly indicates the prevalence of parasympathetic activity during both NREM and REM sleep. These studies also show intermittent increases of LF components in the electrocardiogram, indicating intermittent sympathetic nervous system activation during REM sleep. Studies also show that the HR acceleration occurs at least 10 beats before EEG arousal [231].

The effect of sleep on cardiac rhythm has been studied in healthy individuals using Holter monitor (see Chap. 47).

Cardiac Output

Cardiac output falls progressively during sleep, with the greatest decrement occurring during the last sleep cycle, particularly during the last REM sleep cycle early in the morning [228, 237]. This may help explain why normal individuals and patients with cardiopulmonary disease are most likely to die during the hours of early morning (see Chap. 47). Maximal oxygen desaturation and periodic breathing are also noted at this time.

Systemic Arterial Blood Pressure

BP falls by approximately 5–14 % during NREM sleep and swings up and down during REM sleep with an overall increase by about 5 % above that noted in NREM sleep. There is a sharp rise in BP around the time of awakening [228, 229, 238–240]. These changes are related to alterations in the ANS [18]. Coote [241] concluded that the fall in BP during NREM sleep was secondary to a reduction in cardiac output, whereas the BP changes during REM sleep resulted from alterations in cardiac output and PVR.

Pulmonary Arterial Pressure

Pulmonary arterial pressure rises slightly during sleep. During wakefulness, the mean value is 18/8 mm Hg; that during sleep is 23/12 mm Hg [242].

Baroreflex Function

There is alteration of baroreflex function, measured indirectly by BRS during sleep as described above.

Peripheral Vascular Resistance

During NREM sleep, PVR remains unchanged or may fall slightly, whereas in REM sleep there is a decrease in PVR due to vasodilation, of the Splanchnic vessels [228, 243, 244].

Systemic Blood Flow

Cutaneous, muscular, and mesenteric vascular blood flow shows little change during NREM sleep, but during REM sleep, there is profound vasodilation resulting in increased blood flow in the mesenteric and renal vascular beds [36–39, 228, 244, 245]. However, there is vasoconstriction causing decreased blood flow in the skeletal muscular and cutaneous vascular beds during REM sleep [36–39, 244]. Mullen et al. [246] reported a decrease of plasma renin activity (PRA) in humans during REM sleep, which indirectly suggests increased renal blood flow.

Cerebral Blood Flow

Cerebral blood flow (CBF) and cerebral metabolic rate for glucose and oxygen decrease by 5–23 % during NREM sleep, whereas these values increase to 10 % below up to 41 % above the waking levels during REM sleep [247–255]. These data indirectly suggest [247, 255] that NREM sleep is the state of resting brain with reduced neuronal activity, decreased synaptic transmission, and depressed cerebral metabolism, both glucose and brain oxygen metabolism. CBF is noted to be lower in NREM than in REM sleep, lower at the end of the night compared with that at the beginning of the night, and lower in postsleep wakefulness than presleep wakefulness [255]. Cerebral metabolic rate for oxygen and glucose also decreases in postsleep wakefulness and toward the end of the night compared with the values noted in presleep wakefulness and the beginning of the night [255]. This decreased metabolism, reduced CBF, and reduced anaerobic glycolysis (i.e., there is a greater decrease in glucose utilization compared with oxygen utilization) all support restorative functions of sleep [255].

In the last decade, Maquet and his group (see also Chap. 21) and others[256–274] have made significant contributions using positron emission tomography with [^{15}O]-labeled water or [^{18}F]fluorodeoxyglucose and functional

magnetic resonance imaging (MRI) to understand the functional neuroanatomy in normal human sleep. These studies have shown major differences of brain activation during wakefulness, NREM sleep, and REM sleep. During NREM sleep, there is a global decrease in CBF with a regional decrement of CBF in the dorsal pons, mesencephalon, thalami, basal ganglia, basal forebrain, anterior hypothalamus, prefrontal cortex, anterior cingulate cortex, and precuneus [263–265]. These studies confirmed in humans the existence of brain stem–thalamocortical circuits responsible for the NREM sleep-generating mechanisms and correlate with the electrophysiological findings of hyperpolarization of thalamic neurons with generation of sleep spindles, K complexes, and delta and very slow oscillations [260, 265]. The pattern of deactivation in NREM sleep is not homogeneous. The least active areas in NREM sleep were noted in the dorsolateral prefrontal (DLPF) and orbito-frontoparietal and, less consistently, the temporal and insular regions [257, 260, 264]. The primary cortices are the least deactivated areas [264]. However, recent advances in neuroimaging techniques capturing images with higher spatial and temporal resolution have shown that NREM sleep state may not particularly be a state of brain quiescence. Using simultaneous EEG/ event-related functional magnetic resonance imaging (fMRI), Macquet and his group [274, 275] have detected regionally specific increase in activities during SWS in brain stem, cerebellum, ventral prefrontal cortex, posterior cingulate cortex/precuneus and parahippocampal areas in addition to areas generating fast and slow spindles. These findings suggest that during NREM sleep, brain is actively involved in generating synchronized slow waves and spindles which have important implications for memory processing.

In contrast, REM sleep represents an active brain state with increased neuronal activity and increased metabolism. The largest increases during REM sleep are noted in the hypothalamus and the brain stem structures, and the smallest increases are in the cerebral cortex and white matter. REM sleep is characterized by increased neuronal activity, energy requirements, and CBF with regional activations in the pontine tegmentum, thalamus, amygdala, anterior cingulate cortex, hippocampus, temporal and occipital regions, basal forebrain, cerebellum, and caudate nucleus [274]. In contrast, there is regional deactivation in the DLPF, posterior cingulate gyrus, precuneus, and inferior parietal cortex [256, 264, 266]. REM sleep-related activation of the pontine tegmentum, thalamic nuclei, and basal forebrain supports the REM sleep-generating mechanisms in these regions [270]. An activation of limbic and paralimbic structures including the amygdala, hippocampal formation, and anterior cingulate cortex supports the modulatory role of these structures during REM sleep during generation of pontine-geniculate-occipital waves, a major component of phasic REM sleep and HRV in REM sleep [263], and participation of REM sleep in memory processing. REM sleep also showed regional deactivation in the DLPF, precuneus, posterior cingulate cortex, temporoparietal region, and inferior parietal lobule [256, 264, 273, 274].

In the resting state, there are intense neuronal activities both in wakefulness and sleep that can be detected in fMRI as fluctuations of the blood oxygen level-dependent (BOLD) fMRI. These resting state networks (RSN) in sleep and wakefulness showing spontaneous fluctuating neuronal activities suggest that these RSN play an important role in synaptic homeostasis and brain function [276–278].

There are three mechanisms controlling CBF [279]: cerebral autoregulation, cerebral metabolism, and respiratory blood gases (arterial PO_2 and arterial PCO_2). Cerebral autoregulation is determined by the intrinsic properties of the muscles of the cerebral arterioles. Cerebral autoregulation is normally maintained between the mean systemic arterial pressures of 150 and 60 mm Hg [279]; as the systemic BP falls, cerebral blood vessels dilate in response to changes in transmural pressure, whereas in cases of a rise in BP, the cerebral vessels constrict, thus protecting the brain from fluctuations in systemic BP. This systemic autoregulation may break down in disease states such as stroke, encephalitis, hypertensive crisis, acute head injury, and excessive antihypertensive therapy [279].

There is circadian variation in BP: a reduction during sleep and an increased awakening [280, 281]. Dipping of BP of 10–20 % during sleep compared to mean awake daytime values is physiologic, and these individuals are called "dippers" [280, 281]. There are certain individuals in whom the nocturnal systolic BP during sleep does not fall below 10 % of baseline waking value, and they are known as "nondippers". There are also individuals known as "reverse dippers" ("risers") in whom BP does not drop but actually increases during sleep periods. Those individuals considered "extreme dippers," in whom BP falls excessively, as well as nondippers and reverse dippers, are at higher risk for stroke than dippers [280–283]. Finally, both hypercapnia and hypoxia would cause vasodilation, with hypercapnia causing stronger vasodilation in the cerebral circulation.

Summary and Clinical Implications

These hemodynamic changes in the cardiovascular system result from alterations in the ANS [10, 12, 18, 46, 241]. In general, parasympathetic activity predominates during both NREM and REM sleep and is most predominant during

REM sleep. In addition, there is sympathetic inhibition during REM sleep. The sympathetic activity during REM sleep is decreased in cardiac, renal, and splanchnic vessels but increased in skeletal muscles, owing to an alteration in the brain stem sympathetic controlling mechanism. Furthermore, during phasic REM sleep, BP and HR are unstable owing to phasic vagal inhibition and sympathetic activation resulting from changes in brain stem neural activity. HR and BP therefore fluctuate with up and down swing of the BP and HR during REM sleep. Because of these hemodynamic and sympathetic alterations during REM sleep, which is prominent during the last third of total sleep in the early hours of the morning, increased platelet aggregability, plaque rupture, and coronary arterial spasm could be initiated, possibly triggering thrombotic events causing myocardial infarction, ventricular arrhythmias, or even sudden cardiac death [282–285] (see Chaps. 11 and 47). As stated previously, those patients who are nondippers, extreme dippers, and reverse dippers are at higher risk for cardiovascular or cerebrovascular events causing infarctions and periventricular hyperlucencies on MRI. Meta-analysis of epidemiologic studies provides support to the circadian variation in cardiovascular and cerebrovascular events, with the highest rates of events occurring during the early morning hours [284, 285].

Gastrointestinal Physiology During Sleep

A brief summary of the physiology of the gastrointestinal tract during sleep is given in this section. For a more detailed discussion, readers are referred to the writings of Orr [286–289]. Gastrointestinal changes include alterations in gastric acid secretion, gastric volume and motility, swallowing, and esophageal peristalsis and intestinal motility (Table 11.3).

Studying the physiology of the gastrointestinal system has been difficult traditionally because of the lack of adequate technique. Techniques as well as facilities for making simultaneous polysomnographic (PSG) recordings are now available, allowing study of the alterations in gastrointestinal physiology during different stages of sleep. Before the advent of these techniques, scattered reports generally showed decreased motor and secretory functions during sleep. Subsequent methods have produced better and more consistent results, although findings are still somewhat contradictory overall. There is a dearth of adequate studies using PSG and other modern techniques to understand the physiological alterations of gastrointestinal motility and secretions during sleep. The activity of the gastrointestinal tract is controlled by the ANS and the enteric nervous system which is an intrinsic system within the walls of the visceral organs that work closely with the ANS.

Esophageal Function

There are profound alterations in esophageal function during sleep [289–292]. Gastroesophageal reflux (GER) is the most common upper gastrointestinal problem. GER occurs most commonly postprandially during wakefulness, but also occurs during sleep but is less frequent. The availability of the method to measure GER during sleep by 24-h esophageal pH monitoring [293] has advanced our understanding of esophageal function and swallowing during sleep. Waking reflux events are rapidly cleared within 1–2 min, whereas sleep reflux events persist longer, causing longer acid contact. Sleep alters normal response to acid mucosal contact [294]. During wakefulness GER causes increased salivary flow and increased swallowing with the complaints of heartburn. In contrast, during sleep salivary flow and swallowing are considerably decreased, causing prolongation of acid mucosal contact. This predisposes to development of esophagitis, for which there are two other factors: decreased esophageal peristalsis in sleep, particularly SWS, and proximal migration of gastric contents in the distal part of the esophagus [289]. The refluxed acid contents are harmful not only to the esophagus but also to the tracheobronchial tree [286–289, 295].

There are two esophageal sphincters, the upper esophageal sphincter (UES) and the lower esophageal sphincter (LES), acting as barriers to reflux. The third barrier is the epiglottis [295]. The LES is the primary barrier to GER, and both the UES and the LES act as barriers to pharyngoesophageal reflux [289, 295, 296]. In a recent paper, Eastwood et al. [297] simultaneously monitored the functions of the LES and UES during PSG studies in 10 normal volunteers and found a decrement of UES pressure during SWS, particularly in the expiratory phase of breathing. In contrast to other investigators [289, 295, 298], Eastwood et al. [297] did not find an alteration of LES pressure. UES pressure is generated mainly by the cricopharyngeus and to a certain extent by inferior pharyngeal constrictor muscles. LES pressure is generated by contractions of the esophageal smooth muscles and the diaphragm. Pandolfino et al. [298] studied 15 normal subjects using a solid-state high-resolution manometry recording from the hypopharynx to the stomach with simultaneous measurement of lower esophageal pH. These authors noted that the majority of postprandial transient LES relaxations were associated with brief periods of UES relaxations.

The relationship of GER and sleep is reciprocal: sleep affects GER and GER in turn affects sleep. Sleep-related prolonged esophageal acid clearance and acid-mucosa contact result from several sleep-related physiological alterations, which include decreased salivary production and swallowing as well as decreased conscious perception of

heartburn and arousal, and delayed gastric emptying [286–289]. In normal individuals who experience episodes of GER, there is generally a reduction in LES pressure [286–289, 295, 296]. Lipan et al. [299] postulated that reflux may advance to the laryngopharynx and into the nasopharynx and paranasal sinuses as a result of a laryngopharyngeal reflux. These authors suggested that breakdown of the following barriers to reflux may cause the laryngopharyngeal reflex: the LES and UES, esophageal motility, esophageal acid clearance, and pharyngeal and laryngeal mucosal resistance. This suggestion is in agreement with that of Orr [295].

Gastric Acid Secretion

During wakefulness, gastric acid secretion depends on food ingestion, increased salivation, and the activity of the gastric vagus nerve. Moore and Englert [300] and Orr [289, 295] showed a clear circadian rhythm for gastric acid secretion in humans. Moore and Englert [300] noted peak gastric acid secretion between 10:00 P.M. and 2:00 A.M. in patients with duodenal ulcer. Figure 11.10 (adapted from Moore and Halberg [301]) schematically shows mean 24-h values for gastric acid secretion in patients with peptic ulcer and normal controls. Acid secretion increases in these patients considerably during the day and at night [302, 303]. The importance of vagal stimulation for the control of circadian oscillation of gastric acid secretion has been demonstrated by the absence of circadian rhythm for gastric acid secretion following vagotomy [304].

Several studies have attempted to understand gastric acid secretion during different stages of sleep, but the results have not been consistent because of methodological flaws and cumbersome techniques [289, 290, 301–308]. An important study was made by Orr et al. [308], who examined five duodenal ulcer patients for five consecutive nights using PSG technique and continuous aspiration of gastric contents. They found no relationship between acid secretion and different stages of sleep or REM versus NREM sleep. The most striking finding was failure of inhibition of acid secretion during the first 2 h of sleep, a result that agrees with the previous study by Levin and associates [302].

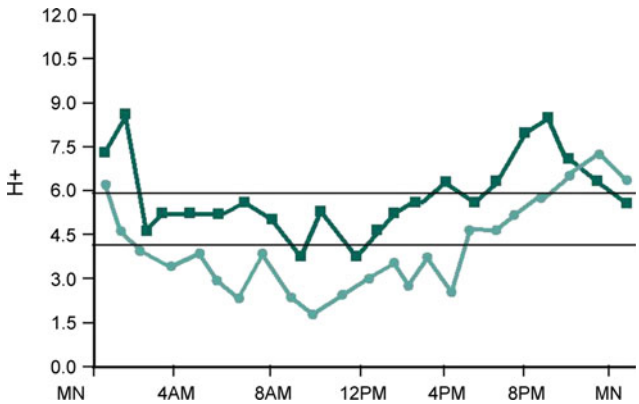

Fig. 11.10 Mean 24-h values for gastric acid secretion from patients with active peptic ulcer disease (*dark blue rectangles*) and normal controls (*light blue circles*) shown schematically. The ordinate shows hydrochloric acid (H^b) secretion in milliequivalents (Adapted from Moore and Halberg [301])

Gastric Motility

Findings regarding gastric motility have been contradictory. Both inhibition and enhancement of gastric motility have been noted during sleep [289–292]. Finch et al. [309] showed that gastroduodenal motility during sleep was related to sleep-stage shifts and body movements. Orr [286, 289] reported that, although no definite statement regarding gastric motility can be made, there seems to be overall inhibition of gastric motor function during sleep.

Intestinal Motility

Although methods are now available to accurately measure intestinal motility, the results of motility studies during sleep are contradictory [286, 288, 289]. A special pattern of motor activity, called *migrating motor complex* (MMC), recurs every 90 min in the stomach and small intestine [310, 311]. This periodicity of the gut motor activity is similar to the cyclic REM-NREM sleep. In fact, a circadian rhythm in the propagation of the MMC has been documented with the slowest velocity occurring during sleep [312–314]. The MMC distribution among REM sleep and NREM sleep stages are random without any consistent relationship, although MMS is modulated by sleep [310]. During both nocturnal and diurnal sleep, MMC cycle length and duration showed a significant reduction [310]. Specifically, the MMC and REM cycles are independent. Consistent abnormalities in the MMC in different bowel diseases have not been documented [289].

Orr [289] summarized the studies from the literature to indicate that there is decreased colonic motility in the transverse, descending, and sigmoid colon. Rao and Welcher [315] observed increased periodic rectal motor activity during sleep; the majority of these contractions are propagated in the retrograde direction and, at the same time, the anal canal pressure is consistently above the pressure of the rectum, thus preventing the passive escape of rectal contents during sleep.

Summary and Clinical Relevance

Patients with peptic ulcer disease may have repeated arousals and awakenings as a result of episodes of nocturnal epigastric pain and failure of inhibition of gastric acid secretion that occurs after sleep onset.

Sleep-related GER, by causing marked prolongation of esophageal acid clearance time, may cause mucosal damage giving rise to esophagitis, laryngopharyngitis, pulmonary aspiration, and exacerbation of bronchial asthma [287, 288, 289, 295, 296]. GER includes esophageal syndrome and extraesophageal complications [316]. Several factors are implicated in the pathogenesis of esophageal syndrome [289, 295]: hiatal hernia, reduced LES pressure, prolonged esophageal acid clearance, and delayed gastric emptying. The UES prevents pharyngoesophageal reflux, and thus loss of UES pressure during sleep makes one vulnerable to reflux of esophageal contents into the pharynx and tracheobronchial tree, which is the most dreaded complication of sleep-related GER. It should be noted that OSAS also predisposes to nocturnal GER disease. Orr et al. [317] have clearly shown that sleep is a significant risk factor for acid migration to the proximal esophagus with prolongation of the acid clearance time, contributing to the extraesophageal complications of reflux such as laryngopharyngitis and pulmonary aspirations.

Patients with functional bowel disorders (e.g., irritable bowel syndrome) have increased sleep complaints, but their sleep architecture does not differ from normal controls [289]. The actual mechanism of sleep disturbance in dysfunctional bowel disorders remains to be determined. Finally, Orr [289] suggested that alterations of the periodic rectal motor contractions and anal canal pressure during sleep in sleeping individuals with diabetes may explain the loss of rectal continence in this condition.

Thermal Regulation in Sleep

Changes in Body Temperature and Circadian Rhythm (See also Chap. 8…)

That body temperature follows a circadian rhythm independent of the sleep–wake rhythm [318] has been demonstrated in experiments involving desynchronization and resynchronization of human circadian rhythms. It has been shown that, when all environmental cues (*zeitgebers*) are removed, the endogenous rhythms are freed from the influence of exogenous rhythms and a free-running rhythm ensues. During this time, it is clear that body temperature has a rhythm independent of the sleep–wake rhythm (Fig. 11.11) [319]. Nevertheless, body temperature has been linked intimately to the sleep–wake cycle [320, 321]. Body temperature begins to fall with the onset of sleep, and the lowest temperature is noted during the third sleep cycle [322].

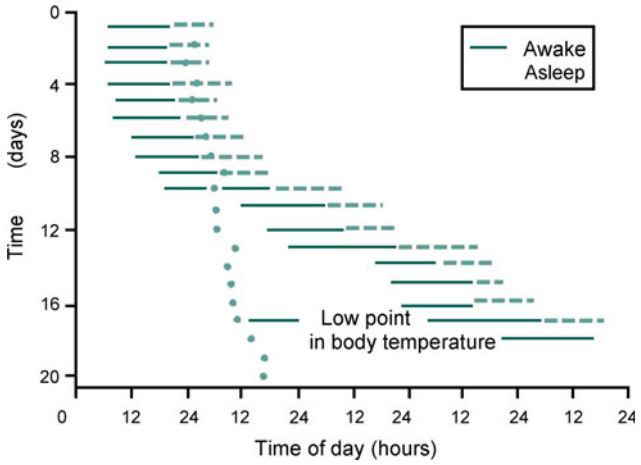

Fig. 11.11 Synchronized (light-entrained) and desynchronized (free-running) rhythms in a person showing dissociation between body temperature and sleep-activity cycles (Reproduced with permission from Aschoff [319])

Role of REM Sleep in Thermal Regulation

During REM sleep, the thermoregulating mechanism appears to be inoperative [320, 323, 324]. Body temperature increases during REM sleep, and cyclic changes in the temperature occur throughout this period. Thermoregulatory responses such as sweating and panting are noted in NREM sleep but are absent in REM sleep; in fact, animals display a state of poikilothermia during REM sleep. However, Bach et al. [321] stated that in contrast to animals, thermoregulation in adult human is not completely abolished during REM sleep but is simply impaired. Brain temperature rises during REM sleep which may be related to all increase in blood supply to the brain causing depression of brain cooling [325]. Szymusiak and McGinty [326] speculated that REM sleep, by elevating brain temperature or by reversing the cooling trend in SWS, prepares the body for behavioral activation. It should be noted that the loss of thermoregulation in REM sleep is not related to inhibition of motor control but is determined by central integration or thermoafferent pathways, or may be due to both mechanisms [320].

Mechanism of Thermoregulation in Sleep

The function of sleep appears to be energy conservation, as evidenced by a reduction in body temperature and metabolism during sleep, especially NREM sleep [322, 323, 327]. Body temperature follows a sinusoidal rhythm with a peak around

9:00 P.M. and a minimum (nadir) around 5:00 A.M. as a result of circadian rhythmicity [328], which is controlled by the master clock in the suprachiasmatic nucleus (SCN). The neural projections from the SCN to the preoptic nucleus of the anterior hypothalamus (POAH) as well as several other brain structures participating in the regulation of sleep and wakefulness are well documented [329]. The circadian system influences core body temperature and the sleep–wake cycle through these connections. At sleep onset, there is a reduction of core body temperature. Exercise or passive body heating causes a rebound stimulating the homeostatic thermostat, permitting peripheral heat loss by vasodilation with a decline in body temperature at sleep onset. Sleep onset latency is shortened, and SWS is increased by peripheral heat loss (e.g., after a hot bath) [330]. This could also be achieved by simply warming the feet [331, 332]. Thermoregulatory effects are also observed after sedative-hypnotic administration. The somnogenic effects of melatonin [333–335] and the benzodiazepines [336–339] are accompanied by a decrease in core body temperature. In contrast, caffeine and amphetamines decrease sleep propensity and increase body temperature [340]. The question is whether sleep onset affects body temperature or body temperature affects sleep onset. The independent circadian rhythm of body temperature appears to be unrelated to a reduction of motor activities at sleep onset [46, 322]. A reduction of body temperature and peripheral heat loss promote sleep onset and amount of SWS; sleep in turn causes a further decrease in body temperature and increases heat loss, thus consolidating sleep. The body temperature and sleep regulation are therefore interrelated. The thermoregulatory changes function as physiological triggers [318] for sleep onset.

Thermosensitive neurons are located mainly in the GABAergic median preoptic nucleus (MnPN) of the anterior hypothalamus (POAH) which received inputs from the skin and thermosensitive neurons in the brain [341]. MnPn and the ventrolateral preoptic (VLPO) nucleus of the POAH are also responsible for generation of NREM sleep [342]. Thus, POAH region is responsible for both the thermoregulation and NREM sleep. Electrical stimulation of the POAH region will cause cutaneous vasodilation, panting, suppression of shivering and decreased body temperature promoting heat dissipation. A POAH lesion suppresses both NREM sleep and thermoregulation. Physical warming [341, 343] or chemical stimulation [344] of the POAH may initiate sleep onset. In the V POAH, warm-sensitive neurons increase firing rates at sleep onset and decrease the rates at sleep offset [345]. An immunocytochemical study by Sherin et al. [346] showed activation of POAH neurons during sleep. These findings provide evidence for a role of temperature in sleep regulation. The conclusive evidence is provided by the observation of increased firing rates of warm-sensitive neurons in the POAH and other brain areas participating in sleep regulation following application of heat to peripheral skin [345, 346], probably through a neural pathway between the peripheral skin and sleep-regulating regions of the brain. Van Someren [347] proposed a thermoregulatory signaling pathway to the circadian system (SCN) promoting circadian regulation of sleep and body temperature. Gilbert et al. [339] suggested a model to show how thermoregulatory changes (e.g., an increase in peripheral temperature and heat loss or a decrease in core body temperature) trigger sleep–wake-promoting areas of the brain directly or via POAH thermosensitive neurons to initiate and consolidate sleep, taking into consideration also the circadian control of sleep and body temperature via the SCN.

MacFadyen et al. [348] observed increased SWS after 2–3 days of fasting in humans, suggesting that the length of hypometabolism helps conserve energy. As stated previously, the POAH neurons participate in both NREM sleep and thermoregulation. McGinty and Szymusiak [349] also cited evidence in support of this hypothesis: POAH warming will facilitate SWS, whereas lesions will suppress it; microinjections of putative sleep factors into the POAH will promote SWS. Szymusiak and McGinty [326, 350] also hypothesized that the neuronal mechanisms in the POAH regions are responsible for both thermoregulation and SWS generation, and that SWS is essentially a thermoregulatory process. Although thermoregulation and sleep are clearly linked, they are also unquestionably separate (Fig. 11.11) [351].

Clinical Relevance

Changes in thermoregulatory function have been noted in some insomniacs and elderly poor sleepers [352–354]. For example, in patients with sleep-onset insomnia [352], the core body temperature rhythm is delayed, suggesting that these people attempt to initiate sleep before the nocturnal dip in body temperature [339]. Similarly, in elderly poor sleepers, there is advancing of the core body temperature rhythm, indicating that these individuals attempt to sleep after the decline in core body temperature [339, 353] or attenuation of the circadian decline in core body temperature [335]. It has been suggested that age-related impairment of the heat loss mechanism or phase advance in body temperature rhythm may partly explain sleep initiation or maintenance difficulty in the elderly [321]. Therefore, thermal manipulation (e.g., behavior to enhance peripheral heat loss) may improve sleep [321, 355]. People with cold feet (e.g., vasospastic syndrome) with impaired heat loss have also prolonged sleep onset latency [339, 356].

Jet lag and shift work may disrupt this linkage of thermoregulation and SWS generation and change the rhythms of sleep and body temperature, which may cause difficulty in

initiating and maintaining sleep and disorganization of sleep architecture and daytime function [320].

Menopausal hot flashes are thought to be a disorder of thermoregulation initiating within the preoptic anterior hypothalamic area. Woodward and Freedman [357] performed 24-h ambulatory recordings of hot flashes and all-night sleep characteristics on 12 postmenopausal women with hot flashes and 7 without hot flashes to determine the effect of hot flashes on sleep patterns. They found that hot flashes were associated with increased stage 4 sleep and that hot flashes occurring in the 2 h before sleep onset were positively correlated with the amount of SWS. They concluded that the central thermoregulatory mechanism underlying hot flashes may affect hypnogenic pathways, inducing sleep and heat loss in the absence of a thermal load in these patients. Menopausal hot flashes (HFs) have a circadian rhythm peaking in the evening around 6:25 PM [358]. HFs can be measured objectively using sternal skin conductance which measures sweating [358]. HFs triggered by a slight rise of core body temperature are manifested by profuse sweating, feeling of intense heat, peripheral vasodilation and sleep disturbances due in part to estrogen depletion [359]. Awakenings and arousals may be triggered by HFs in the first but not the second half of the night because in the second half of the night, REM sleep dominates impairing thermoregulatory mechanism [358].

It has been suggested that environmental temperature and hyperthermia play a role in SIDS [360]. However, multiple factors (e.g., sleep-related respiratory dysrhythmias and CNS disorders, particularly in the region of the arcuate nucleus in the medulla) are implicated in SIDS, and the primary cause of the syndrome remains unknown. Finally, the suggestion that thermoregulatory dysfunction may cause sleep disturbance in patients with depression [361] has no compelling evidence to support it.

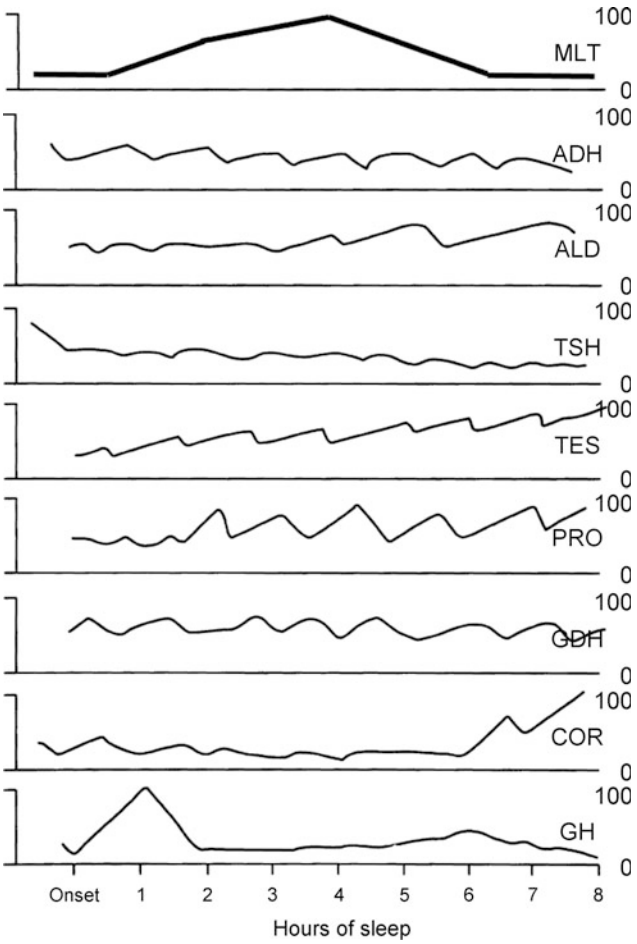

Fig. 11.12 Schematic representation of the plasma levels of hormones in an adult during 8 h of sleep. *Zero* indicates lowest secretory episode and 100 indicates peak. *MLT* melatonin; *ADH* antidiuretic hormone; *ALD* aldosterone; *TSH* thyroid-stimulating hormone; *TES* testosterone; *PRO* prolactin; *GDH* gonadotropic hormone; *COR* cortisol; *GH* growth hormone. (Modified from Rubin [369])

Endocrine Regulation in Sleep

Neuroendocrine secretion appears to be under both circadian control (that is, it shows circadian rhythm in the plasma concentrations of the hormones) and sleep–wake homeostasis. The characteristic pattern of endocrine gland secretion is episodic or pulsatile secretion every 1–2 h, which suggests ultradian rhythmicity. Hormone secretions are thus governed by both the internal biological clock located in the suprachiasmatic nuclei and the stages of sleep. For example, adrenocorticotropic hormone (ACTH), cortisol, and melatonin rhythms are determined by the circadian clock, whereas growth hormone (GH), prolactin, thyroid-stimulating hormone (TSH), and renin rhythms are sleep related. Current evidence indicates that most likely an interaction between the circadian pacemaker and the timing of sleep–wakefulness as well as age, and other diurnal events (e.g., food intake, stress, exercise) determine the daily hormone profiles [362–367]. Changes in the secretion of some major hormones during sleep are described in the following paragraphs. Figure 11.12 shows a schematic of the patterns of neuroendocrine secretion during sleep in an adult human. It is evident from the figure that during the first part of the night the plasma GH level is high and the cortisol level is low, whereas during the later part of the night GH level is low and cortisol level is high, suggesting a reciprocal interaction of the hypothalamic–pituitary–adrenocortical axis and the hypothalamic–pituitary–somatostatin system [368]. Thus there are 24-h oscillations of circulating levels of various endocrine secretions showing a time-of-day dependence [366]. These are driven not only by the endogenous circadian rhythms but also by sleep–wakefulness and behavioral or environmental factors [366].

Growth Hormone

Hypothalamic GH-releasing hormone (GHRH) stimulates release of GH from the anterior pituitary in a pulsatile fashion. In contrast, hypothalamic somatostatin inhibits release of GH [367, 368, 370]. Ghrelin, an appetite-stimulant gastric peptide, also stimulates GH secretion [371]. Sleep, particularly SWS, is associated with increased GH, GHRH, and ghrelin levels. GH secretion occurs shortly after sleep onset during SWS and is inhibited during awakenings and sleep fragmentation. A sexual dimorphism has been noted in GH secretion [365, 366]. Men secrete GH with increased peak amplitude during SWS but also secrete in discrete pulses throughout the day; however, in women, in addition to the GH pulse during first SWS episode, GH is secreted in non-discrete peaks throughout a 24-h cycle. Agents promoting SWS (e.g., γ-hydroxybutyrate) will encourage GH secretion. GH has an anabolic function that is mediated by insulin-like growth factor-I produced in the liver and other organs [368, 370].

Takahashi et al. [372] observed that the plasma concentration of GH peaked 90 min after sleep onset in seven of eight normal subjects and lasted approximately 1.5–2.5 h. The peak is related to SWS (stages 3 and 4 of NREM sleep). Several subsequent reports showed nocturnal peaks of GH in association with SWS [357, 365, 373–379]. Although the major peak in plasma GH occurs during the early part of nocturnal sleep, it has been shown that, in approximately one-fourth of young, healthy men, peaks in circulating GH occur before sleep onset [378]. Sleep deprivation causes suppression of GH secretion, which may be an age-dependent phenomenon that develops during early childhood. The sleep-related release of GH is absent before age 3 months and is reduced in old age [367, 368, 377, 379, 380, 381]. It should be noted that GH secretion is regulated physiologically by opposite actions of GHRH and somatostatin [382]. It has been suggested that somatostatin may induce sleep deterioration in the elderly [382]. Van Cauter and Plat [367, 381] suggested that age-related decrements in GH secretion play a major role in the hyposomatotropism of senescence. The timing of the release of GH shifts if sleep is phase advanced or phase delayed, suggesting a close relationship between episodic GH secretion and sleep [383]. Sadamatsu et al. [384] measured 24-h rhythms of plasma GH, prolactin, and TSH in nine normal adult men by means of serial blood sampling at 30-min intervals. Their findings suggested two mechanisms regulating GH secretion: one that is sleep-independent and has an ultradian rhythm and another that is sleep-dependent.

There is some evidence of possible circadian influences on the regulation of GH secretion from a jet lag study by Goldstein and associates [385] and a study of GH secretory rate in night workers by Weibel et al. [386]. Increased GH secretion has been noted after flights both eastward and westward [385].

The tightly linked normal relationship between GH and SWS is disrupted during sleep disturbances (see later under *Clinical Relevance*). It is notable that such a tight relationship is observed only in humans and baboons, and not in rhesus monkeys and dogs [387], a fact that may relate to the monophasic sleep patterns observed in baboons and humans [369].

An activation of hypothalamic GHRH neurons promotes both the onset of SWS and the peak GH levels, suggesting a direct link between SWS and GH secretion [367, 368, 370, 388]. Furthermore, the GHRH gene is found in the mouse in the same region regulating NREM sleep in the hypothalamus [389]. Experimentally, both intravenous [390] and intranasal [391] administration of GHRH in young men promoted sleep [368]. Many hypothalamic GHRH neurons are thought to be GABAergic [368, 392]. It is notable that POAH GABAergic neurons are important in initiating NREM sleep (see Chaps. 2, 5 and 8), strengthening the link between GHRH and sleep-promoting neurons in the anterior hypothalamus.

Adrenocorticotropic Hormone and Cortisol Secretion

The 24-h ACTH-cortisol rhythm is primarily controlled by circadian rhythmicity but clearly modulated by sleep–wake state. Sleep onset is associated with a decrease in cortisol secretion but with a rapid elevation in the later part of the sleep at night and with subsequent decline throughout the day [280, 362, 365–368, 393–397]. These effects of sleep onset and sleep offset are found to be absent during sleep deprivation. Studies have also shown that awakenings causing sleep interruption will increase the pulsatile cortisol secretion [362]. The inhibitory influence of early nocturnal sleep on ACTH-cortisol levels is most marked during SWS [395]. Some studies [398, 399] have documented both a circadian and an ultradian episodic pattern of secretion for cortisol and ACTH. However, it should be noted that, in contrast to nocturnal sleep, daytime sleep fails to significantly inhibit cortisol secretion; this suggests that sleep does not suppress cortisol release at any point of its circadian rhythm, but only within a limited range of entrainment [400, 401].

In general, the circadian rhythm of cortisol secretion remains undisturbed in disease states such as Cushing's syndrome and narcolepsy [402]. With depression, the earlier occurrence of the lowest point of cortisol levels is thought to indicate a circadian phase advance [403]. The failure of

dexamethasone to suppress cortisol secretion in depressed persons is not necessarily positively correlated with reduced REM latencies noted in depression [404]. Sleep deprivation itself may be responsible for such failure, as is noted in normal individuals [405].

Sleep fragmentation is associated with pulsatile increase in cortisol secretion. Primary insomnia patients had higher mean nocturnal cortisol levels [315, 406]. However, in one report [407], nocturnal cortisol levels did not differ between controls and insomnia patients. Sleep deprivation is also associated with hypercortisolism similar to that noted in normal elderly subjects, accompanied by repeated nocturnal awakenings [408].

Prolactin Secretion

The hormone prolactin, synthesized mainly by the anterior pituitary gland, promotes lactation in women and also participates in multiple metabolic and immune functions. Plasma prolactin concentration has long been known to exhibit a sleep-dependent pattern, with the highest levels occurring during sleep and the lowest during waking [365–368, 402, 409–411]. The plasma prolactin level does not seem to have a definite circadian rhythm; it appears to be linked to sleep [409, 410] but is not related to specific sleep stages [402]. The prolactin level begins to rise approximately 60–90 min after sleep onset and peaks in the early morning hours from approximately 5:00 to 7:00 A.M. [412]. Studies by Mendelson et al. [402, 413], Rubin et al. [414], and Van Cauter et al. [415] showed no relationship between prolactin secretion and NREM–REM cycles. Subsequent studies, however, have clearly shown that prolactin secretion is also driven by a sleep-independent circadian pattern [416, 417]. Waldstreicher et al. [416] studied 12 men and 10 women using a constant routine protocol, during which the subjects remained in semirecumbent wakefulness. The authors clearly documented a robust, sleep-independent, endogenous circadian rhythm of prolactin secretion in humans. The authors hypothesized that the endogenous components of the circadian rhythm of prolactin secretion, along with body temperature, urine production, and cortisol, TSH, and melatonin secretion, are driven by a central circadian pacemaker located in the SCN of the hypothalamus [416].

Prolactin secretion is suppressed by dopamine but stimulated by thyrotropin-releasing hormone [402]. Although prolactin secretion is related to sleep, the secretory pattern of prolactin does not decline with age like that of GH [418]. In women who breastfeed and those with hyperprolactinemia, SWS is increased.

Gonadotropic Hormone (Gonadotropin)

The gonadotropin-releasing hormone (GnRH) produced by the hypothalamus stimulates the anterior pituitary gland to secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In men, LH is the stimulus for the secretion of testosterone by the testes, and FSH stimulates spermatogenesis. In women, the ovarian hormones estrogen and progesterone are secreted by the ovaries in response to LH and FSH, which also are responsible for ovarian changes during the menstrual cycle. It has been difficult to study the relationship between FSH and LH plasma levels because of the limitations of assay sensitivity in measurements and the inaccuracies associated with pulsatile secretion of circulating gonadotropin. A clear relationship between FSH and LH plasma levels and the sleep–wake cycle or sleep stages in children or adults has not been found [367]. FSH and LH show a pulsatile pattern of secretion, but there is no clear variation in their diurnal pattern of secretion [365]. In pubertal boys and girls, gonadotropin levels increase during sleep [367, 419–423]. In 62 healthy 6- to 13-year-old girls, Rosenfield et al. [424] observed that plasma LH and FSH levels rose steadily during sleep throughout the prepubertal years. However, these findings are inconsistent in boys [425]. These authors [425] also studied 9- to 15-year-old boys and noted that LH and FSH plasma levels rose steadily during sleep in the late prepubertal years. By using an ultrasensitive immunofluorometric assay to measure plasma LH and deconvolution analysis to depict LH secretory characteristics, it has been possible to show an increase in sleep-associated GnRH and LH secretion during puberty and the prepubertal stage in boys [426]. Nocturnal elevation of gonadotropins is associated with nocturnal rise of testosterone in boys at puberty.

FSH and LH show pulsatile activities throughout the night without showing any relationship to testosterone secretion. During sleep early in puberty [419], however, there is a marked rise of plasma LH concentration, in contrast to testosterone or prolactin. Based on the observation that LH and prolactin secretion precedes testosterone secretion by 60–80 min, Rubin [369] suggested a relationship between these hormones. Some studies in adult men have shown a modest elevation of nocturnal LH and possibly FSH levels [427]. LH and FSH secretion show no distinct circadian rhythms. Plasma testosterone levels rise at sleep onset and continue to rise during sleep at night [428]. The nocturnal rise of testosterone has been found to be linked to REM sleep in some studies [429] as there was attenuation of this nocturnal rise in those who failed to have REM sleep after sleep fragmentation experiments [430]. In older men, the sleep-related rise in testosterone is reduced and the

relationship to REM sleep is lost [431, 432], and the circadian variation of testosterone and LH is reduced [427].

In contrast to normal men, a sleep-related inhibitory effect on LH secretion has been noted in the early parts of the follicular and luteal phases of the menstrual cycle [431–434]. In a more recent study, Klingman et al. [435] noted no circadian rhythm on LH and FSH in women during early follicular phase.

Thyroid-Stimulating Hormone

A distinct circadian rhythm has been established for the secretion of TSH in normal humans [280, 365–367, 398, 435, 436]. There is general agreement that sleep has an inhibitory effect on TSH secretion: TSH levels are low during the daytime, increase rapidly in the early evening, peak shortly before sleep onset, and are followed by a progressive decline during sleep [367, 399, 402, 437]. Sleep deprivation is associated with nocturnal increase in TSH levels [362, 408]; however, during SWS rebound following prior sleep deprivation, there is marked inhibition of nocturnal TSH rise, suggesting that the sleep-associated fall in TSH is related to the SWS stage [438]. The fact that TSH secretion is not suppressed significantly during daytime sleep and the fact that sleep-related inhibition of TSH secretion occurs following nighttime elevation of TSH indicate an interaction between circadian timing and sleep for the control of TSH secretion [362]. TSH is thus controlled by both circadian clock and sleep homeostasis [366, 367]. Exposure to bright light in the early evening can delay the TSH circadian rhythm, whereas exposure late at night or in the early morning can advance it [367, 437].

Melatonin

Melatonin, the hormone of darkness, is synthesized by the pineal gland and released directly into the bloodstream or cerebrospinal fluid [439–447]. The amino acid L-tryptophan, the precursor of melatonin, is converted to 5-hydroxytryptophan by the enzyme tryptophane hydroxylase, followed by decarboxylation to serotonin. The enzymes acetyltransferase and hydroxyindole-*O*-methyltransferase then catalyze serotonin into melatonin (*N*-acetyl-5-methoxytryptamine). It has been clearly shown that the environment light–dark cycle and the SCN act in concert to produce the daily rhythm of melatonin production. Melatonin secretion is controlled by a complex multisynaptic pathway, which can be briefly outlined as follows [439]: impulses from the retinal ganglion cells are transmitted via the retinohypothalamic tract to the SCN, which then sends efferent fibers to the PVN of the hypothalamus and then to the intermediolateral horn cells of the upper thoracic spinal cord, and subsequently to the superior cervical ganglia, which in turn transmit impulses via the postganglionic efferent fibers to the pineal gland. This complex neural pathway is activated during the night, triggering melatonin production, which is suppressed by exposure to bright light. The melatonin circadian rhythm is clearly driven by the circadian rhythm of the SCN through activation of two major melatonin receptors (MT_1 and MT_2) [448–454]. Both receptors are heavily concentrated in the SCN. MT_1 receptors inhibit SCN neuronal activity and MT_2 receptors phase-shift circadian firing rhythms in the SCN. Melatonin begins to rise in the evening on attaining maximum values between 3:00 and 5:00 A.M. and then decreasing to low levels during the day [440–442, 445]. The maximum nocturnal secretion of melatonin has been observed in young children, ages 1–3 years; secretion then begins to fall around puberty and decreases significantly in the elderly [446, 455].

Because of the important effect of melatonin on circadian rhythms and its possible hypnotic effect, there have been a few clinical applications of melatonin that appear promising [448, 449, 452, 456–467]. Placebo-controlled, double-blind studies using a large number of subjects need to be performed, however, before accepting melatonin as a treatment for various sleep disorders. Administration of melatonin has been shown to have some beneficial effects on the symptoms of jet lag [445, 456, 463, 464, 467] and on nighttime alertness and daytime sleep of shift workers [438, 445, 461, 468]. Administration of melatonin has been found to be beneficial in some primary circadian rhythm sleep disorders, such as delayed sleep phase syndrome [456, 469, 470] and non-24-h sleep–wake syndrome [437, 456, 458–460, 471, 472]. In a subgroup of elderly subjects with reduced melatonin secretion at night, beneficial effects of melatonin on sleep disturbances have been noted in those with insomnia [442, 473]. The hypnotic effect of melatonin has been noted in several reports [442, 474–476]. Again, however, placebo-controlled, double-blind studies with large numbers of subjects are needed before considering the clinical applications of melatonin as a hypnotic agent. In conclusion, until further studies are conducted to determine the long-term effects of melatonin, its indiscriminate use (melatonin is available as a nutritional supplement without U. S. Food and Drug Administration control) should be discouraged. Furthermore, melatonin should only be administered to subjects with clearly documented melatonin deficiency [442, 443, 473].

Miscellaneous Hormones

Renin–Angiotensin–Aldosterone System

The renin–angiotensin–aldosterone (RAA) is a complex system [477] is controlled by the ANS, BP variation, serum electrolytes, particularly sodium, and the sleep process.

Renin, an enzyme secreted by the juxtaglomerular cells of the kidneys, acts upon angiotensinogen found in the α_2-globulin fraction of blood to form angiotensin I, which is then converted by a chloride-dependent converting enzyme into angiotensin II; the latter acts upon the zona glomerulosa of the adrenal cortex to stimulate aldosterone secretion. The juxtaglomerular cells act like baroreceptors responding to changes in BP variation during sleep. During NREM sleep, especially SWS, PRA increases, associated with a fall in BP and a reduction of sympathetic activity as indicated by a significant decrement of the LF/HF power ratio in the spectral analysis of electrocardiographic R–R intervals [478]. In contrast, during REM sleep associated with fluctuating BP and intermittently increased sympathetic activity, there is a significant decrement of PRA [246, 477]. Brandenberger et al. [479–481] demonstrated that 24-h variations in PRA are not circadian in nature but are related to sleep processes and are dependent on the regularity and length of the sleep cycles in an ultradian manner. Thus, PRA oscillations are synchronized to the NREM–REM cycles during sleep [481] (Fig. 11.13). Later studies, however, have shown that the RAA system has clear circulation oscillations [280, 482, 483].

During sleep, aldosterone levels are increased compared with levels during wakefulness [484]. Sleep-related aldosterone levels are related to PRA oscillations, whereas during daytime waking periods aldosterone levels parallel cortisol pulses [484]. Some investigators [280], however, noted that the circadian rhythm of aldosterone parallels that of cortisol also at night. Thus, the 24-h aldosterone secretory pattern is influenced by a dual system: renin–angiotensin and ACTH-cortisol. Sleep deprivation modifies the 24-h aldosterone profile by preventing the rise of nocturnal sleep-related aldosterone release, causing an alteration of overnight hydromineral balance [484].

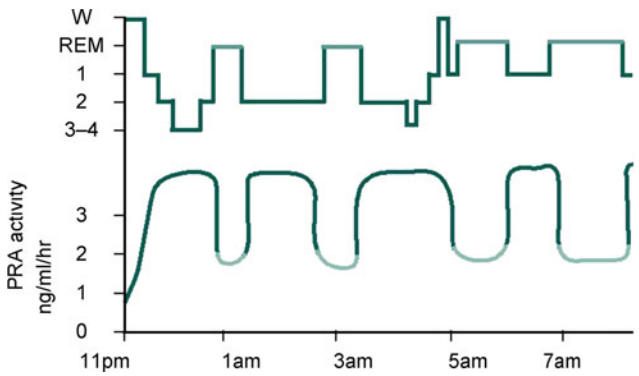

Fig. 11.13 Plasma renin activity profiles schematically shown in a normal subject during sleep at night from 11:00 P.M. to 7:00 A.M.. Note plasma renin activity (PRA) oscillations synchronized to NREM–REM cycling, with the lowest values during REM sleep (Adapted from Brandenberger et al. [481])

Renal Excretion of Water and Electrolytes at Night

In normal persons, nocturnal urine volume and electrolytes decrease owing to decreased glomerular filtration, increased reabsorption of water, increased activation of the RAA system, and decreased sympathetic activity [484, 485]. Antidiuretic hormone (ADH) shows episodic secretion without any relationship to sleep, sleep stages, or circadian system, but the plasma levels of ADH and aldosterone are increased during sleep [370, 414] explaining the reasons for reduced urine production and urinary sodium at night.

Parathyroid Hormone

In normal young men, Chapotot et al. [486] noted a significant increase in levels of plasma parathyroid hormone (PTH or parathormone) during nighttime sleep compared with waking periods but failed to find a significant association with SWS, REM sleep, or plasma ionized calcium and phosphate levels. Their findings demonstrated that the 24-h plasma PTH profile is influenced by sleep processes with a weak circadian component. These findings of Chapotot et al. [486] of a lack of a significant association with sleep stages contradict the earlier observations by Kripke and associates [487] of PTH peaks related to cycles of SWS.

Clinical Relevance

The tightly linked normal relationship between GH and SWS is disrupted during sleep disturbances. For example, in narcolepsy [488], depression of GH secretion is associated with sleep disturbance, and in some cases of insomnia [489], there is a dissociation between SWS and GH secretion. Such dissociation also occurs in old age [377, 465, 466, 490, 491]. These findings suggest that there are independent mechanisms for controlling GH secretion and SWS.

In acromegaly patients, GH secretion remains high throughout sleep and has no relationship to sleep onset or SWS [492, 493]. Diminished, sleep-related secretion of GH is found in both sleep apnea and narcolepsy [494]. In OSAS patients, nocturnal release of GH and prolactin is decreased in untreated apneic subjects but is increased following continuous positive airway pressure (CPAP) treatment [362, 365, 367]. Atrial natriuretic peptide (ANP) is increased in OSAS, resulting in suppression of the RAA system and increased urinary and sodium output [495]. PRA profiles show a flat oscillation in OSAS patients and are normalized after CPAP treatment. The normalization of sodium and urinary output in OSAS patients following CPAP treatment could be related to restoration of normal PRA and aldosterone oscillations as well as decreased release of ANP [495].

The age-related decrease in GH may be related to the reduction of SWS and increased fragmentation of sleep in the elderly. Similarly, decreased prolactin levels in normal elderly subjects may cause increased awakenings and fragmented sleep. The exponential decrease of GH and linear increase in cortisol in old age correlates with age-related decrease in SWS; these changes may impair the anabolic function of sleep in the elderly [362, 365, 367].

Glucose tolerance and thyrotropin concentrations are reduced, whereas evening cortisol concentrations and sympathetic nervous system activity are increased after sleep debt resulting from partial sleep deprivation [365, 367, 408]. Thus, sleep debt has a harmful effect on carbohydrate metabolism and endocrine function. These effects are similar to those noted in normal aging, thus suggesting that sleep debt may increase the severity of age-associated chronic disorders. Age-related sleep fragmentation may also cause increased nocturnal corticotropic activity [363, 365–367, 370]. The pattern of GH secretion associated with clinical depression is contradictory: both impairment and normal sleep-related GH secretion have been noted [402, 489, 496]. GH secretion is somewhat disturbed in alcoholics [497]. Schizophrenia, alcoholism, and depression in adults are associated with impaired sleep-related GH secretion [402]. Whether the impairment is related to an associated decrease in SWS or abnormalities of biogenic amine metabolism in these disorders cannot be stated with certainty. Cushing's syndrome is associated with decreased SWS and GH secretion. Nocturnal GH secretion was found to be higher than normal, and SWS increased, in two patients with thyrotoxicosis [498]. These abnormal findings normalized in response to antithyroid medication.

There is a suggestion that the shift work-related increased incidence of infertility in women may be related to a sleep-related inhibitory effect on gonadotropin release during the follicular phase of the menstrual cycle [499].

Prolonged dyssynchrony or a mismatch between central and peripheral circadian oscillators, and sleep–wake rhythm may impair endocrine homeostasis [366]. Such chronic dyssynchrony as seen in shift work disorder may cause altered immune function, increased tumor growth, increased adiposity, cardiometabolic syndrome (e.g., cardiovascular diseases such as ischemic heart disease) and gastrointestinal disorders [366].

There has been considerable progress in our understanding of how melatonin modulates sleep and circadian phase through activation of the MT_1 and MT_2 melatonin receptors, which inhibit (MT_1 receptors) neuronal activity and phase-shift (MT_2 receptors) circadian firing rhythms in the SCN [448]. This knowledge led to the development and availability of a melatonin receptor agonist (ramelteon) for the treatment of sleep-onset insomnia [454]. Additional melatonin receptor agonists are being developed for treating circadian rhythm disorders and depression. A dysfunction of the multisynaptic pathway from sCN to the pineal gland for melatonin synthesis may abolish melatonin production [439]. Patients with high cervical spinal cord injury affecting this pathway show no circadian rhythm of melatonin, whereas patients with injury below the third thoracic vertebral level sparing this pathway display normal melatonin circadian rhythm.

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Sleep and Immune Regulation

12

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Introduction

While it has long been recognized that inadequate sleep at night is followed by daytime sleepiness, only in the last few decades has sleep deprivation begun to be viewed as a significant health problem with negative consequences including obesity, diabetes, cardiovascular disease, and hypertension. These specific pathologies are all associated with inflammation and emphasize the crucial relationship between sleep and immune function. Given the high prevalence of insufficient sleep that has been reported in both civilian and veteran populations in recent years [1], understanding this relationship has become increasingly important.

Although the research on inflammatory pathologies related to sleep has largely been conducted in the last 20 years, our understanding of this sleep–immune relationship stems from research conducted in the early twentieth century. At that time, scientists in both Japan and France discovered that injecting cerebrospinal fluid from sleep-deprived dogs into well-rested dogs resulted in deep slumber in these otherwise healthy animals [2, 3]. This seminal research was largely unrecognized until the early 1960s, when several independent research groups began to focus their attention on the humoral regulatory mechanisms for sleep, using similar methods to those used by Ishimori and Pieron [4–6]. Following that work, Pappenheimer and colleagues demonstrated a similar transfer of cerebrospinal fluid from sleep-deprived goats to well-rested rats (resulting in sleep induction) and further characterized the sleep-inducing agent as "Factor S," a muramyl peptide [7]. These breakthroughs led directly to our current body of clinical and preclinical studies of sleep and immune function.

Accumulating and novel data from the experimental literature as well as field-based research have provided us with a more comprehensive understanding of this complex relationship. Experimental studies of sleep loss have now examined the sleep–immune relationship across multiple domains, including white blood cell counts, inflammatory mediators, and transcription factors (e.g., [8–10]). This review will present an overview of the current state of the field with respect to both innate and acquired immunity. Additionally, emerging research from clinical trials or intervention studies, which have the potential to further illuminate the bidirectional nature of the relationship between sleep and immunity, will be presented when available.

In order to best understand the sleep–immune relationship, it is also necessary to consider the relationship of hormones with respect to both sleep and immunomodulation. Many hormones demonstrate a circadian pattern, and levels of these hormones can also be affected by sleep loss. Please refer to Fig. 12.1 for a schematic of the diurnal rhythms of immune and endocrine markers and Fig. 12.2 for the impact of sleep deprivation on relevant endocrine markers. While a full description of what is known about the relationship between sleep and endocrine function is beyond the scope of this chapter, we will briefly review sleep-related endocrine effects that facilitate a balanced and well-functioning host defense system, with an emphasis on cortisol and hormones associated with energy regulation and metabolism. For a more comprehensive review of sleep and endocrine relationships, please refer to [11].

Cortisol Cortisol has long been recognized as a powerful immunomodulating hormone with a known diurnal rhythm [12]. The relationships between the diurnal rhythm of cortisol and a range of white blood cells as well as cytokines and their receptors have been well documented [13–15]. The fact that it has endogenous immunomodulating potential has

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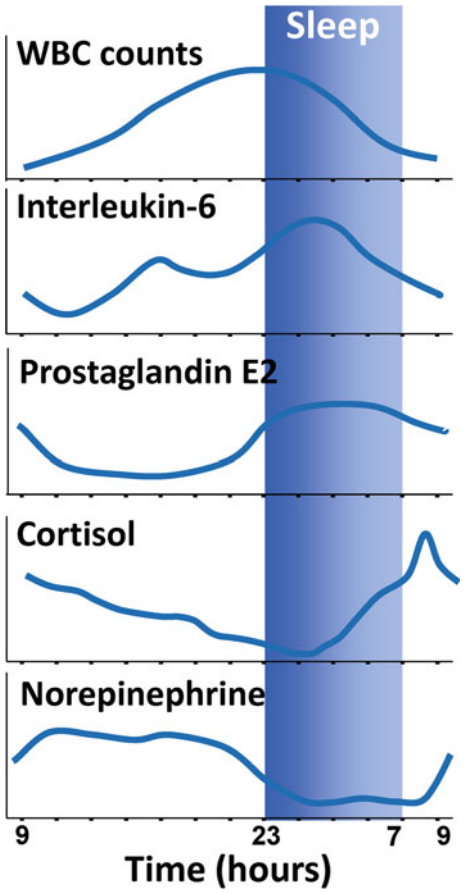

Fig. 12.1 Diurnal rhythms of immune and endocrine markers (schematic). Without sufficient and good quality sleep, rhythms are upregulated or displaced (i.e., shifting of nadirs and peaks)

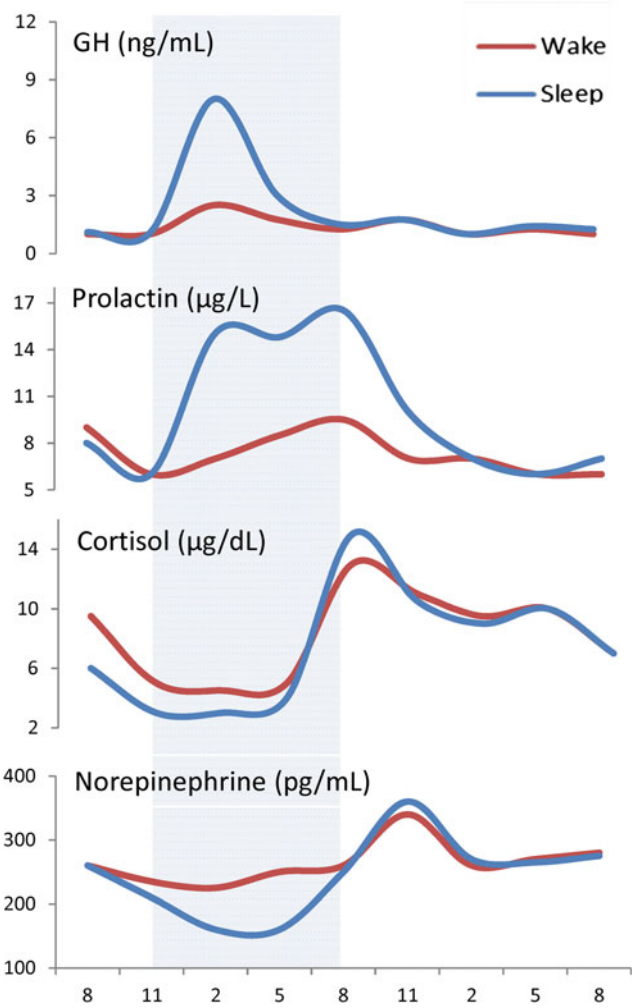

Fig. 12.2 Immunoregulatory hormones are affected by total sleep deprivation (schematic)

also been recognized at least since the 1990s when Pollmächer and colleagues showed that an injection of lipopolysaccharide LPS given in the morning when cortisol is at its peak had a greatly diminished effect on the febrile response, compared to when the challenge was administered in the evening, when cortisol was close to its nadir [16]. This effect was seen despite similar IL-6 and TNF-alpha production in response to challenge, suggesting that the endogenous corticoids have a suppressive effect on the pro-inflammatory effects of these cytokines [16]. In addition, sleep has been shown to be associated with activation of the mineralocorticoid receptor, which has been suggested as a potential mechanism through which sleep supports adaptive immunity [17].

Energy metabolism and adipose tissue hormones It is also known that sleep deprivation alters basal metabolic function, which can contribute to changes in immunological homeostasis [18]. Both total and partial sleep loss have been shown to slow glucose metabolism [19, 20]. Thus, insufficient sleep may be an important contributing mechanism in the clinical development of insulin resistance. Additionally, acute total and sustained partial sleep deprivation have been shown to reduce the diurnal rhythm amplitude [21] and levels [22] of peripheral circulation levels of leptin, an adipocyte hormone that signals satiety to the brain. Levels of ghrelin, a hormone that signals hunger to the brain, and subjective appetite are also increased during partial sleep deprivation [23]. Both changes in insulin resistance and glucose metabolism, and in appetitive hormones may lead to weight gain and changes in adiposity. As adiposity, particularly visceral adiposity, contributes to the production of interleukin 6 (IL-6) and C-reactive protein (CRP) [24, 25], these changes in endocrine system function have a direct impact on the sleep–immune relationship. These hormone changes are particularly relevant when considering the increasing prevalence of obesity [26]

and the development of the metabolic syndrome [27] along with the frequency of chronic insufficient sleep [1], in modern society.

Experimental

Largely conducted in laboratory settings, experimental sleep deprivation (or sleep restriction) studies provide a highly controlled environment in which the effects of sleep loss on immune parameters can be assessed. To date, the vast majority of these studies have been conducted in healthy young adults that have undergone thorough medical screenings in order to provide the clearest understanding of the mechanisms underlying the relationship between sleep and immunity. The field is currently lacking controlled studies that examine how sleep loss affects immune function in potentially more vulnerable populations (e.g., older adults, chronic illness).

Historically, the majority of experimental studies of sleep loss involved acute (total) sleep deprivation—the length of which ranged from 24 to 126 h. Experimental studies of sleep loss have examined the sleep–immune relationship primarily in whole cell counts and in inflammatory mediators of the immune system. There are multiple studies examining how white blood cell counts and differential cells respond under conditions of total sleep deprivation. One of the earliest studies, which was conducted in the 1960s, healthy volunteers were sleep-deprived for up to five nights and days, after which increases in white blood cells, particularly neutrophils, were observed [28]. Subsequent studies of total sleep deprivation report consistent increases in leukocyte number and function [8, 15, 29–31], as well as in some white blood cell count (WBC) subsets (neutrophils [8, 28, 30, 31] and monocytes [8, 15, 30]). Together, these findings collectively suggest that sleep loss activates the innate immune system, as well as the adaptive immune system (discussed below). This conclusion is supported by more recent studies demonstrating that total sleep loss is also associated with upregulation of a range of inflammatory markers, including IL-1 beta, IL-6, CRP TNF-alpha, and prostaglandin E2 in some studies, although results are not as uniformly consistent across studies [32–37].

More recent studies have utilized shortened sleep protocols, ranging from a single night to more chronic sleep restriction paradigms, in which participants' sleep is restricted to a particular shortened length of time each night. It is thought that this model of sleep restriction, rather than the model of total sleep loss, may more closely model the real-world phenomena of chronic insufficient sleep. Similar to participants enrolled in studies of total sleep deprivation, sleep restriction studies typically examine the effects of sleep restriction on healthy adults who typically sleep about 8 h a night. This allows for a controlled dose of sleep loss of similar relative magnitude (compared to habitual duration) across participants. In one of the earliest partial sleep loss studies, participants were restricted to four total hours of sleep per 24 h day over four nights, with sleep opportunities divided into two 2-h naps—one of which occurred in the afternoon and one at night [35]. In this study, no increases in IL-6, TNF-alpha, or TNF-alpha receptors were observed; however, in a parallel total sleep loss condition (see above), increases in TNF-alpha receptors and IL-6 were found [35]. Indeed, effects of partial sleep loss on TNF-alpha and its receptor have been mixed, with some studies finding significant increases (men only [37]) while others do not [35, 38]. IL-6 findings have been more consistent, with deprivation paradigms of sleep restricted to 6 h for 7 nights [37], 4 h/night for 10 nights [33], and 4 nights of sleep restricted to 4 h of split sleep [35] reporting increases in IL-6. Increases in other inflammatory markers have also been observed, including CRP [33, 36, 38] and IL-1 beta [36], although, again, not all studies show this consistent increase [9].

While collectively these experimental, laboratory-based studies of sleep loss demonstrate a significant upregulation of the acute host defense and inflammatory response, there are several additional factors that should be taken into consideration when interpreting these results. Many of these studies are small and thus have the potential to be underpowered, particularly when multiple immune markers are measured. Additionally, basal levels of these immune markers demonstrate considerable variability resulting from a range of factors, including individual factors (stress, temporal proximity to physical activity or meal intake, body mass index, and other metabolic factors), circadian factors (IL-6 in particular has been shown to have circadian variation [13, 39]), and measurement effects (e.g., effects of catheterization [40] and potential sample contamination [41]). All of these factors can increase the variability of the data and have the capability to mask potentially small, yet important changes in immune markers following sleep loss. Collectively, these findings reinforce the need for careful methodological consideration when comparing outcomes across studies.

More recent work has begun to explore the physiological mechanisms underlying the relationships between insufficient sleep, circadian rhythm disruption and negative health outcomes, focusing on the level of gene expression. Moller-Levet and colleagues compared transcriptome analyses after either one week of sufficient sleep (8.5 h/night) or one week of insufficient sleep (5.7 h/night) and found that expression of genes affected by insufficient sleep was associated with not only circadian rhythms and sleep homeostasis (including IL-6), but also oxidative stress and metabolism [10]. A follow-up study by the same research

team found that mis-timed sleep alone also leads to a reduction in rhythmic transcripts [42]. Together, these findings suggest that the immune system is affected by sleep alterations even at the molecular level. We expect that the study of gene expression in relation to sleep loss and immune parameters will be an increasing area of research focus in the future.

In addition to these direct relationships between sleep loss and increases in immune and inflammatory markers, there is a wealth of evidence that sleep supports components of the adaptive immune response. The effects of insufficient sleep on adaptive immune system components have been mostly tested using vaccination models, and exploring the magnitude and time line of the primary antibody response. In one of the first laboratory studies in this area, two groups of adults received a hepatitis A vaccination; one group was deprived of sleep for one night prior to the vaccination, and the other was allowed a full night of sleep. The well-rested group was observed to have an immune response of nearly twice the magnitude of their sleep-deprived comparison subjects [43]. In a follow-up study, vaccination-induced T helper (Th) cell and antibody (AB) responses were monitored over a one-year period following a series of three hepatitis A vaccines, with participants randomized to either sleep or wake the night *following* each vaccine administration. Again, the individuals in the sleep condition had twice the frequency of antigen-specific Th cells and an increased fraction of Th1 cytokine-producing cells; these differences remained significant over the one-year follow-up period [44]. There is also direct evidence that sleep duration can impact the immune systems response to an actual viral challenge, as demonstrated by Cohen and colleagues [45]. In this study that used both field and experimental techniques, habitual sleep duration was assessed via self-report prior to entering the laboratory, where they were then inoculated with a dose of the common cold virus. Participants who slept seven or fewer hours/night were at three times greater risk of developing a cold [45].

Two more recent studies provide additional support for this relationship between sleep and the adaptive immune response. Benedict and colleagues investigated the effects of acute sleep deprivation on the antibody titer response to a novel influenza A H1N1 virus (swine flu) [46]. Twenty-four healthy students received the vaccine after a single night of sleep deprivation or regular sleep. Of note, the antibody response in the sleep-deprived group was 60% lower in the early observation phase of the immune response (day five following the vaccine) although this difference was observed only in males [46]. The authors suggest that acute sleep deprivation may delay the induction of adaptive immune responses in males, but that it does not have lasting effects on the antibody titer response to influenza vaccination, with equivalent responses in both sexes on follow-up days 10, 17, and 52. These results were consistent with those of an earlier pilot study that reported lower antibody titer against a seasonal influenza virus only in the early period (10 days) but not later periods (after 28 days) following a brief exposure to acute sleep deprivation [47]. These studies suggest that insufficient sleep may delay, or at least reduce, the adaptive immune response.

Collectively, these experimental sleep loss studies demonstrate that sleep loss can affect a range of established markers of the inflammatory system, including IL-6, CRP, IL-1 beta, TNF-alpha, and prostaglandin E2. Many of these inflammatory markers are considered to be pro-inflammatory in nature; however, it is important to be mindful that the regulation of inflammatory parameters is complex and is often bidirectional, such that increases in one inflammatory parameter may eventually function to down-regulate another aspect of the system. Additionally, as described above, there is significant variation in the experimental parameters (e.g., the duration and timing of sleep loss, diet, body positional, and activity control of study participant); this, in combination with the study population itself, may help explain patterns of immune responses in a given study compared to another. Replication of specific protocols and expansion of study participants to include more vulnerable populations will provide valuable information to help us better understand the differential pattern of results.

Field and Population Studies

Field studies, which include both epidemiological studies and large-scale non-laboratory-based research, complement experimental or laboratory-based protocols. This area of research helps provide a better understanding of the relationship between sleep and immune function in a real-world setting, allowing for better estimations of the effects of, for example, the chronicity of sleep loss. This real-world validity, however, is countered to some extent by the loss of experimental control when research moves beyond the laboratory. While well-conducted studies are able to control or covary for an appropriate range of factors, they cannot execute the degree of control seen in laboratory studies given their much larger scale. Considered together, experimental and field-based studies provide a more comprehensive picture of the sleep–immune interaction.

There are numerous of epidemiological studies linking short sleep duration with negative health outcomes (e.g., body mass index, risk of hypertension [48, 49]), as well as risk of all-cause mortality. Several meta-analyses have found increased risk of all-cause mortality in both habitual short and long sleep durations, with elevated risks with short sleep of 10–12 and 23–30% with long sleep [50, 51]. While not directly linked with immune function, the overall

relationship between sleep duration and *all*-cause mortality suggests that there may be an underlying shared mechanistic link, and immune function and inflammation is one viable candidate. This hypothesis is supported by other population-based studies that have examined the relationship between sleep duration and inflammatory mediators associated with body mass index (BMI) or adiposity, which we discuss further below.

There is a large base of research demonstrating that insufficient sleep is associated with obesity, both cross-sectionally and prospectively, even when sleep duration is measured objectively [52, 53]. Given that adiposity, particularly visceral adiposity, is associated with higher circulating levels of inflammation [24, 25], the association between sleep and adiposity can also be considered from a perspective of an independent relationship between inflammatory mediators and sleep duration. To date, there are a limited number of studies that can allow for such comparisons. The available data suggest that there is weak evidence for an independent relationship between short sleep and inflammation. In one study of 907 adults (Wisconsin Sleep Cohort study), no relationship between levels of CRP and sleep duration was reported [54], while in another study of over 4600 individuals, sleep disturbances were associated with higher CRP levels in women, but not men [55]. Notably, increases in inflammatory markers associated with long sleep durations have also been reported [56, 57]. While these studies control for a range of potential covariates and comorbid factors, it is still an open question as to whether there is an independent relationship between long sleep durations and inflammation, or rather there is a yet-unidentified/unaddressed factor that is driving this relationship.

These differential results emphasize that very large study samples are required for this area of research, in order to both insure adequate representation across a range of sleep duration and also to allow for statistical control of the contributions of a range of potentially confounding factors. As described in the experimental studies section, methodological variation such as time of day of sample collection and the collection procedures themselves may have an impact on the results, independent from the actual population studied. Interpretation of these findings is also complicated given that epidemiological studies have largely relied on self-reports of habitual sleep duration. Research suggests that healthy population may overestimate by self-report their actigraphically measured sleep duration, while populations with sleep disorders (e.g., insomnia) may over-report time awake/under-report sleep duration [58–60].

Self-assessment of sleep duration via a sleep diary and objective sleep duration, as measured by a night of polysomnography, may lead to differing outcomes, however. Objectively measured shorter sleep duration has been found to be correlated with fasting levels of TNF-alpha, after controlling for covariates; however, in the same study, self-reported longer sleep durations were significantly associated with increased high-sensitivity (hs) CRP and IL-6 [61]. The authors suggest that self-reported sleep duration and single-night polysomnography may be measuring different constructs of sleep [61], which appears supported by the literature on differential findings between objectively and subjectively measured sleep durations described above. Nonetheless, these studies provide more evidence that the inflammatory system is sensitive to actual sleep duration and potentially also by longer-term subjective estimates of sleep patterns. These methodological challenges add an extra layer of complexity in our understanding of study findings, particularly relative to the experimental sleep loss literature. In addition to the investigation of basal changes in inflammatory markers in relationship to sleep duration, a few studies have looked at the inflammatory response or reactivity to challenge, such as to stress. For example, Heffner and colleagues conducted a study in which IL-6 levels were assessed at baseline and 60 min after a stressful testing period in a sample of older adults (greater than 50 years old). Individuals categorized as poor sleepers had a significantly larger inflammatory response to this acute stressor, which was not mediated by negative affect or perceived stress [44].

Field studies have also provided important insights into the relationship between sleep and adaptive immune function. Using the vaccine challenge model, Prather and colleagues investigated whether naturally occurring sleep influenced the specific immune response to a hepatitis B vaccination [62]. This larger study examined relationship between self-reported sleep duration and the primary and secondary antibody response, as well as clinical protection status after the 3rd vaccination in this series. The authors found that shorter sleep duration was associated with lower secondary antibody levels, translating into a 56% increase in secondary antibody levels with each additional hour of sleep [62]. Additionally, shorter sleep durations in this study were associated with a decreased likelihood of being clinically protected after the third vaccine in the series. Specifically, sleeping fewer than 6 h a night was associated with a significant risk of remaining unprotected against hepatitis B infection compared to those sleeping more than seven hours [62]. This relationship between sleep duration and immune response to system challenge is further supported by findings from a large (N = 56,953) study of women, which found that sleeping less than 5 h a night increased the risk of pneumonia by 70% over the four-year observation period, compared to women sleeping 8 h per night [63].

Qualitative aspects of sleep, rather than duration per se, have also been shown to modulate immune function. In one early study, 11 young adults with insomnia, who were otherwise healthy, were compared to 11 age- and sex-matched healthy control subjects. These subjects were studied in the laboratory for four nights; while there were no

differences in mean 24-h levels of IL-6 or tumor necrosis factor, a shift in the secretion timing (from nighttime to daytime) of these cytokines was observed [64]. In a similar study comparing individuals with chronic insomnia to healthy controls, increases in nocturnal IL-6 were observed in the insomnia sample [65]. Total IL-6 levels were inversely correlated with subjective sleep quality and the amount of slow wave sleep and were positively correlated with the amount of wake time at night [65], suggesting that there may be specific relationships between sleep symptoms and immune markers. However, not all studies have reported a relationship between insomnia symptoms and increased markers of inflammation. One large study of 8547 Norwegians with insomnia found no consistent associations with specific symptoms of insomnia and hsCRP levels [66]. Inconsistencies between studies may have largely to do with the wide range of insomnia phenotypes and definitions. For example, more recent findings suggest that inflammatory and other systems abnormalities are present particularly in insomniacs with objectively verified sleep abnormalities (such as short sleep duration, low sleep efficiency) [67].

A growing number of studies have also examined relationships between sleep quality and inflammation, with mixed results. While one large study found that inflammation was not related to an overall index of sleep quality [56], another smaller study found a significant relationship between sleep quality and production of IL-1 beta [68]. Two additional studies report relationships between sleep quality and inflammation in women: one in a female-only study sample (CRP, [69]) and the other in a prospectively assessed, mixed gender sample (multiple inflammatory markers, [70]). Together, this body suggests that there may be some relationship between impaired sleep quality, particularly at the disorder level (e.g., insomnia disorder), and inflammation; however, there are likely multiple factors contributing to these relationships (e.g., sex, medication use, chronicity of sleep disturbance, body mass index) that are yet to be fully understood.

Clinical Trials/Intervention Studies

The studies presented thus far in this chapter have demonstrated the relationship between acute and chronic sleep durations and immune function. There is far more that can still be learned from both experimental and field studies in this area; an exciting new area of research lies in clinical trials and intervention research. Although it is well documented that sleep can successfully be improved (e.g., through treatment of insomnia) [71, 72], few studies to date have incorporated a physiological measurement arm. In the most recent and largest of these studies, 123 older adults were randomized to either cognitive behavioral therapy for insomnia (CBT), Tai Chi Chi (TCC), or a sleep seminar education control (SS) [73]. Treatment was conducted in weekly 2-h group sessions over four months. In addition to CBT outperforming the other two conditions with respect to insomnia remission rates and improvements in sleep parameters, CBT was also associated with a reduced risk of CRP levels at the 16-month follow-up point compared to the SS control condition. Further, remission of insomnia was also associated with lower levels of CRP [73]. The authors suggest that observed inflammatory effects have implications for the cardiovascular morbidity observed with sleep disturbances in epidemiological studies [73].

Two additional studies in medical populations (breast cancer and peritoneal dialysis patients) with insomnia have also demonstrated significant changes in immune markers. In one pilot study, dialysis patients completed either individual CBT-I or a sleep education control condition, and effects on five inflammatory markers were assessed. While sleep quality improved in the intervention group, the authors observed decreases in only one inflammatory marker, IL-1 beta [74]. In another small study, 57 women with insomnia secondary to breast cancer were assigned to CBT or a control condition. The authors report that patients treated with CBT had higher levels of IFN-gamma and a smaller increase in lymphocytes at post-treatment compared to control patients. Additional changes in multiple markers were observed from pre- to post-treatment, including WBCs, lymphocytes, IFN-gamma, and IL-1 beta [75]. Interpretation of specific immune changes following sleep improvement is complex, particularly in these samples of medical populations; however, it does appear that modifying sleep has the potential to effect direct changes in immune function. While more research is needed in this area, these important findings suggest an avenue by which improving sleep can affect underlying medical conditions and also help shed light on our understanding of the mechanisms underlying the sleep duration and health risk epidemiological literature.

Another new area examining the reversibility of inflammatory and autonomic changes related to insufficient sleep is sleep extension. One pilot study in this area assessed 22 adults with hypertension or pre-hypertension and a habitual sleep duration of less than 7 h a night; participants were then randomized to a control condition or an intervention designed to facilitate extension of bedtimes by 60 min/night over a six-week period [76]. Beat-to-beat blood pressure, and stress and inflammatory markers were both assessed pre- and post-treatment in a controlled laboratory setting. Sleep duration increased significantly in the extension group by an average of 35 min/night, and this was accompanied by a significant decrease in systolic blood pressure and

nonsignificant decreases in WBC, IL-6, CRP, and norepinephrine [76]. While small in scale, this study suggests that reversing chronic insufficient sleep even for a period of six weeks can result in significant improvement in autonomic markers related to inflammation.

There is also a small amount of intriguing research that has assessed the relationship between sleep and inflammatory activity in an intervention model by testing the effects of an anti-inflammatory medication (tocilizumab, an antibody against the IL-6 receptor) for six months on sleep disturbances in a small sample of women with rheumatoid arthritis [77]. Researchers found that this IL-6 receptor antibody treatment led to a slight, but significant improvement in sleep quality that was independent of decreased disease activity [77]. This study will require replication but provides more evidence to support the responsivity aspect of the relationship between sleep and immune function, where poor sleep can result in a stronger inflammatory response to stress (see [78]) and reducing the inflammatory response (with use of medication) can improve sleep quality [77].

Conclusion

Accumulating experimental data from laboratory-based studies of sleep loss suggest that insufficient sleep affects basal levels of immune and inflammatory mediators, as well as the inflammatory reactivity to stressors. In field settings, short sleep duration has been associated with increased inflammatory markers, reduced antibody responses, and lower clinical protection induced by vaccinations. Epidemiological and intervention data also suggest that infection rates are higher when sleep durations are lower. This raises the possibility that interventions designed to improve sleep may reduce disease risk to infections through either direct protection by the early and adaptive immune systems or indirect antibody support mechanisms.

While the mechanisms underlying the sleep–immune relationship are yet to be fully understood, preliminary evidence suggests that inflammatory mediators may not only be affected by changes in basal levels of various immune regulatory hormones, but also by changes in receptor density or sensitivity of immune cells to hormonal signals. Future research in this area will benefit from greater understanding of individual differences, and genetic and epigenetic factors so that interventions can be optimized to better address biological system-specific risk.

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Sleep and Memory Consolidation

13

Rebecca M.C. Spencer, Matthew P. Walker, and Robert Stickgold

Introduction

The functions of sleep are not fully understood, a surprising fact given the vast amount of time that this state takes from our lives. One of the most exciting and contentious hypotheses is that sleep makes an important contribution to learning and memory processing. Over the last decade, a large number of studies, from a range of disciplines, have begun to provide a substantive body of evidence supporting this role of sleep in what is becoming known as sleep-dependent memory processing. While this renaissance is relatively recent in the annals of sleep research, the topic itself has a surprisingly long history. The earliest reference to a relationship between sleep and memory is from the Roman rhetorician Quintillian, stating "*It is a curious fact, of which the reason is not obvious, that the interval of a single night will greatly increase the strength of the memory*" and suggesting that "*the power of recollection…undergoes a process of ripening and maturing*" (Quintillian; first century AD). This is striking not only for the level of insight at a time when knowledge of brain function was so anemic, but also considering that it represented the first suggestion of memory requiring a time-dependent process of development, resulting in improved memory recall. Perhaps what is most surprising, however, is that these two fields of research (sleep and memory) then remained separate for almost two millennia.

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In the mid-eighteenth century, the British psychologist David Hartley proposed that the processes of dreaming might alter the strength of associative memory links within the brain [1]. Yet the fields of sleep and memory research remained independent until 1924 when Jenkins and Dallenbach [2] performed the first systematic studies of sleep and memory to test Ebbinghaus' theory of memory decay [3]. Jenkins and Dallenbach [2] showed that memory retention was better following a night of sleep than after an equivalent amount of time awake. However, they concluded that the memory benefit following sleep was simply a passive one, due to a lack of sensory interference in contrast to wake. They did not consider that the physiologic state of sleep itself could actively orchestrate these memory modifications. It is only in the last half-century, following the discovery of rapid eye movement (REM) and non-REM (NREM) sleep, that researchers began testing the hypothesis that specific aspects of sleep physiology may actively participate in memory processing.

This chapter explores what has become known as sleep-dependent memory processing, and its associated brain basis, sleep-dependent plasticity. It is divided into three primary sections: (1) an overview of memory categories and the unique stages of memory development; (2) a review of the specific relationships between sleep and memory, both in humans and in animals; and (3) a brief survey of the wide range of evidence describing sleep-dependent brain plasticity, including human brain imaging studies as well as animal studies of cellular neurophysiology and molecular biology. We close with a consideration of unanswered questions that are the focus of ongoing research.

Delineations and Definitions

Before discussing interactions between sleep and memory, we must first understand what these terms represent and encompass. The process of sleep, with its varied stages and equally diverse physiology and biology, has already been

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described in earlier chapters in this section, clearly demonstrating that sleep itself cannot be treated as a homogeneous state that either does or does not affect memory. Instead, sleep possesses a range of physiologic and neurochemical mechanisms that can contribute to memory consolidation. Moreover, just as sleep cannot be considered homogeneous, the spectrum of memory processes believed to exist in the human brain, and the unique stages that create and sustain memory, are likewise diverse.

Memory Categories

Although often used as a unitary term, "memory" is not a single entity. Human memory has been subjected to several different classification schemes, the most popular being based on the distinction between declarative versus nondeclarative memory [4, 5] (Fig. 13.1a).

Declarative memory is the consciously accessible memories of fact-based information (i.e., knowing "what"). Several subcategories of the declarative system exist, including episodic memory (memory for events of one's past) and semantic memory (memory for general knowledge, not tied to a specific event) [5]. Current neural models of declarative memory formation emphasize the critical importance of structures in the medial temporal lobe, predominantly the hippocampus [6, 7], a structure that is thought to form a contextual retrieval code for neocortically stored information.

In contrast, nondeclarative memory can be regarded as unconsciously acquired learning. The nondeclarative category includes procedural memory (i.e., knowing "how"), such as the learning of habits and motor skills (e.g., playing a piano, athletic sports, surgical skills, etc.), as well as classical conditioning and non-associative learning. The neural basis for nondeclarative learning appears to be more diverse, varying with task characteristics (e.g., motor versus non-motor) [7].

While these categories offer convenient and distinct separations, they rarely operate in isolation in real life. For example, language learning requires a combination of memory sources, ranging from nondeclarative memory for procedural motor programs to articulate speech, to memory of grammatical rules and structure, to aspects of declarative memory for the source of word selection. Such interactions must be kept in mind as we consider the role of sleep in learning and memory.

Memory Stages

Just as memory cannot be considered monolithic, similarly, there does not appear to be one sole event that creates or

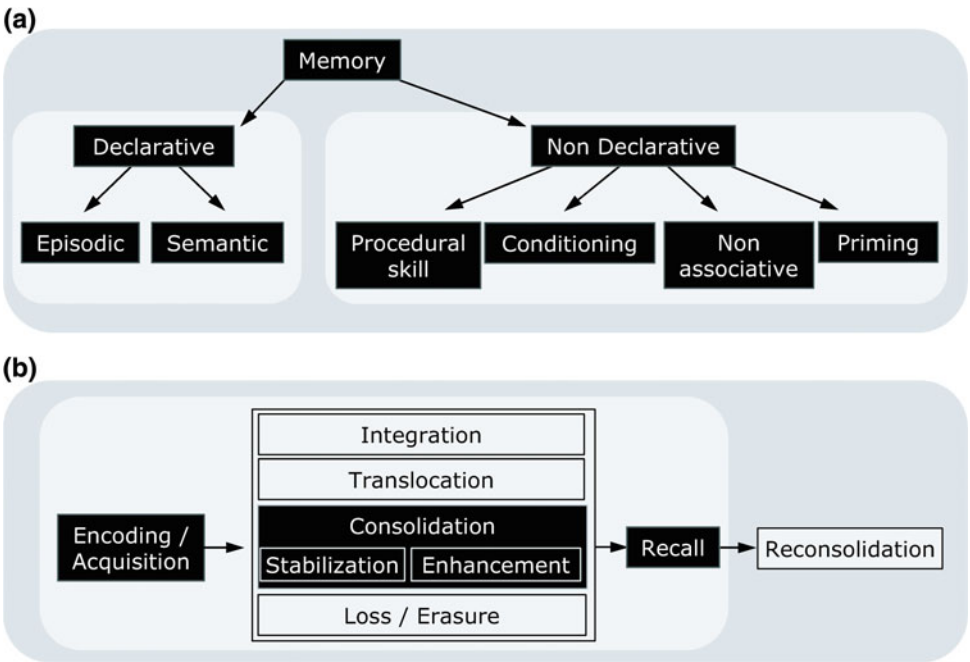

Fig. 13.1 Memory systems and memory stages. **a** Memory systems. Human memory is most commonly divided into declarative forms, with further subdivisions into episodic and semantic, and nondeclarative forms, subdivided into an array of different types including procedural skill memory. **b** Developing stages of memory. Following initial encoding of a memory, several ensuing stages are proposed, beginning with consolidation, as well as integration of the memory representation, and translocation of the representation or erasure of the memory. Also, following later recall, the memory representation is believed to become unstable once again, requiring periods of reconsolidation

sustains it. Instead, memory appears to develop in several unique stages over time (Fig. 13.1b). For example, memories can be initially *encoded* by engaging with an object or performing an action, leading to the formation of a representation of the object or action within the brain. In a subsequent *recall* stage, memories can be actively recalled or recognized by comparison with the representation. However, the memory continues to evolve between encoding and recall through the process of consolidation. Classically, the term *memory consolidation* refers to a process whereby a memory becomes increasingly resistant to interference from competing or disrupting factors in the absence of further practice, through the simple passage of time [8]. That is to say, the memory becomes more stable even with time away from the task.

Important memory stabilization can occur over periods of both wake [9, 10] and sleep [11, 12]. Sleep-dependent consolidation refers to the fact that consolidation is greatest over sleep, compared to wake, for most tasks [13–15]. From this perspective, the enhancement phase of consolidation causes either the active retention of a memory instead of its decay, or the enhancement of a memory over and above its simple maintenance. There is also accumulating evidence that memory consolidation is accompanied by a process of memory integration and generalization [e.g., 16, 17]. Thus, consolidation can be expanded to include more than one phase of post-acquisition memory processing, with each phase occurring in specific brain states such as wake or sleep, or even specific stages of sleep [18].

Although this chapter focuses primarily on the effects of sleep on post-acquisition memory stabilization and generalization, it is important to note that there are additional post-acquisition stages of memory processing that perhaps should also fall under the rubric of consolidation. These include the anatomic reorganization of memory representations (memory translocation), reconsolidation of memory representations following conscious recall (memory reconsolidation), and even the active erasure of memory representations, all of which appear to occur outside of awareness and without additional training or exposure to the original stimuli. It is interesting to note that, while not reviewed here, sleep has been implicated in all of these steps [19–22].

Summary

There are a number of stages of memory processing, which use distinct brain mechanisms to perform separate functions. When multiple classes of memories and the several stages of sleep are combined, one is faced with a truly staggering number of possible ways that sleep might affect memory consolidation.

Behavioral Studies of Sleep and Memory

Evidence of sleep-dependent memory processing has been found in numerous species using a variety of behavioral paradigms. Here, we provide an overview of these studies. The reader is referred to recent reviews for more detail than is provided here [23–25].

Human Studies of Declarative Memory

Much of the early work investigating sleep and memory in humans focused on declarative learning tasks. These studies offered mixed conclusions, some arguing for sleep-dependent memory processing and others against it. For example, De Koninck et al. [26] demonstrated significant increases in post-training REM sleep after intensive foreign language learning, with the degree of successful learning correlating with the percentage increase of REM sleep. Such findings suggest that REM sleep plays an active role in memory consolidation, and that post-training increases reflect a homeostatic response to the increased demands for REM-dependent consolidation.

To the contrary, most recent studies suggest a critical function of slow wave sleep (SWS) in declarative memory consolidation. Perhaps most convincing are studies demonstrating the reactivation of declarative memories during SWS. Rasch et al. [27] taught participants a visuospatial task requiring learning the spatial location of a matrix of images. Learning occurred in the presence of an odor (scent of roses). The experimental odor was re-presented during subsequent SWS for a subset of the participants (Fig. 13.2a). Recall was superior following sleep when the odor present during learning was re-presented during sleep. In a similar study, Rudoy et al. [28] had participants learn a similar visuospatial task, but in this case, each image was paired with a specific sound. Half of these sounds were re-presented during subsequent SWS. Delayed recall was greater for those items for which the associated sound was re-presented during sleep relative to those items for which the associated sound was not re-presented. It is thought that cues presented during sleep, selectively trigger associated memories to be reactivated. Notably, when Rasch et al. [27] presented odors during wake and REM sleep, there was no benefit for subsequent recall beyond that seen in a no-odor (vehicle) control condition (Fig. 13.2b), supporting the specific role of SWS in declarative memory consolidation.

Marshall et al. [29] showed that experimentally boosting human *slow oscillations*, widespread oscillations between "up" and "down" states that are characteristic of SWS, results in improved memory performance the following day. Following learning of a word-pair list, a technique called

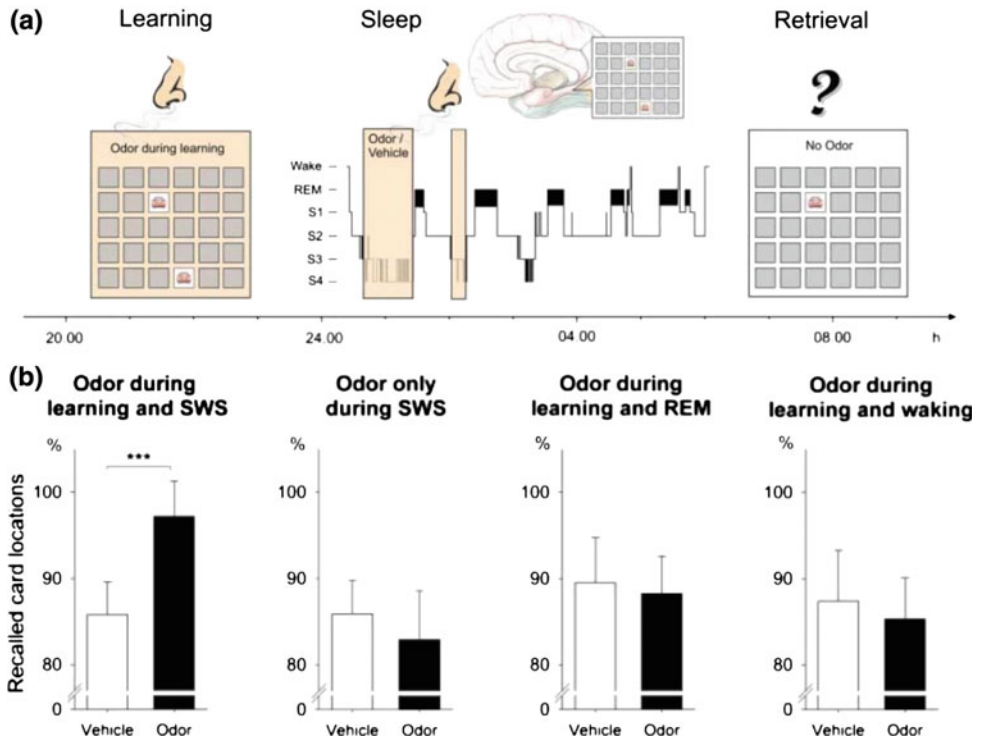

Fig. 13.2 Declarative memory reactivation during slow wave sleep. **a** Subjects performed a visuospatial learning task in the presence of an experimental odor (scent of roses). During subsequent slow wave sleep, this odor or a non-odor vehicle control was presented. Memory for the visuospatial task was tested following sleep. **b** Participants recalled more locations following sleep when the experimental odor was re-presented during slow wave sleep compared to vehicle (*first panel*). Such an effect was not observed if the odor present during slow wave sleep was not also present during learning (*second panel*), if the odor cue was re-presented during REM (*third panel*), or if the odor was re-presented during waking (Permissions needed from Rasch et al. [27])

transcranial direct current stimulation (tDCS) was used to induce these slow oscillation-like (in this case, 0.75 Hz) field potentials during early delta-rich sleep. The tDCS not only increased the amount of delta sleep during the stimulation period (and for some time after), but also enhanced the retention of these hippocampal-dependent factual memories, suggesting a causal benefit of delta sleep neurophysiology.

Memory enhancement reported in this study is striking in the face of earlier studies that showed memory protection but not enhancement. Notably, this study used a classic paired associates task (semantically related word-pair learning). This task tends to show sleep-dependent memory enhancements [30, 31], while those using semantically unrelated word pairs report sleep-dependent memory protection [32, 33]. The nature of the learning task thus shifts from forming and retaining completely novel associations (dog-leaf) to the strengthening or tagging of well-formed associations (dog-bone) for recall at testing [34].

Sleep's role in declarative memory consolidation, rather than being absolute, depends on several aspects of the task including task difficulty, future relevance, and emotional salience. More difficult tasks are thought to benefit most from sleep [12, 35]. This may reflect enhanced consolidation for weak compared to strong memories. For instance, learning a second list of word pairs weakens the memory for the first list. Yet, recall of the first list following sleep is greater than when recalled following an equivalent interval of wake while recall of list two differed little following sleep and wake [36].

The benefit of sleep on declarative memories may also be greatest for memories with clear future relevance. Wilhelm et al. [37] demonstrated this preferential effect of sleep by comparing recall after sleep and wake for two groups of participants: one group was informed that they would be asked to recall the learned word pairs in a subsequent session and a second group was not informed of the later recall. Sleep-dependent enhancement in performance was evident for those who expected to recall the words following the delay interval, whereas there was no difference for sleep and wake groups who performed the surprise delayed recall test. Future relevance implied by associating items with a reward (monetary or points) also yields greater performance benefits following sleep compared to unrewarded items [38, 39].

Emotional salience may cue future relevance as well, as memory for items with negative valence is important for self-preservation. A number of studies have illustrated the

preferential consolidation of negative emotional memories over neutral memories. Hu et al. [40] found greater recognition of emotionally arousing images after sleep compared to wake while no condition differences were found for neutral images. Moreover, when negative items are embedded in neutral scenes, sleep preferentially enhanced recognition of the negative items relative to the neutral items while the scenes themselves, which were neutral in valence, were uninfluenced by the type of interval (sleep vs. wake) [41]. These behavioral effects have been associated with REM sleep [42]. Likewise, oversleep protection of emotional reactivity to negative images is predicted by the time spent in REM sleep [43].

While these examples highlight when sleep functions to stabilize and enhance veridical memories, as discussed earlier, sleep also functions to generalize declarative memories and integrate them into existing representations [44]. Indeed, the end goal of sleep-dependent memory processing may not be simply the enhancement of individual memories in isolation, but instead, the integration of these memories into a common schema and, by doing so, facilitation of the extraction of universal rules, which may be the basis of generalized knowledge. The most basic demonstration of this comes from studies using the Deese–Roediger–McDermott paradigm in which participants are presented with lists of semantically related words (e.g., BOWL, SPOON, MILK) that lack a critical word representing the gist of the list (e.g., CEREAL). When these lists are learned prior to sleep, recall of the list words is greater than following wake. Notably, sleep also yields greater recall of those critical, "gist" words that were never presented. This suggests that declarative memories are generalized and integrated into the existing lexicon over sleep, thereby allowing the extraction of the more general form of the memory after sleep [17, 45, 46].

Sleep-dependent generalization of declarative memories may provide other cognitive benefits of sleep such as enhancing rule learning, decision-making, and creativity. For instance, it has also been demonstrated that, following initial practice on a numeric-sequence problem-solving task, a night of sleep can trigger insight into a hidden rule and thus improve performance strategy the following morning [47]. Likewise, performance on the Iowa gambling task, a measure of affectively guided decision-making, becomes more optimal after sleep as subjects gain more insight into the statistical probabilities of the four decks of cards from which they must choose [48]. Integrating new memories with prior representations may also yield novel, creative solutions [49, 50].

Taken as a whole, these studies suggest a rich and multifaceted role for sleep in the processing of human declarative memories. While SWS is associated with learning of nonemotional veridical memory processing, REM sleep appears to contribute to changes in the emotional memory representation. How sleep facilitates memory generalization and the function of sleep in translocation and reconsolidation of declarative memories are a matter of ongoing research.

Human Studies of Procedural Memory

The benefit of sleep has been demonstrated across a wide variety of procedural tasks spanning the visual, auditory, and motor systems. In this section, we review evidence of procedural memory improvements following sleep as well as possible limitations.

Motor Skill Learning

Motor skill learning is defined as the process by which movements are more quickly and accurately executed after practice [51, 52]. Motor skills are often broadly classified into two forms: motor sequence learning (e.g., learning a piano scale) and motor adaptation (e.g., learning to use a computer mouse) [53].

The movement sequencing task, a common task for measuring sequence learning, requires that subjects repeatedly tap a sequence of response keys as quickly and accurately as possible. With training, movement time decreases, indicating that learning has occurred. A night of sleep can trigger significant performance improvements in speed and accuracy on a sequential finger-tapping task, while equivalent periods of time awake provide little to no benefit [15, 33]. These sleep-dependent benefits appear to be specific to both the motor sequence learned [54, 55] and the hand used to perform the task [56]. Furthermore, the amount of overnight learning expressed the following morning correlated positively with the amount of stage 2 NREM sleep, particularly late in the night (Fig. 13.3) [15]. This late-night stage 2 NREM window corresponds to a time when sleep spindles, a defining electrophysiologic characteristic of stage 2 sleep, reach peak density [57]. Interestingly, spindles have been shown to increase following training on a motor task [58, 59] and are associated with cellular plasticity as discussed later in this chapter.

A more detailed analysis of the performance improvements on the motor sequencing task after sleep provides insight into how improvements come about [60]. Prior to sleep, individual key-press transitions within the sequence are uneven (Fig. 13.4a, light circles), with some transitions seemingly easy (fast) and others problematic (slow), as if the entire sequence was being parsed into smaller subsequences during initial learning (a phenomenon termed *chunking* [61]). Surprisingly, after a night of sleep, the problematic slow transitions are preferentially improved, while transitions that were already mastered prior to sleep did not change (Fig. 13.4a, dark circles). In contrast, if subjects were

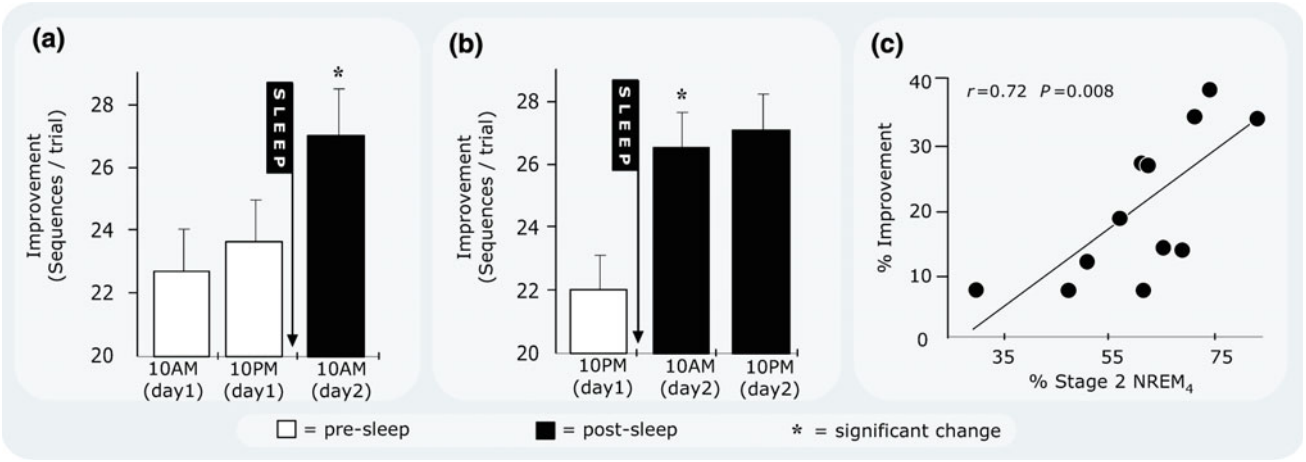

Fig. 13.3 Sleep-dependent motor skill learning in the human brain. **a** Wake 1st: After morning training (10 am, *light blue bar*), subjects showed no significant change in performance when tested after 12 h of wake time (10 pm, *light blue bar*). However, when tested again following a night of sleep (10 am, *dark blue bar*), performance had improved significantly. **b** Sleep 1st: After evening training (10 pm, *light blue bar*), subjects displayed significant performance improvements just 12 h after training following a night of sleep (10 am, *dark blue bar*), yet expressed no further significant change in performance following an additional 12 h of wake time (10 pm, *dark blue bar*). **c** Sleep stage correlation: The amount of overnight improvement on the motor skill task correlated with the percentage of stage 2 NREM sleep in the last (fourth) quarter of the night (stage 2 $NREM_4$). *Asterisk,* significant improvement relative to training; error bars, standard error of the mean (*SEM*)

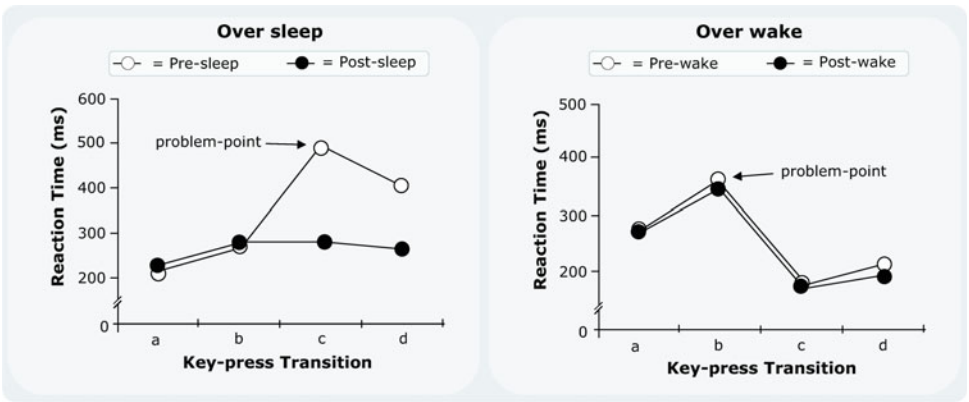

Fig. 13.4 Single-subject examples of changes in transition speeds. Within a five-element motor sequence (e.g., "4-1-3-2-4"), there are four unique key press transitions: (1) from 4 to 1, (2) from 1 to 3, (3) from 3 to 2, and (4) from 2 to 4. **a** The transition profile at the end of training before sleep (*light circles*) demonstrated considerable variability, with certain transitions being particularly slow (most difficult; "problem points"), whereas other transitions appear to be relatively rapid (easy). Following a night of sleep (*dark circles*), there was a specific reduction (improvement) in the time required for the slowest problem point transition. **b** Similarly, at the end of training before a waking interval, transition profiles were uneven (*light circles*), with some particularly slow transitions ("problem points") and other relatively fast transitions (easy). However, in contrast to post-sleep changes, no change in transition profile was observed following 8 h of wakefulness (*dark circles*)

retested after an 8-h waking interval across the day, no such improvement in the profile of key-press transitions, at any location within the sequence, was observed (Fig. 13.4b). These changes suggest that the sleep-dependent consolidation process may involve the unification of smaller motor memory units into one single memory element by selectively improving problem regions of the sequence. This overnight process would therefore offer a greater degree of performance automation and effectively optimize skill speed throughout the entire motor program.

The role of sleep in motor adaptation is less clear. Doyon and colleagues [62, 63] compared off-line changes in motor sequence learning to off-line changes in visuomotor adaptation. To measure adaptation, subjects used a joystick to move a cursor on the screen to a target. After practice, mapping between the joystick space and the cursor on screen

was inverted. Movements that were initially slow and inaccurate under inverted mapping conditions became faster and more accurate over time as participants adapted to the visuospatial shift. While replicating sleep-dependent performance changes on the motor sequence learning task, Doyon and colleagues failed to find preferential changes in performance over sleep on the motor adaptation task. Rather, motor adaptation improved equally over intervals with wake and sleep. These results are in contrast to an earlier study by Huber et al. [64]. Moreover, a rather consistent benefit of sleep has been observed for learning on a mirror tracing task which, like the visuomotor adaptation task of Doyon, requires learning of novel mapping between motor output and visual input. For example, Plihal and Born [65] found improvements in mirror tracing performance following late-night sleep, where REM and stage 2 non-REM dominate, even when early-night sleep was deprived. No such improvements were observed when participants had SWS-rich early-night sleep and late-night sleep was deprived. Moreover, Tamaki [66] found increased sleep spindle amplitude and duration after learning a mirror-tracing task, and this increase was associated with over-sleep improvements in performance.

Conflicting results across studies of motor skill consolidation may reflect limitations on sleep-dependent consolidation of motor skills. For instance, motor skill consolidation over sleep is biased by task difficulty. Kuriyama investigated the effects of increasing task complexity on sleep-dependent motor learning [60]. Subjects trained on a variety of task configurations involving either a short or long motor sequence performed either with one hand (unimanual) or coordinated between two hands (bimanual). Interestingly, the more complex the task became (long sequence, bimanual), the greater the overnight, sleep-dependent memory enhancement. This would indicate that, as task difficulty increases, the overnight sleep-dependent process responds with even greater performance improvements. Consistent with this, sleep was reported to benefit motor sequence learning for adults who were trained to an intermediate level of performance prior to sleep, whereas there was no benefit of sleep for experts [67].

Additionally, performance benefits from sleep are greater when participants are aware of the information to be learned [68]. This was demonstrated in a study comparing implicit motor sequence learning (subjects were not aware that finger responses to visual cues were in a sequence) under conditions which were either contextual—the sequence was embedded in a unique repeating context—or non-contextual. Sleep-dependent consolidation was present for the implicit contextual learning condition but not the non-contextual condition. Given that contextual learning is known to engage the hippocampus [69], we interpret these results as demonstrating the role of the hippocampus in consolidation of motor skills.

Taken together, overnight sleep has been shown to benefit motor skill performance, a benefit primarily associated with stage 2 NREM sleep and associated sleep spindles. Discrepancies across studies may be explained by limitations on this process with preferential consolidation for difficult tasks and those that engage the hippocampus [reviewed in 24].

Perceptual Learning

Karni et al. [70] have demonstrated that learning on a visual texture discrimination task improves significantly following a night of sleep. Furthermore, they established that selective REM, but not NREM sleep appears essential for these performance gains. Using the same task, Stickgold et al. [71] have shown that these enhancements are specifically sleep- and not time-dependent. Specifically, performance gains were correlated positively with the amount of both early-night SWS and late-night REM sleep, and the product of these two sleep parameters explained over 80 % of intersubject variance, an incredibly strong correlation.

Performance on a repeated visual search task also improves with sleep. In this task, participants are presented with arrays of L's in various orientations and must find a hidden T. When displays are repeated, although unbeknownst to the observer, reaction time decreases. In spite of the implicit nature of learning, individuals with medial-temporal lobe lesions (including the hippocampus) fail to learn this task [72]. Geyer et al. [73] demonstrated sleep-dependent improvements on this task, as measured by reduced reaction times to repeated displays further supporting a role of the hippocampus in sleep-dependent consolidation even in the procedural domain.

The Weather Prediction Task is a probabilistic category-learning task in which participants learn to predict the "weather" from a set of cards, each of which has a learned probability of "sun" or "clouds" [74]. Djonlagic et al. [75] found that a group of subjects who slept after observing responses on the task made significantly more accurate weather predictions than a group who stayed awake. Here too, the performance benefits for the sleep group varied by the level of encoding: Those participants for whom the task was less difficult (high accuracy) before sleep showed less improvement than those for whom the task was more difficult (intermediate accuracy). Moreover, when the study was repeated and subjects were required to learn the probabilities through feedback, now sleep had no effect on performance. Given that observational learning is hippocampus-dependent while feedback-based learning of this task is associated with the striatum [e.g., 76], the authors interpreted these results to suggest that sleep may consolidate hippocampal-based learning but not memories encoded in the striatum.

Summary

In summary, delayed off-line learning of many perceptual and motor skills appears to develop during overnight sleep and not across equivalent time periods awake. Such changes have been associated with stage 2 NREM and sleep spindles that are predominantly found in this sleep stage. However, the function of hippocampal-dependent reactivation in SWS is suggested to play a parallel role. How these functions interact across sleep is a matter of ongoing research [e.g., 24, 77]

Animal Studies

Studies using animal models have provided evidence for the role of sleep in primarily hippocampus-dependent tasks. Training on both spatial and shock avoidance tasks triggers alterations in sleep-stage characteristics [78–82], suggesting, as in humans, a homeostatic response to increased demands on sleep-dependent consolidation mechanisms. In one such study, the magnitude of change in sleep architecture following learning demonstrated a strong relationship to initial performance during acquisition, with animals that learned quickly showing the largest change in sleep structure, while those that learned poorly showed relatively little [83].

The benefit of sleep after learning on subsequent performance has been demonstrated in a range of species including non-human primates [84], cats [85], rats [86, 87], starlings [13, 88], honeybees [89], and fruit flies [90]. In one such study, Inostroza et al. [87] examined memory for object-place pairs in rats following an 80-min interval that either contained sleep or was spent fully awake. Memory for the location of objects was greater following sleep, whereas animals performed at chance if kept awake after encoding the object location (Fig. 13.5a). Moreover, sleep did not benefit the memory for a novel object recognition task, which is thought to be encoded independent of the hippocampus (Fig. 13.5b).

Memories are not only protected over sleep but enhanced as demonstrated in starlings, a songbird known for its ability to imitate the sounds of other birds. If two songs are learned in parallel, the memories interfere with one another as seen by impaired performance following an interval spent awake. However, when birds slept following the exposure to the interfering songs, performance improvements were observed, even when sleep followed a significant waking delay. These results suggest that sleep actively restored and enhanced the song memories. Additionally, when interference was presented following sleep, it did not impair performance for the song learned prior to sleep. Collectively, this work in song birds, similar to observations in humans [91], suggests that learning is actively consolidated and

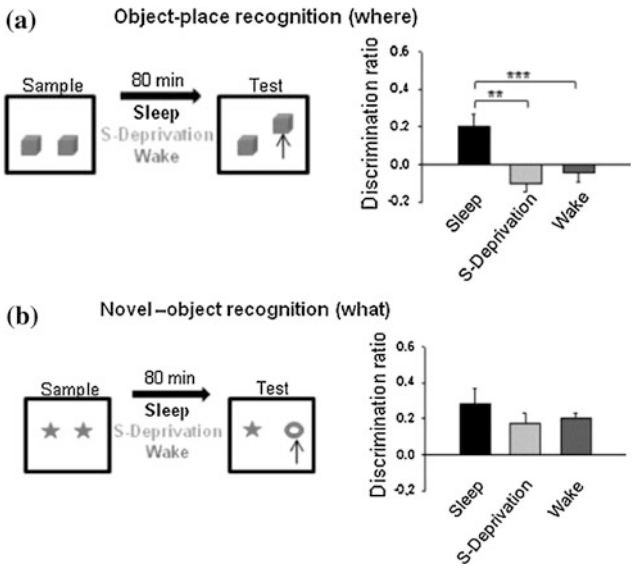

Fig. 13.5 Sleep-dependent learning in rats. **a** Animals learned an object-location task in the morning followed by normal sleep (*Sleep*) or sleep deprivation (*S-Deprivation*). The *Wake* condition took place in the evening when wakefulness is typical (i.e., not sleep deprived). Animals were significantly more likely to identify the misplaced object following sleep compared to both the sleep-deprivation and wake conditions as measured by the discrimination ratio (time spent at novel minus time spent at familiar divided by total exploration time). **b** In the novel-object recognition task, thought to be encoded independent of the hippocampus, animals were probed for their memory of a new object in the arena following sleep. There was no difference in discriminability for the novel object following sleep compared to the sleep-deprivation and wake conditions (Permissions needed from Inostroza et al. [87])

enhanced over sleep, leaving it more resistant to interference after sleep.

Summary

Taken as a whole, behavioral studies in humans and animal models leave little doubt that sleep plays a critical role in post-training memory consolidation. While both declarative and procedural memories have been shown to improve following sleep compared to wake, these memory systems appear to require subtly different sleep stages or even sleep-stage time windows, for consolidation and overnight improvement. With such evidence, it is important to consider the impact of little to no sleep as measured by studies of napping and sleep deprivation.

Sleep Deprivation

Reinforcing the role of sleep in memory consolidation is a wealth of literature illustrating the converse that sleep deprivation results in impaired declarative and procedural learning [80, 89, 92–100]. For example, total sleep deprivation (38 h awake) [101] and sleep restriction (overnight

sleep reduced to 4 h) [102], both yield performance impairments on a number of cognitive tasks including declarative learning.

However, many of these studies have been legitimately criticized for a failure to control for general effects of sleep deprivation on performance [103, 104]. Retesting in a sleep-deprived state may mask evidence of successful consolidation due to lowered alertness and attention. Alternatively, the increased stress of prolonged wakefulness, rather than the lack of sleep itself, may be the cause of unsuccessful consolidation.

More recent studies in both humans and animals have, however, demonstrated that impaired performance can still be seen several days after the end of sleep deprivation, when alertness and attention have returned to normal [105]. In addition, selective deprivation of specific sleep stages inhibits memory consolidation [98, 106], making arguments of sleep deprivation-induced stress relatively untenable, since the stress effects would have to be uniquely produced by deprivation of specific sleep stages during specific time windows following training.

Napping

Given this clear evidence that sleep is advantageous and sleep deprivation is disadvantageous for learning, several studies have asked the question "how much sleep is enough?" These studies have consistently revealed that a nap is sufficient for sleep-dependent changes in declarative [31, 107] and procedural memories [108–112]. Even a very brief nap of 6 min has been reported to increase recall of a declarative, word-list learning task [113]. Nonetheless, more sleep is better. Mednick and colleagues have shown that a 30- to 60-min daytime nap between repeated administrations of a texture discrimination task protects learning from the performance deterioration that is seen when subjects stay awake. If a longer nap period is introduced, ranging from 60 to 90 min and containing both REM sleep and NREM SWS, performance not only returns back to baseline but may be enhanced.

Sleep-Dependent Brain Plasticity

Memory formation depends on brain "plasticity"—lasting structural and functional changes in a neuron's response to a stimulus. The behavioral studies described above indirectly suggest a role of hippocampal plasticity in sleep-dependent memory consolidation, but recent direct evidence of sleep-dependent plasticity greatly strengthens this claim. In this section, we consider a wealth of data describing sleep-dependent brain plasticity at a variety of different levels in both animals and humans, complementing evidence of sleep-dependent changes in behavior.

Neuroimaging Studies

Modification of Post-training Sleep and Brain Activation

Several studies have investigated whether initial daytime training is capable of modifying functional brain activation during later sleep episodes. Based on earlier animal findings (described below), neuroimaging experiments have focused on whether the signature pattern of brain activity elicited while practicing a memory task actually re-emerges, or is "replayed" during sleep.

Maquet and colleagues have shown that patterns of brain activity expressed during motor skill training reappear during subsequent REM sleep, while no such change in REM sleep brain activity occurs in subjects who received no daytime training [114] (Fig. 13.6). Furthermore, these researchers have gone on to show that the extent of learning during daytime practice exhibits a positive relationship to the amount of reactivation during REM sleep [115]. Training on a hippocampus-dependent virtual maze task during the day has similarly been associated with a subsequent increase in hippocampal reactivation in NREM SWS [116], with the magnitude of reactivation correlating with performance on the task the following day, suggesting a function for neuronal replay. Such findings suggest that it is not simply experiencing the task that modifies subsequent sleep physiology, but the process of learning itself, and that this reactivation can lead to next-day behavioral improvements.

Overnight Reorganization of Memory Representations

An alternative approach to investigate sleep-dependent plasticity is to compare patterns of brain activation after a night of sleep. In contrast to measuring changes in functional activity *during* sleep, this approach aims to determine whether there is evidence that the neural representation of a memory has been reorganized following a night of sleep and whether this reorganization differs from that which may occur over wake.

With the behavioral characteristics of sleep-dependent motor sequence learning well established, Walker et al. were the first to examine the neural basis of sleep-dependent changes in learning by investigating differences in brain activation before and after sleep using functional magnetic resonance imaging (fMRI) [117]. Following a night of sleep, relative to an equivalent intervening time period awake, increased activation was identified in motor control structures of the right primary motor cortex (Fig. 13.7a) and left cerebellum (Fig. 13.7b)—changes that likely allow faster motor output to the trained, left hand, and more precise mapping of key-press movements post-sleep. There were

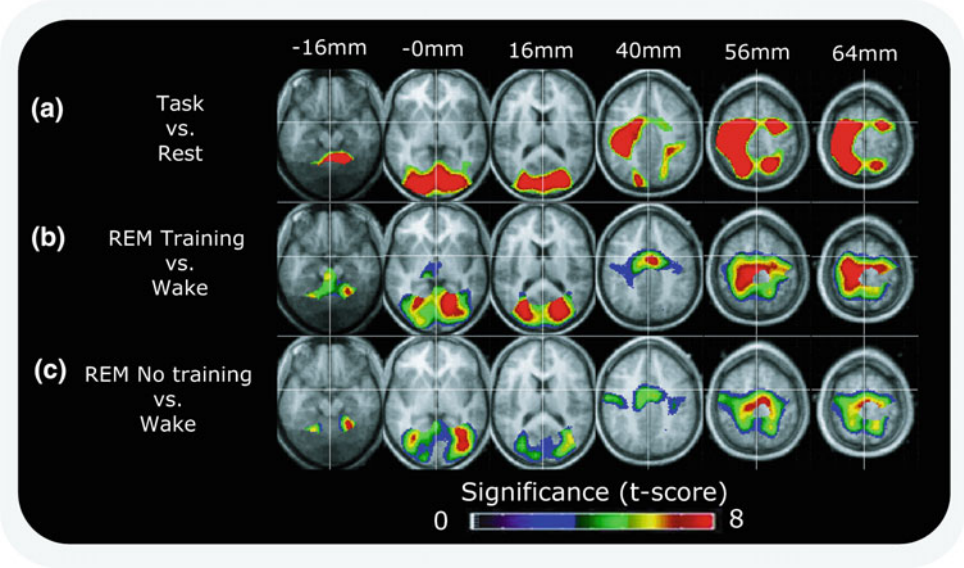

Fig. 13.6 Task-dependent reactivation of human brain activity during REM sleep. Statistical activation maps of different experimental contrasts. Maps are displayed at six different brain levels (from 16 mm below to 64 mm above the bicommissural plane), superimposed on the average magnetic resonance imaging (*MRI*) scan of subjects. All maps are thresholded at $p < 0.001$ (uncorrected), except for A, which is thresholded at voxel-level-corrected $p < 0.05$. **a** Brain regions activated during daytime performance of the motor skill task (Task–Rest). **b** Brain regions activated during subsequent REM sleep in subjects who received daytime training (REM Sleep Training–Rest); note considerable overlap with daytime task-dependent activity patterns. **c** Brain regions activated during REM sleep in subjects who did not receive any daytime training (REM Sleep No Training–Rest) (Reproduced with permission from Maquet et al. [114])

also regions of increased activation in the right medial prefrontal lobe and hippocampus (Fig. 13.7c, d), structures that support improved sequencing of motor movements in the correct order. In contrast, decreased activity post-sleep was identified bilaterally in the parietal cortices (Fig. 13.7e), possibly reflecting a reduced need for conscious spatial monitoring, and throughout the limbic system (Fig. 13.7f–h), indicating a decreased emotional task burden. In total, these results suggest that sleep-dependent motor learning is associated with a large-scale plastic reorganization of memory throughout several brain regions, allowing skilled motor movements to be executed more quickly, more accurately, and more automatically following sleep.

Debas et al. [62] contrasted changes in neural activation following sleep and wake for a motor skill learning task and a motor adaptation task. Consistent with their behavioral observations described above, there was an increase in activation in the primary motor cortex, the cerebellum, and the striatum for the motor sequence learning task following the off-line interval, with the activation of the striatum specifically modulated by sleep. However, there were no sleep-specific changes in neural activation patterns in conjunction with the motor adaptation task, consistent with the observation of limited over-sleep change in performance for this task.

Visual skill learning is also associated with underlying cortical plasticity. Post-sleep performance was associated with significantly increased activity not only in the primary visual cortex, but also in several downstream visual processing regions following sleep, at the occipital–temporal junction and in the medial temporal and inferior parietal lobes (regions involved in object detection and identification) [118]. These findings strengthen the claim that a night of sleep reorganizes the representation of a visual skill memory, with greater activation throughout the visual system following sleep likely offering improved identification of both the visual stimulus form and its location in space.

While most studies of over-sleep neural reorganization have focused on procedural learning, the neural basis of declarative memory consolidation has more recently been investigated. Takashima et al. [119] examined the long-term effects of a nap following the encoding phase of a picture recognition task. Picture recognition and the associated neural correlates were measured following a delay of 1, 2, 30, and 90 days. Following a delay of 1 day, the amount of time spent in SWS correlated positively with recognition performance and negatively with hippocampal activity during correct recognition. With time, recognition was associated with a decrease in the hippocampus activation coupled with a corresponding increase in ventromedial prefrontal cortex activation. This result is interpreted to suggest that SWS is associated with transfer of memories from the labile storage in the hippocampus to a more permanent representation in the cortex.

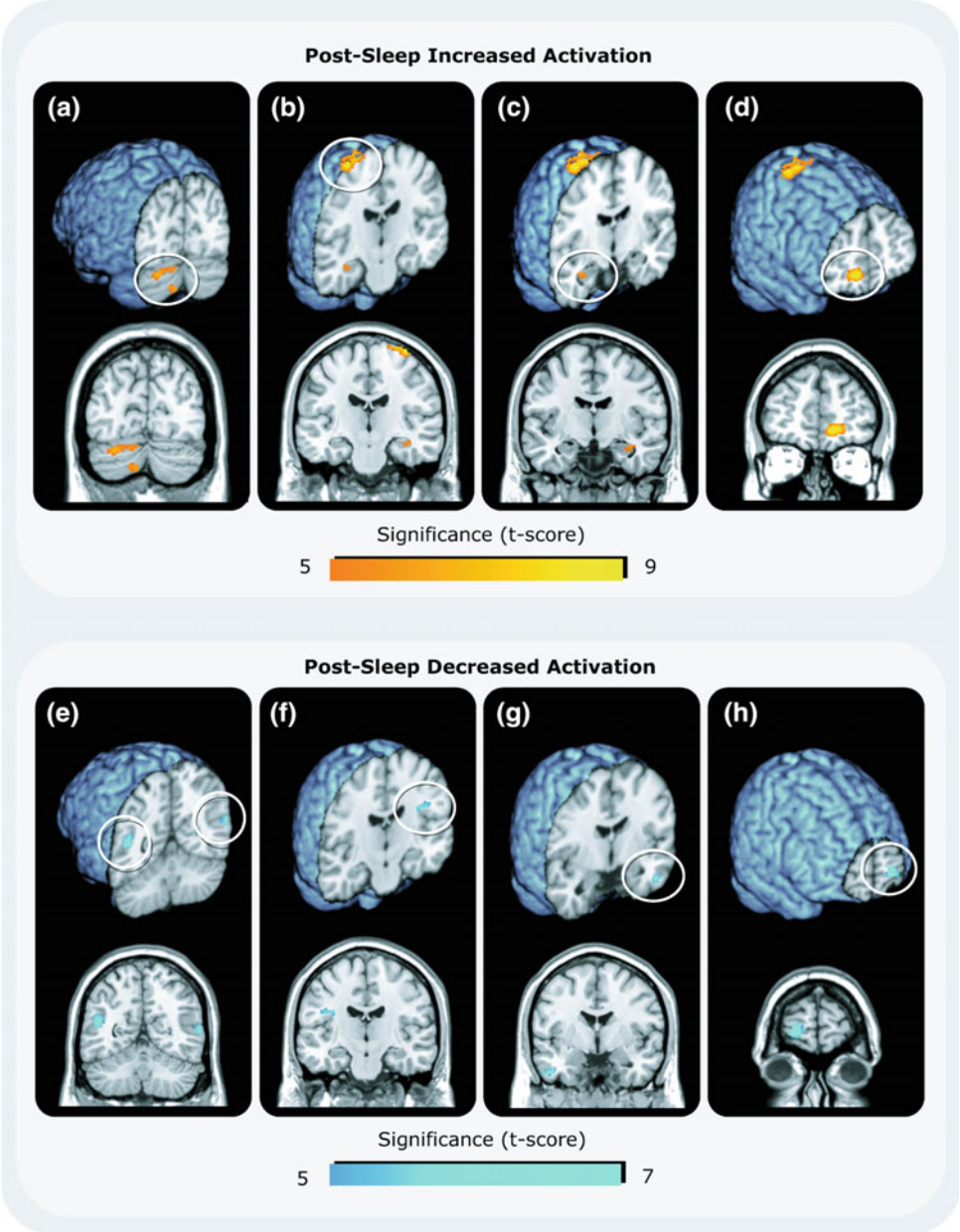

Fig. 13.7 Sleep-dependent motor memory reorganization. Subjects were trained on a sleep-dependent motor skill task and retested 12 h later, either following a night of sleep or following intervening wakefulness, during a functional MRI (*fMRI*) brain scanning session. Scans after sleep and wakefulness were compared (subtracted), resulting in regions showing increased fMRI activity post-sleep (in *red/yellow*; **a**–**d**) or decreased signal activity (in *blue*; **e**–**h**) post-sleep, relative to post-wakefulness. Activation patterns are displayed on three-dimensional rendered brains (*top panel* of each graphic), together with corresponding coronal sections (*bottom panel* of each graphic). Following sleep, regions of increased activation were identified in the right primary motor cortex (**b**), the left cerebellum (**a**), the right hippocampus (**c**), and the right medial prefrontal cortex (**d**). Regions of decreased activity post-sleep were expressed bilaterally in the parietal lobes (**e**), together with the left insula cortex (**f**), left temporal pole (**g**), and left frontopolar area (**h**), all regions of the extended limbic system. All data are displayed at a corrected threshold of $p < 0.05$

Overnight reorganization of emotional declarative memories has been the focus of many recent studies [120–122]. Similar to non-emotional declarative memories, memory for negative images following sleep is associated with less diffuse hippocampal activation. Specifically, Payne and Kensinger [120] examined changes in neural activity associated with an emotional picture recognition task following retention intervals with sleep or wake. Patterns of neural activation associated with successful recognition were distinct following sleep versus wake. After an interval of daytime wake, successful recognition of the negative images was associated with activation in a broad network including the lateral prefrontal,

parietal, and medial temporal lobes (including the hippocampus). In contrast, recognition performance following sleep was concentrated to a smaller network including the ventromedial prefrontal cortex, left amygdala, and cingulate gyrus.

Summary

Learning and memory are dependent on processes of brain plasticity, and sleep-dependent learning and memory consolidation must be mediated by such processes. Using brain imaging techniques, several studies have now identified changes in (1) the patterns of functional brain activity during post-training sleep periods (both REM and NREM) and (2) the reorganization of newly formed memories following a night of sleep. These plastic brain changes likely contribute to the refinement of the memory representations, resulting in improved next-day behavioral performance.

Electrophysiologic Studies

Evidence of sleep-dependent neuronal replay of waking experiences has accumulated from studies using multi-electrode recordings in the hippocampus of rodents. During waking exploration, the pattern of neural firing in hippocampal CA1 and CA3 cells, known as "place cells," is predictable as these cells exhibit an increased firing rate when the animal is in a particular location in space [123]. Initially, Wilson and McNaughton [124] observed that place cells that fired together during waking exploration tended to also fire together during subsequent sleep. Notably, in a subsequent study, Skaggs and McNaughton [125] found that not only was the same neural ensemble active, but cells were reactivated in the same order during sleep as they were during waking behavior. Dave and Margoliash [126, 127] have also shown that waking patterns of premotor activity observed during song learning in the zebra finch are also replayed during sleep, with a temporal structural similar to that seen in wakefulness.

Similar to studies in humans using contextual cues (odors, sounds) associated with learning to reactivate memories during sleep, Bendor and Wilson [128] selectively reactivated memories in rats during sleep and measured associated hippocampal replay. Prior to sleep, rats learned to move either left or right depending on a sound cue. During subsequent non-REM sleep, neurons associated with learning of this task were reactivated in the absence of any sound cue. However, when a task-related sound cue was presented, neurons associated with movements in the direction corresponding to that sound cue were preferentially fired. These results demonstrate a direct association between recent learning and the content of hippocampal replay.

Replay occurs in conjunction with sharp wave/ripple complexes in the hippocampus. Sharp waves are fast depolarizing events that overlap with high-frequency local field potential oscillations (ripples) and originate from pyramidal neurons in the CA1 region of the hippocampus [129–132]. Ripples have been associated with long-term potentiation (LTP), believed to be a physiologic mediator of memory formation [133, 134]; the frequency of ripples is conducive for LTP [135] and experimental suppression of hippocampal ripples has been shown to impair memory [136, 137].

Sleep spindles, generated by the thalamus and spread throughout the neocortex, co-occur with sharp wave/ripple complexes [138]. Rosanova and Ulrich [139] have shown that spike trains designed to mimic sleep spindles, delivered in vivo, produce both short-term and LTP. Moreover, functional connectivity between the hippocampus and the neocortex is increased in conjunction with spindles [140]. Thus, while behavioral evidence suggests that sleep spindles are associated with sleep-dependent performance changes, physiologically, spindles have been shown to support plasticity. Consistent with this, pharmacological manipulations which enhance spindle density in humans increase memory performance [141].

Together these data indicate that sleep-dependent reactivation of temporal patterns of network activity consistently occurs following learning experiences during wakefulness, across a broad spectrum of species. Neuronal replay of recent memories in the hippocampus via ripple events co-occurs with widespread neocortical activity driven by spindles. Such a mechanism is consistent with the proposal of hippocampal–neocortical transfer of memories over sleep, making memories less resistant to interference as new memories are encoded in the hippocampus [131, 142].

Cellular Studies

Sleep-dependent plasticity at the cellular level has been elegantly demonstrated during early post-natal development of the cat visual system [143, 144]. Under normal circumstances, brief periods of monocular visual deprivation during critical periods of development lead to the remodeling of synaptic connectivity, with the deprived eye's inputs to cortical neurons being first functionally weakened and then anatomically diminished [145]. Frank et al. [146] demonstrated that when 6 h of monocular deprivation are followed by 6 h of sleep, the size of the shift in cortical representation doubles. In contrast, if the cats are kept awake for these same 6 h (in the dark, without input to either eye), a nonsignificant *reduction* in the size of the shift occurs. Thus, sleep can contribute as much to developmental changes in synaptic connectivity as does visual experience, presumably by enhancing the initial changes occurring during a prior period of monocular deprivation. In contrast, sleep deprivation

results in a loss of previously formed, experience-dependent synaptic change, consistent with behavioral studies in humans [71].

Shaffery et al. [147] have reported complimentary findings of sleep-dependent plasticity in the rat visual cortex, suggesting that REM sleep, in conjunction with visual experience, modulates the initial time course of visual cortex maturation. In rats under 30 days of age, electrical stimulation produces increased excitability (potentiation) in specific layers of the visual cortex, while stimulation after this early developmental stage is unable to produce such potentiation. Depriving rats of REM sleep during this period can extend the window of plasticity by as much as 7 additional days, suggesting events occurring during REM sleep normally control the duration of this period of experience-dependent plasticity.

Molecular Studies

At the molecular level, Smith et al. [148] have shown that administration of protein synthesis inhibitors to rats during REM sleep windows thought to be critical for consolidation prevents behavioral improvement following the sleep period, while rats receiving saline injections show normal sleep-dependent learning. Such protein synthesis could reflect a fundamental mechanism regulating plasticity, namely the activation of genetic cascades that produce key molecules for synaptic remodeling. Such gene inductions during sleep have been the focus of more recent investigations. In their initial studies, Cirelli and Tononi reported that several of the known "immediate early genes" (IEGs) are specifically downregulated during sleep [149–151]. These findings have been used to argue that sleep is incapable of supporting plasticity and hence memory consolidation [103]. However, ample, more recent research by Cirelli et al. [152] has described approximately 100 genes that are specifically upregulated during sleep—almost the same number that are upregulated during wakefulness.

This extensive upregulation of genes was seen in the absence of any specific learning tasks being performed prior to sleep. Insofar as this upregulation is related to learning and memory consolidation, one might expect that such gene induction would only be seen after training on tasks that undergo sleep-dependent consolidation. Indeed, Ribeiro et al. [153, 154] have found upregulation of *zif*-268 and other plasticity-associated IEGs [155] in rats during REM sleep following exposure to a rich sensorimotor environment or induced hippocampal LTP, but found *zif*-268 downregulation during both SWS and REM sleep in the absence of such exposure. Thus, there appears to be a window for increased neuronal plasticity during REM sleep periods following enriched waking experience (Fig. 13.8).

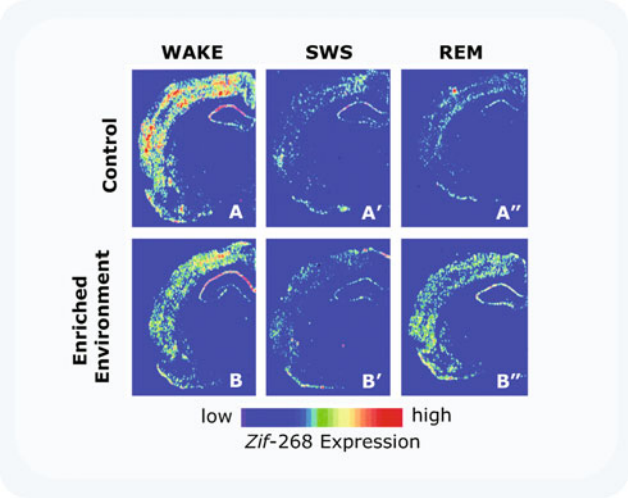

Fig. 13.8 Experience-dependent upregulation of *zif*-268 gene expression during wakefulness (WAKE) and slow-wave sleep (*SWS*) and REM sleep (REM) states in the rat. Autoradiograms of frontal coronal brain sections whose gene expression levels best represent the means for each group studied. In controls, *zif*-268 expression decreased from WAKE (A) to SWS (A′) and REM (A″). In enriched-environment animals, *zif*-268 levels decreased from WAKE (B) to SWS (B′), but increased from the latter to REM (B″). This effect was particularly noticeable in the cerebral cortex and the hippocampus (Reproduced with permission from Ribeiro et al. [153])

Summary

These studies at the cellular and molecular level illustrate the physiological basis of the changes in memory over sleep observed in behavioral studies. Although initial work failed to integrate behavioral changes with physiological findings, recent studies have successfully demonstrated sleep-dependent plasticity directly associated with waking behavior. While further work is needed to continue to integrate measures of plasticity and behavioral changes over sleep, evidence is accumulating in support for this relationship.

Unresolved Questions

Over the last several years, as evidence of sleep's role in learning and memory consolidation has grown, some researchers have raised questions concerning the nature of this relationship and specific mechanisms that are necessary to support it. Having focused our attention so far on the evidence in support of sleep's role, we turn now to concerns

and objections to this research, many of which hold clinical relevance.

Antidepressants, Sleep, and Memory

A recurring issue in the sleep and memory debate has been the REM sleep suppressant effects of monoamine oxidase inhibitors (MAOIs) and other antidepressants and the impact, or lack thereof, on memory functioning. These findings appear to suggest REM suppressants can be taken for years with no deleterious effects on learning [103, 104, 156]. First, although MAOIs appear to reduce REM sleep to a greater or lesser extent early in medication [157, 158], REM sleep re-emerges later in the course of medication [159–161], suggesting a strong REM compensatory mechanism. Furthermore, there is a potent REM rebound during periods when medication is paused—the so-called drug holidays [160, 162, 163]. As such, the claim that patients live for years without REM sleep is unfounded.

It is also important to keep in mind that most of these studies use a single test of memory which does not address the question of intact or impaired sleep-dependent learning, which requires a retest following sleep. No studies, to date, have retested performance following sleep, or recorded subjects' sleep to determine the extent of REM suppression. As a result, current studies are not conclusive regarding the role of post-training REM sleep in memory consolidation. A systematic study focusing on the effects of antidepressant medication on memory consolidation represents an important future goal, particularly considering the implications of such sleep-dependent memory impairment as a consequence of these drugs.

State Versus Trait

Some physiological measures of sleep that have been associated with memory have high within-subject correlations overtime, suggesting that they are a stable trait or phenotype. For instance, twin studies indicate that a significant proportion of the variability in stage 2 NREM and SWS is genetically determined [164]. Likewise, Geiger et al. [165] found low intra-individual (night-to-night) variability and high inter-individual variability in sleep-stage distributions and spectral power including the spindle range (sigma power). Of note, sigma power correlated with IQ. Thus, it is possible that associations between over-sleep changes in performance with sleep physiology, particularly sleep spindles, reflects these known associations between phenotypes. While research disentangling the state and trait relationships is ongoing, Schabus et al. [166] found state-specific spindle increases following learning in addition to the baseline association between spindles and cognitive abilities. This suggests that spindles, and perhaps other sleep features, may play both a state and trait role in learning.

Contributions of Sleep Micro- and macrostructure

As reviewed here, it is apparent that sleep spindles, occurring predominately in NREM, contribute to sleep-dependent hippocampal plasticity. However, it is clear that other aspects of sleep microstructure and macrostructure contribute to memory consolidation and how these factors work independent of or in conjunction with NREM sleep spindles has yet to be elucidated. For instance, Datta has suggested that ponto-geniculo-occipital (PGO) waves present in REM sleep underlie consolidation. PGO waves increase following training on an avoidance task and the increase is proportional to the degree of retention of performance over sleep [167]. These results imply that more time in REM sleep should be associated with greater memory consolidation. Given that Datta's observations were based on an avoidance task in which a foot shock is delivered, one possibility is that the role of PGO waves and, more generally, REM sleep may be restricted to aversive memory processing as suggested in human studies cited above. Likewise, it has been suggested that the macrostructure of sleep is important. Ficca and colleagues have reported that pre-sleep learning can result in an increase in the number of sleep cycles across the night and an increase in cycle time, and this increase is proportional to post-sleep performance [168]. Disturbing sleep cycle organization also resulted in impaired verbal recall following sleep [169]. More than likely memories evolve throughout sleep and reported associations with sleep micro and macrostructure may reflect the predominant contributing process. How the form of memory processing changes across a bout of sleep continues to provide fuel for theoretical debate [24] and future research.

Summary

Over the last 25 years, the field of sleep and memory research has grown exponentially. These reports, ranging from studies of cellular and molecular processes in animals to behavioral studies in humans, have provided a wealth of converging evidence that sleep-dependent mechanisms of neural plasticity lead to the consolidation of learning and memory across a range of animal species.

At the molecular level, a significant number of genes appear to be upregulated specifically in brain tissue during sleep. IEGs related to synaptic plasticity, including *zif*-286, are upregulated during REM sleep expressly in response to environmental or direct electrical stimulation of the

hippocampus. In rats, patterns of neuronal activation expressed during waking exploration reappear during subsequent sleep, and, in humans, patterns of regional brain activation seen during daytime task training are repeated during subsequent REM sleep.

At the electrophysiologic level, studies have shown enhanced hippocampal plasticity in conjunction with sleep spindles. In humans, spindle density increases following training on a declarative memory task, and, again, this increase correlates with subsequent improvement on the task.

At the behavioral level, animal studies have found robust increases in REM sleep following task training and decrements in performance after REM deprivation, even when retesting is delayed up to a week after the end of deprivation. In contrast, several animal studies have failed to find evidence of either increased REM sleep or deterioration following deprivation. Most likely, this reflects a combination of methodologic problems and conditions under which consolidation is, in fact, not sleep-dependent. Similarly, human studies have provided examples in which increases in REM sleep are seen following training; REM, SWS, or stage 2 NREM deprivation diminishes subsequent performance; and overnight improvement correlates with REM, SWS, or stage 2 NREM sleep.

In the end, the question appears not to be whether sleep mediates learning and memory consolidation, but instead, how and when it does so. The future of the field is truly exciting, and the challenge to neuroscience will be to both uncover the mechanisms of brain plasticity that underlie sleep-dependent memory consolidation, and to expand our understanding of sleep's role in memory processes beyond simple consolidation, into the constellation of additional processes that are critical for efficient memory development. Work across the neurosciences will be necessary to answer these questions, but with the current rate of growth of research in the field, the next decade should provide important advances in our understanding of this critical function of sleep. By way of this multidisciplinary approach, and with a measured appreciation that sleep plays a fundamental role in consolidating and reforming memories, we can look forward to new advances in treating disorders of memory, and perhaps even improving the capacity of our own.

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Dreaming and Sleep Disorder

14

James F. Pagel and Seithikurippu R. Pandi-Perumal

A Short History of Dream Study

Dreams are ubiquitous yet poorly defined cognitive experiences that have been the focus of human interest and study since the dawn of recorded history. In the ancient Sumerian city of Ladak, about 6000 years ago, King Gudea inscribed multiple copies of a dream instructing him to orient his temple to the cardinal points. The dreams experienced by rulers, priests, and prophets were thought to be messages from gods, resulting in the incorporation of dreams and nightmares onto the walls of Egyptian Tombs, as well as into the texts of the Torah, the Bhagavad Gita, the Bible, and the Koran [1]. The ancient Greeks incorporated dreams as reflections of physical and psychological health into the Asclepius (the god of medicine) temple cults where patients slept at the foot of the god and reported their dreams in the morning to the priests. This ritual and the results of each prescribed treatment were recorded, laying an epistemological groundwork for the field of medicine. Dreams were an early focus of philosophy as reflected in Plato's records, in which Socrates was asking, "What proof could you give if anyone should ask us now, at the present moment, whether we are asleep and our thoughts are a dream, or whether we are awake and talking to each other in the waking condition?" [2]. In the seventeenth century, René Descartes developed the process of logic that we now call the scientific method based on a series of dreams. He first used that method in an attempt to differentiate his waking consciousness from that of his dreams, and like modern theorists found evidence through addressing the processes of memory. "I should no longer fear lest those things that are daily shown me by my senses are false; rather the hyperbolic doubts of the last few days ought to be rejected as worthy of derision—especially the principal doubt regarding sleep, which I did not distinguish from being awake. For I now notice that a very great difference exists between these two; dreams are never joined with all the other actions of life by the memory, as is the case with those actions that occur when one is awake" [3]. The philosophers, artists, and writers of the nineteenth century found much of the creative inspiration for modernism in the extreme experiences of nightmares and dreams [4]. Freud [5] at the turn of the twentieth century incorporated this perspective into the diagnostic and therapeutic process of psychoanalysis, in which dreams supplied insight into the psychodynamics of psychiatric illness. For much of that century, dreams were used and viewed as markers for the role of the unconscious. When in the 1950s sleep researchers at the University Chicago noted the strange phenomena of repetitious conjugate eye movements occurring periodically during the night, the immediate question was as to whether this physiological state (i.e., rapid eye movement or REM sleep) might be related to dreaming. When Dement awakened test subjects during this REM sleep state, most reported dreaming [6]. For many, this finding was the psychoanalytic "smoking gun" demonstrating a biological basis for postulated psychoanalytical constructs of brain function.

REM Sleep and Neuroconsciousness Theories

In the last 50 years, the scientific focus on dreaming has been on REM sleep as a scientifically measurable correlate of dreaming. Hobson and McCarley incorporated this perspective in their theory of activation-synthesis, proposing that all cognitive behaviors, both conscious and non-conscious, reflect physiological activity occurring in the central nervous system (CNS) [7]. Dreaming was viewed as a higher cerebral cognitive process utilizing the CNS activation associated with the primitive electrophysiologic-activated state of REM

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sleep. A derivative of activation-synthesis, Activation, Integration, Modulation (AIM) theory, is currently the most fully developed and widely accepted theory of CNS functioning [8]. It is a primary postulate of AIM that the neurons and neurochemicals that modulate REM sleep also alter dreaming. Modern measures of the "dream" (e.g., REM sleep and associated position emission tomography [PET] and functional magnetic resonance imaging [fMRI] activity) are often confounded with the cognitive experience of dreaming. Research into the neuroanatomy, neurochemistry, and electrophysiology of REM sleep is often presented as dream research [9].

Defining Dreaming

The lack of an accepted definition for dream has created considerable confusion in the literature [10, 11]. In this chapter, a psychologically based definition will be used: dream is defined phenomenologically as cognition characterized by the presence of images, emotions, memories, as well as CNS activity that typifies dreaming.

The Neurochemistry of REM Sleep and Dreaming

The neurotransmitter acetylcholine was the first neurochemical discovered thought to trigger REM sleep. This effect is modulated by a wide spectrum of neuromodulators including serotonin, norepinephrine, and dopamine. It has been presumed that any neurochemical which alters REM sleep should alter dreaming [12]. Anti-cholinesterase inhibitors are agents known to produce an increase in acetylcholine levels and are reported in some studies to induce increased REM sleep percentages on polysomnography [13]. These agents are used as nerve gas agents and pesticides, and at low doses, donepezil, rivastigmine, and similar nutritional supplements are used to treat Alzheimer's disease. Case reports and small uncontrolled studies have been used to support utilization of these agents in attempting to increase dream intensity and lucidity [14, 15]. Data derived from clinical trials indicate a very different neurochemical association between medications and dreaming. A wide spectrum of agents including REM sleep suppressants, anesthetics, and anti-infectives induces nightmares and abnormal/disturbed dreaming in greater than 1 % of subjects enrolled in clinical trials [16] (Table 14.1). Donepezil is not included in this list, since during clinical trials, only 3 of 747 subjects reported changes in dreaming. Rivastigmine induced no reports of changes in dreaming in 1634 subjects [17]. Clinical trials include a large number of subjects, a control group, and methodology that avoid the plethora of competing variables and biases that characterize much dream research. Clinical trial data indicate that the medications utilized to suppress nightmares, alpha-adrenergic and beta-blocking anti-hypertensive medications, exert primary effects on norepinephrine, while suppressing or having minimal effect on REM sleep [18]. Medications that increase or suppress REM sleep have minimal effects on dreaming. Medications that alter dreaming often have no effect on REM sleep.

REM Sleep and Dreaming

After 50 years of research, we now understand far more about the electrophysiology, neuroanatomy, and neurochemistry of REM sleep than we understand about the cognitive state of dreaming. Multiple studies have demonstrated a bidirectional dissociation between REM sleep and dreaming. Dreaming can occur without REM sleep, and REM sleep can occur without dreaming [19–21]. Those researchers who are reluctant to separate REM sleep from dreaming have suggested a theory of covert REM sleep: when dreaming (defined as bizarre or hallucinatory mentation) is reported, REM sleep must have occurred whether or not it is evident on polysomnography [22]. Many neuroscientists have asserted that dreaming occurs during other stages of sleep but has a special relationship with REM sleep. According to these researchers, REM sleep dreams are the most emotional, vivid, bizarre, have the highest recall of any sleep state, are the only dream state with lucidity, and the only sleep mentation with "dream-like" content [23, 24].

Dream Bizarreness. In the 1950s, Hall and Van der Castle designed an analytic scale used for recording and statistically comparing dream content [25]. This classic and well-validated scale did not address bizarreness, a characteristic that has become important to dream scientists attempting to support a special relationship between REM sleep and dreaming. The Hobson bizarreness scale was developed that rates bizarreness based on the storyline content of the dream. Dreams that include incongruous, uncertain, and discontinuous wording and story are rated as the most bizarre [26]. Since REM sleep dreams tend to be longer and include more words and a more developed storyline, studies using this bizarreness scale consistently demonstrate that REM sleep dreams are the most bizarre. Bizarreness ratings for dreaming based on sleep state of origin vary markedly based on the scale utilized [27]. When factors such as hallucination, confusion, and atypical behavior are included in the assessment, the non-REM (NREM) sleep dream experiences of sleep onset and arousal

Table 14.1 Medications reported to induce nightmares and disturbed/abnormal dreaming in >1 % of clinical trial (ct) subjects

Affected neuroreceptor—drug class	Patient reports of nightmares and/or disturbed/abnormal dreaming
Norepinephrine—beta blockers	
Atenolol	CT [nightmares 3/20 patients]
Bisoprolol	CT [nightmares 3/68 patients]
Labetalol	CT [nightmares 5/175 patients]
Oxprenolol	CT [nightmares 11/130 patients]
Propranolol	CT [nightmares 8/107 patients]
Norepinephrine affecting agents	
Guanethidine	CT [nightmares 4/48 patients]
Serotonin—SSRI—antidepressants	
Fluoxetine	CT [nightmares 1–5 %—greater frequency in OCD and bulemia trials
Escitalopram oxalate	CT [Abnormal dreaming—1 % of 999 patients]
Nefazodone	CT [nightmares 3 % (372) vs. 2 % control]
Paroxetine	CT [nightmares 4 % (392) vs. 1 % control]
Agents affecting serotonin and norepinephrine—antidepressants	
Desvenlafaxine	CT [Abnormal dreams 4 % [400 mg] 2–3 % at lower doses vs. 1 % placebo]
Duloxetine	CT [2 % abnormal dreams (N = 3917) vs. <1 % placebo (N = 2548)]
Mirtazapine	CT [4 % abnormal dreams (N = 453) vs. 1 % placebo (N = 361)]
Risperidone	CT [1 % increased dream activity—2607 patients]
Venlafaxine	CT [nightmares 4 % (N = 1033) vs. 3 % control]
Dopamine agonists	
Amantadine	CT [5 % report abnormal dreams]: CR [1]
Levodopa	CT [nightmares 2/9 patients]
Ropinirole	CT [3 % (208) report abnormal dreaming vs. 2 % placebo]
Selegiline	CT [2/49 reporting vivid dreams]
Dopamine—amphetamine like agents	
Bethanidine	CT [nightmares 2/44 patients]
Fenfluramine	CT [nightmares 7/28 patients]: CR [1] de and re-challenge
Phenmetrazine	CT [nightmares 3/81 patients]
GABA	
Gaba hydroxy butyrate	CT [nightmares >1 % 473 patients]
Triazolam	CT [nightmares—7/21 patients]
Zopiclone	CT [nightmares in 3–5/83 patients]
Anti-infectives and immunosuppressants	
Amantadine	CT [5 % reporting abnormal dreams]: CR [1]
Fleroxacin	CT [nightmares in 7/84 patients]
Gusperimus	CT [nightmares in 13/36 patient]
Antipsychotics	
Clozapine	CT [4 % nightmares]
Antihistamine	
Chlorpheniramine	CT [nightmares in 4/80 patients]
ACE inhibitors	
Enalapril	CT [0.5–1 % abnormal dreaming—2987 patients]
Losartan potassium	CT [>1 % dream abnormality—858 patients]
Quinapril	CT [>3 % nightmares]
Other agents	
Sodium oxybate	CT—Nightmares in 3/102 subjects vs. 0/34 in control group

disorders of deep sleep are far more bizarre than those associated with REM sleep [9].

Vivid Dreams. If vivid is defined as an intense visual experience, the hypnagogic phenomena of sleep onset are clearly more vivid and more hallucinatory than REM sleep dreams. Methodologically controlled dream content analysis reveals that the primary correlate for dream content is waking experience (continuity) [21]. Such studies have not revealed a sleep stage correlate for content; however, if vivid is defined as content that is most like wake, the anxiety dreams of light sleep (Stage-2) have more continuity with the waking experience as do the dreams of REM sleep [9].

Lucid Dreaming. Lucid dreaming is often characterized as occurring only during REM sleep; however, this postulate was developed during the period, in which all dreaming was presumed to be related to REM sleep. Even those who initially described the state noted that up to 18 % of lucid dreams were reported from sleep onset, a period during which REM sleep rarely occurs [28]. During lucid dreaming, rather than the brain stem activation classically associated with REM sleep, multiple CNS sites are activated that are normally de-activated during REM sleep including the bilateral precuneus, cuneus, parietal lobules, prefrontal, and occipito-temporal cortices—sites associated with waking visual perceptual control and not usually associated with dreaming [29]. From an electrophysiological standpoint, the signaling criteria used in establishing the state of lucidity occur during episodes of arousal. The high level of alpha frequency associated with lucid dreaming has also led to suggestions that lucid dreaming may be a state of consciously controlled sleep offset between sleep and waking [30].

Empirical Evidence. Good empirical evidence refutes many of the postulates that have been used to support the perspective that a special relationship exists between REM sleep and dreaming. Sleep onset and REM sleep, both states that are close to waking, have similar recall frequency and content when length of the report is taken into account [19]. Dream content studies designed to eliminate transfer effects and researcher bias have indicated that the content of REM sleep dreaming may not be significantly different from the content of NREM sleep dreams [31]. Today, it remains problematic as to how our understandings of REM sleep electrophysiology, neuroanatomy, and neurochemistry can be applied to the cognitive state of dreaming.

The Sleep/Dream States—REM Sleep Dreaming

All mammals, almost all monotremes, and many birds demonstrate the electrophysiological state of REM sleep. Most humans, even those with extensive neurological damage, have episodes of REM sleep which persist even in very old age.

The dreams of all electrophysiologically described sleep states differ phenomenologically from each other. REM sleep dreams differ from other dreams. The best evidence for this difference is in the number of words and length of report—REM sleep dreams are longer than other dreams [32]. In part, at least, due to their length, REM sleep dreams are more likely to be organized into full narrative structures than are other dreams [4, 9]. Because of their length and narrative structure, REM sleep dreams are often the classic big dreams of psychoanalysis, creative discovery, religious, and ecstatic insight. The narrative structure associated with REM sleep dreams most resemble the narrative genre of personal experiences that we call "soap operas" [33].

Nightmares. Nightmares are the most common of all the parasomnias. They are more closely tied to REM sleep than are other dreams. Except in individuals with Post-traumatic stress disorder (PTSD), nightmares occur almost exclusively during REM sleep. Five percent of the general population report nightmares to be a problem, and among insomniacs, nightmares are reported at even higher frequencies [34]. For those who suffer from nightmares, it is the associated distress, rather than the frequency of occurrence that is most closely tied to waking dysfunction. When an individual experiences significant psychological or physical trauma, recurrent nightmares can mark the failure of CNS systems involved in emotional processing [35]. Nightmares are the most commonly reported symptom of PTSD. Recurrent nightmares that disturb sleep in individuals without a history of trauma denote the presence of nightmare disorder [36].

REM Sleep Parasomnias. The other REM sleep parasomnias that frequently include dream content include sleep paralysis; that often includes dreams with negative and frightening content, developed in great detail, and associated with distress that extends into awakening. The dreams of REM sleep behavior disorder (RBD) can be physically aggressive interactions in which the dreamer is attacked by unfamiliar people or animals. Individuals with RBD sometimes exhibit complex and violent behaviors associated with their dream mentation. Injuries to the sleeper or bed-partner are the most common symptom that leads them to seek medical attention. On video-polysomnographic monitoring, most of these individuals demonstrate increased muscle activity during REM sleep, a state that is normally characterized by motor atonia. This motor block that keeps us from moving during dreaming—fails, and individuals with RBD apparently act out their dreams. The parasomnias of RBD sometimes occur outside of REM sleep [37]. Dreaming bizarreness (both scales) and thought processing characteristics as based on work by Wolman and Kozmova for REM sleep dreams are summarized in Box 14.1 [38].

Box 14.1—REM Sleep Dreams: Formal Characteristics, Bizarreness, and Thought Processing

Formal Characteristics

- Coherent dream sequences
  - Detailed plot, character, or actions
- High recall
- Increased length of report
- Disturbing, intense emotions (nightmares and sleep paralysis)
- Potential lucidity
- Recurrent (reality based) PTSD
  - Comparative reality-based memory

Bizarreness

[Hobson Scale]
Discontinuities—high, Incongruities—high, and Uncertainties—high
[Hunt Scale]
Hallucinations—low, Clouding/confusion—low, and General—high—(uncanny emotion)

Rational Thought Processing

- Analytical—high
- Perceptual—high
- Memory and time awareness—high
- Affective—high
- Executive—high
- Subjective—high
- Intuitive/projective—high
- Operational—mod

Adapted and updated from Pagel and Helfter [16].

Some clinical trials did not query as to dream-associated drug side effects. This is particularly true for older medications >20 years.

The Sleep/Dream States—Sleep Onset

Despite high dream recall frequency (>80 %), the cognitive associations of sleep onset (Stage 1) have received only limited study. Most of what we know of sleep-onset dreaming comes from the study of hypnagogic parasomnias. Hypnagogic hallucinations commonly occur in otherwise normal people at the onset of sleep. These are true hallucinations, most often auditory but frequently visual, and seemingly real to the dreamer. These experiences can be quite bizarre and frightening, ranging from the sounds of a dog barking, a baby crying, or an alarm ringing that wakes the dreamer, to the extreme experience of suffocation at the hands of a succubus. Artists and writers have sometimes induced hypnagogic dreaming and used the resultant dream experiences in their work. Both Salvador Dali and John Keats, known to have used this technique, would attempt to fall asleep while sitting in a chair and holding a coin between thumb and index finger. When they fell asleep, their hands would relax, and the coin would fall into a dish set beside the chair and startling them to awake. There are those who insist that sleep-onset dreams are less bizarre than REM sleep dreams [23]. The surrealistic images that Salvador Dali derived using this technique argue otherwise. Sleep paralysis, most often associated with REM sleep and commonly present in patients with narcolepsy, can also occur at sleep onset. More than half the Americans queried report having experienced either sleep paralysis or hypnagogic hallucinations [39].

Sleep-onset dreams differ from the dreams of other stages of sleep. They are short in duration. They include intense visual imagery and only limited content or story. They can be reality based (particularly in individuals with PTSD) and are sometimes associated with intense distress and anxiety. Each occurs at the initiation of perceptual dissociation that marks the onset of sleep, forming a snapshot of non-perceptual visual consciousness present at sleep onset. These sleep-onset dreams convey an apparent perceptual consciousness but without perception and with limited associated content and memories, without control, yet with intense emotion, visual intensity, and detailed recall. Recent brain scanning studies indicate that compared to other sleep/dream states, large areas of the visual cortex continue to maintain activity despite the eyes-closed perceptual isolation of the state [40]. Sleep-onset dreams include apparently "bizarre" hallucinations, extreme emotional distress, and intense disassociation from reality, yet based on the Hobson scale, sleep-onset dreams due to their short and limited storyline scale are consistently rated as less bizarre than REM sleep dreams. Sleep-onset dream scores are completely different when based on alternative bizarreness scale scores developed by Hunt [27]. Formal characteristics, comparative bizarreness per scale, and characteristic dream state associated thought processes are included in Box 14.2.

Box 14.2—Sleep-Onset Dreaming [Formal Characteristics, Assessment of Bizarreness, and Thought Process]

Formal Characteristics

- Primarily visual hallucinations perceived as potentially real
- Coherent dream stories
- High recall
- Potential lucidity

- Impression of falling (Sleep Starts)
- Intense anxiety (PTSD, Sleep Paralysis)
- Recurrent (reality based) PTSD

Bizarreness

[Hobson Scale]
Discontinuities—high, Incongruities—low, and Uncertainties—low
[Hunt Scale]
Hallucinations—high, Clouding/confusion—high, and General—high (emotion, bizarre personification)

Rational Thought Processing

- Analytical—low
- Perceptual—high
- Memory and time awareness—high
- Affective—high
- Executive—low
- Subjective—high
- Intuitive/projective—low
- Operational—low

The Sleep/Dream States—Stage 2 Dreaming

Most of sleep is Stage 2, a stage that can be viewed as the junkyard of sleep, including all of sleep that is not sleep-onset, REM sleep, or deep sleep. Dream recall frequency is generally low, in the range of 40 %, and varies across the night. Since Stage 2 includes a majority of sleep, dream researchers in attempting to emphasize the association between REM sleep and dreaming have often extended this low recall percentage to NREM sleep [41]. Stage 2 dreams are often fragmentary containing thought-like content and disconnected visual imagery in which the dreamer is emotionally uninvolved. It has been suggested that this "degraded" mentation might be memory remnants from preceding REM sleep state or thoughts that developed after awakening [22]. Stage 2 dreams include fewer elements, a rather fragmented narrative structure, predominantly static impressions, and less emotional self-participatory involvement. The dream-like parasomnias associated with Stage 2 include sleep talking, anxiety dreams, and the brief moments of terror we call sleep panic attacks. These parasomnias share the characteristics of anxiousness and day reflective content. Panic attacks can include extreme emotion. Stage 2 dreams may extend throughout the night. They are rarely profound or particularly interesting. The formal characteristics, bizarreness, and thought processing of Stage 2 dreams and parasomnias are summarized in Box 14.3.

Box 14.3—Stage 2 Dreams: Formal Characteristics, Bizarreness, and Thought Process
Formal Characteristics

- Day reflective content
- Associated anxiety and panic
- Variable recall across night

Bizarreness

[Hobson Scale]
Discontinuities—low, Incongruities—low, and Uncertainties—low
[Hunt Scale]
Hallucinations—low, Clouding/confusion—low, and General—low

Rational Thought Processing

- Analytical—low
- Perceptual—mod (perceptual integration associated with K-complexes)
- Memory and time awareness—low
- Affective—low
- Executive—low
- Subjective—low
- Intuitive/projective—low
- Operational—mod (potential for arousal)

The Sleep/Dream States—Deep Sleep

Deep sleep (Stage 3) differs markedly from other stages of sleep. During deep sleep, perceptions are fully blocked, and we may not respond to pain. Tertiary aspects of consciousness are absent, and there is no volitional or executive control. During deep sleep, frontal cortex activity drops to a very low level. This is the one conscious state, during which the default network is minimally active and apparently decoupled, potentially contributing to an alteration or suspension of consciousness during deep sleep [42]. The reduced recall from this stage may be due in part to its cognitive distance from waking [43]. The dreams of deep sleep that we do remember differ markedly from waking consciousness. The dream content of deep sleep is most often reported as an emotion, a visual color, or perhaps an awareness that dreaming has occurred. Behaviorally, we would understand very little about the mental activity of deep sleep if it were not for the remarkable parasomnias (e.g., sleep terrors, somnambulism, and confusional arousals) occurring in this stage. These parasomnias (particularly somnambulism) are associated with autonomic

"zombie-like" motor activity during which complicated but common waking tasks can be clumsily accomplished (e.g., opening a door or window, preparing food, walking down stairs, picking up and loading a weapon, and running down the street). Computation is only minimally possible, and combination locks can be useful for patients wanting to protect themselves from the more dangerous nocturnal behaviors outside their room. Deep sleep parasomnias often include intense fear and extreme emotions, usually negative, frequently occurring in association with autonomic discharge (sweating, shaking, flushing, and nausea). The dreamer can become extremely angry, hitting out when awake occurring without the subject's conscious waking knowledge. The emotional outbursts of night terrors include a fright-ridden cry, sweating, flushing, and apparent abject terror. Confusional arousals typically include disorientation, slow speech, diminished mentation, and inappropriate behaviors that can be vigorous, highly resistive, and violent [44]. The arousal disorders are the most bizarre and emotional of the dream-associated parasomnias. They are frightening and disturbing to the observer. The formal characteristics of deep sleep dreaming as well as characteristic thought and bizarreness are specified in Box 14.4.

Box 14.4—Deep Sleep Dreaming: Formal Characteristics, Bizarreness, and Thought Process

- Somnambulism (sleepwalking)—Autonomic and inappropriate behaviors, frantic attempts to escape a perceived threat, fragmentary recall
- Confusional Arousals—Mental confusion and disorientation on arousal from sleep, inappropriate and violent behaviors
- Night Terrors—Incoherent vocalizations, extreme fear, intense autonomic discharge, confusion and disorientation, and fragmentary recall

Formal Characteristics

- Mental confusion and disorientation on arousal
- Fragmentary recall
- Autonomic and inappropriate behaviors
- Frantic attempts to escape a perceived threat

Bizarreness

[Hobson scale]
Discontinuities—low, Incongruities—low, and Uncertainties—high (explicit vagueness)
[Hunt Scale]
Hallucinations—low, Clouding/confusion—high (low recall), and General—high (emotion, bizarre personification)

Thought Process

- Analytical—low
- Perceptual—low
- Memory and time awareness—low
- Affective—high
- Executive—low
- Subjective—low
- Intuitive/projective—low
- Operational—low

Dreamless Sleep?

Since dreams are reported from all stages of sleep and since CNS activity in various forms is maintained throughout sleep, the question can be raised as to whether, like thought in waking, cognitive mentation (dreaming) may persist throughout sleep. Many years ago, Descartes suggested that dreamless sleep was a state of non-consciousness. He suggested that sleep without dreaming could not exist. Since "thinking" defined consciousness, a non-thinking, non-dreaming state could be neither conscious nor alive [3].

Variables Affecting Dream Recall. Individuals will sometimes report an absence of dreaming even when awakened during states characterized by high dream recall such as REM sleep and sleep onset. A reported lack of dream recall occurs even more often during episodes of Stage-2 and Stage-3 when reported dream recall declines to approximately 40 % of awakenings [19]. In other words, up to 1/3 of sleep in otherwise normal individuals can be considered to be "dreamless." Memory instability during the state transition from sleep to waking likely accounts for an overall 20 % of reported loss of dream recall, since that is the portion of dream recall typically lost even in the high recall states of sleep onset and REM sleep. The further diminution of recall from Stage 2 may be due to low dream probability secondary to low emotionality, uninteresting content, and anxiety-based characteristics of dreaming in that state. The lower levels of dream recall from Stage 3 (deep sleep) are most likely based on the stage's difference from waking [45].

There are a variety of reasons that individuals do not recall dreams. Variables known to affect the process of recall include time since dreaming and distraction after waking [46]. Dream content characteristics including salience and emotion can increase our tendency to recall a particular dream [47]. A lack of interest in dreaming, particularly in individuals without creative outlets, is also associated with diminished recall [48]. Some personality types (thick boundaries) have diminished dream recall [49]. Other

variables known to alter recall include gender, age, type of report collection (diary, awakening, and interview), and perceived definition of dream by both subject and researcher [50]. Dream studies are also extremely susceptible to collection, transference factors, methodology, and researcher bias [21, 51].

Non-dreamers. A loss of dreaming has been reported after extensive damage to the basilar bi-frontal cortex damage [52]. While rare, 1/262 (0.38 %) of sleep clinic patients will report after questionnaires and interview that they have never experienced a dream. These individuals report a lack of dream recall even when awakened multiple times during REM sleep and NREM sleep [53]. It has been suggested that these individuals are dreaming, but they just do not remember their dreams on waking. Current dream research, however, suggests that dreaming requires and uses many of the same memory systems that are required for waking functioning [54]. If the lack of dream recall indicates that memory systems are somehow compromised, waking memory impairment should be apparent (it was not for these individuals). The question remains as to whether these individuals, those who have experienced major brain trauma, or other individuals who occasionally report a lack of dream recall on awakening are truly experiencing dreamless sleep.

Dreaming in Other Sleep and Psychiatric Disorders

Obstructive Sleep Apnea (OSA) and Insomnia. Individuals with the complaint of insomnia report a higher frequency of both dream and nightmare recall [55]. However, when sleep is objectively measured in these patients, recall is significantly lower for those with lower sleep quality (prolonged latency, decreased time and efficiency, and increased wake after sleep onset [WASO]) [56]. Individuals who have recently developed PTSD and associated nightmares are likely to have at least mild sleep apnea [57]. In individuals with more severe sleep apnea, however, while dream recall is maintained, nightmares occur at a significantly lower frequency [58]. These studies suggest the possibility that for milder levels of both OSA and insomnia, increased arousals may contribute to increased dream and nightmare recall. However, as sleep becomes increasingly disturbed as the disorders worsen, dream recall declines. The initial approach to the diagnosis and treatment of most parasomnias requires polysomnographic study, in part to diagnose and treat OSA and periodic limb movement disorder (PLMD), and associated arousals that can contribute to increased expression of parasomnias.

Psychiatric Disorders. An extensive psychoanalytic-based literature has addressed the role of dreaming in the diagnosis and treatment of psychiatric disorders. A majority of these studies are clinical case reports. There are very few psychoanalytic dream content studies that use scientific methodology such as control groups and statistical analysis to control for conflicting variables. Recent studies that have controlled for the wide spectrum of variables known to affect dream content have been unable to demonstrate clear psychiatric diagnostic correlates for dream content: the two primary and persistent correlates for dream content and recall are clearly gender and waking experience (continuity) [21]. Recently, large diagnostic databases have become available, some including psychological questionnaires and questions regarding dreaming and nightmares. Some of these studies reopen the psychoanalytic question for the role of dreaming and nightmares in psychiatry, suggesting correlates for dream content for a wide spectrum of psychiatric diagnoses [59]. None of these studies, to this point, have used validated dream content questionnaires (e.g., Hall and Vander Castle), and addressed known conflicting variables including continuity, definition, transference, and researcher bias (particularly a problem when new questionnaires are utilized—note the discussion of dream bizarreness scales in this text). Continuity is a particularly difficult variable to control for such studies. It is not surprising that depressed patients might have more negative dreams, and violent patients have more dreams of aggression—such dreams reflect continuity with their waking experience.

Post-traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is the only psychiatric disorder clearly secondary to the environmental factors (major psychological or physical trauma). It is also the only psychiatric disorder in which the most common symptom is dream based, with recurrent distressing nightmares the most common symptom [60]. PTSD is a diagnosis for which psychoanalytic theory and practice have been utilized with particular intensity, and after all, it was Freud's perspective that all psychiatric disorders had a "traumatic trigger" [61]. Nightmares are more closely tied to REM sleep than other dreams. While in patients with PTSD these nightmares can occur at sleep onset and outside REM sleep, sleep-onset REM sleep periods and increased REM sleep pressure (short REM sleep latencies) are often present [62]. Due to these characteristics, activation-synthesis and the other neuroconsciousness theories have proven to be more coherent when used to address nightmares than when forcefully applied to all forms of dreaming [63]. Brain scanning studies have lent support to various theories that propose a function for REM sleep in emotional regulation by demonstrating that many of the neuroanatomic areas involved in the processing of fear and negative emotions have increased activity during REM sleep [64]. It has been proposed that PTSD nightmares occur secondary to the failure of a system of fear-memory

extinction that functions during REM sleep dreaming. The trauma-related nightmares of PTSD could mark the failure of this system [34, 35]. Central to this theory is the suggestion that nightmares reflect psychopathology, and that changes in nightmare prevalence, frequency, and severity, reflect a patient's emotional pressure and distress. [60]. Behavioral approaches to nightmare therapy (exposure/extinction and imagery) as well as the use of alpha-agonist medications (primarily prazosin) can lead to a marked reduction in nightmare frequency. Treatment can lead to decreased nightmare distress and improved sleep [18]. PTSD is a common and physiologically dangerous diagnosis that often has a chronic and persistent course. Currently available therapeutic approaches have limited efficacy [65]. However, the long-term benefits for nightmare suppression therapies have yet to be shown [66].

The Future of Dream Science

In the years since the initial excitement surrounding the discovery of REM sleep, the percentage of scientific papers addressing dreaming has declined [67]. Fifty years ago, the field of sleep medicine was dominated by dream-based psychodynamic perspectives. The associated focus on REM sleep as dreaming led to great leaps in our understanding of the neurophysiology of REM sleep, yet contributed little to our understanding of dreaming. In the mainstream of allopathic sleep medicine, the cognitive state of dreaming is considered primarily in association with disruptive behaviors, parasomnias, affecting sleep. Today, empiric dream science rests on smaller studies addressing competing variables, methodology, validity, and definition that have quietly persisted in a field dominated by grand yet experimentally unsubstantiated theories. The cognitive states of dreaming have been the focus of only minimal study. The future of dream science is wide open.

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Study Design and Analysis in Sleep Medicine

15

Vincent A. DeBari

Introduction

The proper design and analysis of studies in sleep medicine is a critical aspect of research in this field. Likewise, the practice of evidence-based medicine demands that the clinician apply principles of epidemiology and biostatistics to his or her analysis of the literature. In this chapter, the fundamental principles of epidemiology and biostatistics will be presented by focusing on specific examples from the field of sleep disorders.

Clearly, this chapter cannot be an exhaustive tome on research methodology. The aim is to provide a vehicle in which basic principles of epidemiology and biostatistics can be presented in a manner which allows a better understanding of the strength of evidence provided by studies in sleep medicine.

An in-depth presentation of both of these areas of research methodology can be found in numerous books dedicated to them. It is hoped that this chapter will acquaint the reader with basic constructs in the design and analysis of sleep medicine studies in a decidedly non-mathematical manner. For the practicing sleep medicine physician for whom this chapter is intended, the widely available statistical software packages limit the need for detailed mathematical derivations. Practical concepts serve well in this regard.

Classification of Research Designs

Figure 15.1 presents a schematic representation of the hierarchy of research designs. Fundamentally, all modalities of clinical research can be classified as either *observational* or *interventional*. The simplest description of the difference between these methods is that in an observational study, the outcomes and exposures are preexisting, whereas in the interventional study, the researcher provides some (usually) therapeutic measure in an attempt to influence the outcome. In other words, in the former, the investigator is simply an observer (hence the term, *observational* study). These models range from the most basic observational activity, the *case report,* to the, generally, most definitive model, the *cohort study*.

Observational Studies

The value of case reports has been the subject of considerable debate among clinical researchers. Primarily, this negative attitude comes from a preponderance of cases that provide limited insight into the nature of the disease entity under investigation; these vignettes are simply "me too" reports of well-studied clinical conditions for which a minor variation in presentation or outcome is of some educational interest. On the other hand, documentation of a single case of an entirely novel clinical condition ultimately may lead to studies yielding potentially valuable insights into epidemiologic issues related to this condition. These could include both numerical estimates of the prevalence or incidence of the condition and its association with exposures from the environment, pathophysiological or pharmacologic risks, and infectious agents.

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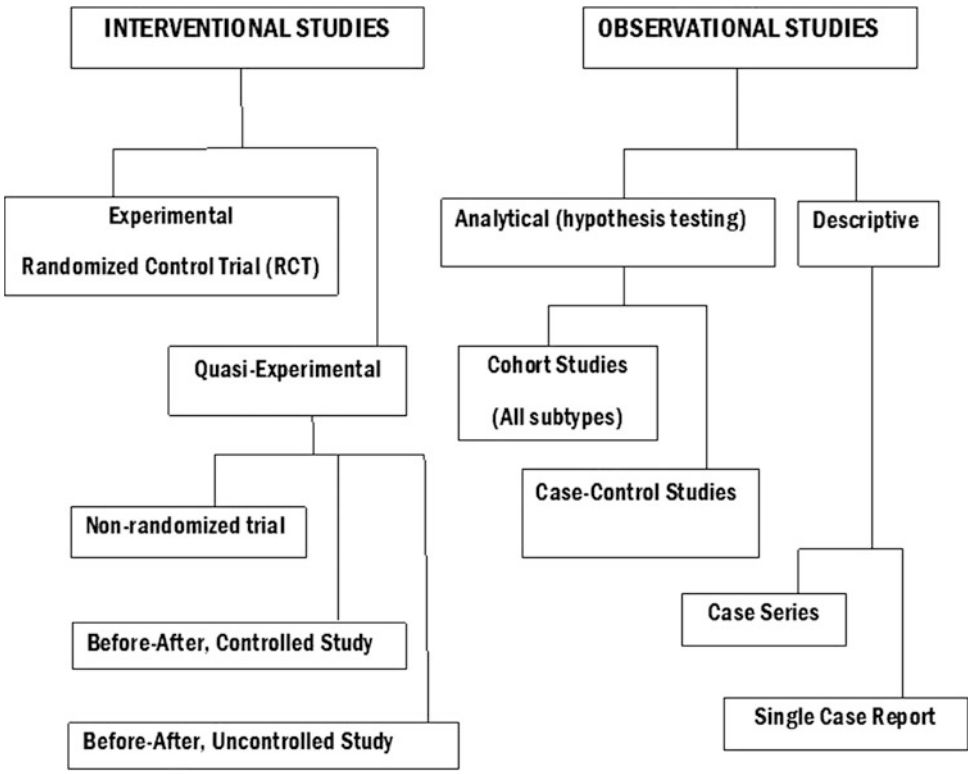

Fig. 15.1 Overview of analytical approaches in clinical research

Hierarchically, the next category of observational studies is the *case series*. As the name implies, this group of studies presents detailed accounts of multiple cases (typically three or more) of a given condition. For epidemiological utility, the cases within the series usually have some degree of commonality beyond the clinical outcome. Thus, in their entirety, they present a cohesive group of entities which are, not only, related to outcome but by the presence of one or more potentially common exposures. Of course, the great danger in attempting to relate these exposures to the outcomes presented by these cases is the temptation to attribute the status of association or, worse yet, of causality to these observations. However, careful documentation of a series of related cases can be valuable in identifying epidemiological factors related to the disease under investigation. Thus, a carefully presented case series is an important first step in the analytical study of diseases because of its ability to generate one or more hypotheses, which can be tested in a formal, analytical manner. This leads to the next group of observational designs, the *hypothesis testing* or *analytical* studies. In this group of observational studies, formal statistical approaches are used to glean information on the occurrence and on the associations of the outcomes with exposures that might ultimately be found to be risk factors for a given outcome.

The most basic of the analytical designs is the *case–control study* (Fig. 15.2). In this model, the individuals with a given clinical outcome (symptom, disease, or syndrome), i.e., *cases,* are compared in some manner with a *control* group of usually healthy individuals or individuals not exhibiting any symptomatology similar to the *case* group. Thus, the comparison is made between the two groups and subject inclusion in either group is based simply on which group the individual belongs. Once the groups have been delineated, the investigator examines such issue differences in numerical occurrence between the groups (incidence or prevalence), quantitative differences between observed exposures or putative risk factors, and associations between these exposures and the occurrence of disease. Lam et al. [1] effectively used this design to examine association of daytime sleepiness and restless legs syndrome with type 2 myotonic dystrophy (DM2).

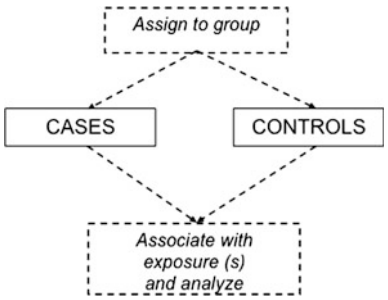

Fig. 15.2 Basic flow chart for the case–control study. Assignment to group is based on the presence (*cases*) or absence (*controls*) of the clinical entity of interest

Most case–control studies are retrospective, but this is not an absolute: Subjects can be recruited into the assigned groups in a prospective fashion. Case–control studies have the advantage of being able to study relatively rare conditions in which the numbers of cases are small. To increase the statistical power of the study (more on this, later), the number of controls is often increased from two to ten times the number of cases. For example, in the previously cited paper [1], there were 54 DM2 subjects enrolled in the study, but these patients were compared with a control group of 104 individuals drawn from the general clinic population of the authors' institution.

Case–control studies, especially retrospective ones, however, have several drawbacks. The degree of risk imposed by a given exposure is difficult to ascertain. In fact, there is no way of determining whether a control will eventually exhibit symptoms suggesting of the disease state present in the cases. Moreover, the primary patient record, which is surveyed for the pertinent data, may not have included relevant information—or may have large amounts of data excluded. Therefore, in case–control studies, the *odds ratio* (OR) rather than *relative risk* (or *risk ratio*, RR) is used to provide an estimate of the magnitude of effect. Another drawback of case–control studies is the difficulty in obtaining *longitudinal* data; the data obtained from most case–control studies is *cross-sectional*, based on observations of simultaneously occurring events such as outcomes and exposures. All these factors lead to the consideration of the case–control study as a relatively weak design from the point of view of strength of medical evidence. The aforementioned technique of increasing the size of the control group (or having a large number of cases) and the use of matching for age, gender, or other potential confounders can increase the evidentiary value of the study.

A far stronger and more versatile group of studies are the *cohort* studies (Fig. 15.3). These start with a group of individuals with a common attribute or clinical finding. For example, the cohort might be drawn from the general public or some subset of the general public. This would be considered to be a *population-based* cohort study such as that conducted by Lai et al. [2] on the risk of type 2 diabetes mellitus (DM type 2) in subjects with non-apnea sleep disorders. In this study, the cohort was drawn from a large health insurance database of Taiwanese subjects. Another possibility would be to select an at-risk cohort sharing some common clinical entity, e.g., congestive heart failure, DM type 2, or obstructive sleep apnea. Cleator et al. [3] developed a cohort based on severe obesity (BMI > 40 kg/m^2) in a group of British subjects. They examined point prevalence and differences in characteristics such as age, gender and data from several questionnaire-based instruments (e.g., the Pittsburgh Sleep Quality Index, the Epworth Sleepiness Score, and the night eating questionnaire). In either type of

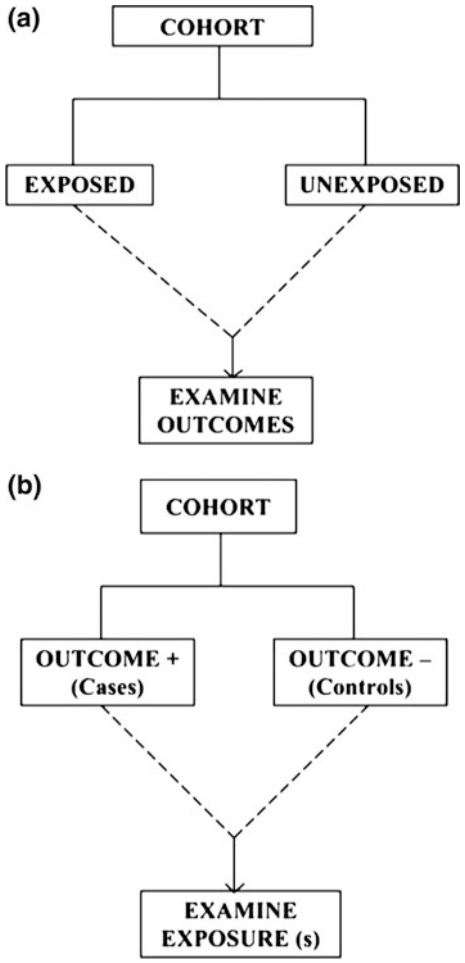

Fig. 15.3 Flow charts for cohort studies. **a** The cohort is bifurcated into subjects with and subjects without a putative risk factor (exposure). **b** The cohort is divided based on the presence or absence of a given outcome or symptomatology. This is referred to as cohort-nested case–control study

cohort study, the cohort can be divided into two or more comparative groups based on some exposure including genotypic or phenotypic *biomarkers*, (Fig. 15.3a) or by the presence or absence of some additional symptomatology or comorbidity (Fig. 15.3b). The latter study is referred to as a *cohort-nested* (or just, "*nested*") case–control study.

Cohort studies may be either retrospective or prospective and have several advantages over case–control studies. Cohort studies, as noted above, offer a degree of versatility difficult to obtain in case–control studies. They may, for example, contain several arms, i.e., essentially substudies examining more than one facet of the cohort. They also provide longitudinal data in a far more facile manner than case–control studies. Also, in the case of prospective cohort studies, potential biases can be negated by careful planning and early consideration of confounding factors. An important thing to remember in the case of all observational studies is that association, except in several very rare cases,

never implies causality. Cause-and-effect is virtually always the domain of the interventional study. This leads to an examination of that group of studies.

Interventional Studies

Among interventional studies, as noted in Fig. 15.1, we consider several designs, *experimental* and *quasi-experimental*. In both types, the investigator provides one or more *independent variables*, almost always related to treatment (the intervention or interventions) and examines one or more *dependent variables*, related to outcomes.

In medical disciplines, the experimental design is typified by the *randomized controlled trial* (RCT). As the name implies, the subjects are randomly assigned to groups. The manner in which they are randomized may vary from simple randomization methods, requiring nothing more than a coin toss (although assignment in modern studies is based not on the heads or tails result of a flipped coin but rather on the use of a computer-generated random number) to more complex randomization schemes. These include several variations of randomization in *block*s of various sizes used to avoid unequal distributions of one or more potential *confounders*, variables which might introduce a bias into the study.

Another issue in the RCT is the comparison group. As noted above, by virtual definition, the group receiving the active intervention will be compared with the control group. In the past, the expectation in examining most RCTs was that the control group would be given a *placebo*, essentially a mimic of the active treatment that is expected to lack any activity, in and of itself. However, with the plethora of treatment options available today, the use of a placebo renders the ethical use of an expectedly ineffective placebo ethically dubious, particularly when effective therapy is available to clinicians. Thus, a technique that is used in many modern studies is to compare the experimental intervention with a therapy of established efficacy. Chihara et al. [4] randomized ninety-three subjects to three groups: Auto-adjusting positive airway pressure (APAP) was applied to one group, and APAP with pressure flexing devices (A-Flex and C-Flex) were provided to the other two groups.

Occasionally, evaluations are often performed initially with a *non-inferiority* study such as the study by White and Shafazand [5] which examined the hypothesis that treatment with a mandibular advancement device is just as effective as continuous positive airway pressure). As the name implies, the object of this type of study is to establish that the experimental treatment performs no poorer than the treatment with established efficacy by a level known as the *non-inferiority margin* [6]. As will be discussed further in this chapter, the statistical approach used in the analysis of non-inferiority trials is somewhat different than a "head-to-head" trial in that the investigators, *a priori*, account only for the possibility that the experimental maneuver will be no worse than the comparator or control modality.

At this point, several additional aspects of the RCT should be mentioned. Investigators are often faced with the need to control for differences in dosing schedule or route of administration between the experimental intervention and the comparator. In this case, the need to include placebos for both differences becomes apparent. This maneuver, called a *double-dummy*, is frequently employed in the RCT and is exemplified by the study by Valente et al. [7] comparing sublingual and oral Zolpidem to initiate sleep onset in healthy subjects.

In addition to the RCT, other interventional models are occasionally used in interventional studies. Foremost among these are *quasi-experimental* studies, in which the subjects are not randomized [8]. One of the most commonly used quasi-experimental approaches is the *pre-* and *post*-model, in which the individual essentially acts as his or her own control. Such a study was conducted by Wei et al. [9] to determine the value of implanting blue-light blocking intraocular lenses in improvement of the quality of sleep in cataract patients. It should be recognized that in the absence of an external control, differences in the dependent variable before treatment and after treatment may be solely a function of some unknown confounder, e.g., time. Thus, a study such as this can be strengthened by the addition of a control group in which the difference in the dependent variable is also measured.

In terms of analyzing the result of an interventional study, the research team needs to determine whether only subjects who completed the study, as designed, should be included in the data analysis—or whether all subjects initially enrolled should be included. The former analytical approach is called *per protocol* analysis, and the latter, *intention-to-treat* (ITT) analysis. In that, it gives a better gauge of the overall utility of a given treatment, and most studies, today, use ITT as the primary approach to analysis.

Factors Involved in Determining Validity

Validity, in essence, deals with the correctness of conclusions drawn from an experiment. Various facets (construct validity, content validity, face validity, and predictive validity) can be examined separately; however, in most sleep studies (as is the case with most examples of clinical research), two main components of validity are examined: *internal validity* and *external validity*.

When designing a study, invariably a group or groups of subjects are examined in terms of their response (a dependent variable) to an intervention (an independent variable) or the association or differences of some outcome variable with respect to some exposure or predictor variable (more on this further in this chapter). The first issue relating to the process of relating dependent variables or outcomes to independent variables or exposures is the correctness of the process, i.e., getting the right answer about the individuals that the researchers, i.e., studied. This is internal validity. However, the ultimate goal is to determine whether that answer is applicable to the population which is represented by the sample used in the research. The ability to generalize from the sample to the population is external validity. In order to achieve external validity, the investigators must, first and foremost, apply appropriate inclusion and exclusion criteria to the process of subject recruitment. Simply put, the sample must be representative of the population with which the study deals. Clearly, then, the sample should have the demographic and clinical characteristics of the population of interest (inclusion criteria) and avoid subjects with demographic or clinical characteristics that render them different (exclusion criteria) from the population of interest.

Basics of Statistical Analysis in Clinical Research

Fundamentally, the application of statistical methods in clinical research serves two purposes: first, to compare the result of an observation or experiment with that result which would occur purely by chance, and second, to determine the magnitude of the observed effect so that the clinician can interpret just how useful the information garnered from a study might be to the provider as well as the patient. This section will review the basic steps that are taken in the analysis of different types of data emanating from research studies.

Variables in Clinical Studies

The data from clinical studies can be categorized as variables in terms of both how the investigator obtained it (a relational description) and the kind of information it provides (a functional description). In the first case, the question asked is "did the observer provide, as part of the protocol, the variable in question or was that variable the expected result of the experiment?" If the former, the variable is an *independent variable*; if the latter, it is a *dependent variable*. It is easy to see how this applies in an interventional study: The intervention is the independent variable and the result, as measured, is the dependent variable, but what of observational studies, in which the investigator does not apply the intervention? In this case, one may reasonably consider the construct in which the study exists as an experiment of nature. In other words, the experiment has already occurred through genetic, pathophysiologic, nutritional, or other epidemiological forces. Thus, the role of the researcher is to simply analyze the result, in terms of some independent variable (as noted above, the *exposure*), and a dependent variable, the *outcome*.

Variables are also described in terms of their functionality as measurements. This is often called the *levels of measurement*. A convenient approach is to consider three broad categories of data: *quantitative*, *qualitative,* and *ordinal*. In the former, two subtypes are included: *interval* and *ratio* data. Interval data are those which provide numerical values with a continuum that lacks a set zero value or for which a zero value is arbitrary. Temperature scales other than absolute are examples of this type of data. Ratio data have a true zero value and numbers in a ratio data set are referenced directly to that zero value. So, temperatures from the Celsius or Fahrenheit scale being interval in nature and not referenced to a non-arbitrary zero point are interval in nature: 40 °C is not half as warm as 80 °C. On the other hand, a serum analyte, e.g., glucose of 200 mg/dl is, indeed, twice the actual concentration of a serum glucose level of 100 mg/dl. These are ratio data because they can be referenced to a theoretical level of 0 mg/dl. Another set of descriptors used for quantitative data (not included in Fig. 15.3) is *continuous* and *discreet*. Continuous data are those which are infinitely divisible, limited only by our instruments of measurement. Discreet data are indivisible: They are either naturally discreet (number of siblings or copies of an amplified gene) or conveniently discreet such as age, most often recorded to the completed year of life. For all of the aforementioned quantitative data, descriptive statistics reasonably include properties of their distribution including measures of the central tendency (*mean*, *median,* and *mode*) and measures of *dispersion* ("variability," to be discussed later in this chapter).

Quantitative data are easily recognized in that rather than having numerical values, they have names, i.e., are *nominal* or *categorical.* They can range from *dichotomous* (dead, alive, or exposure present/absent) to categories with multiple descriptive choices such as race and ethnicity. In describing these data, only a number of subjects with the quality apply.

Ordinal data represent a sort of hybrid: They are described with numbers but the numerical values are purely representative of degree rather than any true mathematical relationship. Several types of ordinal data are encountered in clinical studies. Most commonly used are the *visual analog scale* (VAS) and the *Likert* scale. In a VAS, the numerical values represent the intensity of a measurement on a mathematical continuum and, as conceptually analog, can be

subdivided to some degree. An example of a VAS is the commonly used clinical pain scale which ranges from 0 (no pain) to 10 (worst pain imaginable). In this scale, being conceptually analog, a patient's response such as "5.5" would be acceptable (however, would ordinarily be given a value of 5 or 6). In a Likert scale, commonly used in survey instruments such as questionnaires, an item is generally given a numerical value indicating a property such as frequency, with "never" being assigned a value of 0 and "always" having a value of 5. Likert items are virtually always treated as discreet values. It is easy to recognize that ordinal numbers are purely representative and arbitrary. An individual who describes his or her pain as an "8" does not necessarily have twice as much pain as an individual whose pain is described as "4." This being the case, we treat the numerical values emanating from an ordinal scale differently than we do true quantitative data. In terms of descriptive statistics, the central tendency of an ordinal data set is best described by the median and the dispersion by some measure of range, such as minimum–maximum or *interquartile range* (IQR), the 25th to 75th percentile of values.

There are also clinical scales, such as the Acute Physiology and Chronic Health Evaluation (APACHE II) and the Pneumonia Severity Index (PSI) which are based on the totality of a group of clinical signs and symptoms. There is no consensus as to whether these should be treated as discreet interval data or ordinal data; however, the wide range of values attributable to these scales suggests that there is an inherent mathematical relationship among scores from these clinical scales. Moreover, global scores from questionnaires utilizing Likert items are frequently treated as interval data.

Descriptive Statistics

That branch of biostatistics that examines how values of a variable are distributed is called *descriptive statistics*. In the case of qualitative data, descriptive statistics, as previously noted, is limited simply to counts, i.e., number of subjects exhibiting a particular quality. Of course, a necessary outcome of that description, albeit secondary, is the proportion (percentage or percent) of subjects with that quality.

Quantitative data, however, are examined in terms of how they are distributed. They are described in terms of their central tendencies and dispersion. Precisely, *how* they are distributed generally determines the choice of central tendency and unit(s) of dispersion.

It is extremely important to recognize whether a set of quantitative data is distributed *normally* (described by a *Gaussian* distribution). The reason for this is because when inferential statistical methods (collectively, those statistical tests which provide information about how likely or unlikely what we have observed has occurred purely by chance) are applied, the nature of the distribution will bear on this choice in nearly all cases.

The normal distribution is easily recognized as the classic "bell curve," i.e., it has two "tails" set about a central tendency. Examples of this distribution abound in the literature and can easily be located in elementary statistics texts and on the Internet. The tails are symmetrical, that is they lack *skewness* and are neither too peaked nor too flat (the degree of "peakedness" or flatness is called *kurtosis*). The range of values between the points of inflection on both the rising and falling sides of the distribution curve is equivalent to roughly 67 % of all the values in the data set. This is ± 1 *standard deviation* (SD). Taking twice this value, 2 SD, yields approximately 95 % of the values and, at 3 SD, over 99 % of the values are accounted for. For data which are normally distributed, the branch of inferential statistical tests known as *parametric* (because they are based on the actual value of the parameter or variable) methods can be applied. With the exception of extremely large data sets for which the choice is unnecessary, those data sets that are not normally distributed should be subjected to *nonparametric* tests, which are generally based on rank order of the parameter rather than the parameter itself. Ordinal data are always treated with nonparametric methods, as the parameter is essentially meaningless from a mathematical standpoint.

The question then arises, how is one to determine whether a data set is normally distributed or at least approximates a normal distribution well enough to warrant the application of parametric tests? Simply graphing the values as a differential distribution plot (number or percentage of subjects vs. the incremental value of the variable), in most cases, requires a very large sample to visually observe a normal distribution. This conundrum has been addressed many times in the statistics literature, and the approach most often taken is to apply one of the more commonly used "normality tests," collectively, a group of statistical maneuvers designed to determine how much the distribution of a variable differs from a normal distribution. Some of the most common tests are based on the comparison of a simulated distribution best fit to a normal distribution with the actual distribution of the data. A good example of this is the Lilliefors (Kolmogorov–Smirnov) test, which dates back to 1967 [10]. The normality tests developed by D'Agostino and Pearson [11] take a different approach, in which a parameter, K^2, summarizes the skewness and kurtosis of the distribution. Thus, the fit to normality is based on the actual shape of the distribution.

At this point, it might be wise to recognize that remarkably few physiologic parameters distribute normally. In many cases, a *log-normal* distribution is observed, in which case the distribution exhibits considerable skew to the right, i.e., toward increasing values of the variable. In this case, simply transforming the data by taking the log of the

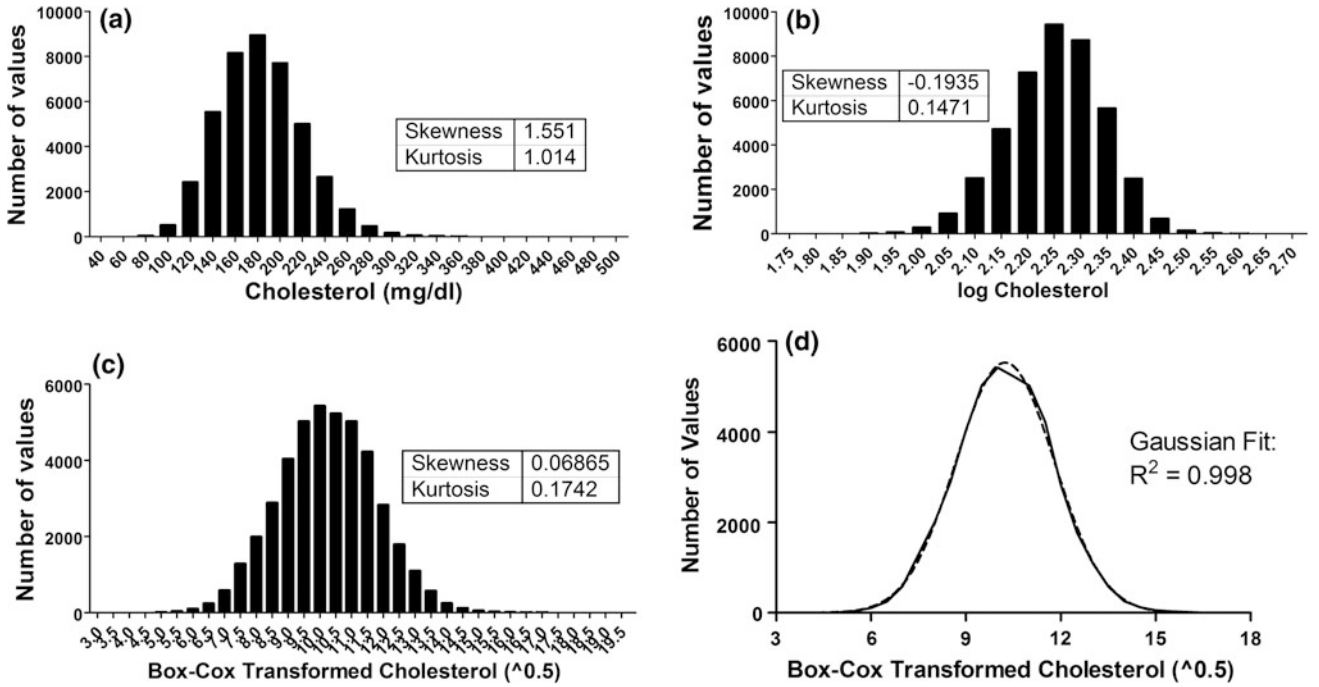

Fig. 15.4 Transformations of a large database of cholesterol measurements in the general population. The untransformed (raw) data are shown in (**a**). **b** and **c** are, respectively, a log transform and a power (Box-Cox) transform of these data. **d** The distribution in (**c**) (*solid line*) is fitted to a Gaussian (normal) distribution (*dashed line*) and shown to exhibit a very strong fit, as described by the value of R^2

variable will provide a reasonable fit to normality. Another approach is the *power-normal* or *Box-Cox* transformation [12] that will occasionally provide a better fit than a simple log transformation. In Fig. 15.4, a large database of over 44,000 serum total cholesterol samples is depicted prior to transformation (Fig. 15.4a) and after log (Fig. 15.4b) and Box-Cox (Fig. 15.4c) transformations. In Fig. 15.4d, the Box-Cox transformed data distribution is compared with the best-fitted Gaussian distribution. The fit to normality is extremely strong, as demonstrated by the R^2 value of 0.998 (more on the "R^2" later in this chapter).

Caution in interpreting normality tests is always warranted. There are numerous assumptions in the development of these tests that lead to potential errors in their misapplication. Realistically, very small samples cannot be expected to provide a reasonable interpretation of fit to normality for a given variable. Similarly, testing very large samples will often result in a test result suggesting a deviation from normality when, in fact, the fit to normality is excellent.

Real or Chance: Hypothesis Testing

Earlier, the differentiation of chance occurrence from something likely to be a real phenomenon was noted to be the primary purpose of biostatistical analysis. The conceptual approach that is taken in this regard is to provide evidence about the unlikelihood of a chance occurrence. This is done with a theoretical device called the *null hypothesis*, symbolized as H_0. One can liken this approach to playing "devil's advocate" in that what an investigator does with this device is to, *a priori*, assume that the hypothesis of true interest, called the *alternate hypothesis* (H_A), is likely to be real only if H_0 can be rejected with some satisfactory assurance of certainty. It is important at this point to keep in mind the fact that sleep medicine researchers, as is the case with scientists in any field, cannot "prove" anything; they simply attempt to demonstrate that a given phenomenon is quite unlikely to have occurred purely by chance. How sure does one need to be? This level of assuredness is given the designation, alpha (α). By tradition, the value of α is almost invariably set at 0.05, the equivalent of 95 % certainty about the decision to reject H_0. The error in deciding to reject H_0 when, in fact, it is operant, is called a *type I or alpha error*.

The converse can also be in effect: One can accept H_0 when, in fact, it should be rejected. This is called a *type II* or *beta* (β) error. Beta is a measure of how well the construct in H_A holds in terms of the percent of times the experiment can be repeated and the authentically valid conclusion reached. The level of β usually accepted in clinical studies is minimally 0.20 (20 %). This relates to the *power* of an experiment or observation, where power is defined as β.

Thus, a clinical study usually is set to provide a power of ≥ 0.8 (80 %). Power depends on several factors: The value

of α, i.e., 0.05, is invariably preset. The other factors are the difference between the groups being compared (for group-wise comparisons, obviously) in terms of the difference in the means and the size of the SD for each group. Finally, and generally the parameter of interest in power analysis is the sample size! A study with too few subjects to reasonably assert acceptance of H_0 is, thus, said to be "underpowered." In any event, acceptance of H_0 in any clinical study should be met with considerable caution. Even if the study has "adequate" power, most investigators would eschew the verbiage, "there was no difference" or "there was no association" and instead choose to say, "no difference (or no association) could be detected".

The precise nature of the H_A will determine how H_0 is phrased. For example, if an investigator is attempting to demonstrate a difference between two groups of subjects, the H_0 will be stated as "there is no difference between group A and group B." Similarly, if there are more than two groups being compared in terms of a difference in the level of some quantitative variable, H_0 would be stated as, "there is no difference *among* the groups being compared." In the case of examining the association of two quantitative or ordinal variables, H_0 would be, "there is no correlation between variable *A* and variable *B*" and, in associating two nominal variables, "there is no association between exposure *A* and outcome *B*".

P-values, Confidence Intervals, and Measures of Effect Size

Having established a "comfort level" about assuredness for rejecting H_0, i.e., $\alpha = 0.05$ or 95 %, it is obviously necessary to have a value with which to compare α. This value is the *p-value,* and for any given test statistic, this is based on the sample size, the magnitude of the difference between the groups for whatever parameter has been evaluated, and the degree of dispersion in each group for the parameter. For the $p < \alpha$, H_0 is rejected and the difference is said to be *statistically significant*. Of course, at a level where p is barely less than α, the certainty is only approximately better than 95 %. However, at very small values of p, the certainty with which H_0 can be rejected is substantially greater; a *p*-value 0.0001 represents a level of assuredness of 99.99 %. Although some software routines can detect *p*-values <0.0001, most often, this is the smallest value usually reported.

An alternative to rejecting H_0 based on *p*-values is the examination of *confidence intervals*. Confidence intervals can be calculated at any desired level but are most often calculated at the 95 % level. They result from the central limit theorem which allows us to determine numerical properties of a population based on the *standard error of the mean* (SEM) for the sample. Thus, confidence intervals (abbreviated *CI*) represent the upper and lower limits of values that can be expected to be observed in a population based on the sample. So, a 95 % CI of 2 units to 4 units means that one could be 95 % sure that any value between 2 units and 4 units would belong to the population being studied.

Confidence intervals are particularly useful when evaluating *magnitudes of effect*. These include ratios of effect in the treatment group compared to placebo, or cases versus controls, or similarly, the association of any given exposure with disease group compared to the effect of that exposure on a group without disease. They include *relative risk* (also called *risk ratio*, *RR*), the risk of morbidity or mortality in the presence of a given exposure, *odds ratio* (*OR*), the odds that given exposure is associated with a given disease or with death, compared with the odds that it is not. The OR is appropriately used for retrospective studies whereas the RR is used for prospective observational studies or for interventional studies. Other magnitude-of-effect measures include the *hazard ratio* (*HR*), which is the difference between the risks in two groups and is analogous to RR except that it is derived from longitudinal studies of *time to event*, such as *survival analysis* and *absolute risk reduction* (*ARR*). Although ARR, as such, is not often used, its reciprocal (1/ARR) yields the *number needed to treat* (*NNT*) which, in an interventional study, allows the investigator to estimate the number of subjects that need to be treated to affect one "success" compared to the number with placebo or comparator control. In a study examining the association of a treatment or exposure that may be harmful, the corresponding effect measure is the *number needed to harm* or *NNH*. These effect measures are summarized in Table 15.1.

In the case of ratio measures such as OR, RR, or HR, whenever the confidence intervals do not include the value 1, the *p*-value will almost always be <0.05. In fact, it is only the vagaries of software programming that occasionally will provide a *p*-value of, perhaps, 0.045 when the 95 % CI interval is, say, 0.98 to 3.52, i.e., the lower or upper confidence limit is very close to unity. In such a case, perhaps it is wisest to suggest that a trend toward statistical significance

Table 15.1 Commonly used magnitude-of-event measures for categorical variables

Odds ratio (OR): $A \times D/B \times C$
Relative risk (RR): $A/(A + B)/C/(C + D)$ [this is the exposed or experimental event rate (EER), given by $A/(A + B)$ divided by the control event rate, $C/(C + D)$]
Absolute risk reduction (ARR): EER—CER
Number needed to treat: 1/ARR

Letters *A*, *B*, *C,* and *D* refer to the cells as shown in the contingency table in Fig. 15.5

exists. For absolute magnitude-of-effect measures such as ARR or *difference in proportions*, the value that must be excluded from the CI is zero.

Examining Groupwise Differences in Quantitative Parameters

One of the most basic needs in clinical science is to determine whether two groups, e.g., a case group and a control group, differ in the presentation of some variable. In other words, is the level of some parameter different in the two samples?

First, consider the case of two groups. Here, the distinction between parametric and nonparametric methods must be made. When data are demonstrably not normally distributed, a nonparametric test should be used, as these rank-based (rather than parameter-based) tests do not require the condition of normality to be extant. Wei et al. [9] used the *Wilcoxon signed rank test* to examine differences in a pretest versus posttest scores in a quasi-experimental study noted earlier in this chapter. This test is a *paired test*, i.e., it requires that the groups being compared are identical (or almost so, in that matched controls are frequently treated as subjects paired with case or treatment groups) and, in this respect, differ from independently assorted or unpaired groups. In the latter case, the use of the *Wilcoxon rank sum test* (or the similarly designed *Mann–Whitney test*) would be the appropriate analytical approach. These nonparametric tests should always be used when comparing ordinal data. The ranked nature of the design of these tests actually matches the ranking inherent in ordinal scales.

When two groupwise quantitative differences are normally distributed (or can safely be assumed to be normally distributed), *t-tests* are invariably used. It should also be recognized that when very large samples are being compared such as the case in population-based cohort studies [2], *t*-tests may be safely used even if normality cannot be demonstrated as, with large samples, parametric methods are suitably robust. These very well-known tests are based on an extension of the *standard difference test* (the *Z-test*) which relies on the normal distribution to evaluate *p*-values. This extension dates back to the early twentieth century when W. S. Gosset, a quality control chemist for the Guinness brewery in Dublin, developed the *t*-distribution. To keep his employer's competitors unaware of this development, he published this under the self-deprecating pseudonym, "Student"; thus, the *t-test* is sometimes referred to as "*Student's t-test.*" The *t*-test for two groupwise comparisons is also modified to account for independently assorted groups (the *unpaired t-test*) and for paired groups (the *paired t-test*). It should also be noted that both *Z*-tests and *t*-tests can be used to evaluate the null hypothesis that a sample does not differ from a known population. This is the so-called one-sample *Z*-test or *t*-test.

Analysis of Variance (ANOVA)

Having considered, above, cases in which two groups were compared, consider the case of more than two groups. Chihara et al. [4] evaluated the results of three treatment groups: APAP, APAP with A-Flex, and APAP with C-Flex. Differences among the three groups were evaluated by ANOVA, in this case a *one-way ANOVA for independently assorted samples* (remember that these groups were randomized and, thus, completely different subjects). If a study were to compare the same subjects with measurements at different time periods, e.g., cortisol levels at different times of the day, a *repeated-measures* ANOVA would be the appropriate analytical approach.

The relevant test statistic for ANOVA is the *F-ratio*, the ratio of the within-sample and between-sample variances. These are calculated at different degrees of freedom and, as expected, depend on the number of groups and sample sizes.

As ANOVA tests the null hypothesis that there is no difference *among* the groups, when a *p*-value less than α is obtained, the null hypothesis is rejected: There is a statistically significant difference among the groups. However, that still leaves the investigator to determine which groups are different than which other groups. There are several approaches to this. The simplest (and, unfortunately, least reliable) is the application of the *Bonferroni* correction to *t*-tests of the various pairs. This correction, in its simplest form, is simply α divided by the number of groups to account for multiple comparisons. Better approaches are available, including *Tukey's*, the *Studentized Newman–Keuls*, *Dunnett's*, *Scheffe's,* and *Holm's* tests.

One-way ANOVA, as described above, is a parametric test and, as was the case with two groupwise comparisons, require the assumption that our groups be normally distributed. When this assumption cannot be met, there are nonparametric options available based, as was the case with the Wilcoxon and Mann–Whitney tests, on ranks rather than the actual value of the variable. In the case of independently assorted groups, the *Kruskal–Wallis test* is the nonparametric analog; the *Friedman test* is the nonparametric analog of the one-way ANOVA for repeated measures.

Several variations in ANOVA exist. The case of two independent variables provides a need to apply *two-way ANOVA*. For example, subjects are randomized to three groups, a control group, a group given a putative therapeutic agent at dose A, and the third group given the agent at dose B. Clearly, the groups (representing one independent variable) are randomly assorted. Now another independent variable is introduced: time, i.e., the investigator wants to

examine an outcome (the dependent variable) at 1, 6, and 24 h. In this case, the outcome can be assessed at different times for the different groups based on the interaction between the two independent variables. The specific example used here is called a mixed-model 2-way ANOVA because it incorporates both a repeated-measures variable (time) and an independently assorted variable (group) into the analysis.

Another useful derivative of ANOVA is called analysis of covariance (ANCOVA). This can best be conceptualized as a combination of ANOVA and regression analysis.

For the effect size of the differences between (or among) continuous variables, several measures have been developed. Perhaps best known are those developed by Cohen [13], the parameter d for two groupwise comparisons [14] and f^2 for comparisons of >2 groups, as in ANOVA.

Measures of Association with Quantitative Variables: Correlation and Regression

The previous section described the measures used to compare quantitative data when the need was to examine a single variable in two or more groups. There is often the need to see whether two different continuous variables are associated or vary with one another. This issue is addressed using two interrelated but, nevertheless distinct approaches, *correlation* and *regression*.

Correlation is assessed by either of two methods depending, once again, on whether or not we can assume that the data at hand are normally distributed or not. For correlation, the null hypothesis is "there is no association between the variables" (usually a dependent variable and an independent variable), i.e., any presumed relationship between the two variables has occurred purely by chance.

If the data are (or can reasonably assumed to be) normally distributed, the method of choice would be Pearson's product–moment method. This generates a test statistic, R (or r) called the Pearson *correlation coefficient*. This coefficient has values ranging from −1 (a perfect negative correlation) through 0 (no correlation at all) to +1 (a perfect positive correlation). One can derive a p-value from R, depending on the number of degrees of freedom. This can create some degree of misunderstanding about the strength of the association: A value of R that is quite weak can yield a p-value that suggests very strong statistical significance. In that case, it should be recognized that the correlation may not have occurred purely by chance; however, the association lacks the strength necessary for it to be of any use. Thus, R is, as noted above, an appropriate measure of effect size. Jiang et al. [15] used Pearson's correlation analysis to assess the strength of the relationship between Montreal Cognitive Assessment (MoCA) scores and sleep efficiency; they also determined negative associations between MoCA scores and the Pittsburgh Sleep Quality index, the arousal index, and sleep latency.

In the event that we are dealing with data that are not normally distributed, most often Spearman's correlation analysis will be applied. This is related to Pearson's method, but rather than use the actual value of the variable, the two variables are ranked separately, and these ranks are then mathematically processed in a manner somewhat similar to its parametric counterpart (Pearson's). The relevant correlation coefficient is, in recent years, indicated by a subscript s, i.e., R_s or r_s. In older work, one may see the Greek letter rho (ρ) used for Spearman's correlation coefficient. In a study of endothelial dysfunction and OSA, Jafari and Mohsenin [16] used Spearman's correlation to examine the relationship between flow mediated vasodilation (FMD) and endoglin and between FMD and fms-like tyrosine kinase. Under certain circumstances usually involving ordinal data, one of several variations in Kendall's tau (τ) may be more appropriate as a measure of nonparametric correlation.

A related process is the development of a mathematical model that describes the relationship between two variables. Intuitively, one recognizes that for the case of linear relationships, the mathematical model that would describe the dependence of a variable on another variable would suggest the correlation of the two variables. In fact, this is nearly always the case with linear regression, as computed by ordinary least-squares (OLS) analysis, in which the mathematical approach is to minimize the distance in both the x and y directions between the coordinates of the x, y pairs and the line describing the relationship between the dependent (always on the y-axis) and the independent variable (on the x-axis). This analysis yields not only a mathematical description of the line (slope and y-intercept) but also the *coefficient of determination*, R^2 (or r^2). The formerly only "intuitive" relationship now is established formally in that $R = (R^2)^{1/2}$, i.e., the Pearson correlation coefficient (but not Spearman's correlation coefficient) is the square root of the coefficient of determination. The null hypothesis for linear regression can be stated as follows: The slope of the line describing the linear relationship between the dependent and independent variables is zero, i.e., parallel to the x-axis. It should also be noted that the coefficient of determination provides an estimate of the strength of the relationship in that if converted to a percent value, it gives an estimate of how well the data are represented by the linear model. A confidence band at the 95 % inclusion level can also be developed.

Not unexpectedly, the mathematical model describing the relationship between two variables need not be a straight line; in fact, there are numerous models that describe nonlinear relationships between two variables. Modern computer software can easily perform curve-fitting routines that,

again, not only provide the mathematical model of the relationship but also provide a coefficient of determination. This may be especially useful for circumstances in which it is necessary to predict the value of a dependent variable from an independent variable when the best-fit model is not a straight line. Nonlinear regression is a complex issue and should be approached with considerable caution, notwithstanding the ease of performance with modern software routines.

Another area related to regression analysis is based on models where time is the independent variable. These models are frequently seen in time-to-event analytics, usually termed *survival analysis.* This will be discussed further on.

Measures of Association with Categorical Variables

Just as was done with quantitative variables, the relationship between categorical variables can be ascertained. In this case, the dependent variable is usually described as an outcome while the dependent variable is called the exposure (in the case of an observational study) or the treatment/intervention in the case of experimental or quasi-experimental investigation. The process of relating these variables is, strictly speaking, not called correlation, a term that in statistical terminology is limited to quantitative association. It should be described, simply, as association.

The construct for the association of a categorical exposure with a categorical outcome is nearly invariably set up as a *cross-tabulation* or *contingency table*. In this tabulation, the absolute counts are input into columns (representing outcomes) and rows (representing exposures or treatments). In Fig. 15.5, just such tabulation is represented. Using either of several analytical approaches, one can derive the level of statistical significance. For simple 2 × 2 tabulations, the best approach is the use of *Fisher's exact test*, because it provides a computed exact *p*-value, obviating the need for an intermediate test statistic. However, because of the arithmetically cumbersome nature of the calculation, some software routines limit the total number of observations (the total count for all four cells) to not much more than one thousand. For larger samples and for contingency tables, more expansive than 2 × 2, the *chi-square test* is invariably used, as was the case in the study by Lai et al. [2] in which the very large sample size (>45,000) precluded the use of Fisher's exact test. Computationally, chi-square is not difficult to perform, but performs poorly when any of the cells have fewer than ten counts. In this case, the deficit may be partially overcome with the use of a correction factor (the *Yates correction*). In the case of analysis where one or more cells has fewer than ten counts, Fisher's exact test should be used. In addition to ascertaining the level of statistical significance, magnitude-of-effect measures can also be calculated from contingency tables (Table 15.1).

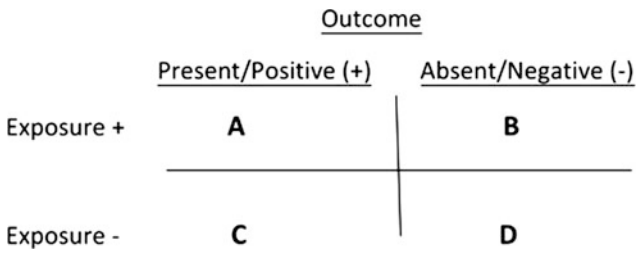

Fig. 15.5 Cross-tabulation of exposures and outcomes for categorical variables. This is commonly referred to as a contingency table

Logistic Regression

In the two previous sections, measures were described that evaluated the association between continuous or ordinal variables (correlation) and the association between categorical variables (contingency table analysis). There exists an extremely useful analytic approach that can be used to associate a (usually binary) categorical outcome, e.g., the presence or absence of disease, with a continuous exposure variable. This analysis yields a curve of probability of the outcome versus the value of the predictor variable (Fig. 15.6).

Logistic regression is also extremely useful in that it allows one to consider potential confounders as covariates in a *multivariable* analysis, i.e., a model in which a given outcome can be evaluated as being associated with more than one predictor variable. Thus, in the event that a significant difference in one or more potential confounders exists between subjects with two different outcomes, those potential confounders can be used to adjust the OR for the primary exposure. Precisely how different the characteristic

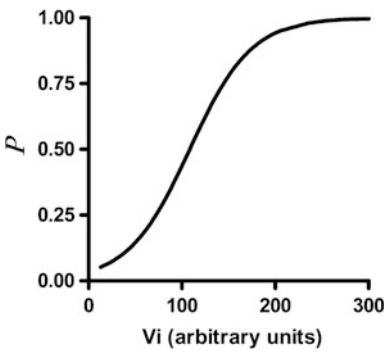

Fig. 15.6 Logit curve resulting from logistic regression analysis. The probability (*P*) is given as a function of some independent variable (Vi). Note that this *P* is an estimate of the true probability of an outcome as a function of the value of the continuous independent variable and is distinct from the *p*-value

should be in order to consider it as a covariate is a subject of some debate but, generally, *p*-values in excess of $\alpha = 0.05$ are considered; minimally 0.1 but often ≥ 0.25 [17].

Time-to-event Analysis

An important aspect of clinical research is the determination of how long it takes for a given exposure or treatment to cause a clinically relevant event to occur. Because this technique, time-to-event analysis, is so often applied to time to death, it is frequently called *survival analysis*. Usually, the technique that is used to perform this analysis is the *Kaplan–Meier* (*K–M*) *method*. In K–M analysis, the percent of individuals not exhibiting an event is plotted, invariably in a stepwise fashion, versus time. Thus, simple inspection of this specialized regression analysis gives the probability of an event occurring over a specified period of time. Figure 15.7 shows data from the Lai et al.'s study [2] in which K–M analysis is used to examine the probability, over a 14-year period, of development of DM type 2 between non-apnea sleep disorders and the cohort to which they were compared. As noted, the *log-rank test* was used to compare the two curves. The log-rank test is a nonparametric method that can be used whenever the hazard ratio is relatively constant over time; a condition described as *proportional hazards*, as described by Cox [18].

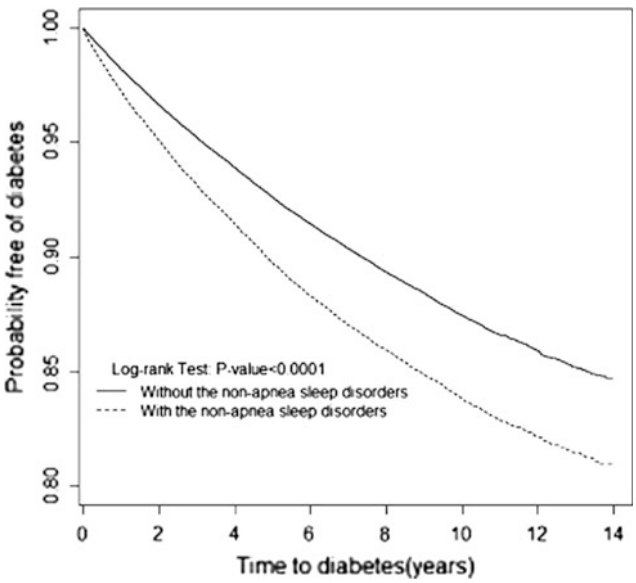

Fig. 15.7 Kaplan–Meier plot of the probability of not having type 2 diabetes (DM2) in patients with and without non-apnea sleep disorders. The log-rank test yielded a highly significant *p*-value (<0.0001), suggesting that patients with non-apnea sleep disorders are more likely to develop DM2 over the time period covered by the study. Note that the probability (*Y*) axis ranges only from 0.80 to 1.00, giving a visually exaggerated suggestion of the actual difference which, at 12 years, is only ~5 %. From Lai et al. [2]

The Cox regression model, as is the case with logistic regression, is adaptable to multivariable models, and is often used to adjust hazard ratios based on the presence of covariates which might be expected to alter the HR resulting from the primary exposure.

Using Questionnaire-type Instruments

Sleep medicine specialists make frequent use of questionnaires. Earlier in this chapter, the ESS and PSQI, both of which see frequent application, were mentioned. These and other questionnaire tools are useful in that they simplify the gathering of relevant survey data but are fraught with potential information biases that should be recognized. First and foremost, they depend upon self-reporting; thus, both are dependent on the recall and forthrightness of the study subjects. Another difficulty is the requirement that cultural and linguistic subtleties are taken into consideration, i.e., that the instrument, as originally developed, is extensible to other cultures and languages.

The most common and, perhaps best, validation parameter for questionnaires is *Cronbach's alpha* [19]. Alpha is a measure of the reliability of the survey instrument and has values ranging between 0 and 1. Generally values ≥ 0.7 are considered good but Tavakol and Dennick [20] caution against high values of alpha (≥ 0.9), which may suggest redundancy of test items.

Investigators attempting to use survey instruments of the questionnaire type should assure themselves that the instrument is valid for the particular population to which the study is intended to be generalizable. For example, Baumgartel et al. [21] studied the reliability of the ESS in pregnant women. Similarly, in evaluating the published results of a survey, the reader is cautioned to examine the available literature to be assured that the authors have validated these tools for their population.

Evaluating Agreement Between or Among Observers

In clinical research, the need frequently arises to assess agreement between two or more, usually expert, observers with regard to the subjective evaluation of some test. This can be done by the use of the *intraclass correlation coefficient* (*ICC*), using widely available statistical software packages [22]. The ICC is, fundamentally, an extension of correlation of individual values, as described earlier in this chapter, to values from groups of data. In a manner analogous to ANOVA, the ICC is a function of both within-observer agreement and between/among-observer agreement.

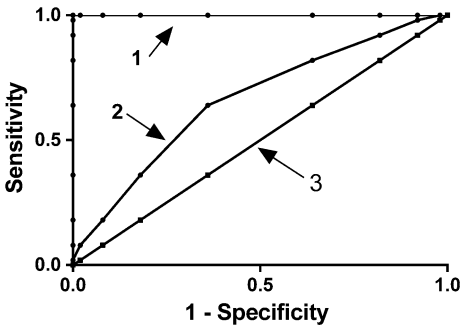

Fig. 15.8 ROC curves of 3 data sets. The area under curve (AUC) *1* is 1.00 that is it represents a test which completely discriminates between two conditions. In curve *2*, the AUC is 0.66, which represents poor discriminatory ability. The line in number *3* is from a test with no discriminatory ability at all; it has an AUC of 0.50 and represents a condition described as "identity"

The kappa statistic (κ) is an alternative to the ICC that has seen wide use in clinical practice, including studies relating to sleep medicine. One such example is a recent study of inter-rater reliability of sleep videofluoroscopy to assess airway obstruction in subjects with OSA by three independent observers [23]. These authors found that depending on the anatomical level studied, values of κ range from 0.635 to 0.938. Values of $\kappa > 0.6$ suggest acceptable agreement.

Specialized Diagnostic Biostatistical Procedures

Basic diagnostic parameters such as *sensitivity*, *specificity*, *positive predictive value* (*PPV*), *negative predictive value* (*NPV*), and *overall test efficiency* (sometimes called *clinical accuracy*) should be familiar to readers of this book. One commonly used (actually required by some standardized publication protocols for diagnostic tests) device to evaluate the utility of diagnostic tests is the *receiver operating characteristic* (*ROC*) *curve*. The ROC curve is a plot of sensitivity (*y*-axis) as a function of 1-specificity (*x*-axis) as demonstrated in Fig. 15.8. The "perfect" test would exhibit a value of 1.0 (100 %) for sensitivity and 0 for 1-specificity (100 % specificity); this point is at the upper left-hand corner of the ROC curve and would result in an *area under the curve* (*AUC,* sometimes called the *c-statistic*) of 1.0. A test with no discriminatory ability (no diagnostic value) would be represented by the *line of identity*, a straight line with a slope = 1.0 (45° angle from the *x*-axis). For this line, the AUC would ½ or 0.5. The point that yields the optimum value of sensitivity and specificity (the *Youden point*) is the point which is tangent to a line parallel to the line of identity at the upper left-hand point of the curve.

ROC curves are frequently used to evaluate diagnostic procedures in sleep medicine, as exemplified by the recent work of Sangal [24] who evaluated the diagnostic efficacy of a group of sleep scales in two groups of subjects with OSA: a group between the ages of 18 and 45 years and a group of subjects with an age >45 years.

Concluding Remarks

This chapter can only serve to introduce fundamental aspects of study design and statistical analysis to those who may require a bit of help in understanding and evaluating the literature in sleep medicine. It was never intended to provide a guide to "do-it-yourself" statistical analysis using one or more of the many commercial statistical software packages or the ever-increasing online, free, statistical computation routines (although some of these are, indeed, quite good). Hopefully, this chapter may have whetted the reader's appetite for more information on the fundamentals of study design and biostatistics. Books by Hulley et al. [25] and Motulsky [26] are highly recommended to the sleep medicine specialist wishing to expand his or her horizons in clinical epidemiology and statistics.

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Part II
Technical Considerations

Instrumentation, Electronics, and Signal Analysis

16

Diane L. Donnelly

Abbreviations

τ	Tau
AC	Alternating current
ACNS	American clinical neurophysiology society
ADC	Analog-to-digital conversion
C	Capacitor
CMRR	Common mode rejection ratio
dB	Decibels
DC	Direct current
DR	Dynamic range
EEG	Electroencephalography
ELI	Voltage–Inductor–Current
HFF	High-frequency filter
HPF	High-pass filter
ICE	Current–Capacitance–Voltage
L	Inductor
LFF	Low-frequency filter
LPF	Low-pass filter
R	Resistor
RC	Tau
X_C	Capacitive reactance
X_L	Inductive reactance
Z	Impedance

Introduction

In order to understand the significance of polysomnographic (PSG) and other clinical neurophysiologic tests to practice first-rate sleep medicine, it is important to have a basic knowledge about the principles of physics and electronics underlying the techniques for recording multiple physiological characteristics. Biological, physical, and chemical environment of the body tissues (e.g., brain, heart, lungs, and others) continually generates electromagnetic signals movements of which tell us about internal physiological changes in the body from which we can differentiate normal from abnormal phenomena. The physiological signals are minute in magnitude and hence must be amplified to recognize them visually. Amplification of essential signals and filtering of unwanted signals are the two most fundamental processes in understanding PSG and other neurophysiologic recording techniques. It should be noted that electrical signals in human body manifested as waveforms are generated by flow of charged ions (e.g., Na, K, Cl) opposed by the resistance and capacitance of the tissues. Using analog and now digital electronic devices, we can measure and analyze current flow and potential differences between different areas of the body and scalp to assess normal functions and alterations by disease. This chapter briefly outlines the basic electronics for sleep specialists and clinical neurophysiologists.

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Definitions and Circuit Analysis

Charge

In a copper wire at room temperature with no externally applied force, the outermost shell of a copper atom loses an electron as a result of surrounding thermal energy. When a copper atom loses a free electron, it becomes a positive ion because electrons carry a negative charge. With no applied force on the wire, electrons continue to move about in a random manner without a net flow. As the electron moves about randomly the positive ion it leaves behind does little more than oscillate in place; the electron thus acts as a charge carrier. Coulombs law states that like charges repel and opposite charges attract and is the reason why free negatively charged electrons are attracted to positive ions. The symbol for charge is "Q." One coulomb of electrons is equal to 6.242×10^{18}. If one coulomb of electrons flows at uniform velocity through a circular cross-sectional area of conductor in one second, the flow of charge is said to be one ampere. Charge or Q may also be expressed as shown in Eq. 16.1 where I equals current and t is time in seconds [1–3]. For current to flow and perform work in a circuit, such as to light an incandescent bulb, electrons must move in the same direction through the load. Recording an electrographic event requires the movement of ions in large populations of neurons. An applied force causes the electrons or ions to move directionally, and in a basic electric circuit, this applied force is the source voltage also referred to as an electromotive force. In the case of a neuron, the applied force is the stimulus (spontaneous or applied) with the electrons replaced by ions. The flow of charge regardless of form is accomplished through the application of an applied force.

$$Q = I * t \tag{16.1}$$

Power Sources

The two types of power sources are alternating current or AC and direct current or DC. The most commonly encountered DC source is the battery. A battery is the conversion of chemical or solar energy using positive and negative electrodes and electrolytes to provide direct current. Direct current moves in one direction and remains constant for the life of the source. Generators on the other hand produce AC power through the use of any number of energy sources to turn a rotor housed in a set of windings called a stator, inducing a voltage in the wires of the stator. One end product is the common 120-V household outlet. In North America, AC power is delivered at 60 Hz, whereas in Europe 50 Hz is the predominant frequency. Both AC and DC provide the electromotive force to move electrons directionally supplying current to power the recording equipment.

Fig. 16.1 Schematic symbol of a resistor

Resistors and Resistance

Resistance is the ability to inhibit the flow of current or charge. Resistance is one of the things that slows down electron movement described earlier. While copper wire has resistive properties, it has better conductive properties which make it ideal for movement of charge. Resistance occurs naturally, and resistors are specifically manufactured for use in circuit design. Resistors behave the same regardless of the type of power applied. The current through a resistor is in phase with the applied voltage. This means both current and voltage follow the same path at the same time. Resistors do not store energy, and they dissipate energy through heat. Figure 16.1 illustrates the schematic symbol of the resistor. The unit of resistance for a resistor is ohms and is indicated by the capital Greek symbol omega "Ω." Resistors can be connected in parallel or series.

The manner in which resistors are connected determines the total resistance of the circuit. Figure 16.2a, b illustrates simple series and parallel resistive circuits, respectively, arrows indicating direction of voltage and current. Notice that in the series circuit, the voltage has only one path to travel; it must pass through each resistor in an orderly manner. In the parallel circuit, the full voltage is applied to each resistor at the same time. When voltage is applied, it pushes the electrons in a uniform direction; in Fig. 16.2a, b, it is through the resistors of the circuit. When electrons are pushed, they develop a charge or Q which is current over time as shown in Eq. 16.1.

As voltage passes through each resistor in the series circuit, some of the supply voltage is lost because the resistor dissipates the supplied energy in the form of heat and this is called voltage drop. The amount of voltage dropped or consumed by each resistor is determined by the size of the resistor and the charge or current through it. In Fig. 16.2a, resistor R_1 receives the full voltage and is the first to consume some of voltage dissipating the energy as heat. Resistor R_2 receives the voltage left over following the voltage drop from R_1, and it too consumes voltage passing on to R_3 the remaining voltage leftover from the source.

In the parallel circuit, the full voltage is impressed upon each resistor immediately. Each resistor drops voltage, and how much voltage is consumed by each resistor is dependent

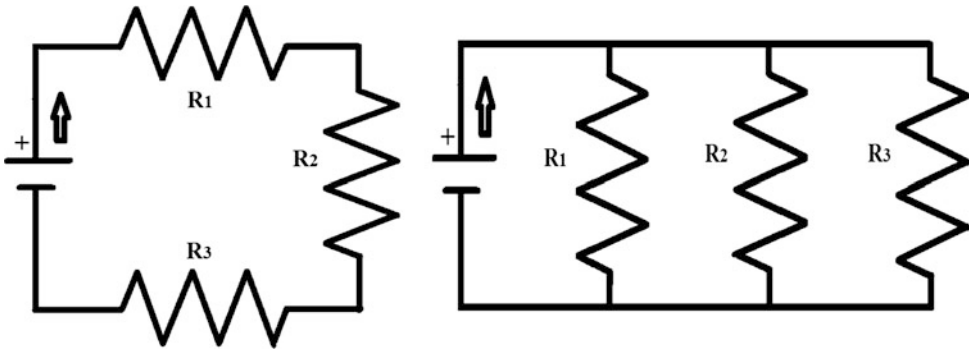


Fig. 16.2 Resistors in series in (**a**) and in parallel in (**b**); *arrow* indicates direction of voltage and current flow

Fig. 16.3 Schematic symbol of a capacitor

upon the resistive value and current through each branch. The relationship between current, voltage, and resistance is explained and easily calculated by Ohm's law discussed further on.

Calculation of the total amount of resistance in a given circuit is different for series or parallel configurations. In a series circuit, the resistance value of each resistor is added to obtain the total resistance of the circuit. The total resistance in a series circuit is higher than the highest value of any single circuit resistor. In a parallel circuit, total resistance is calculated by adding the reciprocal of each individual resistor and then taking the reciprocal of that sum. The total resistance in a parallel circuit is lower than the lowest single resistive value in the circuit. Equations 16.2 and 16.3 illustrate the formulas used to calculate the total resistance in series and parallel resistive circuits, respectively [1–4]. Whether in parallel or series circuit, the current and voltage in a purely resistive circuit are in phase with one another. This means they both follow the same path at the same time.

$$R_T = R_1 + R_2 + R_3 + \cdots + R_n \qquad (16.2)$$

Series Circuit

$$R_T = \frac{1}{\frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} + \cdots + \frac{1}{R_n}} \qquad (16.3)$$

Parallel Circuit

Capacitors and Capacitance

Capacitors are formed by two metal plates or any two conducting surfaces that are separated by a dielectric. A dielectric is an electrical insulator, e.g., air is a dielectric. Two parallel ribbons of wire on a printed circuit board create a capacitor. Power lines running parallel between poles create capacitors by virtue of the definition of a capacitor. An electrode on the surface of the body creates a capacitor. Capacitors are no more than two conductive surfaces separated by a dielectric. There are additional criteria to further define the properties of capacitance; however, this discussion is limited to series and parallel configurations of capacitors and the resistive value they pose in a circuit based on applied frequency. Figure 16.3 shows the schematic symbol of a capacitor.

A capacitor is rated in farads, "*F*" described below, its symbol is "*C*," and the resistance it poses to a circuit is called capacitive reactance symbolized by X_C (X of $_C$) and is calculated as shown in Eq. 16.4 [1, 4].

$$X_C = \frac{1}{2\pi f C} \qquad (16.4)$$

Similar to a resistor, the capacitive reactance or X_C is indicated in ohms "Ω," and unlike a resistor, the capacitive reactance of a capacitor changes with the applied frequency. In Eq. 16.4, the only variable that is not a constant is the frequency or "*f*," the remaining terms are fixed with 2π equivalent to 6.28, and C is the value of the capacitor in farads. In the case of a DC source, "*f*" is equal to zero. If the denominator becomes zero, the resistance is infinite. If that is true what happens when a capacitor is connected across a DC source such as a battery? Electrons move between the battery terminals and the metal surfaces of the capacitor until the capacitor is fully charged with one of the metal conductive plates (positive or negative). You now have an additional power source. How long does this take? The answer depends on time constants. It is important that you understand the behavior of capacitors. Capacitors are effectively an open circuit with a DC source after charging up to their final capacitive value [1, 4].

We still have to account for the energy applied to a capacitor because the law of conservation of energy dictates that energy cannot be lost. Unlike resistors which dissipate energy in heat and drop voltage, capacitors store charge. The ability of a capacitor to store charge is termed capacitance, and its units are farads (*F*), the higher the rating (*F*), the more charge it can store. The symbol of the charge stored on

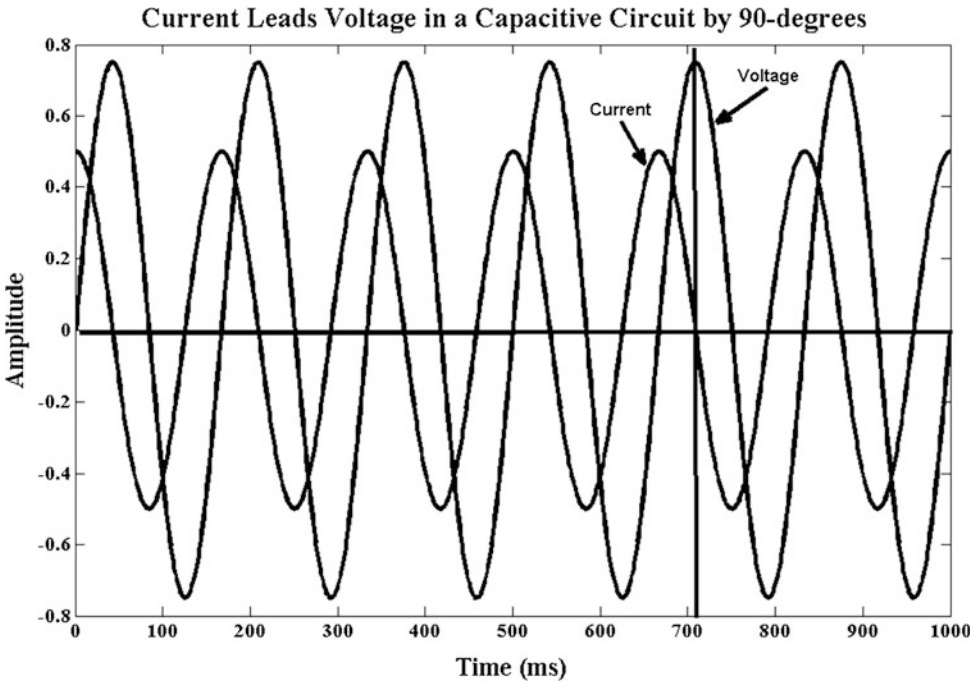


Fig. 16.4 The relationship between current and voltage in a purely capacitive circuit. Voltage lags current by 90°. When the voltage waveform (higher amplitude) is at its peak, the current waveform (lower amplitude) is crossing zero, and this equates to 90°. This is illustrated by the *vertical line* just beyond the 700 ms point. Current flow began 90° prior to any voltage change on the capacitor. Code and output created using MatLab R2012a

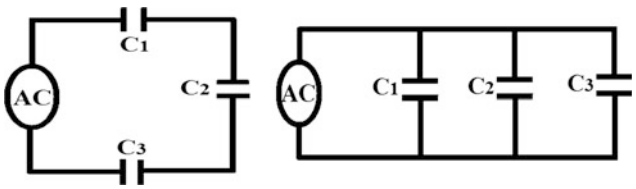


Fig. 16.5 Circuit configurations of capacitors in series (**a**) and in parallel (**b**)

a capacitor is termed "*Q*," because it is electrons that move charging the capacitor. It is the nature of capacitors to resist a change in voltage across them; therefore, the applied voltage lags the current in a purely capacitive circuit by 90°. Figure 16.4 illustrates the phase difference between voltage and current in a purely capacitive circuit. Equation 16.5 states the law of capacitors, where *C* is the capacitor in farads, *Q* is the charge, and *V* is the applied voltage [1, 4].

$$C = \frac{Q}{V} \tag{16.5}$$

Figure 16.5 illustrates capacitors in series (a) and parallel (b) left to right, respectively. In a series, circuit capacitors add like resistors in parallel that is the total capacitance in the circuit is lower than the lowest capacitive value in the entire series circuit. Capacitors in parallel, as you may have guessed, add like resistors in series that is the total capacitance in the circuit is higher than the highest capacitive value in the entire parallel circuit. Formulas for total capacitance in parallel and series circuits are shown in Eqs. 16.6 and 16.7, respectively [1, 3, 4].

$$C_T = C_1 + C_2 + C_3 + \cdots + C_n \tag{16.6}$$
Parallel Circuit

$$C_T = \frac{1}{\frac{1}{C_1} + \frac{1}{C_2} + \frac{1}{C_3} + \cdots + \frac{1}{C_n}} \tag{16.7}$$
Series Circuit

Table 16.1 illustrates the changes in resistance of a 1 μF (10^{-6}) capacitor as the applied frequency increases. Equation 16.4 was used to calculate the change in resistance. It is easily seen that there is a dramatic change in the resistance offered to the circuit by the capacitor as the frequency increases even slightly. This is due to the alternating positive and negative phases of an AC power source. As the alternating phases of the input signal change, more and more rapidly the capacitor ceases to become a resistive factor in the circuit.

Inductors and Inductance

Inductors are coils of wire. The coils of wire can be hollow or the coil can be wrapped around a magnetic or non-magnetic core. Inductors are rated in henries and are indicated by a capital *H* and are identified in a circuit by capital *L*. Figure 16.6 illustrates the circuit schematic symbol for an inductor.

Inductors also store energy, but in a magnetic field, they cannot, however, store energy in the absence of a power source. Once the power source is removed from an inductor, it releases its stored energy. Unlike a capacitor, the resistance of an inductor is directly proportional to the applied

Table 16.1 Capacitive reactance as a result of applied frequency

Capacitor in farads (μF)	Applied frequency	Capacitive reactance (X_C)
1	0.5 Hz	318.3 kΩ
1	1 Hz	159.2 kΩ
1	5 Hz	31.8 kΩ
1	15 Hz	10.6 kΩ
1	20 Hz	8 kΩ
1	25 Hz	6.4 kΩ
1	50 Hz	3.2 kΩ
1	100 Hz	1.59 kΩ
1	1 kHz	159 Ω
1	10 kHz	15.9 Ω
1	100 kHz	1.59 Ω

Fig. 16.6 Schematic symbol of an inductor

frequency of the source. The nature of an inductor is to resist a change in current through it; thus, current lags voltage in a purely inductive circuit by 90°. Like a capacitor, the resistance of an inductor, called inductive reactance which is rated in ohms, is termed X_L (X of $_L$) with symbol Ω and is calculated as indicated in Eq. 16.8 [1].

$$X_L = 2\pi fL \tag{16.8}$$

There is only one variable in Eq. 16.8 that is not a constant, and this is "f" or the applied frequency, 2π is equivalent to 6.28, and L is the measure of the inductor in henries. The phase relationship between an inductor and capacitor is 180°.

Representative circuits for inductors are not shown. The circuit configuration for inductors in series and parallel is identical to the circuit configurations previously shown for resistors and capacitors with the simple change of circuit components to inductors. Figure 16.7 illustrates the output of an inductive circuit with voltage leading current by 90°; this is identical to Fig. 16.4, but voltage and current have changed places. This phase relationship exists because inductors resist a change in current through them so current lags voltage.

It should be remembered that the physical properties of a capacitor cause it to resist an instantaneous change in voltage across it and that an inductor resists an instantaneous change in current through it. This is why each of these properties lags in their respective circuit as illustrated in Fig. 16.7 for inductors and Fig. 16.4 for capacitors.

Circuit calculations for the total inductance of inductors in series or parallel configurations are identical to those of resistors in the same configuration and are shown in Eqs. 16.9 and 16.10, respectively [1].

$$L_T = L_1 + L_2 + L_3 + \cdots + L_n \tag{16.9}$$
Series Circuit

$$L_T = \frac{1}{\frac{1}{L_1} + \frac{1}{L_2} + \frac{1}{L_3} + \cdots + \frac{1}{L_n}} \tag{16.10}$$
Parallel Circuit

Cartesian Plane

A Cartesian plane is a coordinate system with four quadrants that are labeled with Roman numerals I–IV counterclockwise beginning in the upper right quadrant. The "X" or real axis is the horizontal plane, and the "Y" or imaginary axis is the vertical plane. The zero point in the Cartesian coordinate system is where the X and Y axes cross. All X-coordinate points to the left of zero are negative; all X-coordinate points to the right of zero are positive. All Y-coordinate points below zero are negative; all Y-coordinate points above zero are positive. This coordinate system allows for the unique identification of points in space with two specific coordinates, an X value and a Y value. These points are always shown in that order and usually in parentheses as (X, Y). For instance, a point on the Cartesian coordinate system of (3, −3) indicates that it is located three positive units along the X axis horizontally and three negative units along the Y axis vertically, so the point is located in the lower right quadrant or quadrant IV. Figure 16.8 shows an illustration of a Cartesian coordinate system or Cartesian plane.

Here, the Cartesian system is used to create an impedance diagram by plotting resistance, capacitive reactance, and inductive reactance using vectors. Vectors are lines with arrowheads that indicate direction and magnitude. The longer the vector the greater the magnitude of the representative quantity; the arrowhead is an indication of direction. Discussion of phase is not addressed other than what

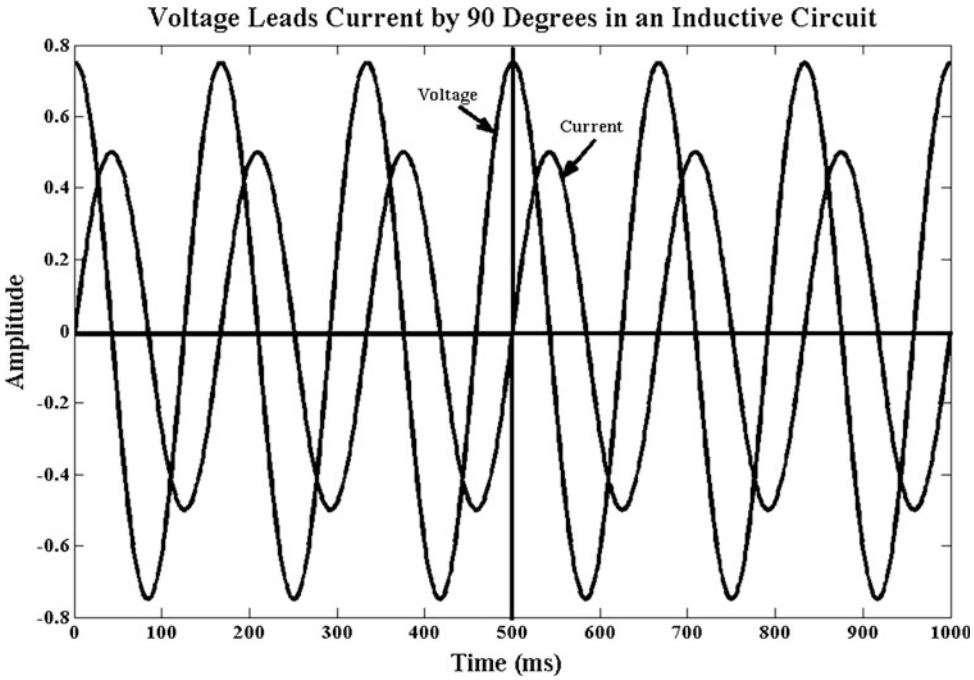


Fig. 16.7 The relationship between current and voltage in a purely inductive circuit. Voltage leads current by 90°. When the voltage waveform (higher amplitude) is at its peak, the current waveform (lower amplitude) is crossing zero, and this equates to 90°. The *vertical line* through the 500 ms point illustrates this point. The voltage through the inductor began 90° prior to current flow. Code and output created using MatLab R2012a

has previously been described in resistive and purely capacitive or inductive circuits. Resistance R is always plotted on the positive X axis, capacitive reactance X_C on the negative Y axis, and inductive reactance X_L on the positive Y axis all by vectors. The phase relationship between inductive and capacitive reactance is 180° which is why X_L points up and X_C points down. The length of the vector indicates the magnitude of the resistance in each case. Because X_C and X_L are 180° out of phase, the smaller value is subtracted from the larger value to determine their combined reactance. The direction, pointing up or down in the impedance diagram, is dependent upon the larger value. The resultant vector will point up if X_L is larger than X_C or will point down if X_C is larger than X_L and should be scaled to indicate the relative reactance value. In Fig. 16.8, X_C is a longer vector than X_L, so capacitive reactance has a higher value than inductive reactance leaving a resultant X_C vector on the Y axis pointing downward. Drawing a straight line from the arrowhead of the resultant vector, here it would be X_C to the vector representing R forms a right triangle. This new line is the hypotenuse of a right triangle, and Pythagoreans theorem shown in Eq. 16.11 is used to calculate this value which is the total impedance of the circuit indicated by the capital letter "Z" [1, 4, 5].

In a circuit containing R, X_L, and X_C, the phase angle between voltage and current is less than 90° and depends on the relative size of the resistor compared to the resultant reactance.

$$Z = \sqrt{(R^2 + (X_{\text{Larger}} - X_{\text{Smaller}})^2)} \tag{16.11}$$

Impedance Z is a complex value; in simple AC circuits such as those with a single voltage or current source, Eq. 16.11 will suffice, but for complex circuitry, more sophisticated circuit analysis is required.

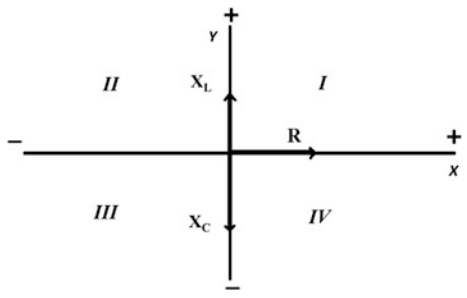


Fig. 16.8 Cartesian coordinate system with labeled quadrants and vectors indicating resistance "R," inductive reactance "X_L," and capacitive reactance "X_C"

Ohm's Law

Ohm's law is the equation that defines the relationship between resistance, voltage, and current. Equation 16.12 illustrates the Ohm's law voltage equation where "R" is resistance, "E" is voltage, and "I" is current, voltage may be shown as "V," and this does not change the formula [1–4].

$$E = I * R \tag{16.12}$$

From Eq. 16.12, it is clear that voltage (E) is directly proportional to resistance and current. Manipulation of this

basic formula reveals that both current (I) and resistance (R) are proportional to the applied voltage and inversely proportional to one another. These relationships are illustrated in Eqs. 16.13 (a) and (b) for current and resistance, respectively [1, 3, 4].

$$\underset{(\mathbf{a})}{I = \frac{E}{R}} \quad \underset{(\mathbf{b})}{R = \frac{E}{I}} \tag{16.13}$$

In Eq. 16.13 (a), for a fixed resistance as the applied voltage increases so does the current. Conversely, if the applied voltage remains the same and the resistance is increased, the current decreases. Using Eq. 16.13 (b), the applied voltage and current resistance are easily calculated.

Power

Power in an electrical circuit is a measure of the rate of performing work and is measured in watts, indicated by a capital "W," and is calculated by the formula in Eq. 16.14 [1]. A light bulb rated 60 W utilizes 60 W of energy, and a 120-W bulb provides more light and consumes more energy.

$$P = E * I \tag{16.14}$$

Through direct substitution of Ohm's law, Eq. 16.13 (a) for current, and Eq. 16.12 for voltage, power can be expressed as indicated in Eqs. 16.15 (a) and (b), respectively.

$$\underset{(\mathbf{a})}{P = \frac{E^2}{R}} \quad \underset{(\mathbf{b})}{P = I^2 * R} \tag{16.15}$$

Kirchhoff's Voltage and Current Laws

Kirchhoff's laws will be defined simply without consideration or explanation of power supply orientation or polarity of any circuit devices. Kirchhoff's voltage law states that the sum of the voltage drops in a closed loop must equal the applied source. Kirchhoff's current law states that the current into a junction, node, or system must equal the current exiting that same junction, node, or system [1–6]. Energy must always be accounted because it cannot be lost. Kirchhoff's voltage and current laws are mathematically stated in Eqs. 16.16 (a) and (b), respectively, and illustrated graphically in Fig. 16.9.

$$\begin{aligned} \Sigma_{\text{Current In}} &= \Sigma_{\text{Current Out}} \quad (\mathbf{a}) \\ \Sigma_{\text{Source}} &= \Sigma_{\text{Voltage Drops}} \quad (\mathbf{b}) \end{aligned} \tag{16.16}$$

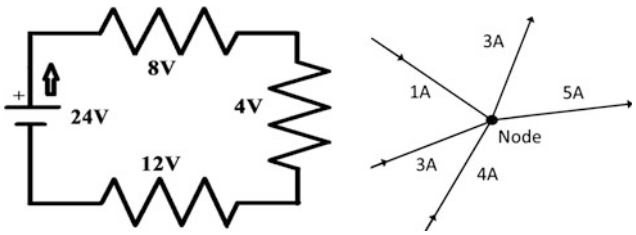


Fig. 16.9 Kirchhoff's voltage law in **a** the sum of the voltage drops 8 V + 12 V + 4 V = 24 V, which equals the source voltage. In **b**, three current values are entering one central node (*arrows* pointing into the node) and two exiting (*arrows* pointing away from the node) current pathways. The sum of the input current is 8 A which equals the sum of the output current meeting the requirements of Kirchhoff's current law

Frequency and Period

Frequency is a rate quantity measured in cycles per second. Frequency is an indication of how often something happens in one second time. The symbol for frequency is lower case "f," and its units are Hertz, abbreviated Hz. Period is a time quantity and is a measure of the time it takes for one cycle of a periodic waveform to occur. The symbol for period is capital "T" and is expressed as a unit of time. Frequency and period are inversely related, as one increases the other decreases. The period of a signal with a frequency of 60 Hz is 1/60th of a second. This means there are 60 cycles per second in a 60 Hz periodic signal, and it takes 1/60th of a second for one of those cycles to occur [1]. If you know one quantity you know the other. Equation 16.17 indicates the inverse relationship between period and frequency.

$$f = \frac{1}{T} \quad T = \frac{1}{f} \tag{16.17}$$

When identifying frequency of any waveform, verify the time line and determine the frequency in one second. Figure 16.10 shows a 3 Hz signal with one period indicated.

Decibels, Logarithms, Gain, and Bode Plots

These topics are discussed briefly because filter frequency response curves are shown in logarithmic scale in "Bode" plots, filters are designed with a cutoff stated in decibels, and gain is usually indicated in decibels. Gain is the output of an amplifier; in neurodiagnostic technology, this is termed a differential amplifier which is a sophisticated device made up of resistors, capacitors, and transistors. When transistors are used in filter design, they are called active filters, whereas passive filters only use resistors and capacitors in their design.

The voltage gain of a circuit denoted "A_V" is a ratio of the output voltage to the input voltage as shown in Eq. 16.18 (a). Gain is a measure of how much larger the output is

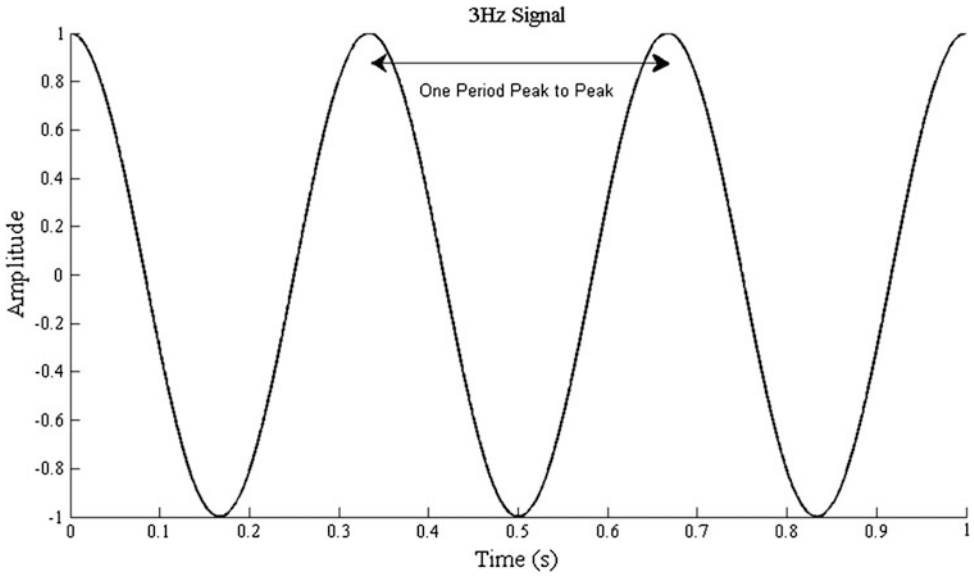


Fig. 16.10 3 Hz signal, its period from one peak to the next, is indicated by the *double arrow*, and this equals one cycle whose period is 1/3 s the inverse of the signal frequency. Code and output created using MatLab R2012a

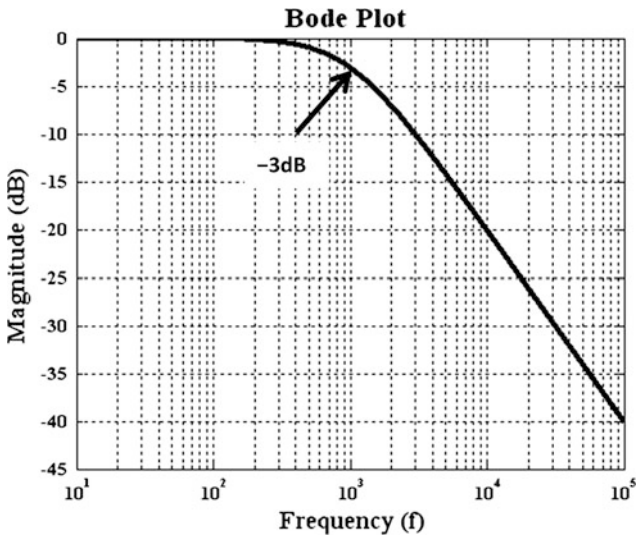


Fig. 16.11 The "y" axis in the Bode plot indicates magnitude in dB, and a logarithmic "x" axis indicates frequency. Maximum signal magnitude begins at "0" and slopes negative as the frequency increases. The −3 dB point or filter cutoff is indicated by the *arrow*, and this is a high-frequency filter (HFF) with cutoff of 1 kHz. Code and output created using MatLab R2012a

compared to the input and is a term used in reference to amplifiers. The voltage gain of an amplifier expressed in decibels (dB) is found by using logarithms as illustrated in Eq. 16.18 (b) [1, 7].

$$\underset{(\mathbf{a})}{A_V = \frac{V_{\text{Out}}}{V_{\text{In}}}} \quad \underset{(\mathbf{b})}{A_{V\text{dB}} = 20\log\frac{V_{\text{Out}}}{V_{\text{In}}}} \tag{16.18}$$

The technical specifications of a machine can indicate the gain in decibels (dB) or as a whole number, i.e., 100,000 that can be obtained by using Eqs. 16.18 (a) and (b). For example, given 1 μV input and an output of 0.1 V, the gain would be 100,000 or 100 dB.

Bode plots represent the frequency response of a filter and are plotted on a log frequency axis. An example of a Bode plot is shown in Fig. 16.11; in this example, the cutoff frequency of the filter is 1 kHz and is indicated on the plot as the −3 dB point.

There are several names for the cutoff of a filter. We already are familiar with −3 dB; there is also f_C for frequency cutoff, and half power point, and there are others. The term half power point means that the effective value of the voltage is 0.707 V, and the signal is now equivalent to half its original power. Rather than introducing additional equations, I will illustrate this property using the power formula of Eq. 16.15(a). In reiteration, I have just stated that −3 dB is equal to the half power point of the signal, and the output effective value has dropped to 0.707 V of its full value [1, 6, 7]. By inserting 0.707 into Eq. 16.15(a) as shown in Eq. 16.19, the output at −3 dB is half the power of the input.

$$P = \frac{E_{\text{Max}}^2}{R} = \frac{(0.707 * E_{\text{Max}})^2}{R} = \frac{0.707^2 * E_{\text{Max}}^2}{R}$$

$$= 0.5 * \frac{E_{\text{Max}}^2}{R} = 0.5 * P \tag{16.19}$$

The Bode plot of Fig. 16.11 is initially flat at zero and does not begin to drop off until the frequency of the signal approaches the filter cutoff. This flat part of the Bode plot is maximum power passing through the filter; any signal in this frequency range is passing through the filter at full amplitude or full power. As frequency increases and nears the −3 dB

point, or the filter cutoff, the amplitude of the input voltage drops to 70.7 % of its maximum value. For the Bode plot of Fig. 16.11, the filter cutoff is 1 kHz; if a 2 V 1 kHz signal was passed through the filter, the output would be 1.414 V or 70.7 % of the input amplitude [1]. This is illustrated in Eq. 16.20 and is called **attenuation**. This is how filters work; they are not perfect, and they incrementally remove the power from the signal as the frequency increases by dropping the signal amplitude.

$$2V * 0.707 = 1.414V \tag{16.20}$$

Filters vary in design and can be cascaded to improve attenuation at the filters cutoff point. In this chapter, we discuss simple single-stage filter circuits with a −3 dB cutoff.

Filters

The three types of filters used in neurodiagnostic equipment are high pass, low pass, and notch [2–6]. The low-pass filter (LPF), in clinical neurophysiology, is commonly referred to as a high-frequency filter (HFF) because it eliminates high frequencies allowing low frequencies to pass up to the design cutoff of the filter. The high-pass filter (HPF) is commonly called a low-frequency filter (LFF) because it excludes low frequencies and passes high frequencies. The notch filter is designed to eliminate a specific frequency band. In North America, power is generated at a frequency of 60 Hz, whereas in Europe it is generated at 50 Hz. In equipment design, the notch filter would be set to match the generated frequency, and thus, in North America, the notch would eliminate 60 Hz, and in Europe, it would eliminate 50 Hz.

What separates a LFF from a HFF is the location of the capacitor in the circuit which dictates filter behavior. If a capacitor is the first component the signal encounters, the capacitor will resist a change in voltage across it and have a very high resistance at low frequencies, and so this must be a low-frequency filter. The high resistance at low frequencies causes these signals to be severely attenuated. As the capacitive reactance of the capacitor decreases with increasing frequency, the filter will incrementally pass the higher-frequency components. When the incoming signal frequency reaches the filter cutoff, 70.7 % of the signal amplitude passes (this assumes a—3 dB design). As frequency increases beyond the −3 dB point, increasing amounts of the signals are passed until the full signal strength is passed through the filter.

If a capacitor is second in line in a filter circuit, the design is that of a high-frequency filter. A high-frequency filter will allow low frequencies to pass until the frequency of the incoming signal approaches the design cutoff of the filter. At the filter cutoff, the signal is attenuated to 70.7 % of its amplitude. Amplitude continues to decrease and is attenuated as frequency increases. The frequencies that filters pass are called the pass band of the filter, and those that are attenuated are considered in the stop band of the filter. In any filter, attenuation is indicated in a Bode plot by the slope of the line, the steeper the slope, the higher the percentage of attenuation with increasing frequency. Figure 16.12a, b illustrates the circuit design, frequency behavior, and the stop and pass bands of high- and low-frequency filters, respectively.

The output of a HFF as illustrated in Fig. 16.12a is taken across the capacitor; for an LFF, the output is taken across the resistor as in Fig. 16.12b. The filter behavior at the respective output can be demonstrated through the use of Eqs. 16.21 (a) and (b) as shown in Table 16.2.

$$\begin{gathered} V_{\text{Out}} = V_{\text{In}} * \frac{X_C}{\sqrt{R^2 + X_C^2}} \\ (\mathbf{a})\ \mathbf{HFF} \\ V_{\text{Out}} = V_{\text{In}} * \frac{R}{\sqrt{R^2 + X_C^2}} \\ (\mathbf{b})\ \mathbf{LFF} \end{gathered} \tag{16.21}$$

The cutoff frequency of a filter is determined by the combination of the resistive and capacitive values of the

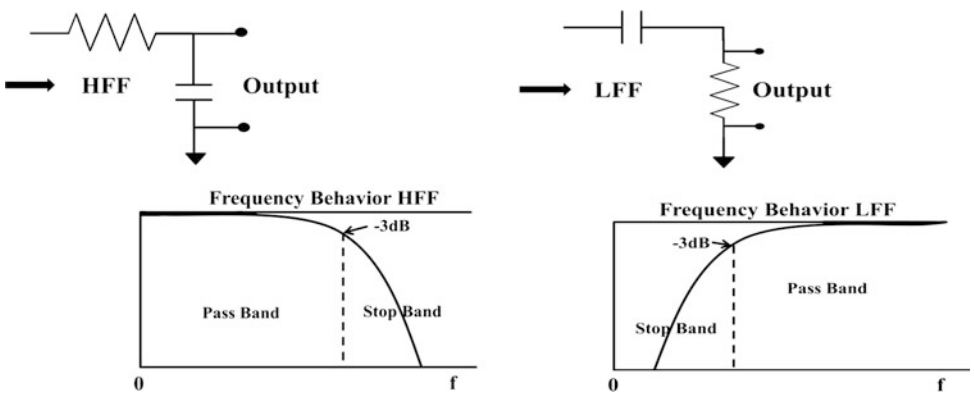


Fig. 16.12 High-frequency filter circuit (**a**), low-frequency filter circuit (**b**). Frequency behavior, −3 dB and the stop and pass bands are identified for each circuit

Table 16.2 Filter output at varying input frequencies with V_{In} 1 V, resistance 5 kΩ, and capacitance 50 nF. Equation 16.4 was used to calculate X_C. Equations 16.21 (a) and (b) were used to calculate V_{Out} for the respective filter

Frequency (f)	Capacitive reactance X_C	V_{Out} HFF	V_{Out} LFF
2 Hz	1.59 MΩ	1 V	0 V
200 Hz	15.9 kΩ	0.95 V	0.30 V
2 kHz	1.59 kΩ	0.30 V	0.95 V
20 kHz	159 Ω	0.03 V	1 V
200 kHz	15.9 Ω	0 V	1 V

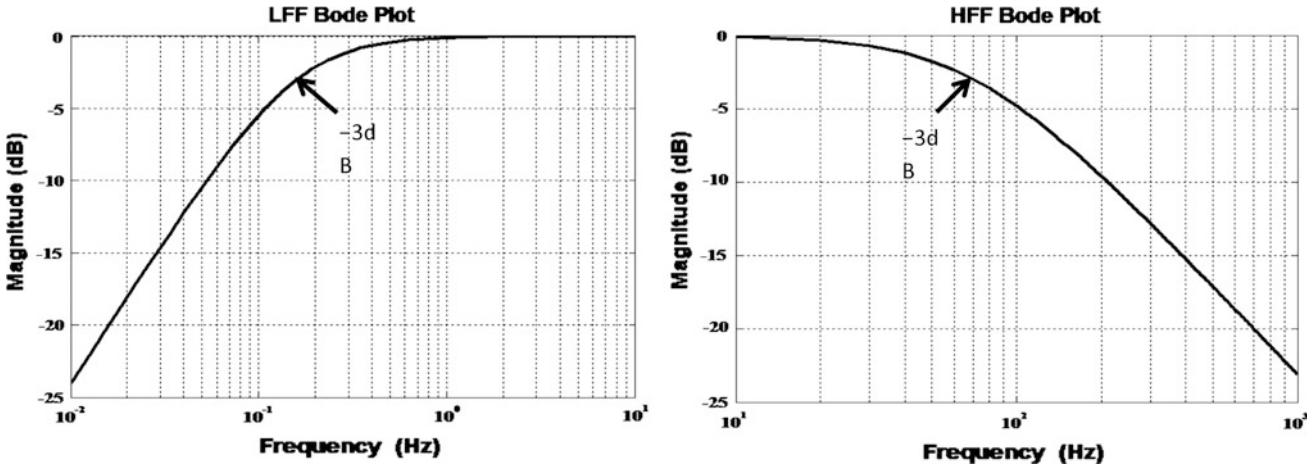


Fig. 16.13 Frequency response plots of the filters in Fig. 16.12a, b, respectively. In **a**, the filter attenuates high frequencies, and in **b**, the filter attenuates low frequencies. An *arrow* indicates the −3 dB point; in (**a**), f_C is 70 Hz, and in (**b**), f_C is 0.16 Hz. Code and output created using MatLab R2012a

filter circuit. This is shown in Eq. 16.22 where 2π is equivalent to 6.28, R is the resistor value in ohms, and C is the capacitor value in farads. The product $R * C$ is called tau, is indicated by the lower case Greek letter τ, represents a time constant, and can be substituted for RC as shown in Eq. 16.22 [1–5]. Time constants are discussed in the next section; however, it is important to understand that filters may be discussed in their cutoff point in Hz or by their time constant tau.

$$f_C = \frac{1}{2\pi RC} = f_C = \frac{1}{2\pi\tau} \tag{16.22}$$

Bode plots of HFF and LFF are shown in Fig. 16.13a, b, respectively. In the Bode plot of Fig. 16.13a, the HFF pass band extends from the vertical axis to the −3 dB point, and beyond the filter cutoff is the filter stop band. This is also true for the LFF Bode plot in Fig. 16.13b; however, the stop band and pass bands are reversed relative to the vertical axis.

Time Constants

A time constant is the product of the resistor and capacitor values in a filter circuit (RC) and is measured in seconds [1–5]. How does the product of a resistor in ohms and a capacitor in farads result in a time quantity? Using formulas already discussed for resistance (R), capacitance (C), and current (I), this can be answered and is shown in Eq. 16.23.

$$RC = \frac{E}{I} * \frac{Q}{E} = \frac{E}{\frac{Q}{t}} * \frac{Q}{E} = t \tag{16.23}$$

Filters may be described in terms of their time constant or frequency cutoff. It is important to be conversant between the two and to understand the behavior of the charge and discharge cycles for each filter. The voltage charge and discharge cycles of a capacitive transient are illustrated in Fig. 16.14a, b, respectively. A typical HFF setting in clinical neurophysiology is 70 Hz, with tau of 2.2 ms, and a 1-Hz LFF is synonymous with tau of 0.159 s. The term tau was introduced in the section on Filters and illustrated in Eq. 16.22, the formula for frequency cutoff of a filter. Equation 16.22 solved for tau is shown in Eq. 16.24.

$$\tau = \frac{1}{2\pi f_C} \tag{16.24}$$

Time constants can quite effectively be explained through the use of calculus; however, I will eliminate derivations and illustrate the equations along with a table. Equation 16.25

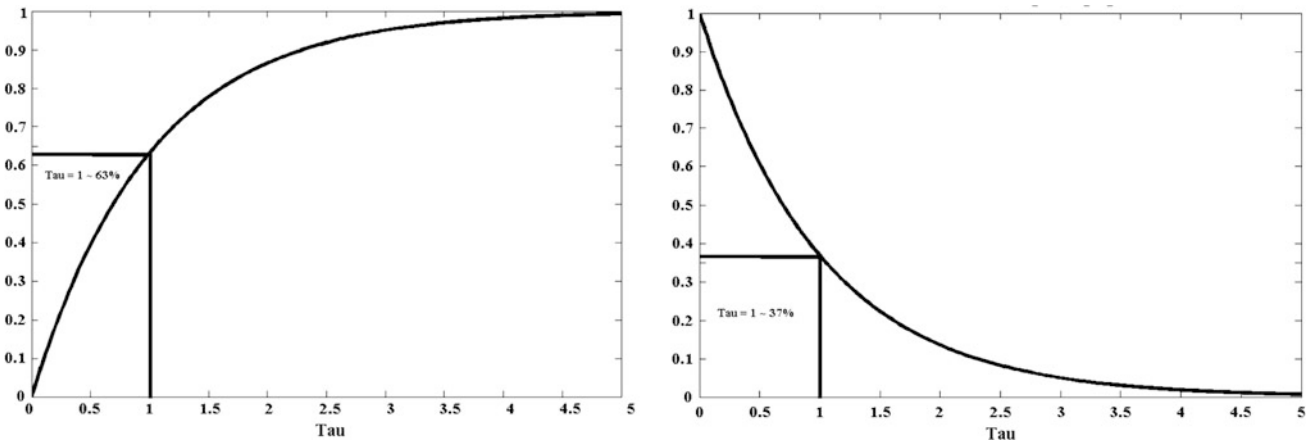


Fig. 16.14 The capacitive transient characteristics of Eqs. 16.25 (a) and (b) are shown in (**a**) and (**b**), respectively. In 1τ, the output has risen to 63 % in (**a**) and declined to 37 % in (**b**). In 5τ, in a DC circuit the components are either fully charged or discharged. Code and output created using MatLab R2012a

Table 16.3 Behavior of rising and decaying exponential time constants 0τ is initial conditions

Tau (τ)	Rise $V(t) = 1 * (1 - e^{\frac{-t}{\tau}})$		Decay $V(t) = 1 * e^{\frac{-t}{\tau}}$	
τ = tau	V	% of rise	V	% of decay
0	0	0	1	0
1	0.63	63	0.37	63
2	0.86	86	0.14	86
3	0.95	95	0.05	95
4	0.98	98	0.02	98
5	0.99	99	0.01	99

(a) and (b) are the rise and decay of voltage in a capacitor, respectively.

$$\underset{(\mathbf{a})}{V(t) = V(1 - e^{\frac{-t}{\tau}})} \quad \underset{(\mathbf{b})}{V(t) = Ve^{\frac{-t}{\tau}}} \tag{16.25}$$

The results of Eqs. 16.25 (a) and (b) are shown graphically in Fig. 16.14a, b respectively and numerically in Table 16.3.

It is clear from Fig. 16.14a, b and the values in Table 16.3 that in five time constants (5τ), the capacitor resistor combination has either completely charged or discharged. Another useful observation is this: Following one time constant, the circuit has completed 63 % of its course regardless of direction, charging, or discharging. With a DC source after 5τ, the capacitor has fully charged, and current has stopped flowing. With a DC source applied after 5tau, the capacitor has fully charged and current has stopped flowing. With an AC source applied charging and discharging of the capacitor alternate with the alternating AC source. The higher the applied frequency of the AC source the faster the alternating state of the capacitor. The higher the frequency the lower the capacitive reactance as illustrated in Eq. 16.4. The higher the frequency, the faster the alternating states. The time constant remains the product of the resistance and capacitance (RC), and this is the design of the circuit.

In terms of Bode plots if the time constant is a small value, the −3 dB point would be further from zero on the frequency scale, and the filter cutoff would be a larger value. If the time constant is a relatively large value, the −3 dB point would be closer to zero on the frequency scale, and the frequency cutoff would be a smaller value. This can be illustrated in several ways: One is using Eqs. 16.25 (a) and (b) to form Table 16.3. Another method is to use Eq. 16.24 to derive tau with various values of f_C as illustrated in Table 16.4. A third way is to view the concept graphically as in Fig. 16.15.

Differential Amplifiers and Polarity Convention

This is a general discussion of the operation of differential amplifiers in clinical neurophysiology. There is no in-depth electrical or electronic explanation, and the internal operation and electrical requirements of the operational amplifier are assumed satisfied.

Differential amplifiers do exactly what their name implies, and they take the difference of two inputs, amplify, and output the result. The schematic diagram of a differential amplifier is indicated in Fig. 16.16.

Table 16.4 The inverse relationship between tau and f_C. Values are rounded up to the highest integer. Note the change in units from seconds (s) to milliseconds (ms) at 3 Hz

Cutoff −3 dB f_C (Hz)	$\tau = \frac{1}{2\pi f_C}$
0.25	0.64 s
0.5	0.32 s
1	0.16 s
1.5	0.11 s
3	53 ms
5	32 ms
10	16 ms
15	10.6 ms
35	4.5 ms
70	2.3 ms
100	1.6 ms

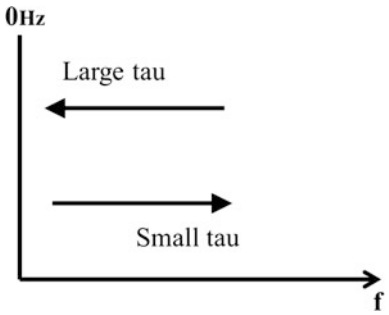
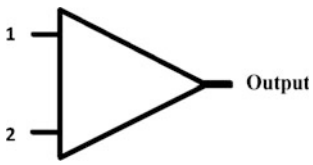


Fig. 16.15 Graphic illustration of the inverse relationship between the filter frequency cutoff and the value of its time constant. Horizontal axis begins at 0 Hz with increasing frequency moving to the right. With larger values of tau, the frequency cutoff moves toward 0 Hz indicated by a lower-frequency value cutoff. With smaller values of tau, the frequency cutoff moves away from 0 Hz taking on a larger-frequency cutoff value

Fig. 16.16 Schematic symbol of a differential amplifier



As can be seen in Fig. 16.16, the amplifier has two inputs, input 1 and input 2, and a single output representing the amplified difference of the two inputs. Input 1 is referred to as the active input and input 2 the reference input [2–6]. Each amplifier represents one channel of digital recording. In clinical neurophysiology, electrodes are connected to the differential amplifier with one on each input. The differential amplifier then subtracts input 2 from input 1, amplifies, and outputs the difference as one channel of recording.

The deflection of the channel output up or down is a result of the polarity convention [4, 5]. All electroencephalography (EEG) machines are designed the same way allowing for a standard definition of polarity. If input 1 is relatively more negative than input 2, the deflection of the output is upward, and if input 2 is more negative than input 1, the deflection of the output is downward. In short, the deflection of the output follows the negativity [4].

Common mode rejection ratio (CMRR) is a design parameter of a differential amplifier. It is a measure of the amplifiers ability to reject common signals [2–7]. Common mode rejection is a ratio of two measured outputs of the amplifier. One output, called A_{Diff}, is measured with a different and controlled voltage level applied to each amplifier input. This may also be accomplished by applying a voltage to one input and grounding the other. The other output termed A_{Com} is measured with an identical, i.e., common and controlled voltage level applied to both amplifier inputs [1, 7]. In this way, it is possible to determine the integrity of the amplifier. Does the amplifier properly take the difference of the inputs, amplify, and output the result and is the output zero when identical voltage levels are applied to both inputs? There are inherent imperfections in electronic design, so the output is rarely if ever zero when identical and controlled voltages are applied to the inputs; however, the output is extremely low. CMRR is indicated in decibels (dB) although it may be shown as a whole number. The equation for CMRR and its conversion to decibels are shown in Eqs. 16.26 (a) and (b) [2, 3, 7].

$$\underset{(\mathbf{a})}{A_{\text{CMRR}} = \frac{A_{\text{Diff}}}{A_{\text{Com}}}} \quad \underset{(\mathbf{b})}{\text{dB}_{\text{CMRR}} = 20\log(A_{\text{CMRR}})} \tag{16.26}$$

This is an important design criterion of the amplifier, the higher the CMRR, the better the component design. Common mode voltage would be noise, such as 60 Hz induced on the electrode wires from a variety of sources. If it is common to both inputs, it should be rejected, and so it is not amplified as part of the signal of interest which could potentially lead to misinterpretation. One way to assist an amplifier to perform up to its design potential is to bundle all

connected electrode wires together. Bundling the wires causes induced noise to be common to all the wires allowing the differential amplifier to remove common mode noise.

Analog-to-Digital Conversion

Neurodiagnostic recording captures analog signals through the application of externally applied electrodes. Analog signals are continuous in time versus a digital signal which is composed of discrete points in time. In older pen and paper machines, it was the analog signal that was captured and faithfully recorded in full. Digital equipment has many advantages over older pen-driven machines; however, computers cannot capture and store signals that are continuous in time; they must be converted to digital form for storage and display. All neurodiagnostic equipments begin with an analog signal, and all convert it to a digital signal through a circuit called an analog-to-digital converter or ADC. Digital signals are discrete points in time represented by 1's and 0's and stored in memory on a computer.

All biological signals are analog, but all stored signals are digitally obtained by sampling and analog-to-digital conversion. The signal being recorded is filtered, sampled at equidistant points in time, and stored transforming it into a digital signal. An ADC has several design parameters, which come in various speeds and have differing degrees of accuracy and resolution, and an input voltage range, but all are rated in the number of bits of information they can store [4, 6, 7]. A bit is a single unit of information represented by a 1 or a 0 in binary notation; calculation of bits is shown in Eq. 16.27.

$$2^n = \#\text{ of bits} \quad 2^4 = 16\text{ bits} \tag{16.27}$$

The design criterion of the ADC dictates the price, and hence the more bits, the higher is the cost. A typical ADC size of 2^{16} is 65,536 bits, and if the ADC had a resolution of 0.06 μV, its dynamic range would be ±1.97 mV. Calculation of dynamic range requires knowledge about the size of the ADC and its resolution. Calculation of dynamic range (DR) indicated in our example is shown in Eq. 16.28.

$$\begin{aligned} \text{DR} &= 2^n * \frac{\text{resolution}}{\text{per bit}} = 65536\text{ bits} * \frac{0.06\ \mu\text{V}}{\text{bit}} \\ &= \pm 0.001966\text{ V} \end{aligned} \tag{16.28}$$

This means that the ADC can assign values to the samples with a minimum or maximum value of 1.97 mV. Without consideration for sign bits, the number of bins available to assign values to these samples is 65,536, with half (32,768) dedicated to the positive values and the other 32,768 is dedicated to the negative values. Each bin in this ADC represents a 60 nV increment, that is 10^{-9}, lending to very accurate placement of the digital samples to match their true analog values. The current American Clinical Neurophysiology Society (ACNS) guideline #8 calls for a minimum of an 11 bit ADC with 12 or higher preferred, to resolve the EEG to 0.5 μV or better and record up to plus or minus several millivolts without clipping [8]. Clipping may occur when the sample falls out of the range of the ADC as it has nowhere left to place a value larger than its dynamic range (positive or negative). Anything beyond these values is assigned to the maximum available value and appears clipped off in the positive or negative range.

Quantization (or signal processing is the process of mapping a large set of input values to a smaller set) is an indication of how much rounding, up or down, the ADC will have to do with the samples taken to make the value "fit" into its available steps [6, 7]. The higher the number of bits, the less rounding the ADC has to do, and thus, the sample will be assigned a value closer to its actual value. Our example of ±32,768 available steps at a resolution of 0.06 μV decreases the quantization error, which is defined as the round-off error introduced by quantization, for example, a decimal number of 12.65 representing as 13 in which there is an inherent error. This is what a larger number of bits does; it provides more alternatives for the ADC to more accurately represent the value of the samples taken as they are converted to digital form.

Nyquist Theorem

We need to sample and convert analog to digital signal, but we do not know yet how often to sample. This is where the Nyquist sampling theorem will help. Nyquist theorem states that a band-limited signal can be faithfully reproduced, providing the sampling rate is twice the maximum frequency of the signal being sampled [4–6]. For example, if the highest frequency content of a signal of interest is 70 Hz, then per Nyquist theorem it must be sampled at a **minimum** of 140 samples per second or 140 Hz for perfect reconstruction. What happens to the information between each sample? It is discarded, and the computer does not store any information other than the value of the analog signal at the time a sample is taken. One must understand the frequency content of a signal and ensure Nyquist criterion is met to obtain perfect reconstruction of an analog signal in digital form. If Nyquist theorem is not followed, "**aliasing**" of the signal occurs. Aliasing describes a situation that generates false (i.e., alias) frequency signals with jagged distortions making it difficult to recognize the original signal. Aliasing results in misinterpretation of the recorded signal because the original signal can no longer be perfectly reconstructed from its digital samples as there is not enough information from which to properly reconstruct the signal [4–6].

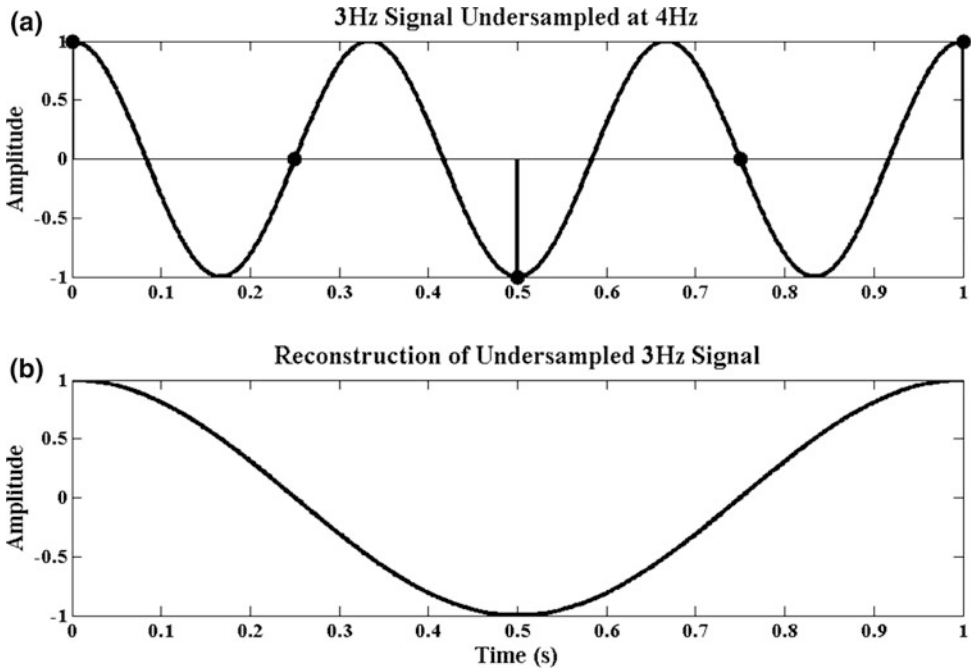


Fig. 16.17 The consequences of violating Nyquist sampling criteria. In **a**, 3 Hz signal is sampled at 4 Hz. In **b**, it has been reconstructed from its samples and appears to have been a 0.5-Hz signal, and this is aliasing, improper reconstruction due to insufficient sampling. Code and output created using MatLab R2012a

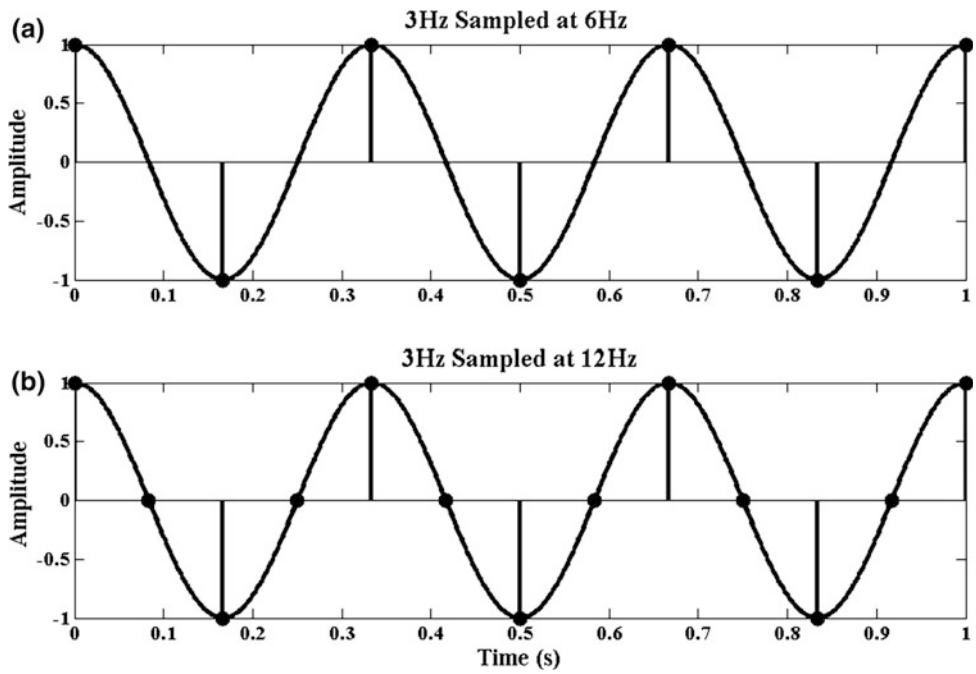


Fig. 16.18 In **a**, 3-Hz signal is sampled at 6 Hz meeting Nyquist criteria, and in **b**, the signal is over sampled at four times the signal frequency or 12 Hz. Perfect reconstruction is virtually ensured in both (**a**) and (**b**); however, (**b**) provides additional information for reconstruction with preserved morphology. Code and output created using MatLab R2012a

To faithfully follow the Nyquist theorem, the signal is filtered before sampling so the maximum frequency is known and Nyquist sampling theorem can be applied. In practice, sampling is performed at a higher rate than Nyquist theorem. The current American Clinical Neurophysiology Society (ACNS) guideline #8 requires a minimum sampling rate of three times the highest frequency content of the signal [8]. Higher sampling rate or over sampling is preferable and not generally an issue as the cost of storage is fairly inexpensive. More storage capacity is needed with a higher sampling rate because the faster a signal is sampled the more discrete points in time are taken that must be stored by the analog-to-digital converter. Taking constant snapshots of an event at evenly spaced intervals, stacking up all the snapshots sequentially, and flipping through them will give a fairly accurate and animated picture of the event. If sufficient snapshots are not available, there would be missing information and voids without properly depicting the event as it

occurred. During sampling, the values are briefly held up in a sample, and the circuit reassembled time locked and then displayed as "*X*" number of channels.

Figure 16.17a illustrates a 3 Hz signal that has been under sampled at 4 Hz violating Nyquist criteria. Note that the samples would never faithfully reproduce a 3 Hz signal, and on reconstruction, it would appear to have been a 0.5 Hz signal as shown in Fig. 16.17b; this is **aliasing**. Remember information between samples is lost, and the only values available to reconstruct the signal are the stored sampled values.

In Fig. 16.18a, the 3 Hz signal has been sampled at 6 Hz, meeting Nyquist criteria; notice, however, that only the peaks have been captured during sampling. While this would be sufficient to reconstruct the original signal, its morphology could be compromised upon reconstruction. It may appear to have had sharper peaks than the original signal. It is best to oversample as in Fig. 16.18b to capture additional information and ensure reconstruction.

Conclusion

The recording of a biological signal requires the application of electrodes that interface with sophisticated electronic equipment in order to capture and record minute electrical activity generated by the movement of ions in biological tissue. Neurodiagnostic machines have a variety of settings that must be adjusted during the course of the recording to enhance data acquisition providing meticulous recording.

In order to appropriately adjust variables, it is vital to possess an understanding of the controls available, the appropriateness of making variable adjustments, and a complete understanding of the effect on the integrity of the recording.

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An Overview of Polysomnographic Technique

17

Nic Butkov and Sharon A. Keenan

Introduction

The term *polysomnography* (PSG) was proposed by Holland et al. [1] in 1974 to describe the recording, analysis, and interpretation of multiple, simultaneous physiologic characteristics during sleep. PSG is an essential tool in the formulation of diagnoses for sleep disorder patients and in the enhancement of our understanding of normal sleep [2–14]. It is a complex procedure that should be performed by trained technologists. Innovations for monitoring changes in physiology during sleep continue to hold great promise in the quest to understand healthy sleep and to diagnose sleep disorders.

Over the past decade, PSG has been increasingly employed in the diagnosis and treatment of complicated sleep-related breathing disorders (SRBDs), as seen in patients with chronic obstructive pulmonary disease (COPD), neuromuscular disease, congestive heart failure (CHF), obesity hypoventilation syndrome (OHS), and patients using opioid medications, whereas limited-channel home sleep apnea testing (HSAT) is increasingly used for diagnosing uncomplicated obstructive sleep apnea (OSA) [15–17]. Overnight in-laboratory PSG remains the gold standard when comprehensive physiologic sleep measures are required. These measures are particularly relevant as newer methods of nocturnal noninvasive ventilation (NIV) treatments are being developed. The importance of properly diagnosing patients with complicated SRBD and evaluating treatment response to NIV within the context of multiple physiologic parameters cannot be understated.

This chapter is a review of the technical aspects of PSG, describing traditional, classic in-laboratory PSG recording techniques. Problems likely to be encountered during a recording are examined, as are ways to alleviate them. Figures and tracing samples augment the text and help identify artifacts. Elsewhere in this volume, specified protocols are discussed and physiologic recording techniques are reviewed in detail.

Clinical Indications for PSG

According to the 2005 American Academy of Sleep Medicine (AASM) guidelines [18], attended PSG is considered the standard of practice for: (see also Chap. 26)

- Diagnosis of SRBD
- Positive airway pressure titration
- Preoperative assessment for snoring or OSA
- Evaluating results of the following treatments:
  - Oral appliances for moderate to severe OSA
  - Surgical procedures for moderate to severe OSA
  - Surgical or dental procedures in SRBD for return of symptoms.
- Treatment results requiring follow-up PSG:
  - Substantial weight loss or gain (10 % of body weight)
  - When clinical response is insufficient or when symptoms return.
- Patients with systolic or diastolic heart failure and nocturnal symptoms of SRBD
- Patients whose symptoms continue despite optimal management of CHF
- Neuromuscular disorders with sleep-related symptoms
- Narcolepsy (Multiple Sleep Latency Test [MSLT] after PSG)
- Periodic limb movement disorder in cases secondary to complaints by patient or observer (movements during sleep, frequent awakenings, excessive daytime sleepiness).

According to the AASM guidelines, PSG is not required to diagnose:

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- Uncomplicated Parasomnias
- Seizure disorders, unless suspected nocturnal seizures
- Restless legs syndrome
- Common, uncomplicated, non-injurious events (arousals, nightmares, enuresis, sleep-talking, bruxism)
- Circadian rhythm disorders.

Diagnosis with clinical evaluation alone is the standard in these cases. Standard evaluation includes history, details of behavior, age of onset, time, frequency, regularity, and duration.

Patient Contact

A number of factors need to be kept in mind when a PSG is scheduled. Issues such as shift work, time zone change, or suspected advanced or delayed sleep phase syndrome should be taken into consideration. The study should be conducted during the patient's usual major sleep period, to avoid confounding circadian rhythm factors.

When the PSG is scheduled, the patient is sent a questionnaire about his or her sleep–wake history and a sleep diary that solicits information about major sleep periods and naps for 2 weeks prior to the study (Appendix 17.1). Information is provided to the patient about the purpose and procedures of the sleep study. The goal is to make the patient's experience of the sleep study as uncomplicated and comfortable as possible.

In the sleep laboratory setting, the technologist should ensure that patients are familiar with the surroundings and that they receive explicit information about the process. Patients should be made aware that someone will be monitoring their sleep throughout the entire study and told how to contact the technologist if necessary.

Before the study is undertaken, a full medical, psychiatric, and drug history should be completed and made available to the technologist performing the study. This information is necessary for correct interpretation of the data, and it allows the technologist to anticipate difficulties that may arise during the study. Technologists must also understand what questions the study seeks to answer. This enhances their ability to make protocol adjustments when necessary and ensures that the most pertinent information is recorded.

Prestudy Questionnaire

It is not uncommon for patients, particularly those with excessive sleepiness, to have a diminished capacity to evaluate their level of alertness [19]. In addition, patients with difficulty initiating and maintaining sleep often report a subjective evaluation of their total sleep time and quality that is at odds with the objective data collected in the laboratory. For these reasons, it is recommended that subjective data be collected systematically as part of the sleep laboratory evaluation.

The Stanford Sleepiness Scale (SSS) [20, 21] (Appendix 17.2) is an instrument used to assess a patient's subjective evaluation of sleepiness prior to the PSG. The SSS is presented to the patient immediately before the beginning of the study. Patients respond to a series of phrases by selecting the set of adjectives most closely corresponding to their current state of sleepiness or alertness. The scale is used extensively in both clinical and research environments. However, it has two noteworthy limitations: It is not suitable for children who have a limited vocabulary or for adults whose primary language is not English. In these situations, a linear analog scale is recommended to provide an introspective measure of sleepiness (see Appendix 17.2). One end of the scale represents extreme sleepiness and the other end alertness. Patients mark the scale to describe their state just prior to testing.

Another instrument, the Epworth Sleepiness Scale [22], lends information about chronic sleepiness. Patients are asked to report the likelihood of dozing in situations such as riding as a passenger in a car, watching television, and the like.

Patients are also asked about their medication history, smoking history, any unusual events during the course of the day, their last meal prior to the study, alcohol intake, and a sleep history for the last 24 h, including naps. Involvement of the patient in providing this information usually translates into increased cooperation for the study. A technologist's complete awareness of specific patient idiosyncrasies, in the context of the questions to be addressed by the study, ensures a good foundation for the collection of high-quality data.

Recording Parameters

A conventional PSG recording montage used in clinical sleep studies typically includes the following parameters:

- Central, frontal, and occipital electroencephalogram (EEG)
- The recording of eye movements (electrooculogram or EOG)
- The recording of chin muscle activity (chin electromyogram or EMG)
- The recording of leg muscle activity (right and left anterior tibialis EMG)
- The electrocardiogram (ECG)
- Nasal and oral airflow

- Respiratory effort (based on chest and abdomen excursion)
- Pulse oximetry.

Additional parameters can be added depending on the intent of the study. For example, when PSG is used in conjunction with noninvasive ventilation, additional parameters would typically include delivered positive airway pressures, estimated tidal volumes, inspiratory to expiratory ratios, leak values, and other essential data relevant for comprehensive treatment evaluation. On the other hand, if PSG is used with the intent of evaluating nocturnal seizures or parasomnias, additional recording parameters might include an expanded number of EEG channels and possibly additional limb EMG channels.

Understanding the Equipment

PSG Amplifiers

Although PSG equipment has undergone many changes since the early days of analog paper-based recordings, the basic concepts of bio-physiologic data collection remain the same. Bioelectrical signals, such as the EEG, EOG, EMG, and ECG, are derived from surface electrodes attached directly to the patient's skin. Other signals, such as those representing respiratory airflow and effort, are derived from transducers that respond to certain physiologic markers, such as changes in temperature or pressure, or body motion.

The signals received by the PSG equipment are extremely low in voltage (generally measured in microvolts) and must be greatly amplified to be converted into visible tracings. The key component of every PSG recording system is the bank of amplifiers used for processing the derived signals. In the past, these amplifiers were large in size and constituted a major part of the polysomnograph. In the present day, the amplifiers have been miniaturized and are typically integrated with the electrode jack box in the patient's room. The amplified signals are converted into digital form and transmitted by cable to the computer in the control room.

The amplifiers used in PSG recordings are described as differential amplifiers, specially designed to preserve essential physiologic data while rejecting undesirable signal interference. The process by which differential amplifiers accomplish this is called common mode rejection. For each physiologic derivation, two signals are compared to each other and only those signals that are dissimilar in voltage or polarity are amplified, while any identical in-phase signals are rejected. For example, when recording EEG activity, signals derived from the C4 electrode are referenced to signals derived from the M1 electrode (see Electrode and Sensor Application Process). The output from this derivation represents only those signals, which are dissimilar in voltage or polarity between the two inputs, while any identical, in-phase signals are rejected (these would include 50 or 60 Hz power line interference, or any other extraneous signals that are identical in both inputs).

It is important to understand that common mode rejection is only effective when the input signals are of equal quality, i.e., the signals are not degraded by high electrode impedances or poor electrical connections. If the signal quality varies significantly between the two inputs to the amplifier, the effect of common mode rejection is diminished and unwanted interfering signals (such as 50 or 60 Hz) will be amplified along with the signals of interest [23].

Gain and Sensitivity

The amount of signal amplification produced by PSG equipment is determined by the amplifier gain, defined as the number of times the raw signal is amplified. On most contemporary equipment, the gain is a fixed value. However, the actual size of the signal on a computer screen can be adjusted by the user. In doing so, the user can choose a specific ratio of input voltage to the vertical height of the signal. This is defined as signal sensitivity, which allows for precise signal measurements. Historically, sensitivity settings for the EEG, EOG, and EMG have been either 50 or 70 μV/cm for adult subjects (higher voltage-per-centimeter values equate to lower displayed amplitudes). For pediatric studies, the EEG channels are typically set to 100 μV/cm because of the higher EEG amplitudes seen in children, which might cause excessive signal blocking if displayed at high sensitivities. It is important to note that unlike sensitivity settings used in paper-based recordings, which were uniformly adjusted to grid marks on paper, sensitivity settings on contemporary digital equipment must be adjusted specifically for the type of display used. The size of the monitor, the available workspace on the monitor screen, and the total number of channels on the screen are all factors that can affect the actual size and aspect ratio of the displayed signals. To ensure consistency in recording and interpreting the polysomnogram, it is recommended that the sensitivity settings (and all other controls) at each workstation within the sleep laboratory are set identically, so that everyone involved in the process views the data in the same way.

Filters

Whereas common mode rejection is intended to eliminate major sources of external signal interference such as 50 or 60 Hz, additional signal conditioning is necessary to minimize localized signal interference within each recorded

Table 17.1 Examples of filter and sampling rate settings for various PSG parameters based on recommendations by the AASM

Recommendations for filter settings and sensitivity for various physiologic parameters				
Channel[a]	Low-frequency filter (Hz)	Time constant (s)	High-frequency filter (Hz)	Sensitivity
EEG	0.3	0.4	35	50 (μV/cm)
EOG	0.3	0.4	35	50 (μV/cm)
EMG	5[b]	0.03	90–120	20–50 (μV/cm)
ECG	1	0.12	15	1 MV/cm
Index of airflow	0.15	5[b]	15	[c]
Index of effort	0.15	5[b]	15	[c]

Some modifications to these settings may be appropriate, based on the types of signals recorded, or the types of transducers used in the study. For example, a lower LFF setting in the respiratory channels may be advantageous, to better resolve the "flattening" effect seen with flow limitation
[a]EEG includes C3/A2, C4/A1, O1/A2, and O2/A1 (or any other EEG derivation). EOG includes right outer canthus and left outer canthus referred to opposite reference (or any other EOG derivation)
[b]If shorter time constant or higher low-frequency filter is available, it should be used. This includes settings for all EMG channels, including mentalis, submental masseter, anterior tibialis, intercostal, and extensor digitorum muscles. Because breathing has such a slow frequency (as compared to the other physiologic parameters), the longest time constant available, or the lowest setting on the low-frequency filter options, would provide the best signal. It is also possible to use a DC amplifier (with no low-frequency filter, time constant = infinity) to record these signals
[c]It is common in clinical practice to index changes in airflow and effort to breathe by displaying qualitative changes in oral/nasal pressure, temperature, and chest and abdominal movement. It is well recognized that quantitative methods (such as endoesophageal pressure changes) provide a more sensitive and accurate measure of work of breathing. Ideally, a multi-method approach is used to increase confidence in detecting events of sleep-related breathing anomalies ECG, electrocardiography; EEG, electroencephalography; EMG, electromyography; EOG, electrooculography

parameter. This is accomplished by the use of low- and high-frequency filters (LFF and HFF). Historically, filters used in EEG and PSG recording equipment were built with resistors and capacitors that limited the range of frequencies allowed to pass through the amplifiers during data collection [24]. These filters were designed to attenuate undesirable signal frequencies relative to a gradually descending curve at each end of the selected frequency bandwidth. Contemporary digital filters are software-based and can be applied or changed either during the recording or during playback. This offers a significant advantage over traditional filtering, because changes can be made at any time without affecting the raw data. However, as with analog filters, caution should be exercised not to overuse digital filtering to the extent that faulty signals are made to appear "clean." When analyzing PSG data, it is essential to understand the effects of filtering on the raw data, making certain that unwanted interference is minimized, yet not completely eliminated, in order to alert the reader if a faulty signal occurs [23].

The selection of filter settings is made on the basis of the desired frequency range to be displayed within each channel. For example, in PSG recordings, EEG data are generally read within a bandwidth of 0.5 and 25 Hz. To preserve each end of the frequency spectrum, the low- and high-frequency filters are set slightly beyond this range; the LFF is generally set to 0.3 Hz and the HFF is set to 30 or 35 Hz. This creates a frequency window of 0.5–25 Hz, with some extra margin at each end to ensure full resolution of EEG waveforms relevant to sleep stage and arousal scoring. Likewise, the LFF and HFF settings for other PSG parameters, such as the EMG and ECG, are set according to the frequency ranges expected to be read within those channels. Table 17.1 presents recommended filter settings for the various PSG parameters.

Bit Resolution and Sampling Rates

Unlike paper-based recording systems of the past that transformed the continuous analog signals into mechanical pen movements, contemporary PSG systems require analog-to-digital converters (ADCs) to convert the analog signals into digital form. The ADC converts the signals by assigning a numeric value to the amplitude of the analog waveforms at predetermined intervals. The number of binary units (bits) used to represent the numeric value of each sampled interval determines the amplitude resolution of the digital recording. For adequate amplitude resolution, a 12-bit or higher system is recommended.

The number of sampled intervals collected within the span of one second is defined as the sampling rate, which

determines the frequency resolution of the recorded waveforms. The reconstruction of a digitized waveform follows the Nyquist theorem, which states that for basic frequency resolution the minimum sampling rate must be twice the rate of the highest frequency sampled (Nyquist rate). While the Nyquist rate is acceptable for processing signals that do not require detailed waveform reconstruction (such as the EMG), sampling rates that are significantly higher than the Nyquist rate are necessary for adequate graphic resolution of waveforms that require close scrutiny (such as EEG, EOG, and ECG waveforms) [25]. In these instances, the sampling rates should be at least 5–10 times higher than the highest frequency expected within the channel.

Unlike digital filtering, bit resolution and sampling rates must be applied during the recording process and cannot be changed afterward. To reduce overall file sizes and processing times, sampling rates can be selected channel by channel, depending on the type of signal recorded. Recommended sampling rates for various PSG parameters are included in Table 17.1.

Also to be considered is the display resolution, which is determined by the resolution of the monitor. The computer screen for review of the recording should have a sufficiently high resolution. Ideally, the screen should be at least 20 in. with a resolution of at least 1600 × 1200 pixels.

Time Scale

Historically, the speed of the chart drive for the recording instrument established the time scale and the epoch length (amount of time per page) of the recording. A common paper speed for traditional PSG was 10 mm/s, providing a 30-s epoch. Another widely accepted paper speed was 15 mm/s, a 20-s epoch length. For patients with suspected sleep-related seizure activity, a paper speed of 30 mm/s enhanced the ability to visualize EEG data. Data such as oxygen saturation and respiratory signals, however, were more easily visualized with slower paper speeds.

The issue of selecting the appropriate paper speed became moot when digital systems became the norm. In the present day, digital technology allows for multiple time-scale settings, which can be applied either during the recording or during playback (Figs. 17.1 and 17.2). For sleep stage and arousal scoring, the 30-s epoch continues to be the established standard [26]; however, alternative time scales can be used for evaluating sleep-related events. For example, an epoch length of 10–15 s can be useful for closely examining EEG or ECG abnormalities, whereas epoch lengths of 2–5 min are useful for evaluating respiratory patterns, periodic limb movements, and oximetry trends.

The Study

Electrode and Sensor Application Process

The quality of the tracing generated in the sleep laboratory depends on the quality of the electrode application [27]. Before any electrode or sensor is applied, the patient should be instructed about the procedure and given an opportunity to ask questions. The first step in the electrode application process involves measurement of the patient's head. The International 10–20 system [28] of electrode placement is used to localize specific electrode sites (Figs. 17.3 and 17.4) (see also Chap. 24). The following sections address the application process for EEG, EOG, EMG, and ECG electrodes.

Electroencephalography

As originally described in the Rechtschaffen and Kales manual [29], standard electrode derivations for monitoring EEG activity during sleep are C3/A2 or C4/A1 for central EEG activity, and O1/A2 or O2/A1 for occipital EEG activity (see also Chap. 18). The AASM Scoring Manual terminology uses the terms "M1" and "M2" instead of "A1" and "A2" for the reference electrodes placed on the mastoid process. In this case, the derivations are C3/M2 or C4/M1, and O1/M2 or O2/M1 (the AASM recommends using C4/M1 and O2/M1 as the default derivations, with C3/M2 and O1/M2 as alternative back-up derivations). The AASM also recommends the use of frontal EEG recordings (F4/M1 and F3/M2) when considering decisions regarding K complexes or slow-wave activity [26].

In some situations, there may be a need for additional electrodes. For example, to rule out the possibility of epileptic seizures during sleep or to detect the presence of other sleep-related EEG abnormalities, it may be necessary to apply the full complement of EEG electrodes according to the International 10–20 system. An abbreviated montage to screen for EEG abnormalities during PSG is discussed in Appendix 17.3. For recording EEG, gold cup electrodes are commonly used. The electrode cups are filled with conductive cream or electrode paste and adhered to the scalp with collodion or with additional electrode paste. The collodion technique [27] has long been an accepted and preferred method of application for EEG scalp and reference electrodes. Other methods using electrode paste and a conductive medium are acceptable and may be preferred in certain conditions.

The International 10–20 system of electrode placement determines the placement of EEG electrodes. Reference electrodes are placed on the bony surface of the mastoid process. A description of the measurement procedure appears in Appendix 17.4.

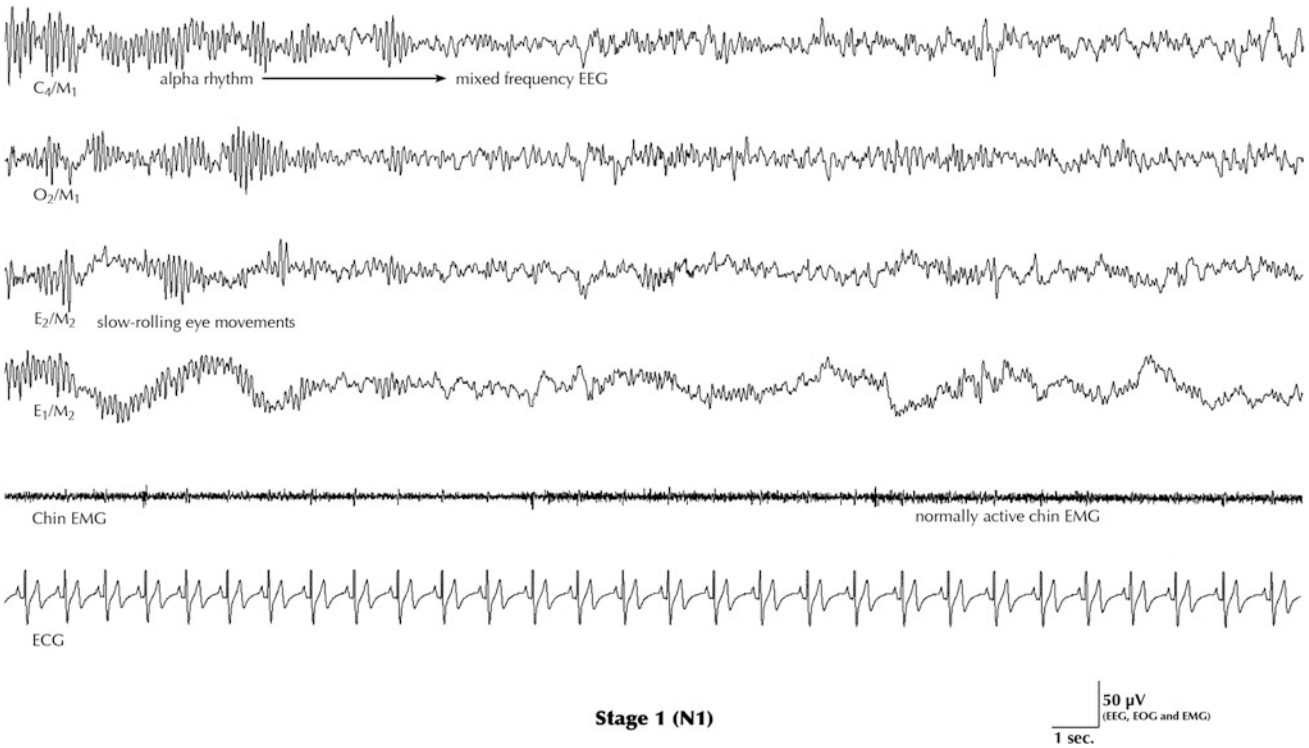

Fig. 17.1 PSG recording viewed in a 30-s epoch window. A time scale of 30 s per epoch provides a high level of detail in the EEG and EOG channels and is the standard scale for scoring sleep stages and arousals. This sample demonstrates the onset of stage 1 sleep. Reprinted with permission from Butkov [23]

Electrooculography

The EOG is a recording of the movement of the corneo-retinal potential difference that exists in the eye. It is the movement of this dipole with respect to the placement of the EOG electrodes that is recorded (Fig. 17.5) (see also Chap. 18). Gold cup electrodes or silver–silver chloride electrodes can be used to record the EOG. EOG electrodes are typically applied to the surface of the skin with an adhesive collar; this method avoids the risk of collodion contacting the patient's eyes.

The AASM Scoring Manual recommends placing the right EOG electrode (E2) one centimeter directly above the right outer canthus (ROC) and the left EOG electrode (E1) one centimeter directly below the left outer canthus (LOC) [26]. Some adjustments might be necessary to these placements, to avoid placing the E2 electrode directly over the right eyebrow or to avoid placing either of the electrodes too close to the sensitive tissue of the eyelid. The AASM also recommends referencing both EOG electrodes to the right mastoid (M2); however, a contralateral reference (E2/M1 and E1/M2) may be preferable for maximizing signal amplitudes in both EOG channels and equalizing the out-of-phase signals deflections seen with conjugate eye movements [30].

It should be noted that many variations of electrode placement and recording derivations have been used in a variety of clinical and research settings. Additional infraorbital and supraorbital electrodes enhance the ability to detect eye movements that occur in the vertical plane and can be particularly useful in the MSLT [31, 32]. Given the existing variations in methodology within the clinical and research environments, it is important to know the exact electrode placements and inputs to the EOG channels when interpretation of EOG activity has significant impact on diagnosis or treatment outcome (Fig. 17.6).

Electromyography

To record chin EMG activity, gold cup or silver–silver chloride electrodes are placed over the mentalis and submentalis muscles. The electrodes can be attached with double-sided electrode collars and paper tape, or they can be adhered with collodion or paste if the patient has a beard. The AASM Scoring Manual recommends placing one electrode on the midline, 1 cm above the inferior edge of the mandible, and two electrodes 2 cm below the inferior edge of the mandible, offset 2 cm to the right and left of midline, respectively [26]. Two of the electrodes are used to create a bipolar EMG recording, while the third electrode serves as a backup. Some practitioners place an electrode over a masseter muscle to better detect bursts of EMG activity associated with bruxism (see Fig. 17.6).

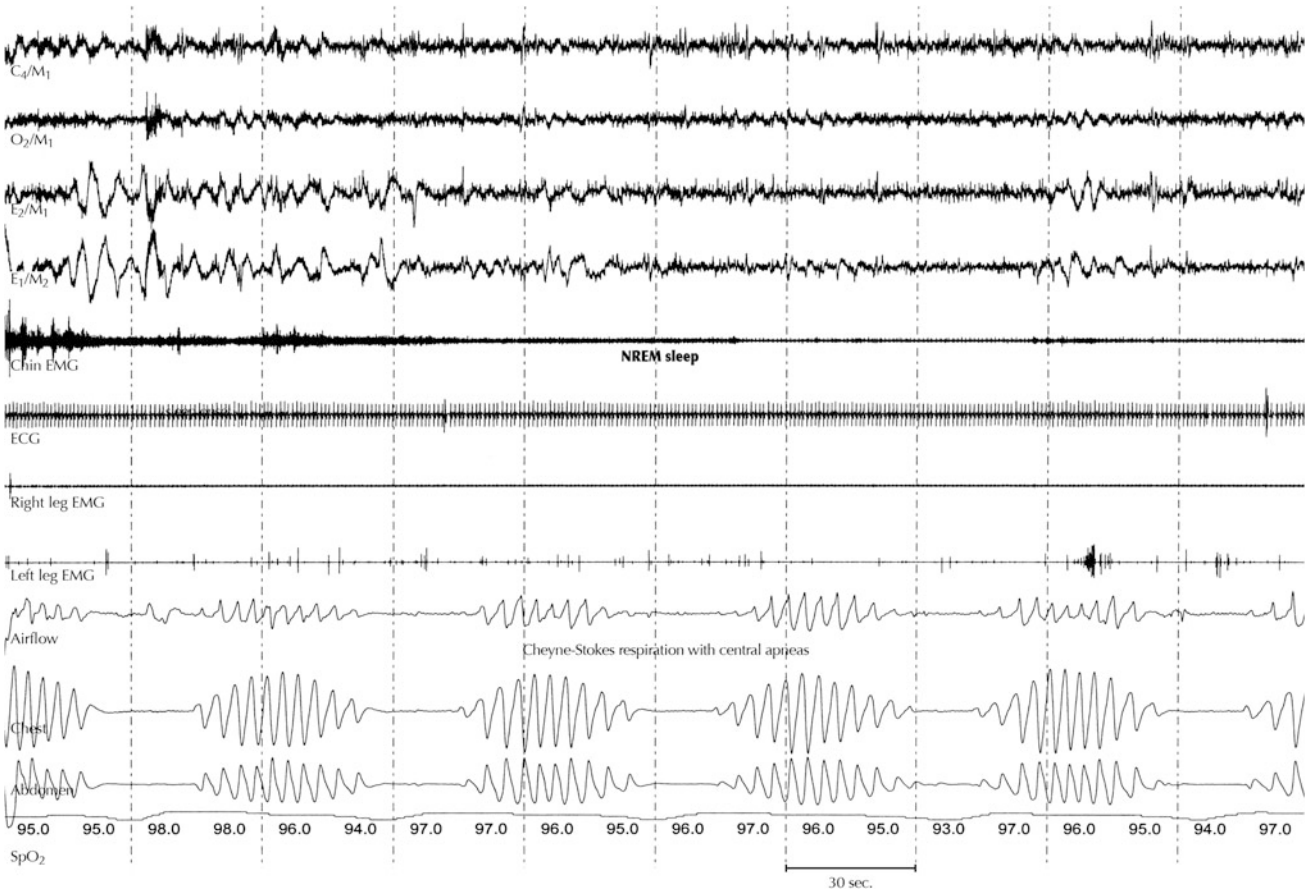

Fig. 17.2 PSG recording viewed in a 5-min epoch window. After scoring sleep stages and arousals in 30-s epochs, the time scale can be compressed into 2- to 5-min epochs, to better discern respiratory patterns while correlating them to the patient's sleep and wake physiology. This example shows a pattern of Cheyne–Stokes respiration emerging with the onset of NREM sleep. Reprinted with permission from Butkov [23]

To record leg EMG, a pair of electrodes is placed over the anterior tibialis muscle of each leg. The electrodes are spaced approximately 2–3 cm apart and referenced to each other in a bipolar derivation.

Electrocardiography

There are a variety of approaches for recording the ECG during PSG. The simplest approach is to use disposable ECG patches with a stress loop incorporated into the lead wire to ensure long-term placement. A modified lead II is obtained by placing an electrode slightly below the right clavicle and referencing it to an electrode placed over the left lower thorax. A third electrode placed slightly below the left clavicle allows for recording a modified lead I (left subclavicular to right subclavicular) and lead III (left subclavicular to left lower thorax) ECG.

Patient Ground and System Reference Electrodes

A single patient ground electrode is applied typically to the patient's forehead, slightly below the hair line. The purpose of a patient ground is to divert excessive 50 or 60 Hz line frequency interference from the patient's body. The input for the ground electrode must be isolated to prevent the possibility of stray current passing through the patient, and only a single ground electrode should be used on the patient to avoid the possibility of creating a ground loop.

If system referencing capabilities are provided by the PSG equipment, then an additional system reference electrode is attached to the patient, typically placed on the midline of the scalp (Cz). System referencing offers a way to select or to change input signal derivations either during data collection or during playback. During data collection, the signals from all of the applied electrodes are initially referenced to the Cz electrode. This configuration is not seen by the operator, but is used as a framework for selecting the desired derivations. For each selected derivation, the computer subtracts the common reference (Cz) from the chosen pair of input signals and displays the resulting derivation on the computer monitor [23].

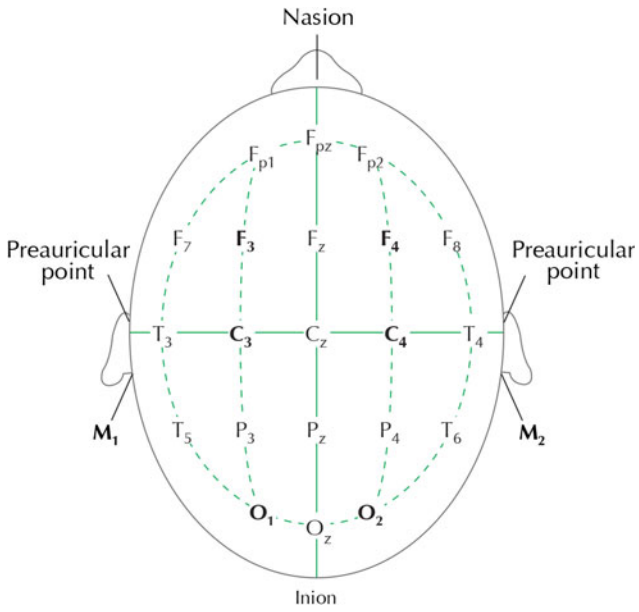

Fig. 17.3 International 10/20 system of electrode placement (*top view*). Reprinted with permission from Butkov [23]

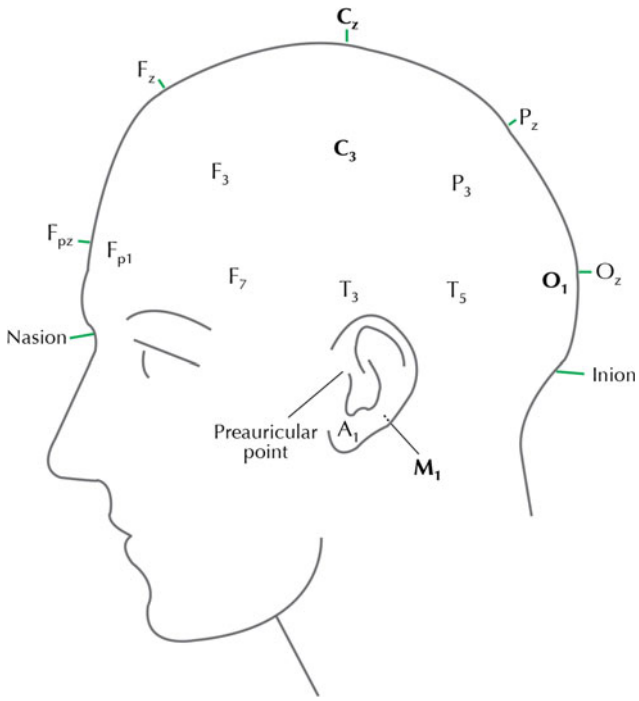

Fig. 17.4 International 10/20 system of electrode placement (*side view*). Reprinted with permission from Butkov [23]

It is important to note that a faulty connection to either the patient ground or the system reference electrode will result in signal degradation that can affect all of the PSG channels. A faulty patient ground connection can cause excessive 50 or 60 Hz interference in the recording, while a faulty system reference connection can cause complete signal loss in all channels (with the exception of any dedicated bipolar or transduced signals that bypass the common reference). Consequently, extra care should be taken to ensure that these two electrodes are properly applied and well maintained throughout the duration of the recording.

Electrode Impedances

Before recording, all electrodes should be visually inspected to check the security of their placement and an impedance check should be performed and documented. An impedance meter is ideally part of the recording system. Alternatively, a separate device can be used. Adjustments should be made to any electrode with impedance readings of greater than 5000 Ω (5 kΩ). Impedance levels are reduced by carefully cleansing and scrubbing each electrode site with a gel-based skin prepping solution before applying the electrode. Only a small area of skin should be scrubbed, no larger than the size of the electrode cup, to prevent electrical bridging and to minimize the occurrence of artifacts in the recording [23].

Physiologic Calibrations

Physiologic calibrations are performed after the electrode and sensor application is complete. This calibration documents proper functioning of the electrodes and other recording devices and provides baseline data for review and comparison when scoring the PSG. The specific instructions given to the patient for this calibration include

- Eyes open, look straight ahead for 30 s.
- Eyes closed, look straight ahead for 30 s.
- Hold head still, look to left and right, up and down. Repeat.
- Hold head still, blink eyes slowly, five times.
- Clench the jaw and grit the teeth.
- Inhale and exhale slowly, three times.
- Hold breath for 10 s.
- Dorsiflex right foot (i.e., bend the foot upward), dorsiflex left foot (this ensures contraction of the tibialis anterior muscle).

As these instructions are given to the patient, the technologist examines the tracings and documents the patient's responses. When the patient stares straight ahead for 30 s with eyes open, the background EEG activity is examined. As the patient looks right and left, the tracing is examined for out-of-phase deflections of the signals associated with recording the EOG. Out-of-phase deflection occurs if the inputs to consecutive channels of the polygraph are E2/M1

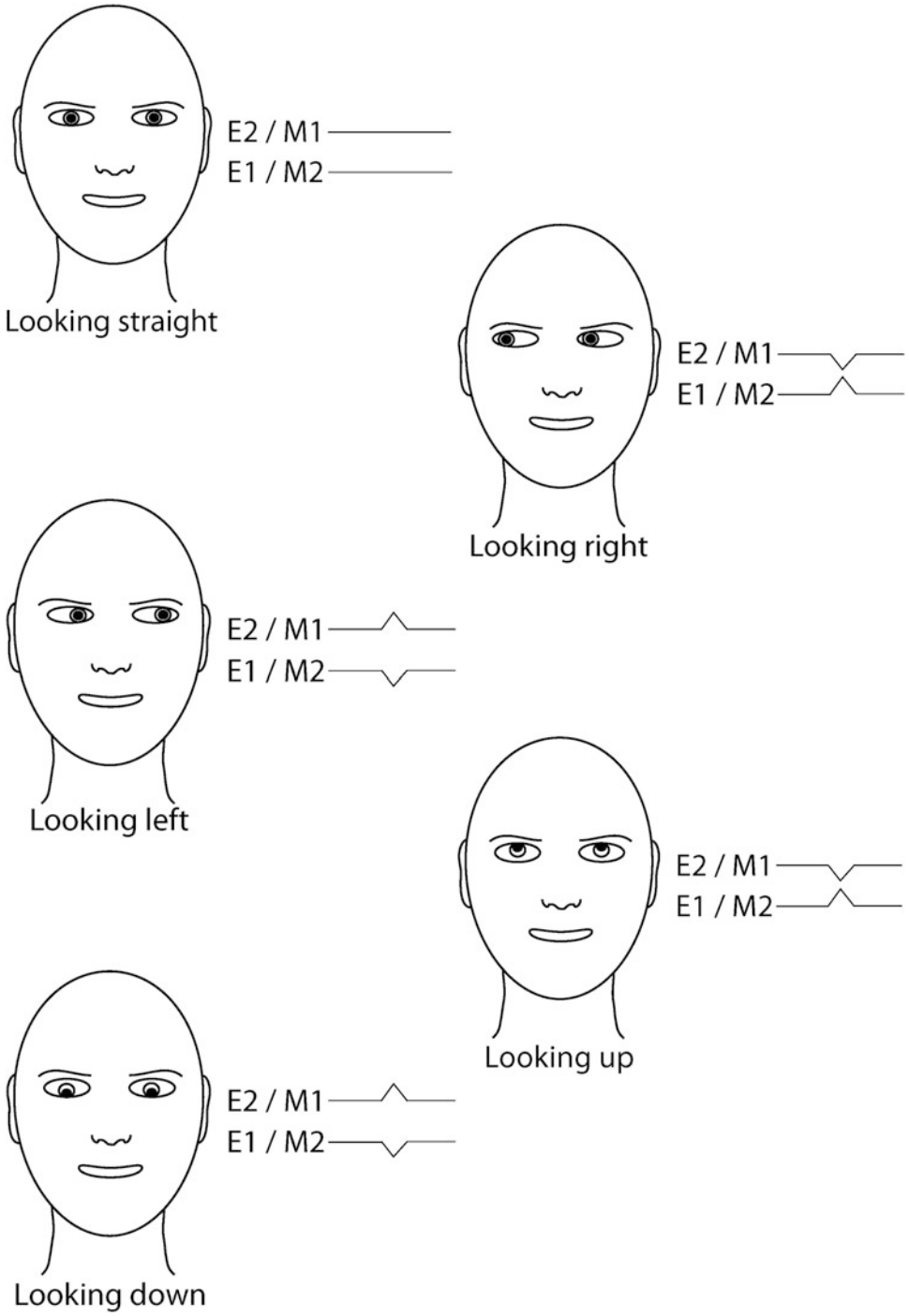

Fig. 17.5 Recording montage for a 2-channel EOG demonstrates out-of-phase deflections in the EOG tracings associated with conjugate eye movements. The deflections in the EOG tracings follow the standard EEG and PSG polarity convention (negative voltage = upward deflection; positive voltage = downward deflection)

for the first EOG channel and E1/M2 for the second. It is also important, when the patient closes his or her eyes, to observe the reactivity of the alpha rhythm seen most prominently in the occipital EEG; alpha rhythm is usually best visualized when the patient's eyes are closed.

The mentalis/submental EMG signal is checked by asking the patient to clench the jaws, grit the teeth, or yawn. The technologist documents proper functioning of the electrodes and amplifiers used to monitor anterior tibialis EMG activity by asking the patient to dorsiflex the right foot and the left foot in turn. If rapid eye movement (REM) sleep behavior disorder is suspected, additional electrodes should be applied to the surface of the skin above the extensor digitorum communis muscles of each arm. Patients are asked to extend their wrists while the technologist examines the recording for the associated increase in amplitude in the corresponding EMG channel.

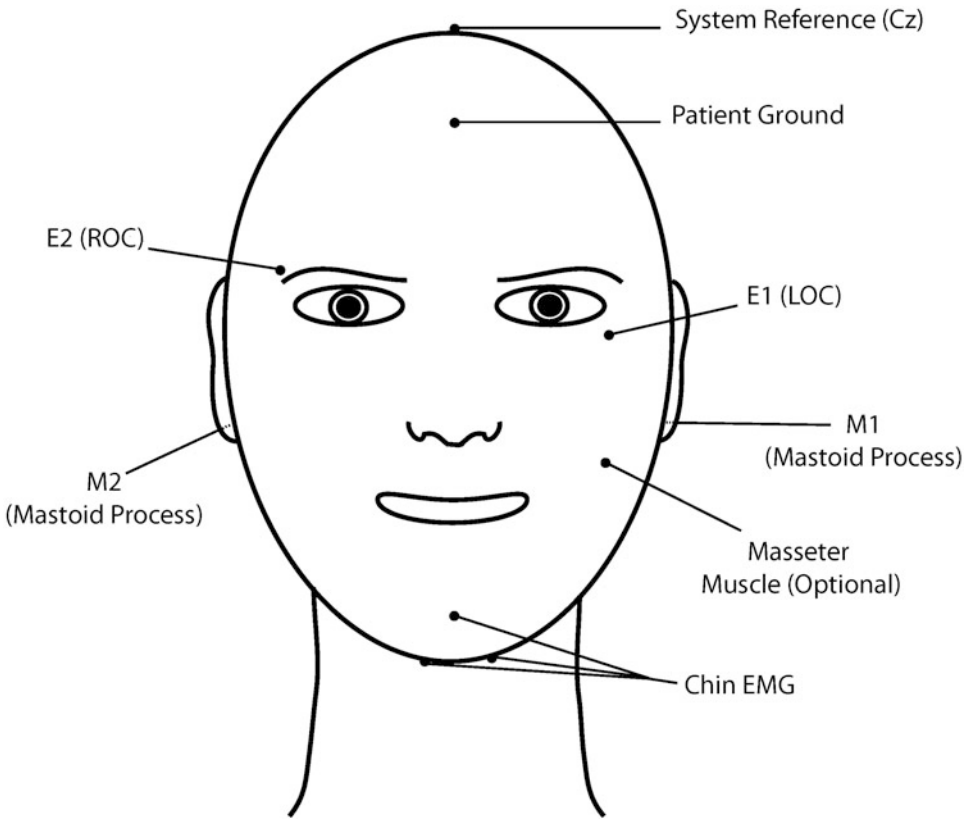

Fig. 17.6 Schematic diagram showing the placement of the EOG, chin EMG, patient ground and system reference electrodes

Inspiration and expiration allow for examination of the channels monitoring airflow and respiratory effort [33, 34]. A suggested convention is that inspiration causes an upward deflection of the signal and expiration a downward deflection. It is important that the signals in all the channels recording respiration are in phase with each other to avoid confusion with paradoxical breathing. The technologist should observe a flattening of the trace for the duration of a voluntary apnea. [Note: It is recommended to include end-tidal or transcutaneous CO_2 monitoring when studying children [35], or adult patients with underlying lung or neuromuscular diseases. The addition of CO_2 monitoring increases the sensitivity of the study of hypoventilation.

If the 50 or 60 Hz notch filter (also called "line filter" or "AC filter") is in use, a brief examination (2–4 s) of portions of the tracing with the filter in the "out" position is essential. This allows for identification of any 50 or 60 Hz interference that may be masked by the filter. Care should be taken to eliminate any source of interference and to ensure that the 50 or 60 Hz notch filter is used only as a last resort. This is most important when recording patients suspected of having seizure activity, because the notch filter attenuates the amplitude of the cortical spike activity seen in association with epileptogenic activity.

The physiologic calibrations enable the technologist to determine the quality of data before the PSG begins. If artifacts are noted during the physiologic calibrations, it is imperative that every effort be made to correct the problem, as the condition is likely to get worse through the remaining portions of the recording. The functioning of alternative backup electrodes should also be examined during this calibration. If any additional monitoring devices are used for the study, the technologist should incorporate the necessary calibrations.

When a satisfactory calibration procedure and all other aspects of patient and equipment preparation are completed, the patient is told to assume a comfortable sleeping position and to try to fall asleep. Then, the lights are turned out in the patient's room and the "lights-out" time is noted on the tracing and in the recording log.

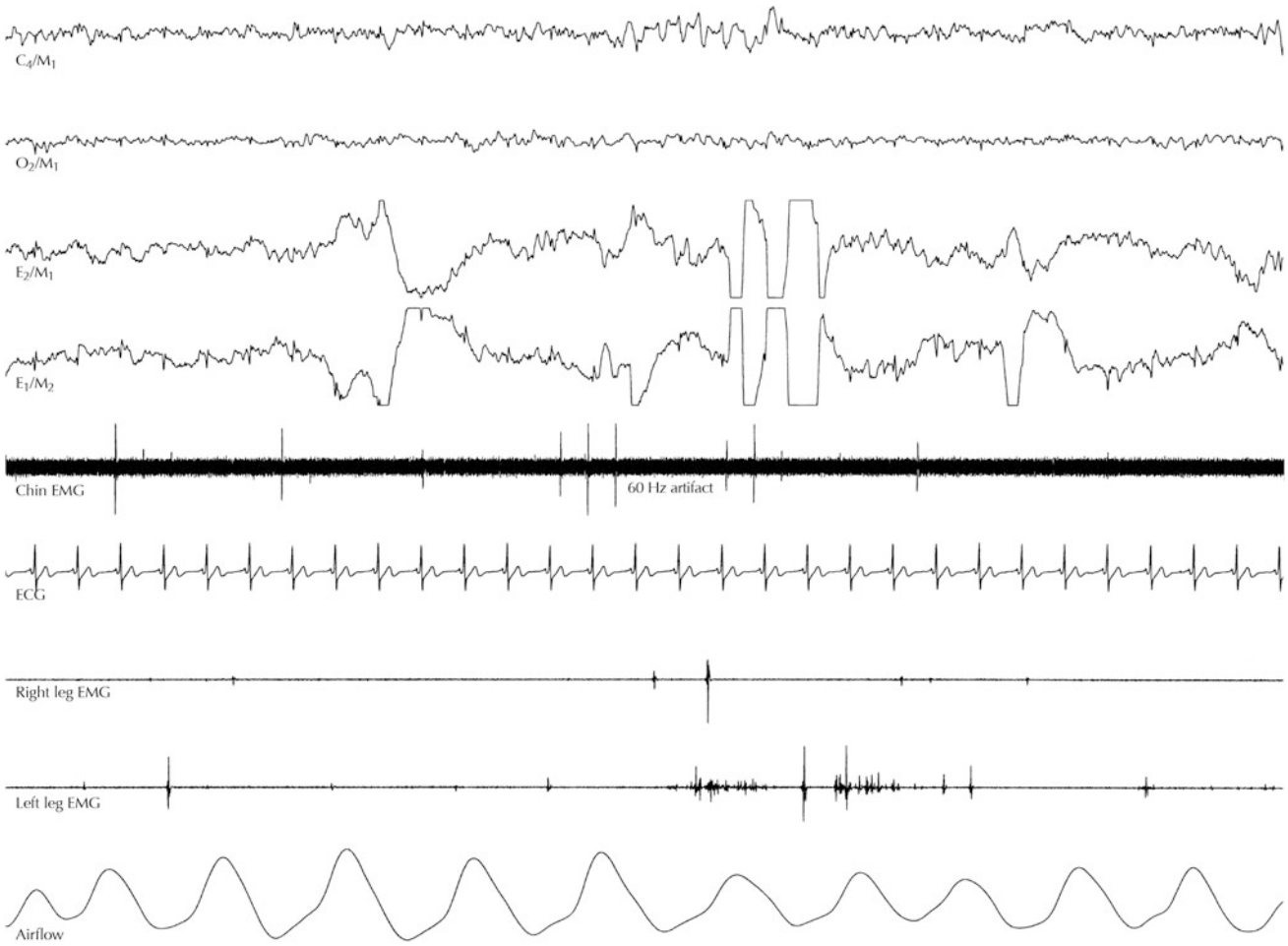

Fig. 17.7 60 Hz artifact. This is an example of 60 Hz artifact in the chin EMG channel caused by faulty electrode connection. Reprinted with permission from Butkov [23]

Monitoring and Recording

Complete documentation for the PSG is essential. This includes patient identification (patient's full name and medical record number), date of recording, and a full description of the study. The name of the technologist performing the recording, as well as those of any technologists who prepared the patient or the equipment, should be noted. In laboratories that use multiple pieces of equipment, the specific instrument used to generate the recording should be identified. This is particularly useful in the event that artifacts are noted during the analysis portion (scoring) of the sleep study.

Specific parameters recorded on each channel should be clearly identified, as should a full description of sensitivity, filter, and calibration settings for each channel. The time of the beginning and end of the recording must be recorded, as well as specific events that occurred during the night. Any changes made to filter, sensitivity, or derivation settings during the recording should be clearly noted in the study.

The technologist is also responsible for providing a clinical description of unusual events. For example, if a patient experiences an epileptic seizure during the study, the clinical manifestations of the seizure must be detailed: deviation of eyes or head to one side or the other, movement of extremities, presence of vomiting or incontinence, duration of the seizure, and postictal status. Similar information should be reported on any clinical event observed in the laboratory, such as somnambulism or clinical features of REM sleep behavior disorder. Physical complaints reported by the patient are also noteworthy. When studying patients with SRBD, documentation of snoring, wheezing, labored breathing, or other descriptive observations of the patient's breathing patterns provide essential information that can assist the reading physician in interpreting the PSG recording.

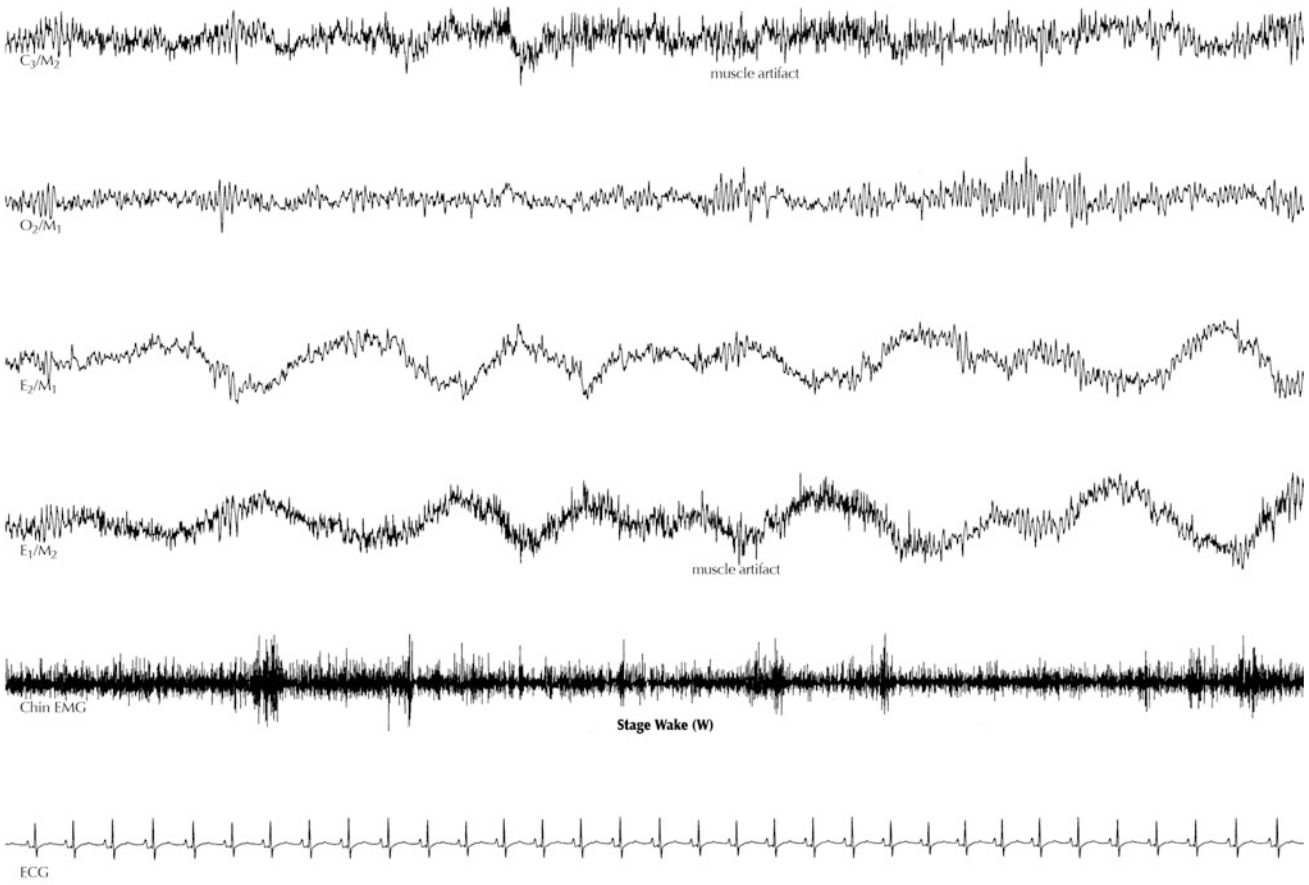

Fig. 17.8 60 Hz Artifact. This is an example of 60 Hz artifact in the chin EMG channel caused by faulty electrode connection. Reprinted with permission from Butkov [23]

Troubleshooting and Artifact Recognition

In general, when difficulties arise during recording, the troubleshooting inquiry begins with the patient and follows the path of the signal to the recording device. More often than not, the problem can be identified as a displaced or faulty electrode or sensor. It is less likely that artifact is the result of a problem with an amplifier. If the artifact is generalized (i.e., in most channels), then the integrity of the ground electrode, system reference electrode, or the cable from the electrode jack box should be checked. If the artifact is localized (i.e., in a limited number of channels), then the question should be: which channels have this artifact in common and what is common to the channels involved? The artifact is probably the result of a problem with an electrode or sensor that is common to both channels. If the artifact is isolated to a single channel, then the problem most likely stems from the specific electrode or sensor used only for that channel. In many instances, localized artifacts can be corrected by changing the derivation(s) to an alternative reference electrode, or by using alternative backup derivations.

50 or 60 Hz Artifact

50 or 60 Hz interference (Figs. 17.7 and 17.8) stems from power line frequency in the vicinity of the study.[1] As described earlier in this chapter, common mode rejection (a function of the PSG differential amplifiers) serves to eliminate 50/60 Hz artifact from the PSG recording. In addition, the patient ground electrode is used to divert stray electrical interference from the patient. The effectiveness of common mode rejection and the function of the patient ground are both dependent on the integrity of the electrode connections to the patient. Consequently, the presence of 50 or 60 Hz artifact is most often caused either by high electrode impedances (which defeat the function of common mode rejection), or by a faulty ground connection (which prevents effective diversion of electrical interference from the patient), or a combination of both. Such 50 or 60 Hz interference can also be aggravated by excessive leakage current, which can stem from any electrical equipment in the vicinity of the study.

[1] 50 Hz is used in most European and Australasian countries; 60 Hz is used in the USA, Canada, and many South American countries.

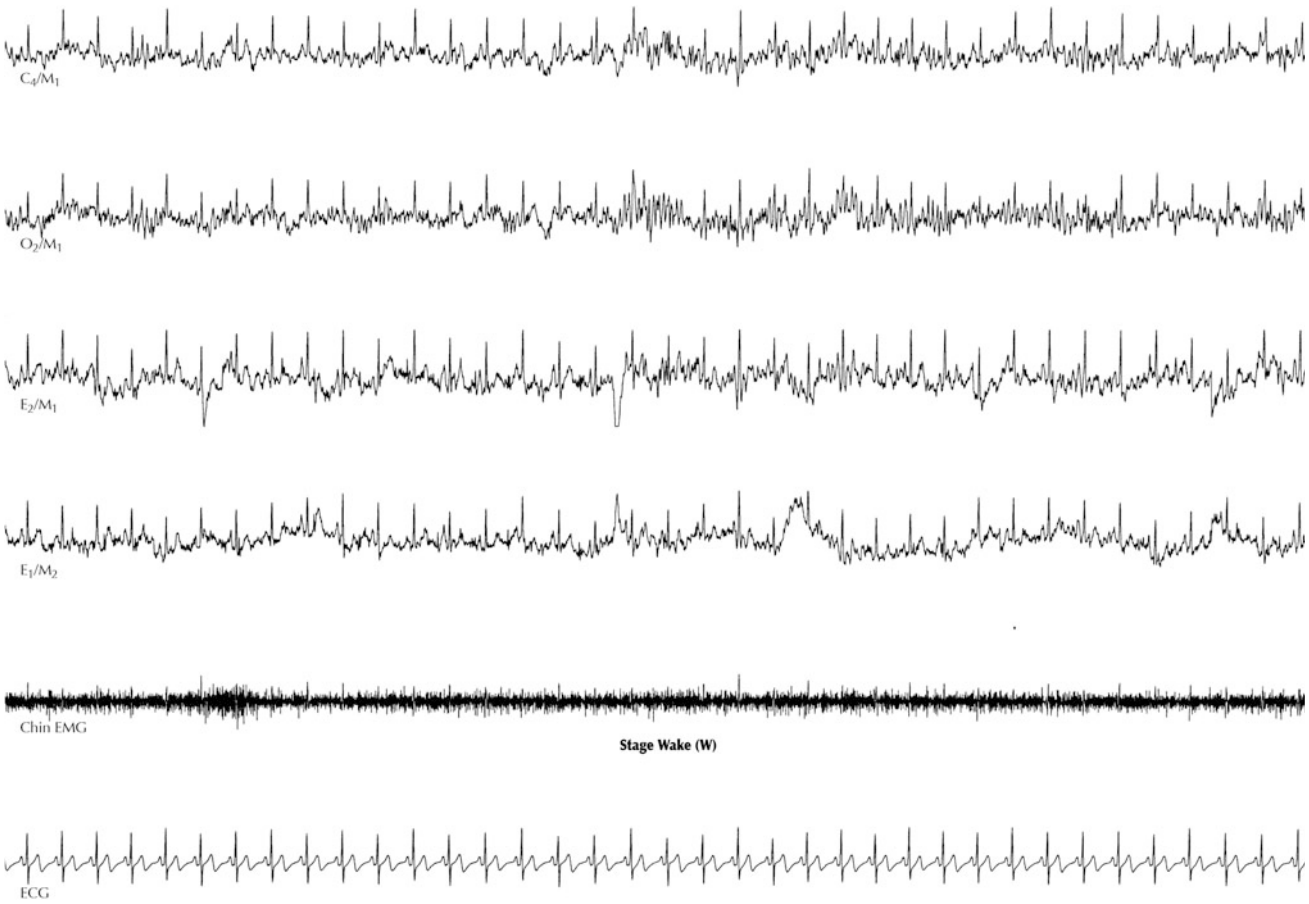

Fig. 17.9 Muscle artifact in the EEG and EOG. This is an example of muscle artifact appearing in the C3/M2 and E1/M2 channels. Because the artifact is identical in both channels sharing the same reference, it is evident that the artifact originates form the M2 electrode. Reprinted with permission from Butkov [23]

It is not recommended to routinely use 50/60 Hz filters to eliminate power line frequency interference, because this only serves to cover up potential problems with the recording and in some instances may attenuate important physiologic data, such as seizure spikes in the EEG. An exception to this is leg EMG recordings, which may require the use of 50/60 Hz filters due to the extended length of the electrode leads, and because in some instances it may be difficult to obtain optimal impedance levels in the leg EMG due to skin conditions or concerns over excessive skin scrubbing. It is recommended that PSG recording systems provide individual channel-by-channel 50/60 Hz filters, so they can be applied only to those channels where needed.

The best insurance against 50 or 60 Hz artifact is to pay close attention to the integrity of the electrode connections to the patient. If problems with 50 or 60 Hz artifacts persist, the laboratory environment should be checked for sources of excessive electrical interference. A common source of interference can be an electric bed, which may need to be unplugged during the study to prevent problems with the recording.

Muscle Artifact

Muscle artifact appearing in the EEG and EOG (Fig. 17.9) can be expected whenever the patient moves or tenses the scalp or facial muscles. Muscle artifact is sometimes confused with 50 or 60 Hz, because both are high-frequency artifacts. Unlike 50/60 Hz, which is uniform in appearance, muscle artifact is irregular and tends to wax and wane with increased or decreased muscle tension. Excessive muscle artifact can be caused by placing the mastoid reference electrodes (M1 and M2) too low or too far from the ear flap (pinna), in close proximity to the muscles of the neck. Repositioning the mastoid electrode to a firm bony area close to the pinna can often help minimize the problem.

ECG Artifact

The presence of ECG artifacts in the EEG and/or EOG channels is common, due to the relatively long inter-electrode distances used in PSG recordings. However, excessive ECG artifacts (Fig. 17.10) can be caused by high electrode impedances in the EEG and EOG channels, or by placing the mastoid reference electrodes (M1 and M2) too low or too far

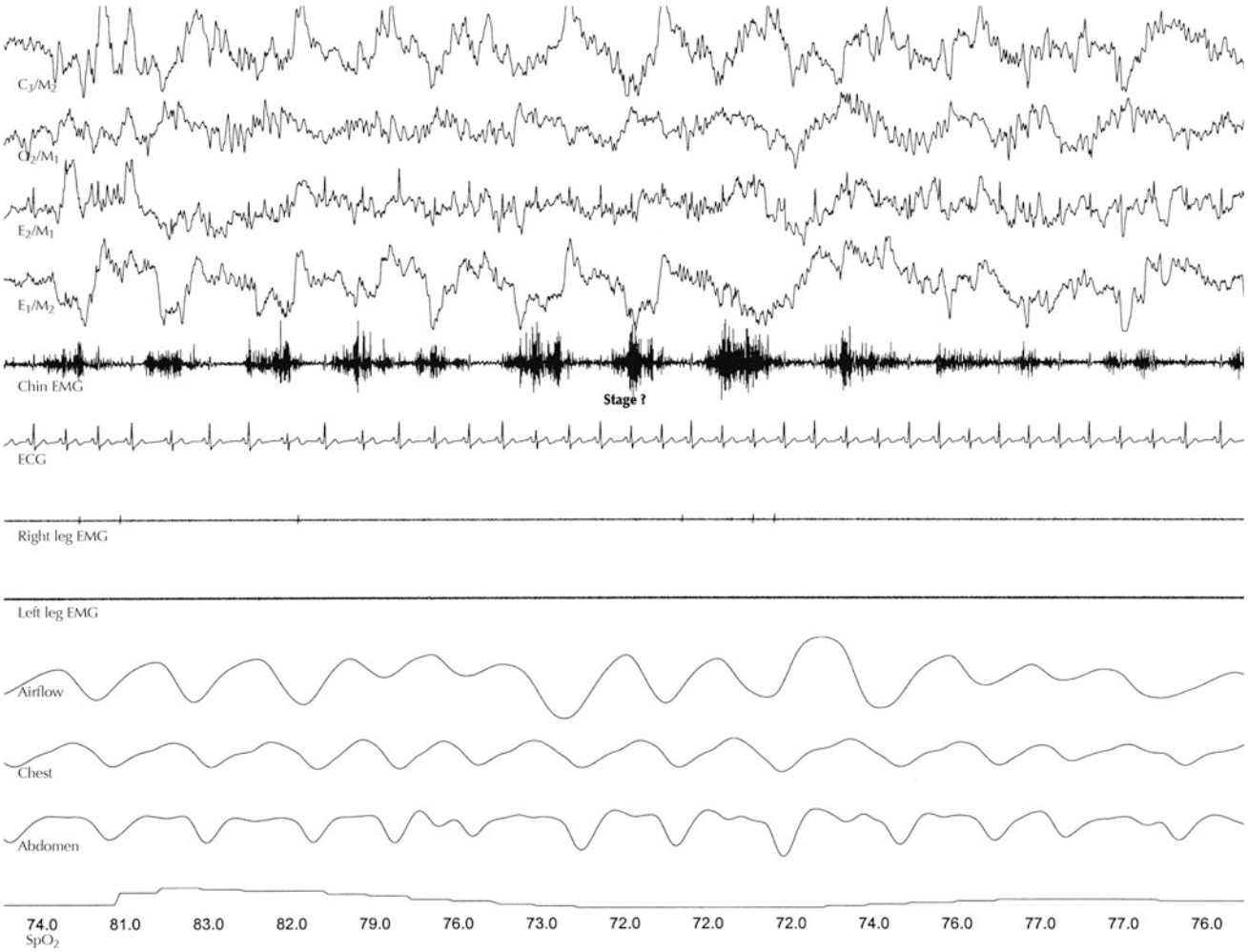

Fig. 17.10 ECG artifact in the EEG and EOG. This is an example of excessive ECG artifact in the EEG and EOG channels. Although small amounts of ECG artifact are sometimes unavoidable, ECG artifacts can be exacerbated by impedance imbalances between the EEG and EOG electrode connections, or by poor placement of the mastoid reference electrode. Reprinted with permission from Butkov [23]

from the pinna. As mentioned above, the reference electrodes are best positioned over a firm bony area close to the pinna, away from muscle or fatty tissue of the neck.

ECG artifact can also be minimized or corrected by combining M1 and M2 as a dual reference. However, this should not be used as routine practice, because it can attenuate the EEG, and because any other form of interference stemming from either of the mastoid reference electrodes can subsequently affect all of the multi-referenced channels.

Slow Frequency Artifacts

Slow frequency artifacts in the EEG or EOG (Fig. 17.11) are most often caused by perspiration or by direct pressure against an electrode. Perspiration induces chemical changes in the electrolyte interface between the electrode and the patient's skin, causing the appearance of slow-oscillating waves in the EEG or EOG, commonly described as "sweat artifact." A similar pattern, although more pronounced and abrupt, can be caused by intermittent pressure against an electrode or by tugging an electrode lead. This is commonly described as "popping artifact." Popping artifact can also be caused by dirty or faulty electrodes, or by electrodes that are loosely attached to the skin.

Both sweat and popping artifacts can be exacerbated by patient movement. Often, these slow frequency artifacts coincide with the patient's respiratory patterns, most likely caused by the slight head movements associated with breathing. Slow frequency artifacts that appear synchronous with breathing are often labeled as "respiration artifacts"; however, this term may be misleading, because the source of the artifact is not respiration, but rather a combination of chemical and mechanical instability of the EEG and EOG electrode–patient interface.

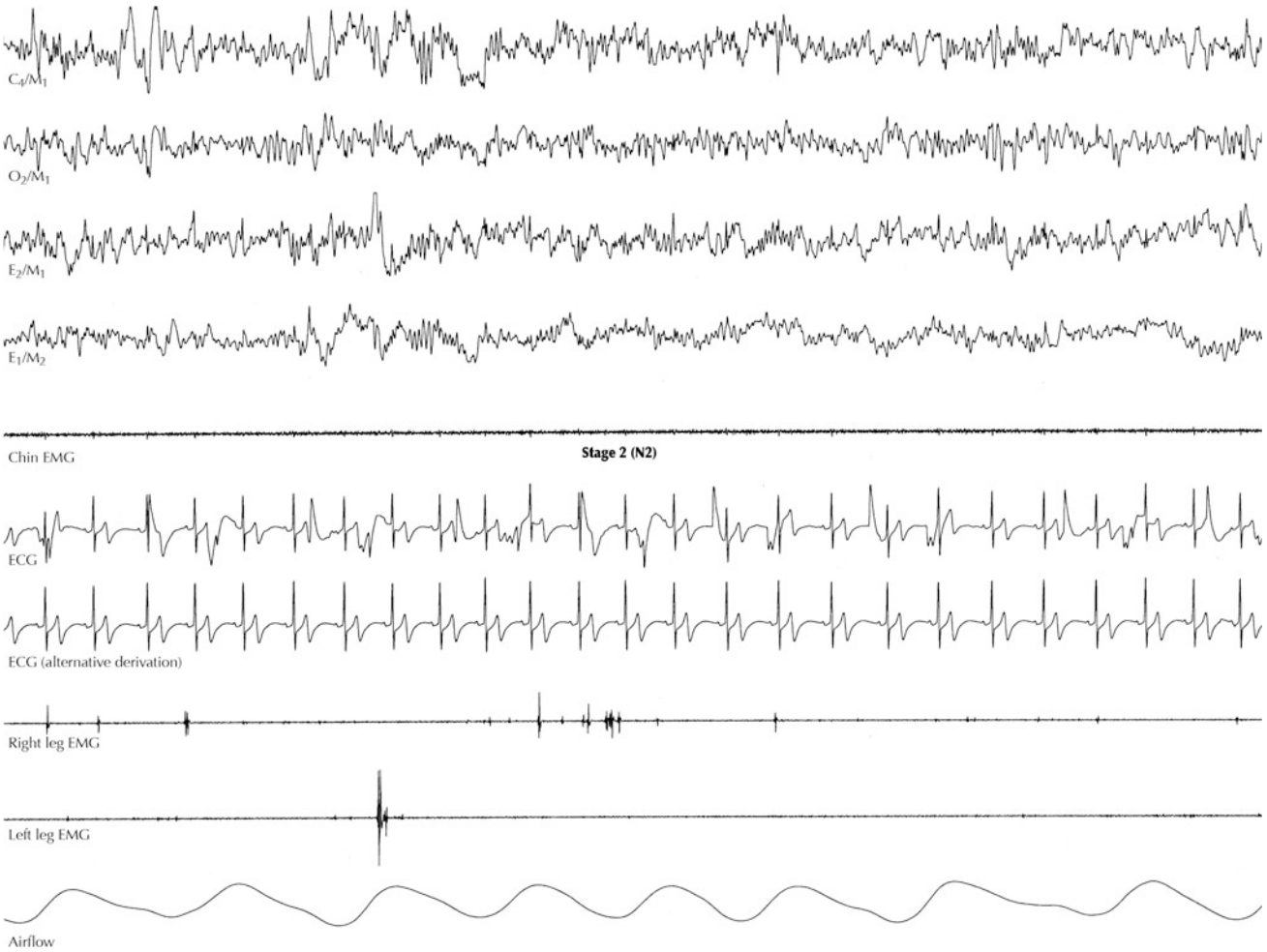

Fig. 17.11 Slow frequency artifacts in the EEG and EOG. The slow frequency artifacts in this example are most likely caused by a combination of sweat and slight rhythmic head motion associated with breathing. The artifacts are limited to the C3/M2 and E1/M2 channels. They are identified by their exaggerated appearance and by lack of correlation with the O2/M1 and E2/M1 derivations. These artifacts can be corrected by changing the affected derivations to C4/M1 and E1/M1. Note also the pattern of "snoring artifact" in the chin EMG channel, which is actually useful for confirming that the patient snores. Reprinted with permission from Butkov [23]

Slow frequency artifacts can be minimized by practicing proper electrode application technique. It is important to make sure that all electrodes are well adhered, with a tight seal between the electrode and the patient's skin. This prevents the electrodes from "floating" over the electrode sites, which can cause signal disruption from even the slightest movement. It is equally important not to spread conductive substances (including skin prepping materials) beyond the boundary of the electrode cup when preparing the electrode site and when applying the electrodes. Additionally, slow frequency artifacts that are caused by perspiration can be reduced by cooling the patient with a fan or air-conditioning.

Artifacts in the ECG Channel

Although ECG voltages are considerably higher than EEG, EOG, or EMG voltages, tracings derived from ECG electrodes can be equally susceptible to artifacts caused by high electrode impedances, faulty connections, pressure against an electrode, sweat, or patient movement. In some instances, artifacts in the ECG can resemble ectopic beats or missed beats. To avoid misinterpreting the ECG, it is useful to compare any questionable tracings to alternative ECG derivations. If the recording equipment provides system referencing, an alternative ECG signal can be obtained from any two electrodes that are sufficiently distant from each other, such as the C4 electrode referenced to one of the left leg electrodes (Fig. 17.12).

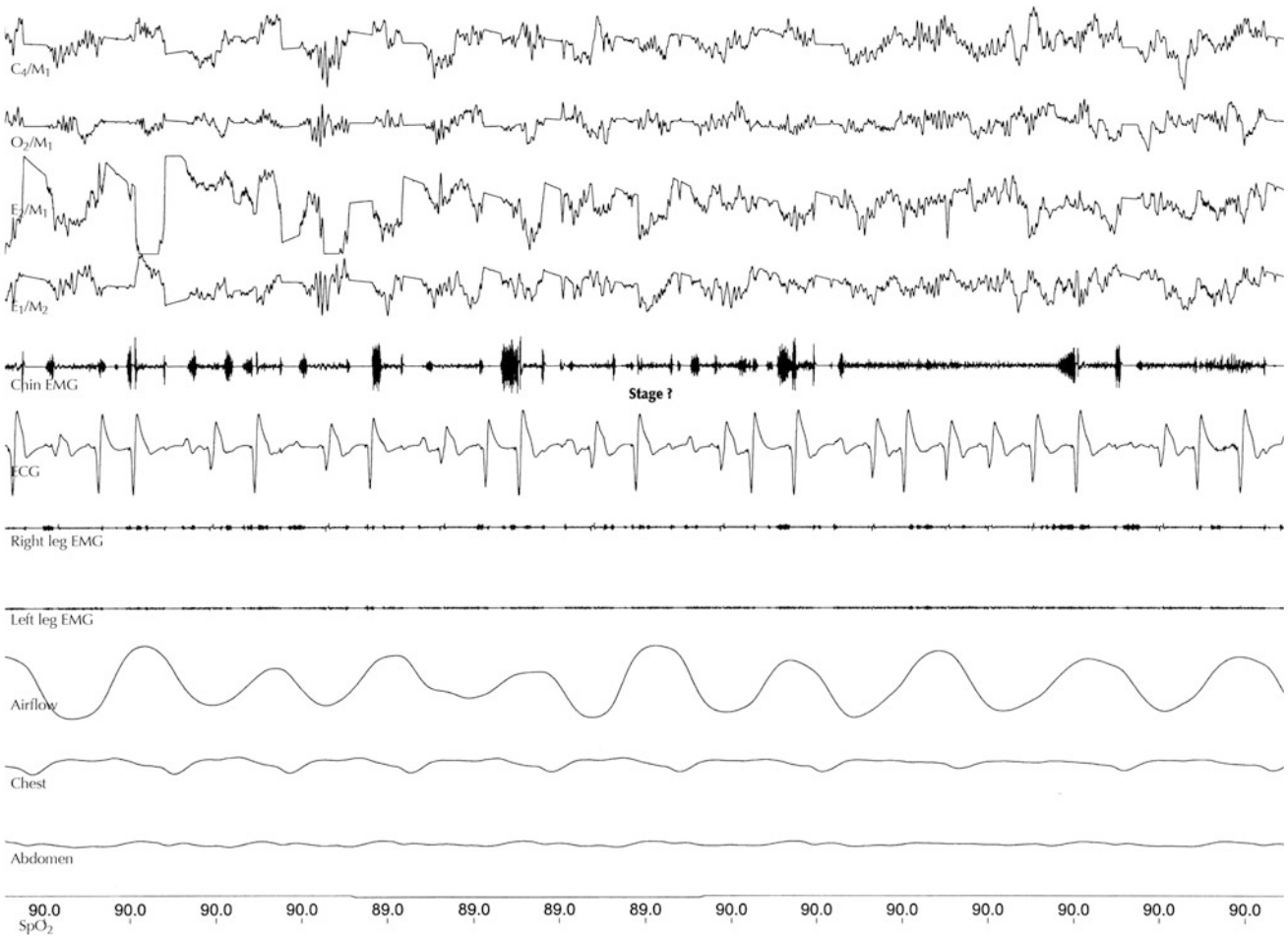

Fig. 17.12 Artifacts in an ECG channel. In this example, the primary ECG channel is distorted with artifact. An alternative ECG derivation has been added to the recording and demonstrates a normal sinus rhythm. The alternative derivation was obtained by referencing an ECG electrode to one of the left leg electrodes. Reprinted with permission from Butkov [23]

Artifacts Caused by a Faulty System Reference

If the PSG recording provides system referencing, it is essential to make certain that the integrity of the system reference electrode is maintained throughout the duration of the study. If the system reference electrode becomes detached, or the signal is degraded, all of the channels relying on the system reference will become affected (Fig. 17.13). Operators of equipment that relies on system referencing must pay close attention to the recording and be able to identify and correct problems with the system reference electrode if they occur.

Artifacts in the Respiratory and Oximetry Channels

For practical reasons, most forms of respiratory monitoring during sleep rely on sensors that provide non-quantitative, indirect representations of respiratory airflow and effort. As such, these representations are often imprecise and subject to many forms of signal distortion. In some instances, artifacts in the respiratory channels can resemble physiologic respiratory events. It is important for those who read the PSG data to be aware of the characteristics and limitations of respiratory sensors and interpret the study accordingly. An advantage of multi-channel PSG recordings is that all

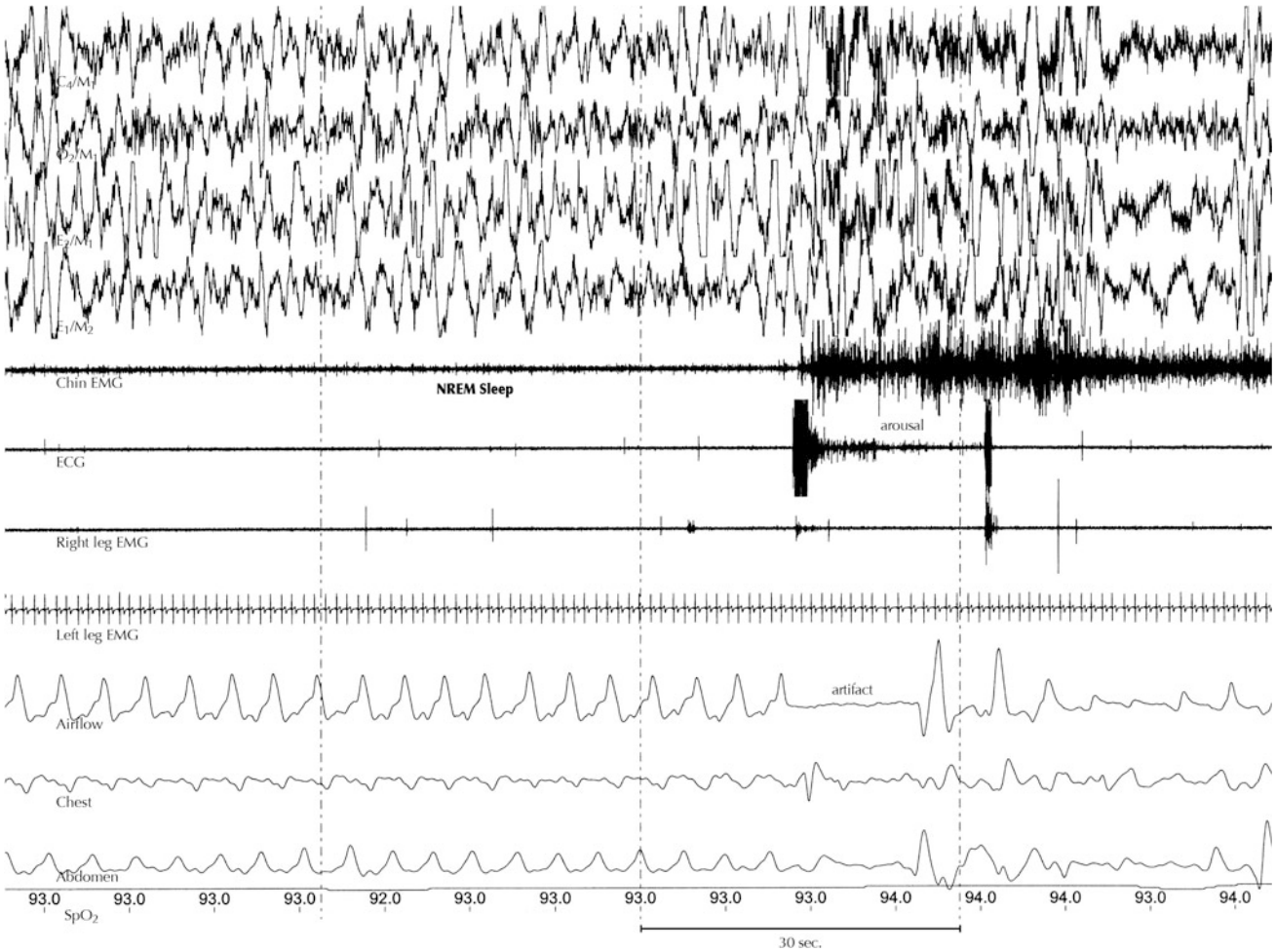

Fig. 17.13 Artifacts originating from the system reference electrode. In this example, a faulty system electrode connection is causing artifacts to appear in all of the channels that are linked to the system reference. Reprinted with permission from Butkov [23]

respiratory data can be evaluated within the context of sleep and wake physiology, thereby helping the reader confirm or refute the validity or etiology of any suspected event (Fig. 17.14).

It is equally important to carefully examine the oximetry tracing and identify any potentially erroneous data. Faulty oximetry tracings can be caused by probe displacement, by over-tightening the probe on a patient's finger, by poor perfusion, by motion artifact, or by placing a probe over painted or artificial nails. Any questionable oximetry data should be flagged, to prevent erroneous interpretation. This especially applies to unattended oximetry recordings, as used with HSAT or overnight oximetry screening (Fig. 17.15).

Using Filters to Correct Artifacts

Changing a filter setting to correct an artifact should always be a last resort. Filters should not be relied upon to "clean up" a poor quality study. However, there are some instances when changing a filter setting can be useful; for example, when attempting to score or read a PSG study with excessive slow-wave artifacts in the EEG or EOG. Unlike analog filters of the past that were limited to only a few specific settings, contemporary digital filters available on some of the more advanced equipment can be configured to virtually any setting. Thus, the reader of the study can choose to make minor filter adjustments, enough to minimize the artifact, yet preserve most of the physiologic data. For example, if slow

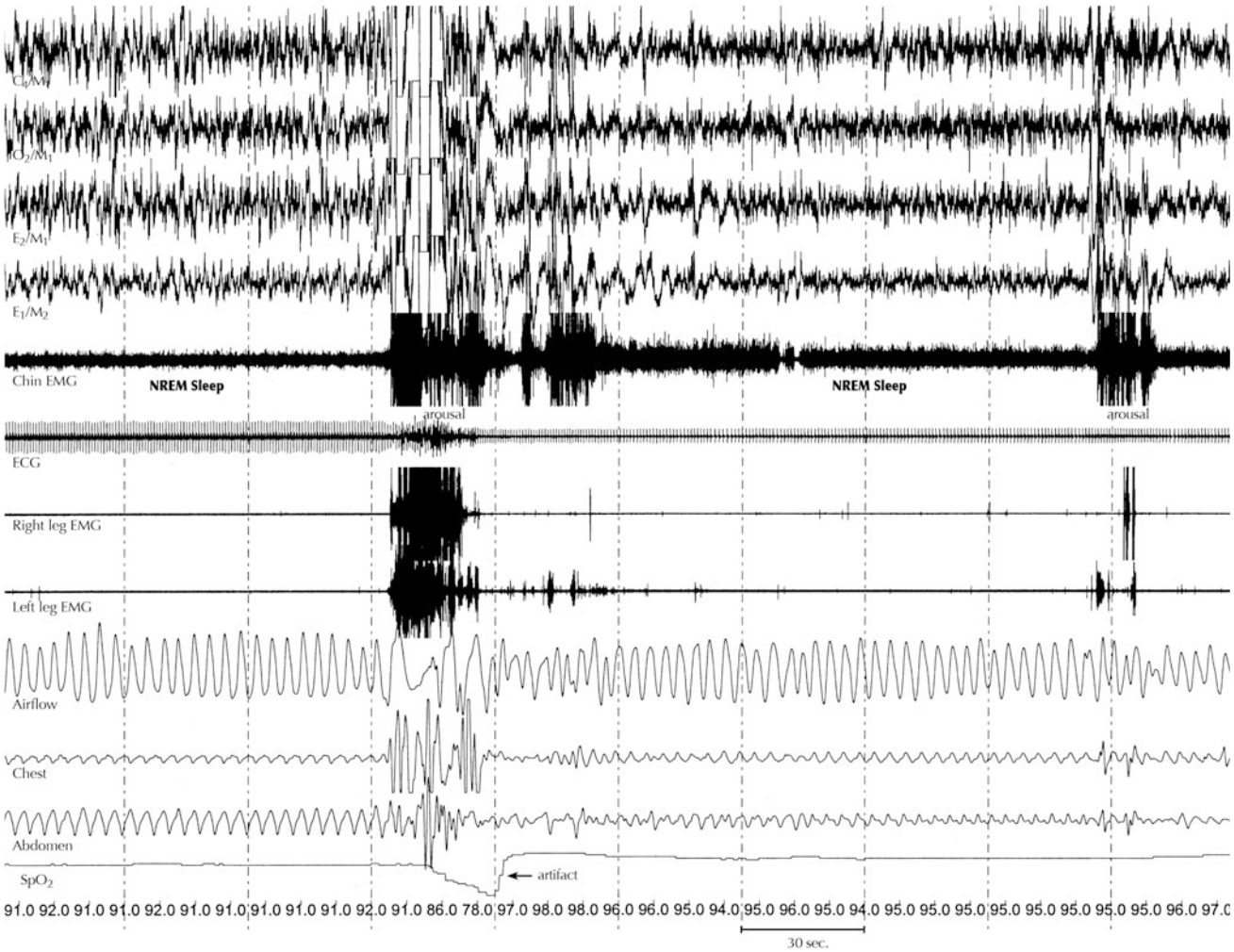

Fig. 17.14 Artifact in the airflow channel resembling an apnea. By examining the respiratory channels within the context of the patient's sleep and wake physiology (as documented by the top channels), it is evident that the apparent "absence of airflow" is actually an artifact caused by patient movement during an arousal. The flattening of the airflow signal may have been caused by the patient's mouth dropping open, or by a dislodged airflow sensor. Note the continued attenuation of the airflow signal following the arousal. This is an example of an artifact that could be erroneously scored as an apneic event. Reprinted with permission from Butkov [23]

artifacts in the EEG are a problem, the low-frequency filter can be adjusted from 0.3 to 0.5 or 0.6 Hz (instead of changing the filter to 1 Hz, which was common practice in the past). This reduces the slow-wave artifacts to a more manageable level, without overly attenuating slow-wave EEG activity (although some attenuation of the EEG can still be expected with *any* increase in the low-frequency filter setting).

As noted before, the best way to minimize recording artifacts and reduce the need for excessive post-collection data manipulation (which can significantly alter the data) is

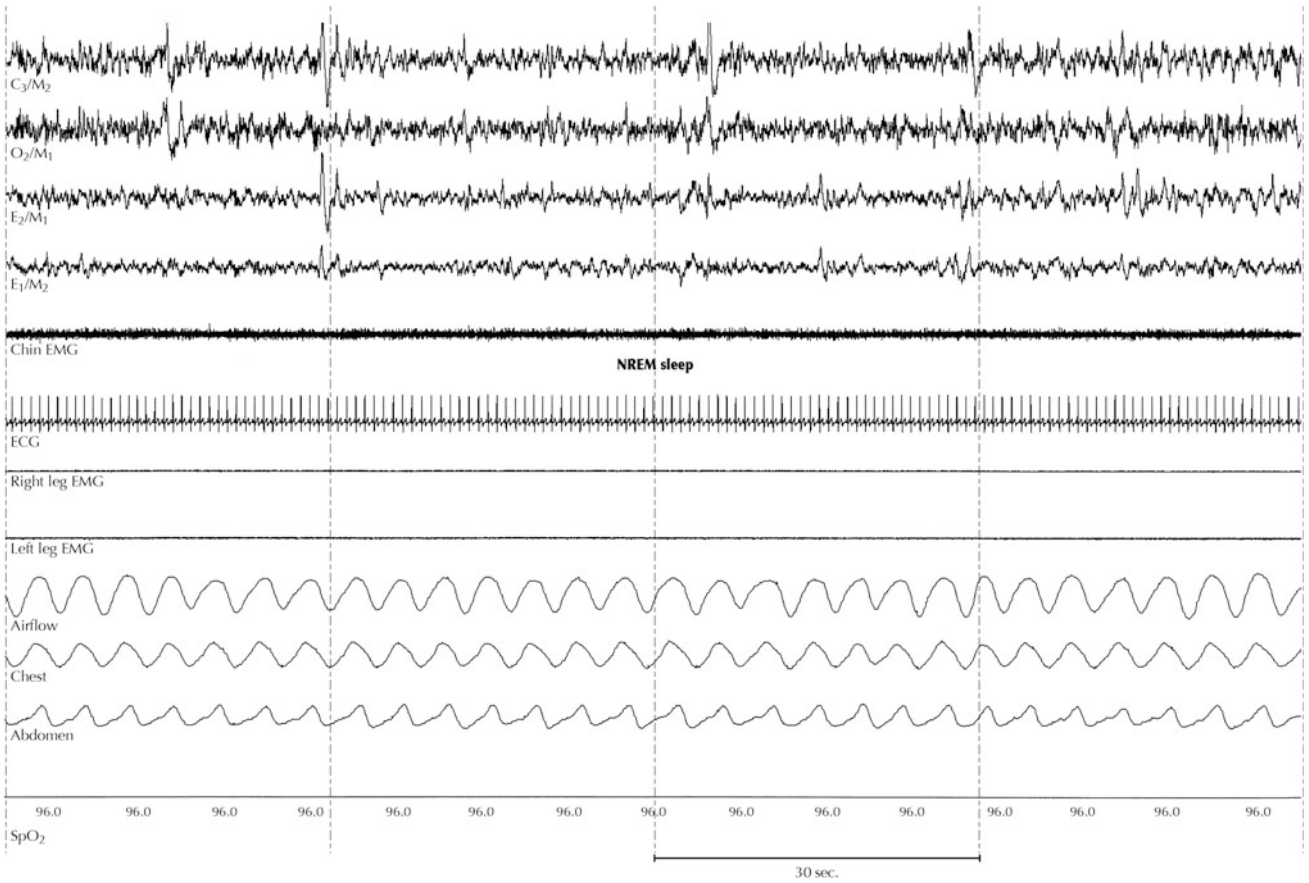

Fig. 17.15 Artifact in the oximetry channel. Artifacts in the oximetry channel are common and may be caused by a number of factors including patient movement or sensor displacement. It is important to identify and delete these artifacts during the scoring and interpretation process, to prevent false oximetry data from appearing on the final report. Reprinted with permission from Butkov [23]

to pay close attention to the quality of the electrode and sensor application.

Ending the Study

Often, clinical circumstances and laboratory protocols dictate whether the patient is awakened at a specific time or allowed to awaken spontaneously. Ideally patients should be allowed to sleep for the duration of their normal sleep period, and any deviation from their normal sleep patterns should be clearly noted. After awakening at the end of the study, the patient should be asked to perform the physiologic calibrations to ensure that the electrodes and other monitoring devices are still functioning properly.

A subjective evaluation is made by the patient. The patient is asked to estimate how long it took to fall asleep, the amount of time spent asleep, and whether there were any

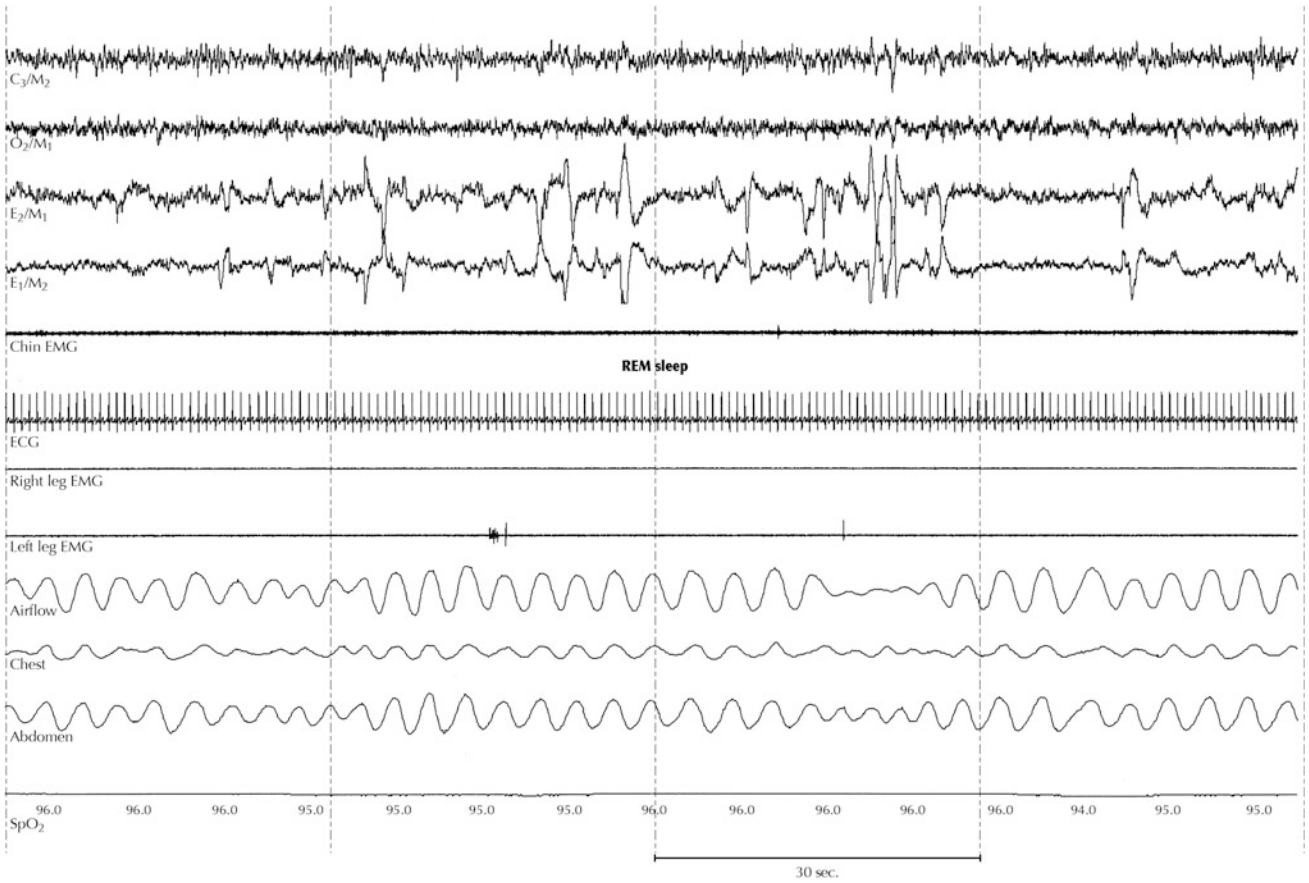

Fig. 17.16 PSG recording sample of non-rapid eye movement (NREM) sleep using time-scale compression. This sample and the samples shown in Figs. 17.17, 17.8, and 17.19 have been compressed to accommodate 4 epochs of data (2 min) to a page. This type of display offers the scorer or interpreter a general overview of the sleep recording, as well as a practical method of counting any prominent sleep-related events such as obstructive apneas, hypopneas, or body movements. The resolution of the EEG data is inadequate, however, for precise EEG evaluation or sleep-stage scoring. This sample shows a normal respiratory pattern during NREM sleep, without any apparent evidence of arousal, movement, or other form of sleep disturbance. Reprinted with permission from Butkov [23]

disruptions during the sleep period. Patients should also report on quality of their sleep and level of alertness upon arousal.

For patient safety, a plan needs to be made for patients leaving the laboratory after a study. A patient who has a severe sleep disorder should avoid driving. An arranged ride or public transportation should be used, particularly if the patient has withdrawn from stimulant medications for the purpose of the study, or was using a pharmaceutical sleeping aid during the study.

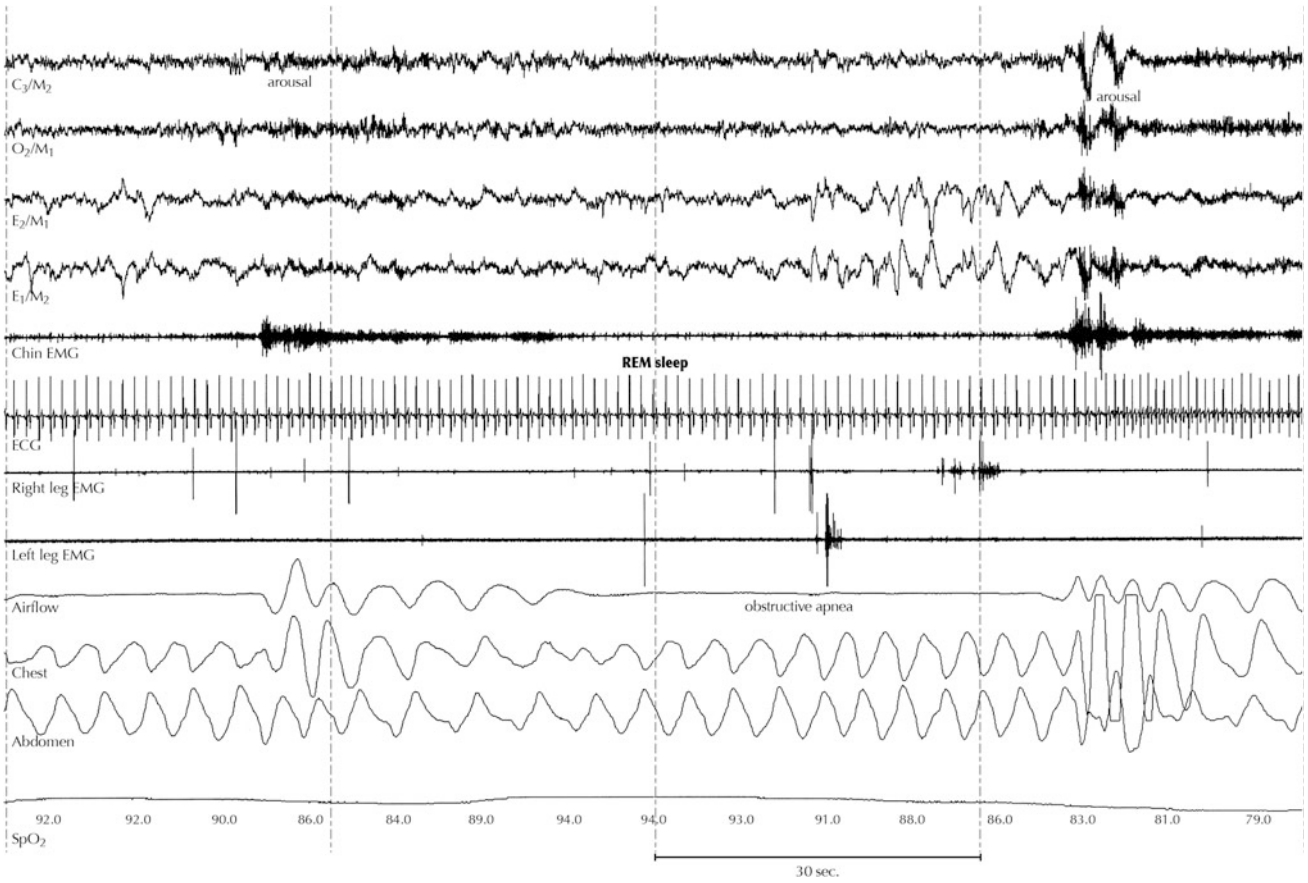

Fig. 17.17 PSG recording sample of REM sleep. Although altered by time-scale compression, the sleep-stage pattern can readily be identified as REM. Note the mild respiratory irregularity, which is a normal variant of REM sleep physiology. Reprinted with permission from Butkov [23]

Perspective on Polysomnography

Technical advances and increases in clinical knowledge provide great potential for our ability to monitor physiologic changes in our quest to understand sleep and its disorders. The *Atlas of Sleep Medicine* [36] provides an excellent review of PSG and hypnogram analysis. Specialized techniques, including pulse transit time, peripheral arterial tonometry, and cyclic alternating patterns, are illustrated and discussed. Special attention is given to motor disorders, sleep and epilepsy, and a variety of other neurologic disorders. A number of other atlases of PSG data have been published [23, 37–42] expanding the knowledge of PSG, normal sleep, and sleep disorders. Access to PSG recording samples is especially helpful for those who wish to expand their scoring and reading skills. Some examples of diagnostic PSG recordings are shown in Figs. 17.16, 17.7, 17.18, 17.19 and 17.20 [23]. Figure 17.21 is an additional (see also Chap. 18) suggested montage for patients with suspected seizure disorder.

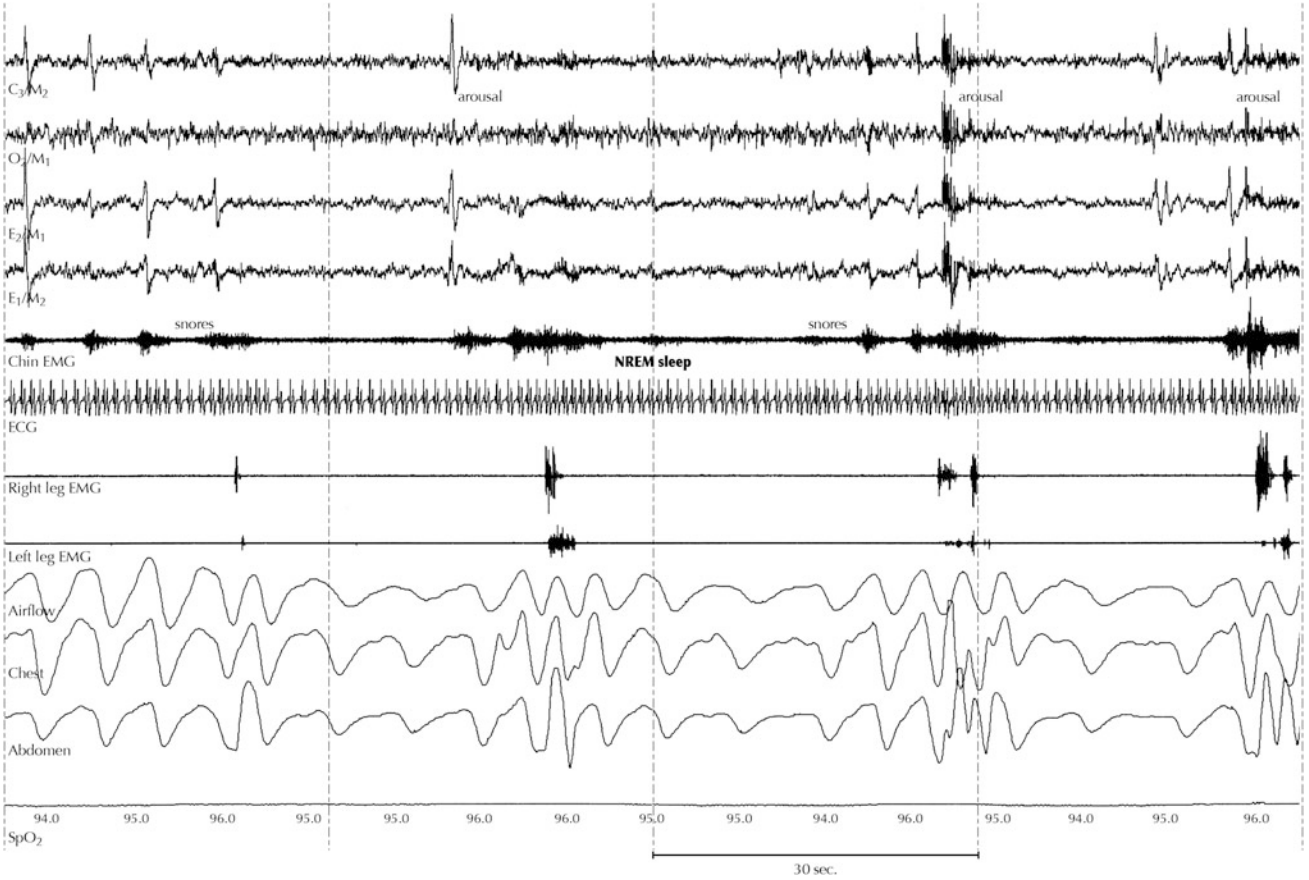

Fig. 17.18 PSG recording sample showing repetitive obstructive apneas occurring during REM sleep. In this example, all the features of classic obstructive sleep apnea are present, including distinct paradoxical (out-of-phase) respiratory effort, instances of complete cessation of airflow, subsequent EEG arousals, and cyclic oxygen desaturations. Reprinted with permission from Butkov [23]

Also recently published is an excellent review of the critical differences between children and adults [35] who have SRBD and restless legs syndrome. It is imperative that we identify sleep disorders as early as possible in order to prevent needless suffering. In order to achieve this goal, it is crucial for clinicians and technologists to understand that the clinical presentation of sleep disorders may be different in children than in adults. For example, as mentioned

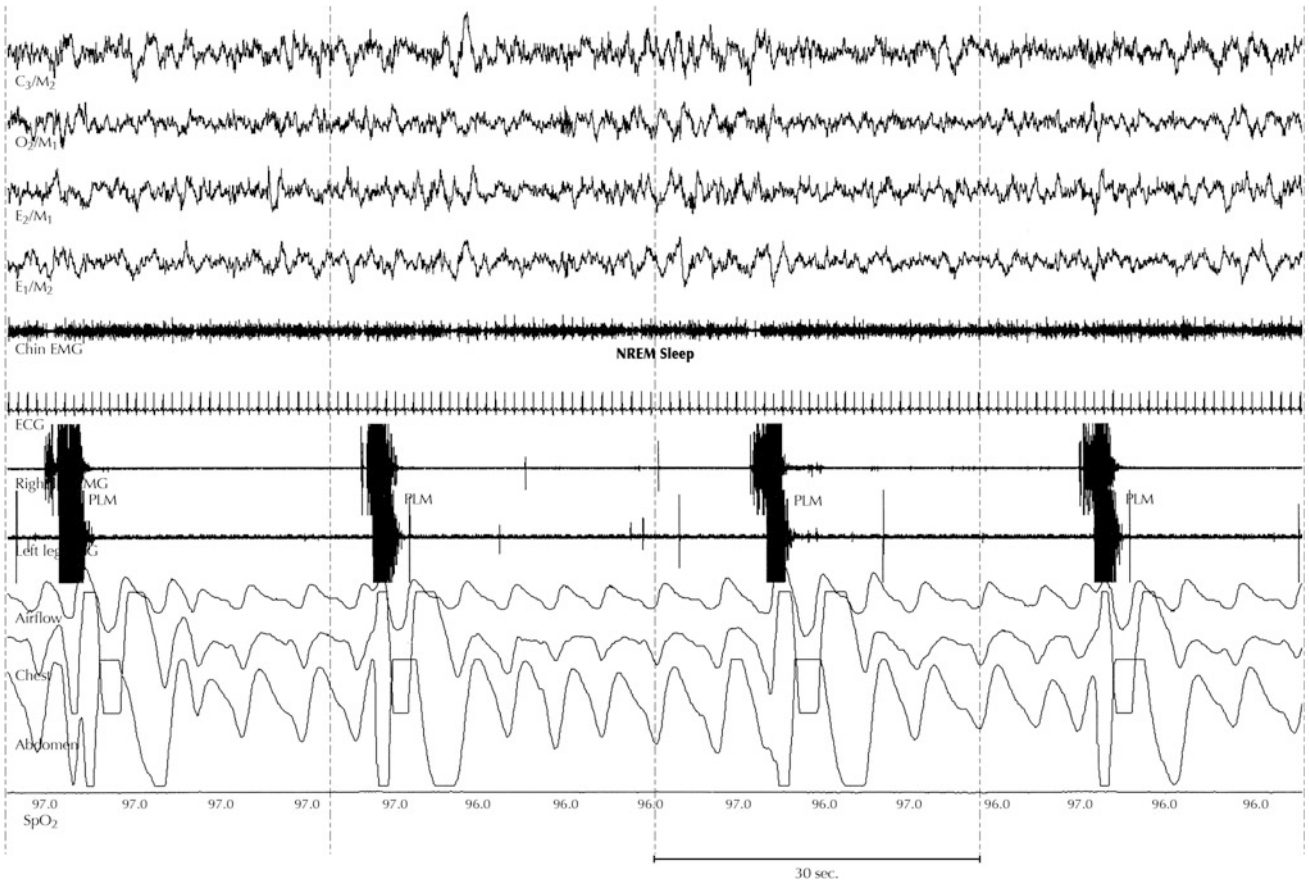

Fig. 17.19 PSG recording sample showing cyclic obstructive hypopneas with minimal O2 desaturation. This example demonstrates a pattern of cyclic obstructive hypopneas, as evidenced by the respiratory tracings in conjunction with snoring artifacts in the chin EMG and arousals occurring at the end of each event. Although these events appear quite obvious, they do not meet current reimbursement criteria for treatment due to lack of sufficient O2 desaturation. Reprinted with permission from Butkov [23]

previously, it is important to record CO_2 changes in children as they may show retention of CO_2 more commonly than dramatic changes in arterial O_2 saturation (as compared to adults with SRBD).

Throughout its evolution, PSG has proven a robust tool for enhancing our understanding of sleep and its disorders. It is an essential diagnostic procedure. Increased public awareness of sleep disorders as a major public health concern will drive the need for diagnosis and treatment. We must be effective and efficient in providing the highest quality of patient care. It is well recognized that questionnaires [43] have proven to be excellent tools in

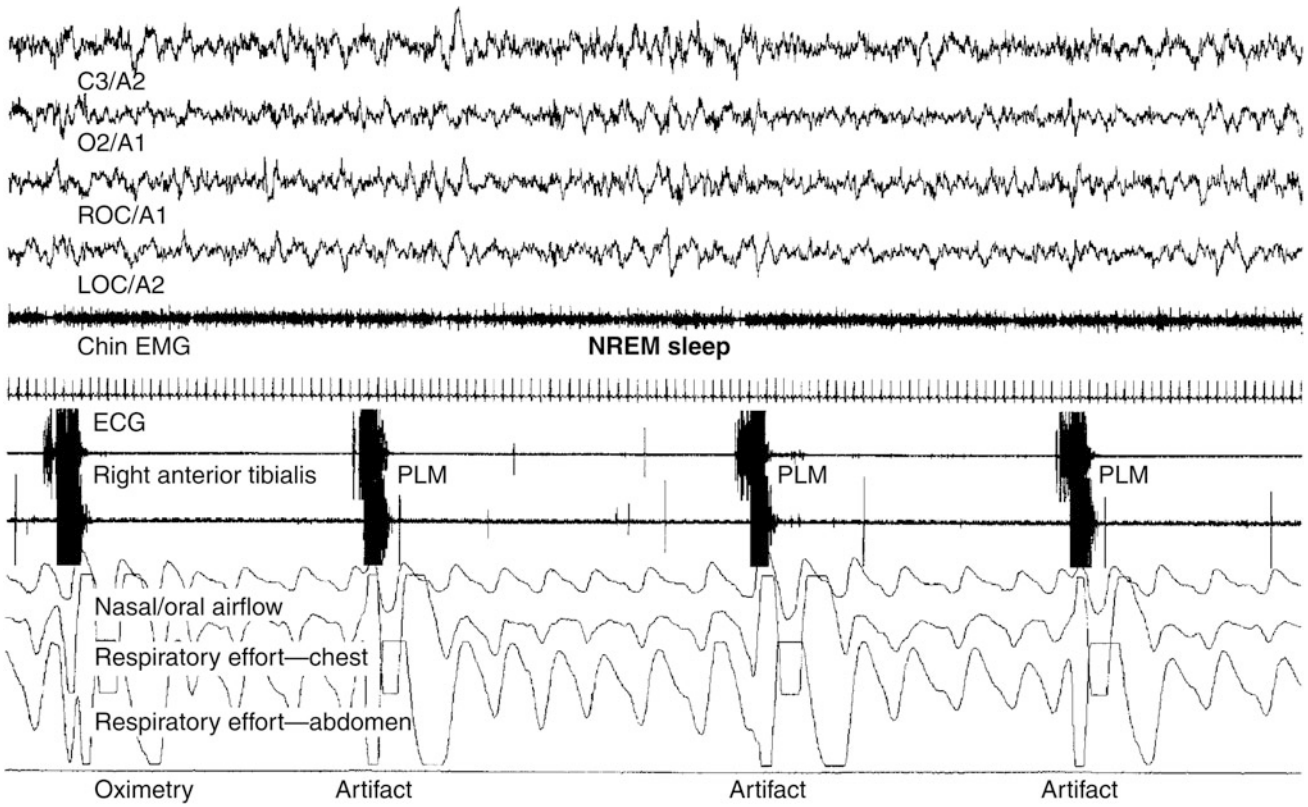

Fig. 17.20 PSG recording sample of periodic limb movements, with artifacts in the respiratory channels that appear similar to cyclic hypopneas. This sample shows a compressed version of the characteristic pattern of periodic limb movements (*PLMs*), recorded by the right and left anterior tibialis EMG. Significant leg and body movements can potentially generate artifacts in the respiratory channels that resemble respiratory events. Note that the pattern of artifact appears similar to the cyclic hypopneas seen in Fig. 17.19. Reprinted with permission from Butkov [23]

helping to triage patients in need of further evaluation. PSG remains the "gold standard" for diagnosis when indicated.

PSG is complex and labor intensive. It requires specialized technical skills and knowledge of normal sleep and sleep disorders. Technologists need to be experts with equipment, competent in dealing with medically ill patients, and capable of dealing with emergencies that may be encountered. The establishment of accredited training programs, standardized board certification requirements, and state licensure are tangible signs of the growth and development of the field of PSG technology.

It is our responsibility to millions of patients awaiting optimal sleep health care to demand that all studies performed during sleep meet the highest standards of practice. With this commitment, we maximize our ability to facilitate improved patient health outcomes for all those suffering from sleep disorders.

Appendix 17.1: Template for 24-h Sleep–Wake Log

This log should be completed by the patient for a period of 2 weeks prior to the study.

For each hour of the day:

indicate sleep or wake time with an (*X*) in the appropriate box(es)
indicate naps with an (*N*) in the appropriate box(es)
indicate periods of extreme sleepiness with an (*S*) in the appropriate box(es)

Date			Date			Date		
Time	Awake	Asleep	Time	Awake	Asleep	Time	Awake	Asleep
12:00			12:00			12:00		
13:00			13:00			13:00		
14:00			14:00			14:00		
15:00			15:00			15:00		
16:00			16:00			16:00		
17:00			17:00			17:00		
18:00			18:00			18:00		
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22:00			22:00			22:00		
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24:00			24:00			24:00		
01:00			01:00			01:00		
02:00			02:00			02:00		
03:00			03:00			03:00		
04:00			04:00			04:00		
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07:00			07:00			07:00		
08:00			08:00			08:00		
09:00			09:00			09:00		
10:00			10:00			10:00		
11:00			11:00			11:00		
Exercise			Exercise			Exercise		
Treatment			Treatment			Treatment		
Sleep quality			Sleep quality			Sleep quality		
Medications			Medications			Medications		
Comments			Comments			Comments		

Appendix 17.2: Subjective Evaluation of Sleepiness

Stanford Sleepiness Scale

1. Feeling active and vital; alert; wide awake.
2. Functioning at a high level, but not at peak; able to concentrate.
3. Relaxed; awake; not at full alertness; responsive.
4. A little foggy; not at peak; let down.
5. Fogginess; beginning to lose interest in remaining awake; slowed down.
6. Sleepiness; prefer to be lying down; fighting sleep; woozy.
7. Almost in reverie; sleep onset soon; lost struggle to remain awake.

Linear Analog Scale/Introspective Measure of Sleepiness

Ask patient to make a mark on the scale that corresponds to state (level of alertness versus sleepiness) prior to testing.

Adapted from Hoddes E, Dement WC, Zarcone V. The development and use of the Stanford Sleepiness Scale (SSS). Psychophysiology 1972;9:150.

Appendix 17.3: Suggested Montages for Recording Sleep-Related Seizure Activity

Montage for a 12-Channel Study

1. Fp1–C3
2. C3–O1
3. Fp1–T3
4. T3–O1
5. Fp2–C4
6. C4–O2
7. Fp2–T4
8. T4–O2
9. EMG: submentalis–mentalis
10. Right outer canthus–left outer canthus
11. Nasal/oral airflow
12. ECG.

Montage for a 21-Channel Study

1. Fp1–F3
2. F3–C3
3. C3–P3
4. P3–O1
5. Fp2–F4
6. F4–C4
7. C4–P4
8. P4–O2
9. Fp1–F7
10. F7–T3
11. T3–T5
12. T5–O1
13. Fp2–F8
14. F8–T4
15. T4–T6
16. T6–O2
17. EMG: mentalis–submentalis
18. Right outer canthus–A1
19. Left outer canthus–A2
20. Nasal/oral airflow
21. ECG (Fig. 17.21).

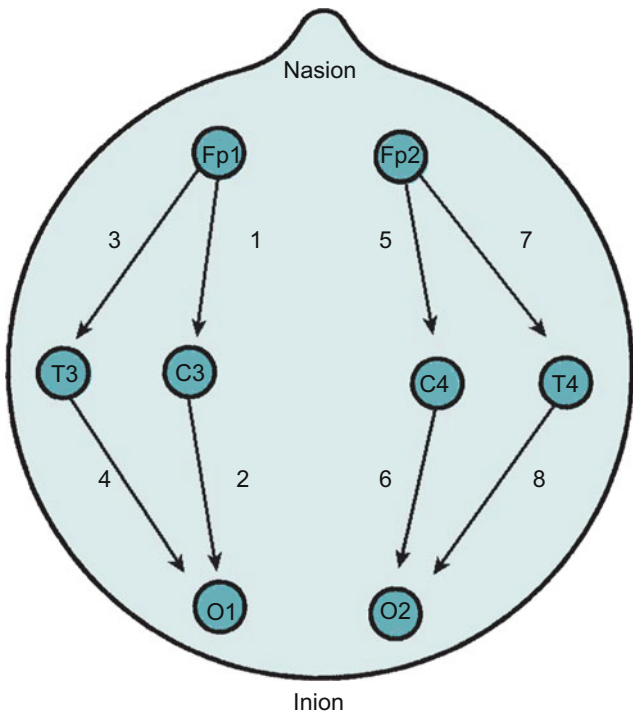

Fig. 17.21 Suggested montage to be used to screen for possible seizure activity during sleep. Use of wide inter-electrode distance affords for a global view of EEG activity and conserves the channels. To more adequately localize epileptogenic activity, a full complement of electrodes should be used. For a more comprehensive review of montages, the reader is referred to standard EEG montages as proposed by American EEG Society Guidelines No. 7, Grass Instruments (1980)

Appendix 17.4: Measuring the Head for C3, C4, O1, and O2

Before measuring the head, it is helpful to make an initial mark at the inion, the nasion, and the two preauricular points.

1. Measure the distance from the nasion to inion along the midline through the vertex. Make a preliminary mark at the midpoint (Cz). An electrode will not be placed on this spot, but it will be used as a landmark.
2. Center this point in the transverse plane by marking the halfway point between the left and right preauricular points. The intersection of marks from steps 1 and 2 gives the precise location of Cz.
3. Reposition the measuring tape at the midline through Cz and mark the points 10 % up from the inion (Oz) and nasion (Fpz).
4. Reposition the measuring tape in the transverse plane, through Cz, and mark 10 % (T3) and 30 % (C3) up from the left preauricular point and 10 % (T4) and 30 % (C4) up from the right preauricular point.
5. Position the tape around the head through Fpz, T3, Oz, and T4. Ten percent of this circumference distance is the distance between Fp1 and Fp2 and between O1 and O2. Mark these four locations on either side of the midline.
6. The second marks for O1 and O2 are made by continuing the horizontal mark for Oz. Do this by holding the tape at T3 and T4 through Oz and extend the horizontal mark to intersect the previous O1 and O2 marks.
7. To establish the final mark for C3, place the tape from O1 to Fp1, and make a mark at the midpoint of this line. When extended, this mark will intersect the previous C3 mark. Repeat on the right side for C4.

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18 Electroencephalography, Electromyography, and Electro-oculography: General Principles and Basic Technology

Sushanth Bhat and Sudhansu Chokroverty

Physiologic Basis of EEG

The traditional scalp EEG (as obtained during PSG) records the difference in electrical potentials between two electrodes placed over the head [2]. The recorded activity results from extracerebral current flow due to summated excitatory postsynaptic potentials (EPSP) and inhibitory postsynaptic potentials (IPSP), rather than from single neurons that have action potentials too localized and too short (generally shorter than 1 ms) to be recorded. On the other hand, EPSP and IPSP currents last for 15–200 ms or more and induce more extensive voltage changes in extracellular space, rendering them easily recordable [3]. The source of the EPSP and IPSP currents, in turn, is the rhythmic oscillations of the thalamocortical neuronal projections to areas of the cortex. This has been experimentally proven; neither lesioning the cerebral cortex nor sectioning the brainstem abolishes sleep spindles, for example, but destruction of the thalamus does [4]. Neurons in other brain structures, including the inferior olivary nucleus, hippocampus, and temporal neocortex, exhibit oscillatory behavior and may play a role in generating EEG rhythms [5]. The scalp EEG recording voltages are attenuated by the skull and intervening tissues (including the cerebrospinal fluid and dura) and reflect about one tenth of the voltage recorded over the cortical surface; they therefore need to be amplified to be interpretable.

Figure 18.1 provides a schematic representation of how synaptic potentials induce voltage changes recorded at the scalp. An excitatory input on a deep dendrite causes positive ions to flow into the pyramidal neuron, resulting in a lack of positive charges, or negativity, outside the neuron. Everywhere else, including the superficial dendrite, positive ions flow out of the cell into the extracellular space to complete the current loop. This results in a relative positivity in the superficial extracellular space. Because the superficial dendrite and surrounding extracellular space are closer to the scalp electrode, a positive deflection is recorded. The separation of superficial positive and deep negative charges allows one to view the pyramidal neuron as a dipole. This permits a more complete analysis of how synaptic potentials result in scalp EEG changes [6].

Methods of EEG Recording

Amplification of the exceedingly minute electracerebral voltage changes into interpretable waveforms is the function of the EEG equipment (Fig. 18.2). EEG voltage changes are transmitted by the electrodes and conducting gel applied to the scalp through electrode wires, which connect the electrodes to the jack box of the EEG equipment. While different types of electrodes are available, most standard laboratories employ gold cup electrodes with holes in the center and silver–silver chloride electrodes for EEG recordings. Silver–silver chloride electrodes need repeated chloriding for proper maintenance. Positive and negative charges are generated between the scalp and recording electrode as a result of ionic dissociation in the electrodes. Paste or conducting gel is used to secure the electrodes. The electrode–electrolyte interface is the most critical link in the EEG machine, as most artifacts originate at this site; careful preparation is therefore very important. The impedance in a pair of electrodes should be measured by an impedance meter and should be less than 5000 (5 K) ohms. High impedance impairs the ability of the electrical signal to reach the amplifier and interferes with the capacity of the amplifier to eliminate environmental noise, thus increasing artifacts [7]. Impedance and impedance-related artifacts are described in greater detail in Chap. 17.

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Electrode Placement, Channels, and Montages

The placement of the electrodes is determined by the 10–20 electrode placement system which is recommended by the International Federation of Societies for EEG and Clinical Neurophysiology and was published by Jasper in 1958 [8]. This system is based on definable anatomical landmarks (see Fig. 24.1) and consists of letters denoting the parts of the brain underneath the area of the scalp and numbers denoting specific locations. The odd numbers refer to the left side of the head, and the even numbers refer to the right side. Important landmarks for measuring include the inion, the nasion, and the right and left preauricular points. The distance from the nasion to inion along the midline through the vertex should be measured. FPz in the midline is 10 % above the nasion of the total distance between the inion and nasion. The electrodes marked FP1 and FP2 are located laterally 10 % above the nasion of the total distance between the inion and nasion measured along the temporal regions through the preauricular points. Oz denotes an electrode placed at a distance of 10 % above the inion of the total distance between the nasion and inion. T3 and T4 electrodes are placed in a location 10 % above the preauricular points of a total distance between the two preauricular points. The rest of the electrodes are located at a distance of 20 % measured from inion to nasion anteroposteriorly or laterally through the ears as well as transversely between the ears. The nomenclature was recently changed to rename T3, T4, T5, and T6 to T7, T8, P7, and P8, respectively, in what has been designated the "Modified Combinatorial Nomenclature."

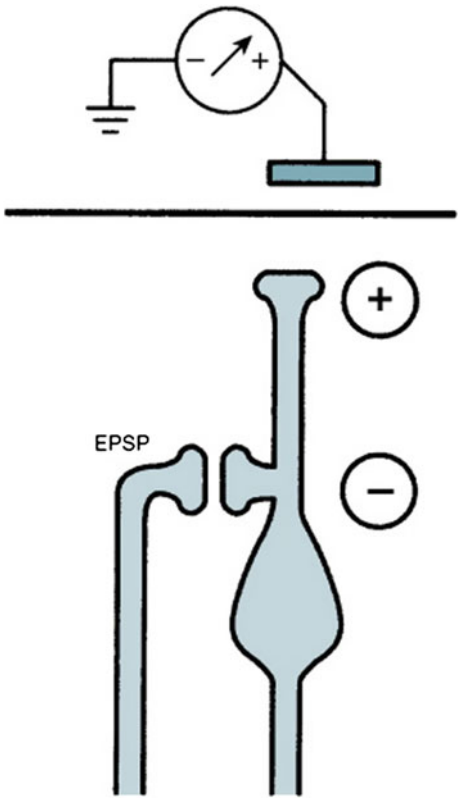

Fig. 18.1 Scalp EEG voltage recordings resulting from an excitatory input on a deep synapse. *EPSP* excitatory postsynaptic potential. Modified from Kandel and Schwartz [69]

Two electrodes connected to each other constitute a *channel* or a *derivation* (e.g., F7-T3 is a channel). A *montage* refers to the manner in which these channels are arranged. Both *bipolar* montages (connection of the electrodes between two relatively active sites over the scalp; e.g., F7-T3) and *referential* montages (connection of the electrodes between an active and relatively inactive site; e.g., F7-M1, F8-M2, and T4-Cz) are recommended. Electrode inputs for digital systems always include one or more additional inputs for reference electrodes. A location between Fpz and Fz is often chosen for the reference electrode but any location on the scalp that is relatively electrically neutral and where firm attachment to the scalp is possible can be used. Reference electrodes are necessary because digital EEG recording is always referential.

Despite the pivotal role that EEG plays in the analysis of sleep, the limited number of inputs available on most PSG equipment results in a less than desirable number of channels dedicated to EEG. In fact, the American Academy of Sleep Medicine (AASM) guidelines [9] call for a minimum of just three channels that record from a single hemisphere and

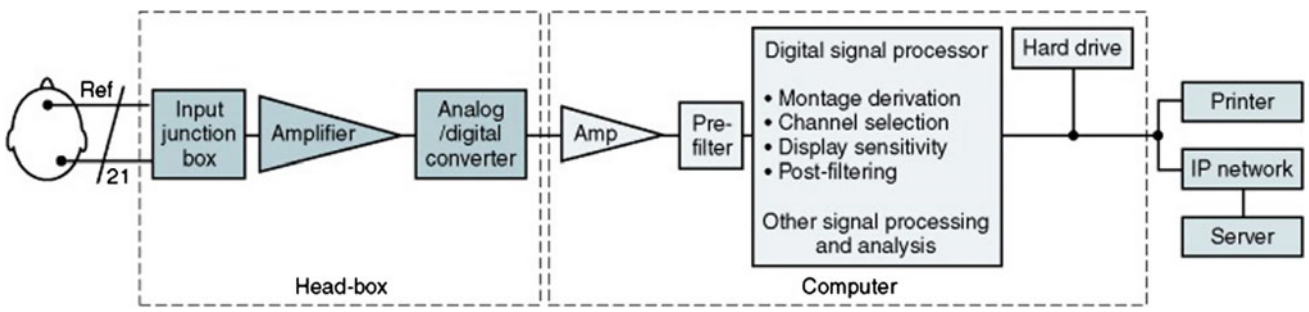

Fig. 18.2 Computer-generated components of a digital polygraph

Table 18.1 Typical overnight polysomnographic montage used in our laboratory

Channel number	Name
1	F3-M2
2	C3-M2
3	T3-M2
4	O1-M2
5	F4-M1
6	C4-M1
7	T4-M1
8	O2-M1
9	Left electro-occulogram (E1-M2)
10	Right electro-oculogram (E2-M2)
11	Chin electromyogram (EMG)
12	ECG
13	Heart Rate
14	Left gastrocnemius EMG
15	Left tibialis anterior EMG
16	Right gastrocnemius EMG
17	Right tibialis anterior EMG
18	Intercostal EMG
19	Oronasal thermistor[a]
20	Nasal pressure transducer[a]
21	Chest
22	Abdomen
23	Snoring
24	Arterial oxygen saturation

Channels 1–8 record electroencephalogram activity from bilateral cerebral hemispheres in a referential chain; electrode designation per the 10-20 International System of electrode placement. M1 and M2, left and right mastoid, respectively. Channel 19 and 20 record airflow ("flow channels"). Channels 21 and 22 record respiratory effort ("effort channels")

[a]In a CPAP titration study, flow channels are replaced by a CPAP signal (C-flow signal)

which do not record from the temporal lobes; such a limited montage would result in an inability to capture focal epileptiform activity arising from the most common location for such discharges (e.g., temporal lobes), as well as missing focal abnormalities from the hemisphere not being recorded [10]. Given the pro-epileptogenic effect of drowsiness and nonrapid eye movement (NREM) sleep, and the fact that nocturnal seizures that are often mistaken for parasomnias and are sometimes encountered during an in-laboratory PSG, it would be unfortunate if a clinically important finding were to be missed or improperly interpreted because of an inadequate number of EEG channels.

For this reason, in our own laboratory, we use between 4 and 8 EEG channels including temporal leads from both hemispheres (Table 18.1); such montages increase the yield of capturing focal or diffuse slow-waves or epileptiform activities compared to recording with 2–4 channels. When nocturnal seizures are suspected, an extended *EEG montage* (Table 18.2; Fig. 18.3), covering bilateral temporal and parasagittal regions and including both bipolar and referential channels is recommended. Full complement of electrodes and special electrode placements (e.g., Tl and T2 electrodes) should be used. Simultaneous video recording (video-PSG study) for correlation of EEG activities with the actual behavior of the patients is crucial. In computerized PSG recordings (digital PSG recordings), which are currently performed in most laboratories, it is easy to change the recording speed from the standard 10 mm per second of the usual sleep recording to 30 mm/s of the standard EEG recording for proper identification of epileptiform discharges.

Differential Amplification and Sensitivity

An understanding of the physiological basis of recorded waveforms is important. While a detailed description of the elementary concepts of electricity, resistance, and capacitance is provided in Chap. 16, and an overview of digital equipment and recording techniques with regards to PSG is provided in Chap. 17, a review of a few key concepts is

Table 18.2 Extended EEG ("seizure") montage

Channel number	Name
1	F4-M1
2	C4-M1
3	O2-M1
4	C3-M2
5	Fp1-F7
6	F7-T3
7	T3-T5
8	T5-O1
9	Fp2-F8
10	F8-T4
11	T4-T6
12	T6-O2
13	Fp1-F3
14	F3-C3
15	C3-P3
16	P3-O1
17	Fp2-F4
18	F4-C4
19	C4-P4
20	P4-O2
21	Left electro-oculogram (E1-M2)
22	Right electro-oculogram (E2-M2)
23	Chin electromyogram (EMG)
24	Right Masseter EMG
25	Left biceps EMG
26	Right biceps EMG
27	Left tibialis anterior EMG
28	Right tibialis anterior EMG
29	Intercostal EMG
30	Oronasal thermistor[a]
31	Nasal pressure transducer[a]
32	Chest
33	Abdomen
34	Snoring
35	Arterial oxygen saturation
36	ECG
37	Heart Rate

Channels 1–20 record electroencephalogram activity from bilateral cerebral hemispheres with referential and bipolar montages including both temporal and parasagittal chains; electrode designation per 10-20 International System of electrode placement. Channel 30 and 31 record airflow ("flow channels"). Channels 32 and 33 record respiratory effort ("effort channels")

[a]In a CPAP titration study, flow channels are replaced by a CPAP signal (C-flow signal)

provided here, especially with regards to EEG recording and analysis. EEG equipment measures and amplifies potential differences, which are always measured between two points; in this case, it is the potential difference between the two scalp electrodes. This is referred to as *differential amplification*. This is an extremely important concept to understand. Figure 18.4 provides an illustration. If electrode A (the "active" electrode) is connected to input 1 of an

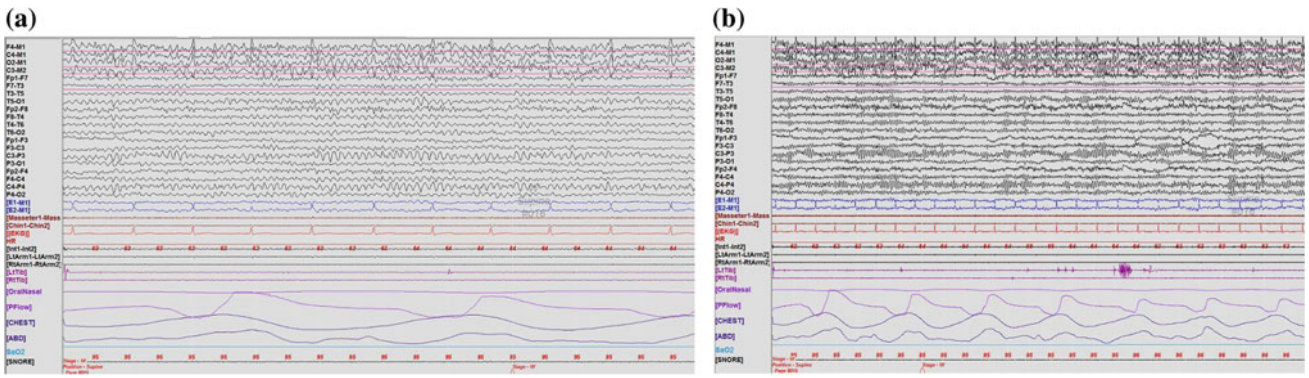

Fig. 18.3 **a** A 10-s and **b** 30-s epoch from the polysomnogram of a 32-year-old man referred to the sleep laboratory for possible OSA. He has a history of epilepsy; hence, an extended EEG ("seizure") montage was requested. Normal awake EEG pattern characterized by symmetrical, sinusoidal posterior dominant alpha rhythm at 9–10 Hz is noted. The top four channels are referential channels connected to the left mastoid. The next 16 are bipolar channels arranged in a double banana montage covering parasagittal and temporal regions as per the International 10–20 electrode placement system. E1-M1 and E2-M1, electrooculogram (EOG) channels; Masseter1-Masseter2 and Chin1-Chin2, masseter (right) and submental electromyogram (EMG); ECG, electrcardiogram; HR, heart rate; Int1-Int2, intercostal EMG; LtArm1-LtArm2; RtArm1-RtArm2, left and right biceps EMG, LTIB; RTIB, left and right tibilais anterior EMG. OroNs1-OroNS2, oronasal airflow (thermistor); PFlow, nasal pressure transducer; Chest and ABD, effort belts; SaO_2, arterial oxygen saturation by finger oximetry. Also included is a snore channel. ECG artifact is noted in the referential leads and EOG leads. Reproduced with permission from: Chokroverty and Thomas [65]

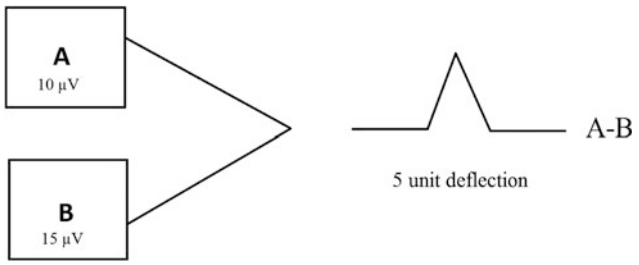

Fig. 18.4 Illustration of the concept of differential amplification. Electrode A, at 10 μV, is connected into input 1 of the differential amplifier, and Electrode B, at 15 μV, is connected into input 2, resulting in the creation of channel A-B. A potential difference of 5 μV results in a corresponding deflection of 5 units in channel A-B. In this case, the deflection is negative or upwards; the direction in any given situation would depend on the polarity convention (see Figs. 18.6 and 18.7 for details)

amplifier and electrode B (the "reference" electrode) is connected to input 2 of the same amplifier, the amplifier would determine the difference between the two inputs (in this case, 5 μV) and there would be a deflection of 5 units. The actual amount of the deflection in millimeters would depend on the sensitivity (see below). Similarly, the direction of the deflection (upwards or downwards) depends on the relative polarity of the two electrodes (as discussed below). The key concept here is that the differential amplifier is displaying the difference between the two electrode inputs rather than absolute voltages; if the two electrodes are at the same voltage, there would be no deflection at all. This does not mean that neither site is electrically active, just that there is no difference in the voltages between the two. This is a useful feature, because environmental noise, which is likely to be the same at the two electrodes, is "subtracted out" and therefore does not contaminate the recording. The *common mode rejection ratio* measures the ability of the amplifier to suppress a signal, such as noise, that is present simultaneously at both electrodes (Fig. 18.5). This ratio should exceed 1000 to 1; most amplifiers currently in service have values that exceed 10,000 to 1. On the other hand, electrodes that are too close to each other may miss significant electrocerebral activity because the area involved is large enough to involve both almost equally; thus the need to reference to a distant electrically inactive site or to use double-distance electrodes as is done, for example, in brain death studies. Analyzing the same EEG using different reformattable montages helps increase the sensitivity of the study overall.

Amplifiers can faithfully amplify input voltages only within a certain range known as the *dynamic range*. Input voltages below the lower limit of the dynamic range are lost in noise; voltages above the upper limit result in a distorted EEG output. Flexible control of amplification within the dynamic range is achieved by manipulating the sensitivity switch. The sensitivity switch is connected to a series of voltage dividers that attenuate the amplified cerebral voltages sufficiently for the EEG record to be interpretable. Sensitivity is defined as the amount of voltage necessary to produce a prespecified output deflection. The usual units are microvolts per millimeter or millivolts per centimeter. In the past, studies were mostly recorded with analog systems, where sensitivity had to be adjusted by the technician as the study was being recorded and could not be manipulated by the polysomnographer at the time of interpretation. With

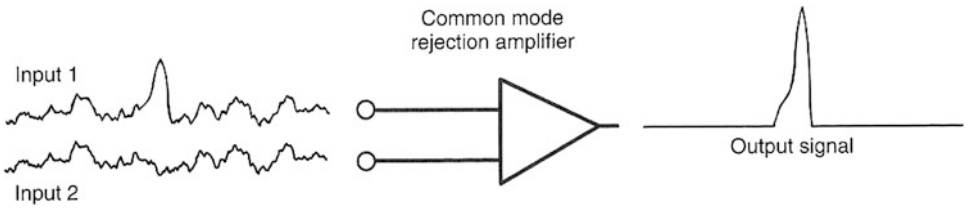

Fig. 18.5 A schematic representation of common mode rejection amplification. The potential difference between the electrodes connected to input 1 and input 2 results in a single amplified upwards deflection. The complex underlying waveform is common to both electrodes, is artifactual and not of biological interest, and represents "noise" that is canceled out by the common mode rejection amplifier. Reproduced and modified with permission from Libenson [5]

virtual replacement of analog with digital systems, the polysomnographer has the freedom to change sensitivity as best suited to the situation. Chapters 16 and 17 discuss analog and digital systems in greater detail.

Polarity Convention

Whereas the sensitivity settings determine the amplitude of waveforms, the positivity or negativity of cerebral activity determines their polarity. The differential amplifier compares relative positivity and negativity at the two electrodes. The resulting deflection is determined according to the polarity convention. If input 1 is negative relative to input 2, or if input 2 is positive relative to input 1, there is an upward, or negative deflection. On the other hand, if input 1 is positive relative to input 2, or if input 2 is negative relative to input 1, there is a downward, or positive deflection. When a number of inputs are connected together as channels in a bipolar EEG montage, the direction of the deflections produced according to the above polarity convention results in the deflections "meeting" at a common point, referred to as a *phase reversal*, which can be used to roughly localize the scalp distribution of those waveforms. Such a phase reversal is due to an area of cortical negativity, although the direction of deflection in any given channel depends on whether the first electrode in the channel is closer or further away from this area of cortical negativity in comparison to the second, resulting in a negative or positive deflection, respectively (Fig. 18.4).

An illustrative example of this concept is provided in Fig. 18.6, which represents a bipolar hypothetical left parasagittal chain. If one were to assume that there is an area

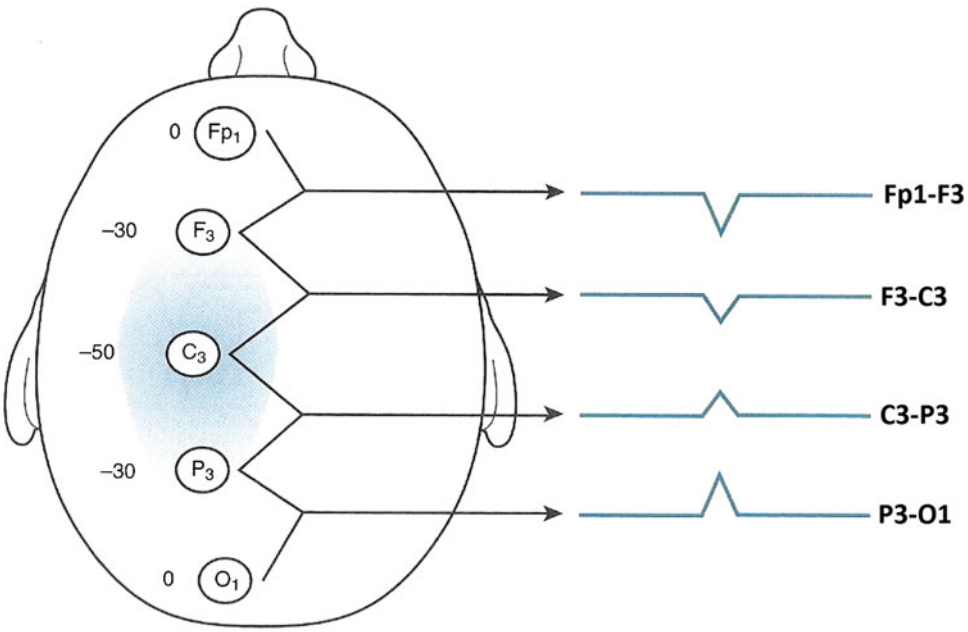

Fig. 18.6 Schematic representation of bipolar montage with an area of cortical negativity at the C3 electrode. There is a phase reversal at C3, the area of maximal cortical negativity. Note that while the maximum deflection is noted in the channels containing the phase reversal (F3-C3 and C3-P3), adjacent channels (FP1-F3 and P3-O1) also show defections predicted by the relative negativity of the individual electrodes, thereby producing a "field." Reproduced and modified with permission from Libenson [5]

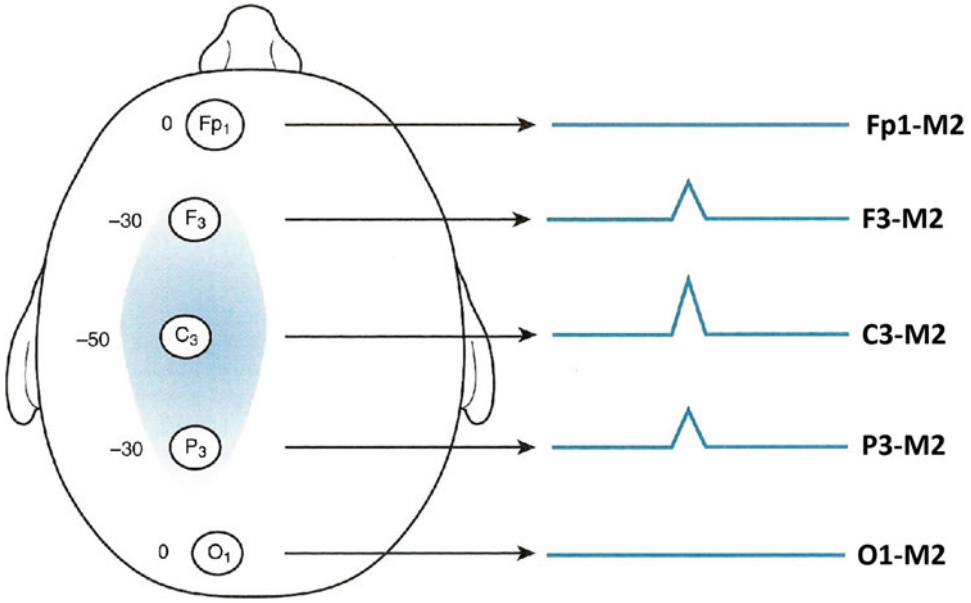

Fig. 18.7 Schematic representation of a referential montage with an area of cortical negativity at the C3 electrode. The montage has been created by connecting electrodes Fp1, C3, P3, and O1 to the contralateral mastoid (M2, not shown). All channels demonstrate negative (upward) deflections, with the waveform being of highest amplitude in the channel containing the electrode with the highest degree of cortical negativity (C3-M2). Adjacent channels demonstrate negative deflections of lower amplitudes, thereby producing a "field." Reproduced and modified with permission from Libenson [5]

of relative cortical negativity at C3 (as typically occurs in epileptogenic foci), then there would be a downward deflection in F3-C3 (because C3 is more negative than F3) and an upward deflection in C3-P3 (because P3 is less negative, or more positive, than C3). However, in practice, epileptogenic foci are rarely so precisely localized, and the area of cortical negativity generally extends beyond a single electrode, i.e., it usually has a "field". Thus, while C3 may be the most negative electrode, its adjacent electrodes, while less negative than C3 itself, are nevertheless more negative than the electrodes farther away from C3 in the montage. The result is that F3 is more negative than Fp1 (causing a positive or downward deflection in Fp1-F3), and P3 is more negative than O1 (causing a negative or upward deflection in P3-O1). Reviewing the entire montage, it is obvious that while a large portion of the left frontotemporal region is involved, the phase reversal is at C3, the area of maximum cortical negativity. The "meeting point" is between the F3-C3 and C3-P3 electrodes, and the common electrode between the two, the site of phase reversal, is C3.

In a referential montage, where each electrode is connected to a common relatively electrically inactive reference electrode (e.g., right mastoid, M2), the same epileptogenic focus would look different. Since every electrode recording from the area of cortical negativity would be more negative than the reference electrode, deflection would always be upwards in channels where M2 is connected to input 2 as is the convention. However, since the degree of deflection of the waveform is dependent on the potential differences between the two electrodes, the amplitude would be highest in that channel where the active electrode is the most negative. Thus, in the example above, the amplitude of the negative potential is highest at C3, the same electrode where a phase reversal occurred on the bipolar montage. But because the area of cortical negativity extends beyond C3 to involve the adjacent electrodes, although to a lesser degree, deflections occur in those channels as well, i.e., there is a field noted even on the referential montage (Fig. 18.7). Thus, while the channel containing the most negative electrode (C3-M2) demonstrates the negative wave with the highest amplitude, adjacent electrodes (F3-M2 and P3-M2) demonstrate negative waves with lower amplitudes, thus producing a field. The ability to view a suspicious waveform (e.g., a spike or sharp wave of potential epileptic significance) in multiple reformattable montages is a benefit of digital recordings.

To summarize, localization of an area of epileptogenic potential or an area showing a focal slow wave, as represented by cortical negativity, is by visualization of phase reversal on bipolar montages, and by maximum waveform amplitude on referential montages.

Filters

Once inputs are subtracted and amplified, the result is passed through a series of filters. The goal of filtering is to attenuate voltages occurring at undesirable frequencies (e.g., environmental noise) without disturbing frequencies found in the biological signal of interest. Filters are described in greater detail in Chap. 16. Briefly, however, a high-pass filter, (also known as a low-frequency filter), allows higher frequency activity to pass unchanged while progressively attenuating lower frequencies (see Fig. 16.12a). This is particularly useful to eliminate artifacts of low frequency such as sweat and respiratory artifact. A low-pass filter (also known as a high-frequency filter), allows lower frequencies to pass unchanged while progressively attenuating higher frequencies (see Fig. 16.12b). This is particularly useful to eliminate high-frequency artifacts such as muscle artifact. A 60-Hz or notch filter is also present in most polygraphic amplifiers. This filter is designed to specifically attenuate the 60-Hz artifact from electrical lines very harshly while attenuating activity of surrounding frequencies less extensively. A similar 50-Hz notch is available in European and certain other countries to match the current in those countries. The notch filter should be used sparingly for at least two reasons. Some biological signals of interest to the polysomnographer have waveforms with important components in the range of 40–80 Hz. Examples include myogenic activity and epileptiform spikes, both of which may be significantly attenuated by the notch filter. For example, use of the notch filter in the chin EMG channel may result in a false impression that tonic EMG has significantly decreased. In addition, the capability of the differential amplifier to reject common signals (see above) should be sufficient to suppress 60-Hz artifact in most cases. Thus, the appearance of 60-Hz artifact usually signals a problem somewhere in the polygraphic circuit that needs to be resolved. Most often the culprit is high impedance at the electrode–scalp interface. Less frequently, defects in the amplifier or grounding of the polygraph are responsible. In these cases, addressing the cause of the 60 Hz rather than using the notch filter is the appropriate course. There are circumstances in which a nearby source of 60 Hz (e.g., a critical piece of medical equipment that cannot be disconnected) renders the EEG uninterpretable. Use of the 60-Hz filter may be justified in these circumstances but must be clearly documented.

Analog and Digital Systems

Until digital PSG recording became the norm, analog systems were used. The analog PSG and EEG machines consisted of an oscillograph in the form of a galvanometer pen unit, with current flow from the amplifier entering a coil attached to the unit, inducing a magnetic field that interacted with the permanent magnetic field in which the coil was placed and causing the deflection of the pen. These have been virtually phased out at this time in favor of digital equipment and hence will not be discussed further.

Modern digital communications technology has allowed miniaturization of what had been much bulkier (if somewhat hardier) solid state components. It has also resulted in some reorganization of the functions of the polygraphic circuit. Digital polygraphs perform all of the functions of the analog polygraphic circuit. However, the ability to digitize the EEG signals allows easier manipulation, transmission, display, and storage that confers some distinct advantages. The ability of the polysomnographer to change sensitivities, montages, and filters while reviewing the study, rather than be limited by decisions taken by the technician at the time the study was recorded, is probably the biggest such benefit.

Recorded signals are still analog signals and need to be presented to the analog to digital converter (ADC). The ADC assesses the voltage of the continuous analog EEG, creates a numerical value corresponding to this voltage, and stores this value in memory. The ADC then repeats this process at a uniform interval (intersample interval). In this manner, a continuous (analog) EEG signal is converted into a series of numerical values representing the voltage of the signal at serial moments in time. Thus, the signal is commonly referred to as "digitized" or a "digital signal." As described in Chap. 16, the reliability of the digital signal is dependent on the sampling rate; if the digitized signal is to reflect the analog signal faithfully, the sampling rate must be at least twice the highest frequency in the analog signal to prevent aliasing (see Figs. 16.17 and 16.18).

The digitized signal is now passed to a computer for storage in memory and further manipulation by a software program. Software programs perform many of the functions of the solid state components of the analog polygraph.

Filtering is an important function performed by software on the digitized EEG signal. Digital filters are computer algorithms that transform digitized EEG by filtering out designated frequencies. Digital filtering [11] can be performed in the frequency domain by computing the Fourier transform of a segment of EEG, replacing coefficients at the frequency one wishes to eliminate by zero, and then reconstituting the EEG by computing the inverse Fourier transform (see further discussion of Fourier analysis below). Digital filtering can also be performed in the time domain by using a moving average method. Such finite impulse response filters are increasingly used in digital EEG machines and allow filtering without phase distortion, an advantage over traditional analog filters [12].

Software can manipulate and analyze digitized EEG signal in more sophisticated ways as well. Spectral analysis is a commonly employed technique relying on the Fourier

theorem and forms the basis of sleep stage scoring software. Pitfalls and limitations of this technique are discussed below. Algorithms designed to detect seizures and epileptiform abnormalities are also commercially available [13]. The clinical utility of these is variable and at present they do not replace a thorough analysis of the original record by a qualified interpreter.

Modified and organized digital signal can be directed from computer memory to a variety of destinations. Polygraphic data must be presented to the interpreter for visual inspection. Polygraphic data in digital systems is typically displayed on monitors. Monitor resolution must be sufficient so that the degree of resolution provided by the ADC is not significantly compromised. For example, if 1024 pixels (a common horizontal resolution in "off the shelf" computer monitors) is available to display 30 s of EEG, at most 1024/30 or 34 pixels can be devoted to display one second of EEG. This is far less than the 256 samples per second horizontal resolution provided by ADCs typically used in contemporary polygraphic systems. While this degree of horizontal resolution may be adequate for sleep stage scoring, it is not sufficient for analysis of epileptiform activity or electrographic seizures. Changing the timebase of the display so that 10 s epochs are displayed on the monitor will triple the horizontal resolution of the monitor in the above example and bring it more into line with the resolution provided by the ADC. Similar considerations pertain to the vertical resolution of the monitor though this is of less concern in polygraphy where less channels of polygraphic recording are typically presented at any time. In general, larger monitors with higher monitor resolution better reflect all the information present in the digitized signal.

Digitized polygraphic data can be transmitted to a printer to generate a "hard copy" polygraphic tracing of selected epochs. Printing an entire polygraph is rarely necessary with digital systems. Digitized data in computer memory must ultimately be transmitted to peripheral devices for storage. A variety of digital storage mediums are available, all of which are less expensive and more convenient than the paper and microfilm required for analog EEG. After security and privacy issues are addressed, digitized polygraphic data can be transmitted via network or the internet to other computers in the clinic, the interpreter's home, or on another continent.

Advantages and Limitations of Digital Recording Systems

Digital recording systems are now the norm and have rendered analog polygraph systems obsolete. With digital systems, there has been a revolution in techniques of data acquisition, display, and storage. Some of these have been alluded to in the discussion above, but to summarize, digital equipment is much less bulkier and conserves space. Previously recorded data can be manipulated retroactively and changes can be applied to the filter settings, sensitivities, and monitor speeds. As a result, artifacts can often be minimized and eliminated, data can be analyzed in multiple ways, and areas of interest can be more easily pinpointed and logged for future reference. Computerized recording makes the EEG paperless, conserving space, and being more environmentally friendly. Digital information is easier to store on inexpensive media such as DVDs, and the digital format translates more easily into databases. For these reasons, digital recording will undoubtedly continue to replace analog polygraphic systems over time.

Spectral Analysis

Spectral analysis is probably the most widely used computerized analysis of digitized EEG [14]. Spectral analysis is based on the Fourier theorem, which states that any waveform can be decomposed into a sum of sine waves at different frequencies with different amplitudes and different phase relationships. When summed, these waves reconstitute the original waveform. The Fourier transformation is a mathematical operation that provides the frequency, amplitude, and phase parameters of each of these component sine waves. Fourier coefficients represent the amplitude and phase relationship at each of the component sine-wave frequencies. Squaring and summing the Fourier coefficients at each frequency provides the power at that frequency. A plot of power at each of the component frequencies is called the power spectrum. The power spectrum allows determination of relative amounts of given frequencies in the waveform over the time segment analyzed.

The fast Fourier transform algorithm allows real-time spectral analysis with contemporary personal computers. Commercially available software packages offer straightforward presentation of the power contained in the traditional frequency bands during a set period of EEG. This allows detection and quantification of frequencies not detected with visual inspection. However, there are many potential pitfalls. Theoretically, the power spectrum is a faithful representation of the original signal only if the original signal is stationary (has stable statistical properties). The EEG signal is clearly not stationary over long periods, although it appears reasonably stationary over brief epochs. In practice, this means that the EEG segment selected for analysis should not include obvious changes such as those due to alerting or drowsiness. In addition, the Fourier theorem assumes that an infinitely long sample is available for analysis. Because, even long samples are clinically impractical, tapering, or "windowing" of the endpoints of the sample is necessary to attenuate the spurious frequencies

(leakage) arising from the segmentation of the signal. Windowing is never completely successful—some leakage is unavoidable. This may affect clinical interpretation when power is displayed in the traditional frequency bands; for example, a reasonable amount of alpha power may leak to the theta band or beta bands. Nonsinusoidal rhythms, such as "spiky alpha" are common in routine EEG. Fourier analysis of a nonsinusoidal rhythm of a set frequency often shows a large peak at that frequency with smaller peaks at harmonics of the frequency. These smaller, higher frequency peaks may lead the interpreter to conclude that cerebral activity at the higher frequency is actually present. The most common pitfall in interpreting power spectra is artifact. Artifact is ubiquitous, often subtle, and can take an almost infinite variety of forms. The computer cannot separate artifact from EEG and includes artifact in the computation of the power spectrum. This can lead to significant misinterpretation. Artifact is much more difficult to recognize in the power spectrum than in the unprocessed EEG. It is therefore very important to review EEG before spectral analysis or interpretation of the power spectrum to prevent analysis of segments contaminated by artifact [15, 16].

Despite these limitations, spectral analysis can play a useful role in the operating room and in routine scoring of sleep studies. A basic understanding of the principles of signal processing and thorough experience in the appearance of various cerebral activities after spectral analysis is necessary. Unprocessed "real" physiologic signal must always be reviewed. Spectral analysis has not demonstrated any consistent clinical utility in routine EEG despite almost two decades of active research. Because the potential for misinterpretation and abuse is high, the major neurologic and neurophysiologic professional organizations have taken strong positions against the use of spectral analysis during routine EEG.

Electro-oculography

Electro-oculography (EOG) recording is crucial to staging sleep accurately. Gold cup or silver–silver chloride electrodes can be used to monitor the EOG. The sensitivity and filter settings for EOG are similar to those used for EEG (see Table 18.3). The two recommended electrodes are labeled E1 (1 cm below the left outer canthus) and E2 (placed 1 cm above the right outer canthus) both referenced to the right mastoid [9]; this arrangement allows simultaneous recording of both vertical eye movements (such as blinking) and horizontal eye movements (both slow and rapid) (Fig. 18.8).

The underlying concept is that the eye is an electric dipole, with relative positivity at the cornea and a relative negativity at the retina. Any eye movement changes the orientation of the dipole, and it is the movement of the dipole that is recorded as a potential difference between the two electrodes used to record the EOG. In this arrangement, conjugate eye movements produce out-of-phase deflections in the two EOG channels whereas the EEG slow activities contaminating the eye electrodes are in phase. For example, when the eyes look to the right (see Fig. 18.8), the cornea of the right eye approaches electrode A in input 1 and electrode A becomes positive relative to the inactive ear. According to the polarity convention, amplifier 1 will register a downward deflection. Simultaneously, the retina of the left eye approaches electrode B connected to input 2. Consequently, electrode B becomes negative relative to the inactive ear and amplifier 2 registers an upward deflection. The out-of-phase deflections in the two adjacent channels indicate that a conjugate eye movement has occurred. Similarly, an upward eye movement results in a downward deflection in amplifier 1 and an upward deflection in amplifier 2. Eye blinks will produce an identical pattern because eye closure results in an upward rotation of the eyeball (Bell's phenomenon).

Table 18.3 Filter and sensitivity settings for polysomnographic studies

Characteristics	High–frequency filter (Hz)	Time-constant (s)	Low Frequency filter (Hz)	Sensitivity
Electroencephalogram	70 or 35	0.4	0.3	5–7 μV/mm
Electro-oculogram	70 or 35	0.4	0.3	5–7 μV/mm
Electromyogram	90	0.04	5.0	2–3 μV/mm
Electrocardiogram	15	0.12	1.0	1 mV/cm to start; adjust
Airflow and effort	15	1	0.1	5–7 μV/mm; adjust

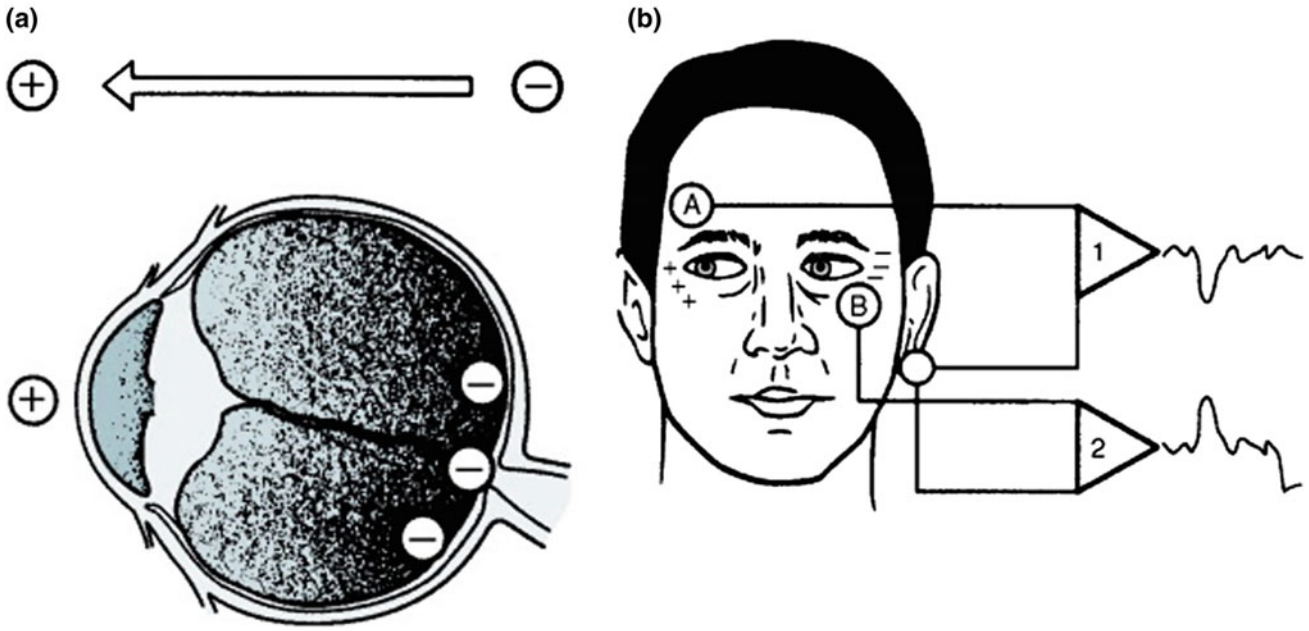

Fig. 18.8 **a** The voltage field generated by the eye can be represented by a simple dipole, the cornea being positive and the retina negative. **b** With the use of two polygraphic channels to detect conjugate eye movements according to the scheme suggested in the sleep scoring manual, eye movements result in out-of-phase potentials in the two channels

Eye movements are general characteristic of the sleep stage in which they occur and are an essential part of scoring. Eye blinks, seen only in wakefulness, are conjugate vertical eye movements occurring at 0.5–2 Hz with the eyes open or closed. REMs (conjugate, irregular, sharp eye movements with an initial deflection of less than half a second) occur in wakefulness along with high chin EMG tone, eye blinks and a posterior dominant rhythm, but also occur in REM sleep, especially in phasic REM where they occur in bursts seen in all directions (horizontal, oblique, and vertical) and are accompanied by low to absent chin EMG tone (interspersed with similar phasic bursting) and a desynchronized, amorphous EEG pattern. The frequency with which bursts of REMs occur in REM sleep, measured as REMs/minute, is called REM density. It typically increases in later REM cycles during the course of a normal PSG; this may be reversed in patients with depression. Slow lateral eye movements (SEMs or SLEMs) are seen in drowsiness and light sleep and are defined as conjugate, sinusoidal, and regular eye movements with an initial deflection of greater than half a second (Fig. 24.9). These eye movements are not under voluntary control and cannot be volitionally simulated. In patients, who do not generate a posterior dominant rhythm, their appearance heralds Stage N1 sleep. While they may persist into Stage N2 during the early part of the night, they generally disappear in Stage N3 and REM sleep. However, patients on antidepressants such as selective serotonin reuptake inhibitors (SSRIs such as fluoxetine and paroxetine) as well as serotonin–norepinephrine reuptake inhibitors (SNRI such as duloxetine) may have unusual eye movements that appear to be a mixture of rapid and slow eye movements occurring well into Stage N3 and often into REM sleep (colloquially referred to among polysomnographers as "Prozac eyes"); their presence makes sleep staging difficult (Fig. 18.9) and can render scoring of a multiple sleep latency testing (MSLT) equally frustrating. The role of EOG in sleep staging is further discussed in Chap. 24.

Santamaria and Chiappa [17] found two types of eye movements in drowsiness, not previously reported, by placing recording electrodes over the globe in addition to traditional EOG; they described small fast irregular eye movements in 60 % of normal subjects in early drowsiness, preceding slow eye movements, as well as small fast rhythmic eye movements in 30 % of normal subjects, usually associated with the traditional slow eye movements. The former did not appear in traditional EOG recordings, and when the latter occasionally did, they were of very low amplitude. These have yet to be validated by other authors.

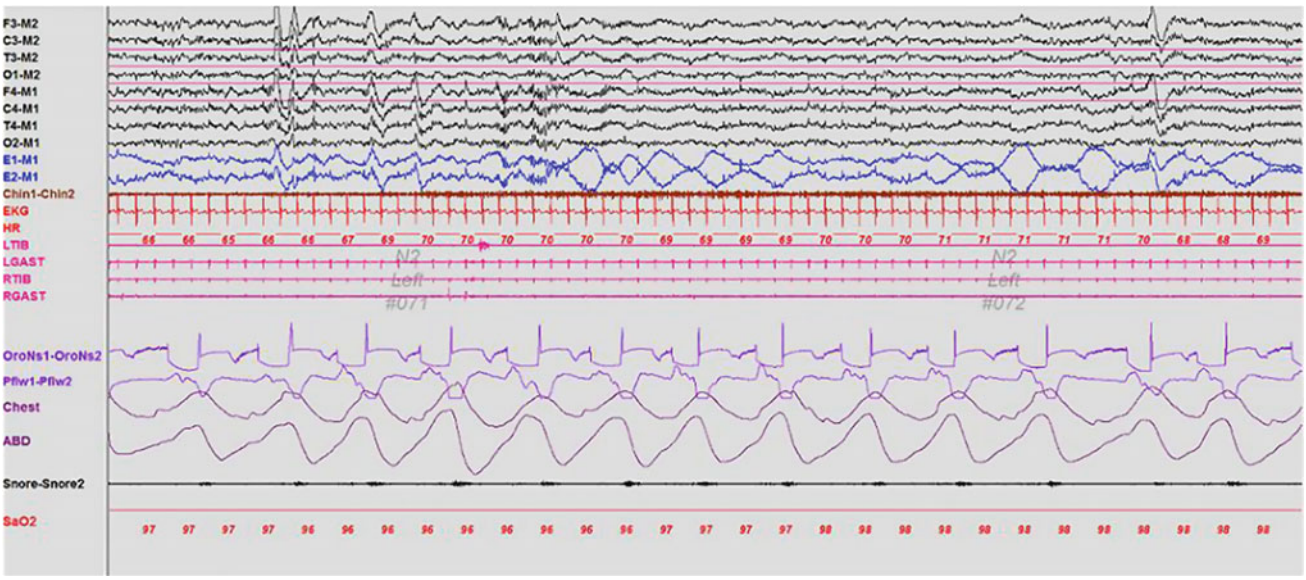

Fig. 18.9 A 60 s epoch from the overnight polysomnogram of a 35-year-old man complaining of excessive daytime sleepiness and with a prior diagnosis of obstructive sleep apnea. He also has a history of depression and is on citalopram, a selective serotonin reuptake inhibitor (SSRI). This epoch represents Stage N2 sleep, as evidenced by the presence of K complexes and sleep spindles. Note the presence of excessive eye movements, representing a combination of slow and rapid eye movements. Eye movements generally do not persist into Stage N2 and beyond but are often seen in patients on SSRIs (colloquially referred to as "Prozac eyes"). Top eight channels; EEG recording with electrodes placed according to the 10–20 international electrode placement system. Chin1-Chin2, submental electromyogram (EMG); ECG, electrcardiogram; HR, heart rate; LTIB; RTIB, left and right tibilais anterior EMG; LGAST; RGAST, left and right gastrocnemius EMG; OroNs1-OroNS2, oronasal airflow; Pflw1-Pflw2, nasal pressure transducer recording; Chest and ABD, effort belts; SaO2, arterial oxygen saturation by finger oximetry. Also included is a snore channel. Reproduced with permission from: Chokroverty and Thomas [65]

Electromyographic Recordings in Sleep Disorders

Electromyography (EMG) channels provide important physiological characteristics that help determine sleep stage, as well as aiding in the diagnosis and classification of a variety of parasomnias [18]. At a minimum, a PSG consists of chin EMG channels recording activity from the mentalis and submental muscles (the mylohyoid and anterior belly of the digastric, supplied by the motor fibers of the trigeminal nerve), and bilateral leg EMG channels recording activity from the tibialis anterior muscles. EMG is recorded using a gold cup or a silver–silver chloride electrode applied to a clean surface using tape or electrode glue. For chin EMG recordings, at least three EMG electrodes are applied so that in the event of a problem with one of the electrodes the additional backup electrode can be connected during the recording without disturbing the patient. The electrode impedance should be less than 5 K. The high- and low-frequency filter settings for the EMG recordings are different from those used for EEG and EOG and are listed in Table 18.3. The sensitivity should be at least 20 μV/cm for mental or submental EMG activity.

As recorded during a PSG, the EMG channels represent the surface recording of intracellular changes occurring as a result of muscle depolarization during contraction. Unlike needle EMG performed in patients with suspected neuromuscular disease in the neurophysiology laboratory, analysis of motor unit morphology and firing pattern is not the focus of these recordings. Rather, the EMG channels provide important information about overall muscle tone. EMG tone is seen to progressively decrease with sleep onset and continue to diminish through nonREM (NREM) sleep to a point where it is at its minimum and almost absent in REM sleep [19]. Phasic bursts (with short durations in the myoclonic range, 20–150 ms and sometimes up to 250 ms) in the chin EMG (as well as limb EMG) are seen in phasic REM sleep.

Lower limb EMGs are generally recorded with electrodes placed over the tibialis anterior muscles 2–2.5 cm apart. The main utility of these channels is to record limb EMGs in patients with periodic limb movements in sleep (PLMS). While generally seen in up to 80 % of patients with restless legs syndrome (RLS, recently renamed Willis-Ekbom disease), PLMS are often seen in normal patients with no daytime complaints, especially those above the age of 65 years. PLMS are also seen in those with a variety of sleep disorders (e.g., REM behavior disorder [RBD] and

narcolepsy, in which they may be abundant in REM sleep), those on antidepressants such as SSRIs and SNRIs. For this reason, a careful sleep history is essential while determining the clinical significance of PLMS. In many cases, PLMS occur in association with respiratory events as part of obstructive sleep apnea (OSA). These are referred to as respiratory related limb movements, and may respond to continuous positive airway pressure (CPAP) treatment. This recognition cannot be made without PSG that allows simultaneous analysis of respiratory and EMG channels, although the bedpartner may often complain of kicking leg movements or similar body flailing by the patient.

Many patients with a history of abnormal movements or behavior in sleep require a more extended EMG montage, which we term a multiple muscle montage (MMM), that includes extra channels recording from additional cranially innervated muscles (e.g., the sternocleidomastoideus, masseter, and other muscles), upper limb (e.g., biceps, triceps, extensor digitorum communis, and flexor digitorum subliminis), and lower limb muscles (e.g., quadriceps, hamstrings, gastrocnemius, and extensor digitorum brevis) and axial muscles (e.g., cervical, thoracic and lumbar paraspinals, rectus abdominis, and intercostal muscles) (Table 18.4). This additional muscle recording is of particular utility in patients with suspected RBD where REM without atonia (RWA) may be missed if an adequate number of muscles are not sampled. While a standard montage for RBD has not yet been agreed upon, Fraucher et al. found that simultaneous recording and quantitative analysis of the mentalis and flexor digitorum superficialis in three second mini-epochs was 100 % specific for RBD, when activity was present in more than 31.9 % of mini-epochs [20]. The heterogeneity of RBD appears to be expressed in the dissociated EMG findings in muscles innervated by the cranial nerves, as well as spinal nerves to the arms and the legs, requiring recording from multiple muscles. Multiple muscle montage recording may also be useful in patients with suspected RLS, as PLMS may also occur in the arm muscles or, rarely, in the axial or cranially innervated muscles (Fig. 18.10). EMG recordings are needed to score excessive fragmentary myoclonus, hypnagogic foot tremor, and alternating leg muscle activation (ALMA), as well as propriospinal myoclonus at sleep onset.

Additional EMG channels aid in the analysis of unusual movements in sleep, especially myoclonus, and help assess their propagation and location of their generators. A dystonic muscle burst refers to a tonic or prolonged EMG activity lasting for 500–1000 ms or longer. Myoclonic muscle bursts are phasic bursts, which are characteristically noted during REM sleep and also during NREM sleep as excessive fragmentary myoclonus. Myoclonic bursts refer to EMG activity lasting for a brief duration of generally 20–150 ms and sometimes up to 250 ms. In patients with tremor, EMG may record rhythmic activity in agonist–antagonist muscle pairs. Physiological analysis of a variety of movements in sleep, many of which are benign phenomena such as hypnic or intensified hypnic jerks [21] is possible when additional muscle electrodes are used.

Recording alae nasi muscle may pick up not only inspiratory activity, but also some expiratory activity [22]. Many upper airway muscles are secondary muscles of respiration. All the facial muscles, including the masseter muscles, show inspiratory bursts during the recordings (Fig. 18.10) [23]. It is often helpful to include intercostal and diaphragmatic EMG channels to record respiratory muscle activity. The intercostal EMG can be recorded from the seventh to ninth intercostal spaces with active electrodes on the anterior axillary line and the reference electrodes on the mid-axillary line. Diaphragmatic muscle activity may be recorded by placing surface electrodes over the right or left side of the umbilicus or over the anterior costal margin. However, these tend to cross-contaminate each other so that recordings from either sites are effectively a mixture of both diaphragmatic and external intercostal muscles. True diaphragmatic activity is typically recorded by intraesophageal recording. Spectral analysis of data from chest wall surface electrodes with simultaneous data obtained from a swallowed bipolar electrode with a double-balloon catheter suggests that the former (i.e., chest wall electrodes) do not accurately reflect diaphragmatic activity [24]. Intercostal EMG is particularly useful in the differentiation between central and obstructive apneas, especially when the respiratory channels are unreliable; continued bursts of activity in these channels during an apneic event would identify it as obstructive while the absence of such bursts would indicate a central event (Fig. 18.11). The 2012 update to the AASM Manual for the Scoring of Sleep and Associated Events [25] recommends the use of the intercostal/diaphragmatic EMG channel for scoring apneas/hypopneas when the airflow channels are unreliable.

In our laboratory, we have designed a hybrid seizure/multiple muscle montage for recording patients who have abnormal behaviors and events in sleep and in whom the differential diagnosis includes seizures and parasomnias. While most PSG machines have a limited number of inputs, precluding full seizure and multiple muscle recordings during the same study, we have found this hybrid montage useful in analyzing such events (Table 18.5).

Table 18.4 Multiple muscle montage (extended EMG channels for parasomnias and other movement disorders in sleep)

Channel number	Name
1	F3-M2
2	C3-M2
3	O1-M2
4	F4-M1
5	C4-M1
6	O2-M1
7	Left electro-oculogram (E1-M2)
8	Right electro-oculogram (E2-M2)
9	Chin electromyogram (EMG)
10	Right Masseter EMG
11	Right sternomastoid EMG
12	Left biceps brachii EMG
13	Left triceps EMG
14	Right biceps brachii EMG
15	Right triceps EMG
16	Right lumbar paraspinals EMG
17	Left quadriceps EMG
18	Left hamstrings EMG
19	Right quadriceps EMG
20	Right hamstrings EMG
21	Left gastrocnemius EMG
22	Left tibialis anterior EMG
23	Right gastrocnemius EMG
24	Right tibialis anterior EMG
25	Intercostal EMG
26	Right lower rectus abdominis EMG
27	Oronasal thermistor[a]
28	Nasal pressure transducer[a]
29	Chest
30	Abdomen
31	Snoring
32	Arterial oxygen saturation
33	ECG
34	Heart rate

Channels 1–6 record electroencephalogram activity from bilateral cerebral hemispheres with referential parasagittal chains. Channels 10–26 record EMG activity, including from additional muscles not routinely studied on typical PSGs. Channels 27 and 28 record airflow ("flow channels"). Channels 29 and 30 record respiratory effort ("effort channels")

[a]In a CPAP titration study, flow channels are replaced by a CPAP signal (C-flow signal)

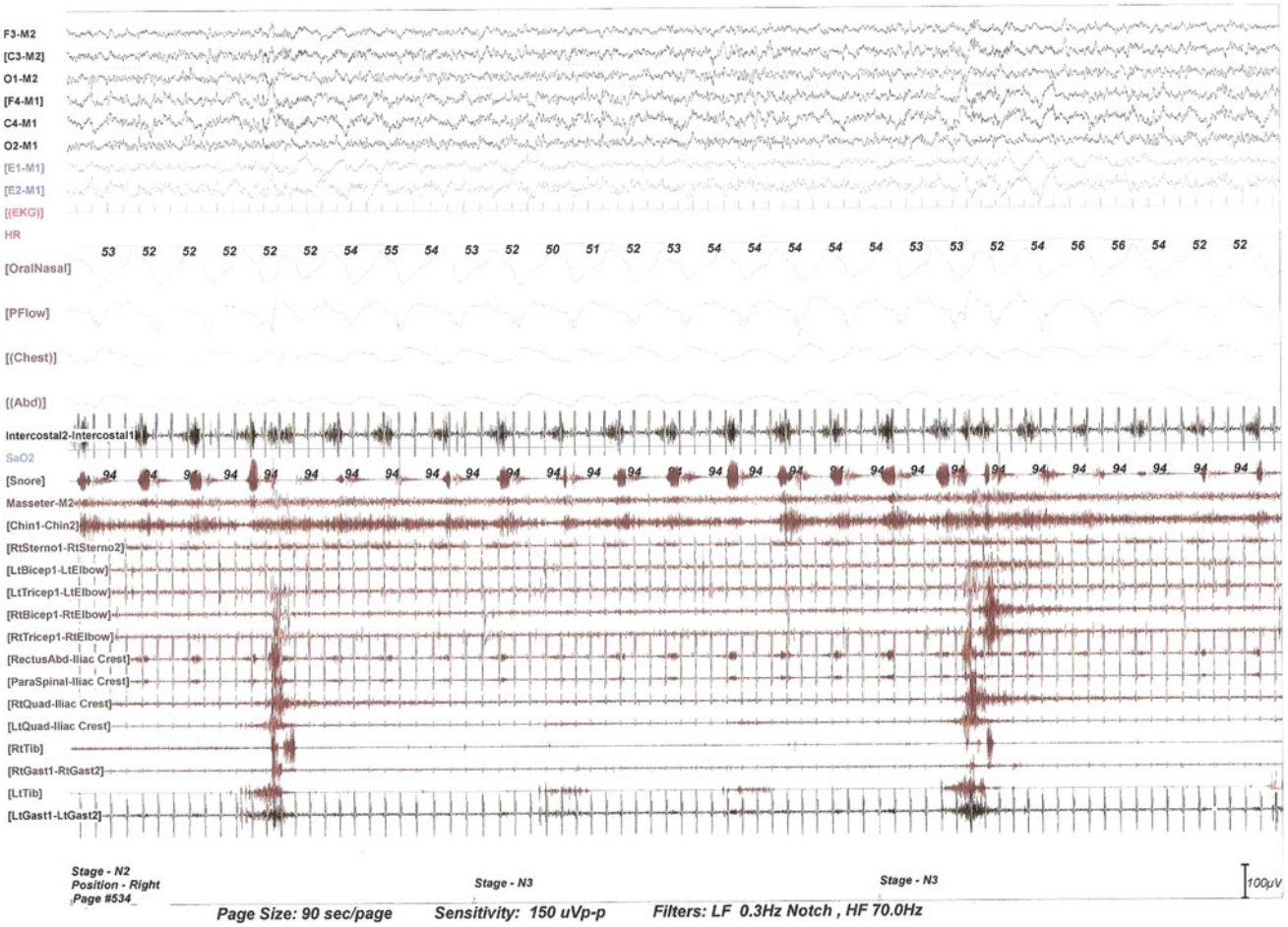

Fig. 18.10 Propriospinal propogation of periodic limb movements of sleep. This 90 s epoch of Stage N3 sleep is taken from the overnight PSG recording using multiple muscle montage in a 66-year-old man with a history of restless legs syndrome (Willis-Ekbom Disease) fulfilling all the essential diagnostic criteria for this. Note periodic limb movements in sleep (PLMS) originating first in the tibialis anterior and propagating up the spinal cord to the quadriceps muscle and subsequently to the rectus abdominis, paraspinals, and then to the biceps and triceps muscle at a very slow speed (note prolonged interburst intervals between the lower limb, trunk, and upper limb muscles). This suggests propagation along slowly conducting propriospinal pathways. It is not possible to measure exact interburst latencies using our PSG equipment. Note also the inspiratory muscle bursts in cranially innervated muscles (secondary respiratory muscles). The upper rectus abdominis and paraspinal muscles are picking up inspiratory bursts from neighboring intercostal and diaphragmatic muscles. Top 6 channels: EEGs (international nomenclature system); E1–M1 and E2–M1: Left and right electro-oculography, respectively; M1: left mastoid; ECG: Electrocardiogram; HR: Heart rate; OralNasal: oralnasal thermistor; PFlow: Nasal pressure transducer; chest and ABD: CHEST and abdominal respiratory effort channels; intercostals: Intercostal EMG from the Right 8th intercostal space; SaO2: oxygen saturation by finger oximetry; channels 18-32: EMGs from masseter, chin (mentalis muscle) sternomastoid, biceps, triceps, rectus abdominis (right), paraspinal (right thoracolumbar), quadriceps (Lt and Rt), gastrocnemius (Gast) (Lt and Rt), and tibialis anterior (Tib) (Lt and Rt), muscles. Reproduced with permission from: Chokroverty and Thomas [65]

Special Techniques for Physiological Characterization of Abnormal Movements

In addition to polymyographic recording to understand the onset and propagation of muscle bursts, other electrophysiological techniques may be needed to characterize the nature of propriospinal myoclonus at sleep onset and other nocturnal muscle jerks.

Propriospinal myoclonus at sleep onset [26] usually originates from a generator in the mid-thoracic region with propagation up and down the spinal cord at a very slow speed (3–5 m/s) using very slowly conducting propriospinal pathways. Surface EMG recording may be obtained for upper thoracic (e.g., second or third intercostal space), mid-thoracic (upper rectus abdominis muscle), lower thoracic (lower rectus abdominis muscle), and lumbar (e.g., quadriceps femoris muscle) regions. The onset of muscle burst, interburst duration in milliseconds and the distance in centimeter between the recordings should be measured. The motor conduction velocity is then computed to

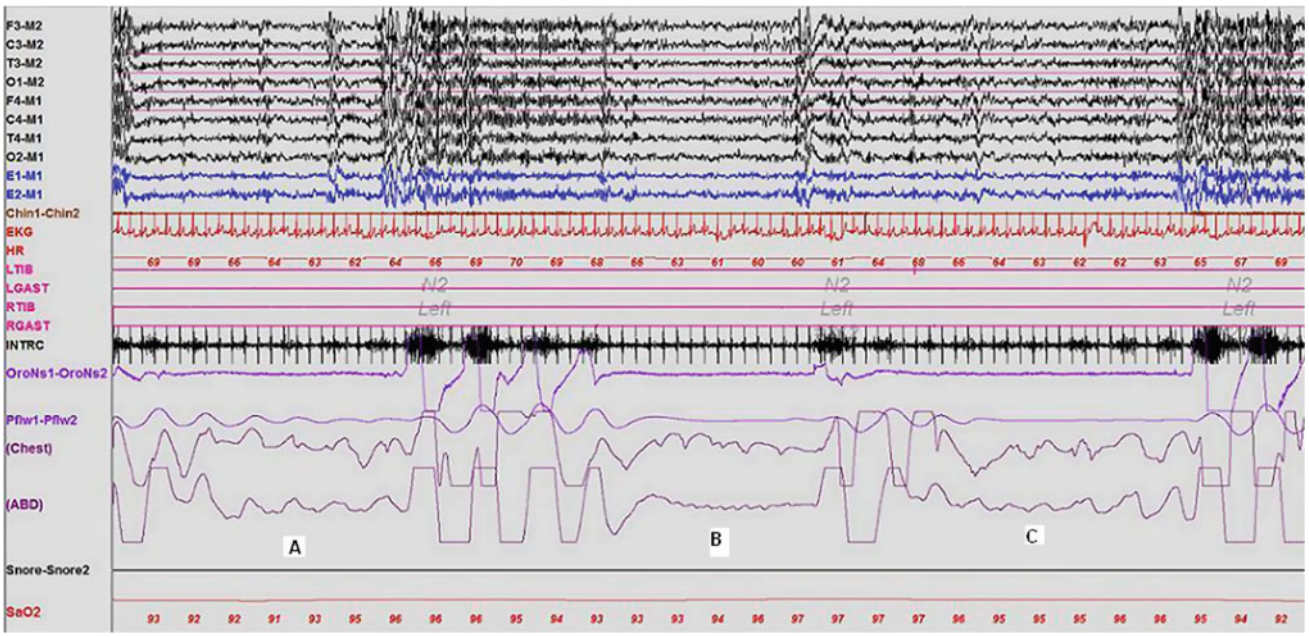

Fig. 18.11 A representative 90 s epoch from the overnight polysomnogram (PSG) of a 46-year-old man with a longstanding history of snoring, witnessed apneas, and excessive daytime sleepiness. Three respiratory events are depicted in this epoch. Note that during the second event (B), the chest lead shows artifacts making it difficult to determine whether it is central or obstructive in nature. However, the intercostal EMG channel (INTRC) shows the absence of inspiratory bursts during the event, confirming that it is a central apnea. Also noted is cardioballistic artifact in the abdomen (ABD) lead, another indicator of a central event. For comparison, the first and third events (A and C) are clearly obstructive apneas, and intercostal EMG bursts continue (albeit at a lower amplitude) throughout their duration. The intercostal EMG channel is often very helpful in distinguishing between obstructive and central apneas when effort channels are unreliable or show artifacts. Top eight channels; EEG recording with electrodes placed according to the 10–20 international electrode placement system. Chin1–Chin2, submental electromyogram (EMG); ECG, electrcardiogram; HR, heart rate; LTIB, RTIB: left and right tibilais anterior EMG; LGAST, RGAST: left and right gastrocnemius EMG; OroNs1-OroNS2, oronasal airflow;. Pflw1-Pflw2, nasal pressure transducer recording; SaO2, arterial oxygen saturation by finger oximetry. Also included is a snore channel. Reproduced with permission from: Chokroverty and Thomas [65]

(distance/interburst time interval) show conduction at a very slow speed. Propogation of muscle bursts up and down the spinal cord at a very slow speed will provide evidence for a propriospinal myolclonus [27].

For abnormal muscle jerks, the technique of back-averaging (EMG-EEG correlation) will tell if the jerks are voluntary or involuntary in nature [28]. A voluntary jerk will produce a Bereitschaftspotential (readiness potential), a characteristic slowly rising negative potential with onset about 500–1000 ms before the onset of the EMG activity from the jerking muscle which is a classic electrophysiologic signature of voluntary movement. A cortical prepotential will be recorded (about 20 ms before the onset from an upper limb muscle or 30–40 ms before the onset from a lower limb muscle) in case of cortical myoclonus whereas no prepotential will be recorded in case of brain stem or spinal myoclonus [29].

Interpreting the EEG

While the main purpose of recording the EEG in sleep studies is to stage sleep, it is vital that the polysomnographer be familiar with normal waking rhythms, be able to identify abnormalities, both epileptiform and nonepileptiform, as well as recognize artifacts that may contaminate a recording, and be a source of confusion. This is especially true since many epileptiform abnormalities become more pronounced during drowsiness and sleep (specifically NREM sleep), and the prolonged nature of sleep recordings (six hours or more over a night), in comparison to the relatively short recording time for routine EEGs (generally 20–30 min) increases the yield of finding abnormalities, giving the polysomnographer a unique opportunity to evaluate potential cerebral dysfunction. Incorporation of multiple EEG electrodes to cover both the temporal and parasagittal regions of the scalp is

Table 18.5 Hybrid EEG/parasomnia montage

Channel number	Name
1	F3-M2
2	C3-M2
3	O1-M2
4	T3-T5
5	T5-O1
6	T4-T6
7	T6-O2
8	C4-P4
9	Left electro-oculogram (E1-M2)
10	Right electro-oculogram (E2-M2)
11	Chin electromyogram (EMG)
12	Right masseter EMG
13	Right sternocleidomastoideus EMG
14	Right biceps brachii EMG
15	Left biceps brachii EMG
16	Right lumbar paraspinals EMG
17	Right quadriceps EMG
18	Left quadriceps EMG
19	Right tibialis EMG
20	Right gastrocnemius EMG
21	Left tibialis EMG
22	Left gastrocnemius EMG
23	Intercostal EMG
24	Right lower rectus abdominis EMG
25	Oronasal thermistor[a]
26	Nasal pressure transducer[a]
27	Chest
28	Abdomen
29	Snoring
30	Arterial oxygen saturation
31	ECG
32	Heart rate

Channels 1–8 record electroencephalogram activity from bilateral cerebral hemispheres in a bipolar montage. Channels 11-24 record EMG activity, including from some additional muscles not routinely studied on typical PSGs. Channels 25 and 26 record airflow ("flow channels"). Channels 27 and 28 record respiratory effort ("effort channels")

[a]In a CPAP titration study, flow channels are replaced by a CPAP signal (C-flow signal)

particularly important for a patient with suspected nocturnal seizure (see also Chap. 44).

Describing EEG Activity

EEG activity is described based on particular characteristics, summarized in Table 18.6 (see also Chap. 24). EEG frequency is measured in hertz (Hz, or cycles per second) and is commonly in the delta, theta, alpha, or beta range. EEG activity is also described on the basis of its distribution (whether localized, i.e., predominantly frontal, temporal, central, occipital, or generalized), amplitude, rhythmicity (whether the waves have a sinusoidal pattern and occur in a set pattern), morphology (e.g., monomorphic [all similar in appearance], or polymorphic [dissimilar]), synchronicity (i.e., occuring simultaneously in both hemispheres), symmetricity (equal amplitude on both sides), regularity (intermittent or continuous), and reactivity (whether the activity changes in response to stimulation).

Table 18.6 Descriptive terminology used in EEG analysis

Frequency
• Delta, theta, alpha or beta range
Distribution
Localized or generalized
Amplitude
Rhythmicity
Morphology
• Monomorphic or polymorphic
Synchronicity
Symmetry
Reactivity

Normal Waking Rhythms

A normal awake adult EEG has a characteristic posterior dominant rhythm (PDR) in the *alpha range*, generally between 8 and 13 Hz. As implied by its name, this rhythm is distributed over the parieto-occipital regions bilaterally, becoming less pronounced anteriorly (i.e., has an anterior-posterior gradient). It is synchronous and symmetric over the two hemispheres. Frequency of the rhythm should not vary by more than 1 Hz, and amplitude should not vary by more than 50 %, between the two hemispheres. The PDR is best seen during quiet alertness with eyes closed and attenuates with eye opening (i.e., it is reactive, see Chap. 24). The PDR may be suppressed in an anxious patient. Up to 10 % of normal adults will show no alpha rhythm during quiet wakefulness. The EEG in these subjects is characterized by low-amplitude (10–20 μV) poorly sustained beta (>13 Hz) and a small amount of theta frequencies. Occasionally, hyperventilation elicits a typical alpha rhythm in such patients. With drowsiness, the PDR slows into the theta range and may be better seen anteriorly before dropping out and being replaced by typical sleep background activities. A PDR slower than in the normal alpha range may be seen in patients with encephalopathies from various causes, both acute (e.g., toxic-metabolic) and chronic (e.g., dementia).

Non-alpha range rhythms may occasionally be seen in normal waking EEGs (e.g., beta rhythms). There are probably at least two beta rhythms, one distributed over the frontal and central regions and the other with a more diffuse distribution. Beta rhythms are present during wakefulness and drowsiness. They may appear more persistent during drowsiness, drop out during deeper sleep, and reappear during REM sleep. Amplitude over the two hemispheres should not vary by more than 50 %. Amplitude of beta activity is less than 20 μV in 98 % of normal drug-free subjects. A persistent beta rhythm with higher amplitude suggests use of sedative-hypnotic medications (generally benzodiazepines and barbiturates) because most such medications increase amplitude of beta activity.

It is important to bear in mind that the EEG in infants and children undergoes significant evolution with increasing brain maturity. A sustained PDR is not seen until approximately 3 months of age. At that time, reactive 3-Hz waves are recorded during wakefulness. Frequency of the parieto-occipital rhythm increases rapidly over the next several years, reaching at least 6 Hz by one year of age and adult values in most children by 8–9 years of age. Greater amounts of random frontocentral theta are seen in children than in adults, but this decreases as the child ages. Brief runs of more sustained low-amplitude (15 μV) frontal 6- to 7-Hz waves are seen in as many as 35 % of adolescents. This rhythm is present during quiet wakefulness with eyes open and may be related to affective arousal.

Whether slowing of the PDR is a natural consequence of aging remains controversial [30, 31]. However, an alpha rhythm with a dominant frequency of less than 8 Hz is always abnormal in adults. Focal temporal theta or delta is seen in as many as 35 % of asymptomatic individuals older than 50 years. Such activity is more commonly noted over the left temporal regions and should probably occupy no more than 5 % of the tracing. More persistent temporal slowing is considered abnormal by most electroencephalographers.

Normal Sleep EEG

This section provides a brief overview of normal EEG changes in sleep from the point of view of the electroencephalographer. Readers are referred to Chap. 24 for a detailed description of the implications of EEG changes for staging sleep while interpreting a PSG.

Stage 1 sleep (equivalent to N1 sleep on PSG) is a transitional stage between wakefulness and Stage 2 sleep, occupying a relatively small percentage of a normal night's sleep, generally less than 5 %. The term "drowsiness," while often used by electroencephalographers, is not a standard part of the polysomnographers' lexicon. Indeed, even within

the electroencephalographer community, the distinction between drowsiness and Stage 1 is often difficult and arbitrary. Drowsiness may be thought to occur with shifting of the posterior rhythms of wakefulness from the characteristic parieto-occipital distribution to the frontocentral or temporal regions. Amplitude of alpha activity may either increase or decrease and frequency of the alpha rhythm may slow. Slow lateral eye movements may appear (Fig. 24.8). Slower theta and delta frequencies may be superimposed in the central or temporal regions. In older patients especially, paroxysmal theta bursts may predominate in one temporal region. Eventually, the PDR disappears altogether. Vertex waves, high-voltage monophasic surface-negative sharp transients with a maximal voltage at the Cz electrode (often with extension of the field to Fz, or less frequently Pz) occur (Fig. 24.9) and may be particularly sharp and of high amplitude in children and young adults.

Stage 2 (equivalent to N2 sleep on PSG), which comprises the bulk of a normal night's sleep in an adult, is characterized by the presence of specific sleep architecture and a synchronized EEG background. Sleep spindles are prominent (see Figs. 24.13 and 24.14). There is a high degree of symmetry and synchrony between the two hemispheres in normal subjects older than one year. Some investigators have proposed a classification of spindles based on topography and frequency [32], but it is not clear that this has clinical utility at this time. K complexes (Fig. 24.12), another feature of N2 sleep, often accompanies sleep spindles. Slow-wave activity may be seen in this stage but does not meet the criteria for Stage 3.

Stage 3 sleep (equivalent to N3 sleep on PSG, see Chap. 24), commonly referred to as "slow-wave sleep," is present when 20 % or more of any epoch is occupied by waves slower than 2 Hz and greater than 75 μ (Fig. 24.16). Electroencephalographers (but not polysomnographers) recognize an additional sleep stage, Stage IV, when the slow waves occupy more than 50 % of the epoch. Vertex waves, sleep spindles, and K complexes may persist in this stage but are much less prominent. The percentage of Stage N3 tends to decrease with age.

REM sleep has very characteristic EEG, EMG, and EOG features. In contrast to Stages 2 through 3 sleep, the background EEG is desynchronised, meaning that it is comprised of low-voltage, mixed-frequency activity similar to Stage 1. Alpha frequencies are often present and may be more persistent than in Stage 1 but are usually 1–2 Hz less than the subject's waking rhythm [33]. Vertex waves, sleep spindles, and K complexes are generally absent, although may occasionally occur, especially in the earlier REM cycles. In fact, REM-spindle sleep (Fig. 18.12), where sleep spindles

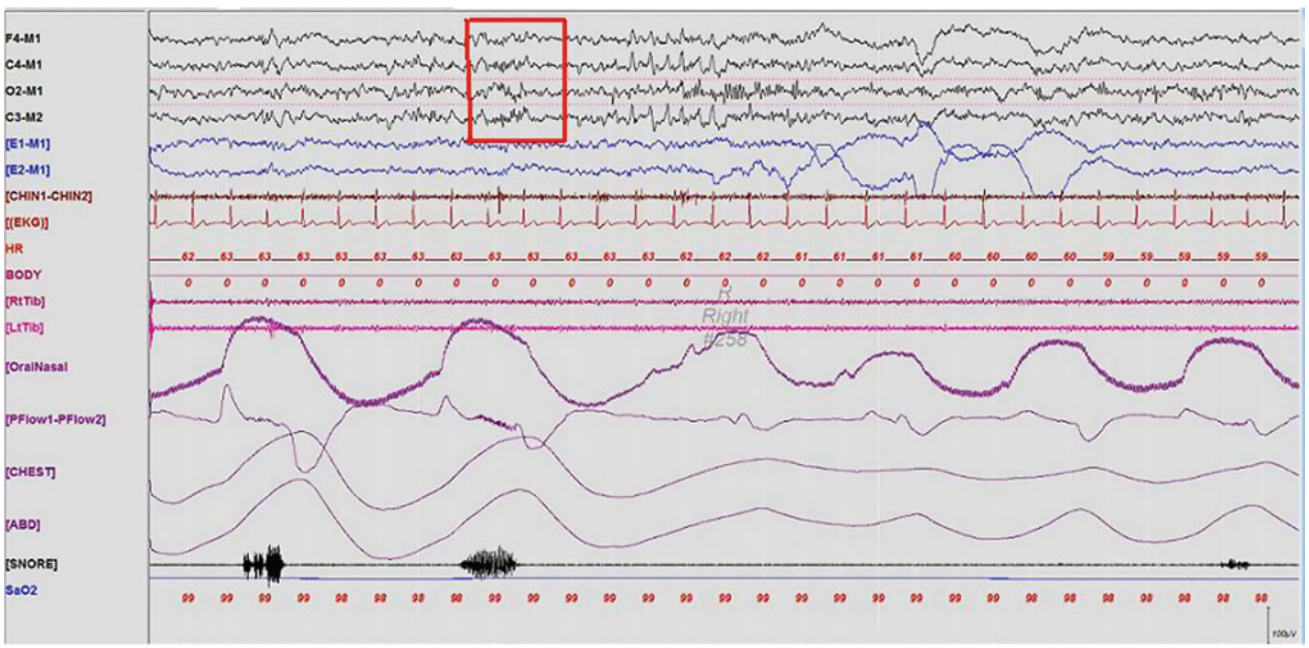

Fig. 18.12 A case of sleep spindles in REM sleep. Shown is a 30 s epoch from the overnight PSG of a 50-year-old woman with difficulty sleeping, loud snoring, and excessive daytime sleepiness for 5 years. Medical history is significant for chronic headaches and hypothyroidism. Nocturnal PSG showed the presence of mild sleep apnea (no respiratory events are occurring in this epoch) with an apnea–hypopnea index of 10/hr. Note the presence of sleep spindles (*box*) during REM sleep. Prominent sawtooth waves of REM sleep in C3- and C4-derived EEG channels, prominent phasic eye movements of REM sleep on electrooculogram channels and decreased chin muscle tone characteristic of REM atonia are seen. Sleep spindles, while characteristic of Stage N2 sleep, may be seen in REM, especially in the early cycles. Reproduced with permission from: Chokroverty and Thomas [65]

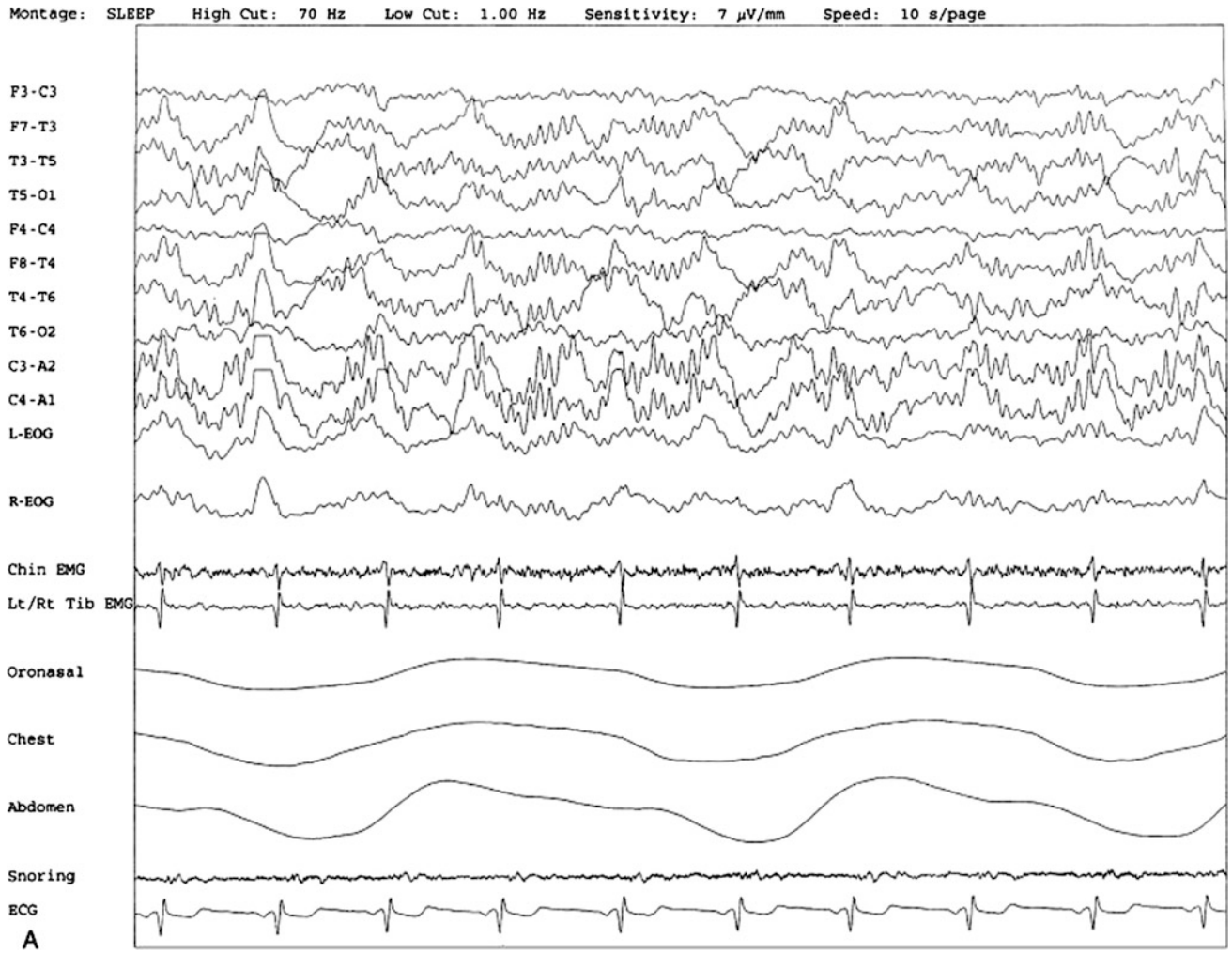

Fig. 18.13 A case of alpha-delta sleep. Ten- and 30-second excerpts from a nocturnal PSG showing alpha–delta sleep in a 30-year-old man with history of snoring for many years. He denied any history of joint or muscle aches and pains. The alpha frequency is intermixed with and superimposed on underlying delta activity. Alpha–delta sleep denotes a nonspecific sleep architectural change noted in many patients with complaints of muscle aches and fibromyalgia. It is also seen in other conditions and many normal individuals. EEG, Top 10 channels; Lt. and Rt. EOG, left and right electrooculograms; chin EMG, EMG of chin; Lt./Rt. Tib. EMG, left/right tibialis anterior EMG; oronasal thermistor; chest and abdomen effort channels; snore monitor; ECG, electrocardiography. Reproduced with permission from: Chokroverty and Thomas [65]. (Figure 9 from Atlas 2nd edition)

intrude on what otherwise meets all the scoring criteria for REM sleep, may be seen in 1–7 % of normal subjects but is more common when sleep is disrupted and after the first night of continuous positive airway pressure treatment [34]. Characteristic sawtooth waves (Fig. 18.12), 2- to 7-Hz sharply contoured triangular waves usually occurring serially for several seconds with highest amplitude over the Cz and Fz electrodes are seen, which usually, but not always, precede a burst of REMs [35]. REM sleep occupies 20–25 % of a night's sleep in a normal adult subject.

An atypical variant is the so-called "alpha-delta sleep" pattern (Fig. 18.13) characterized by persistence of alpha activity overriding the slow waves of Stage N3. It may be seen in Stage N2 as well, obscuring spindles. Its clinical relevance is unknown at this time, but it appears to be associated with unrefreshing sleep and is seen in a variety of conditions associated with muscle aches and pains. Researchers have shown that it can be produced by depriving patients of slow-wave sleep, a process that also elicited complaints of diffuse arthralgias, myalgias, and fatigability, similar to the complaints of the fibromyalgia syndrome. These findings raise the intriguing question whether fibromyalgia is basically a sleep disorder causing musculoskeletal symptoms rather than the other way around, but clearly more research needs to be done in this regard [36–38].

Normal Sleep EEG in Pediatrics

The transition from neonatal to infantile EEG sleep patterns occurs between 1 and 3 months (see also Chap. 52).

The first recordable EEG activity begins at around 8 weeks conceptual age (CA), as a completely low voltage (>25 μV), completely discontinuous background (i.e., the periods of background activity ["burst interval"] are interspersed by periods of background suppression ["interburst interval"]). As the neonate ages, the burst interval increases and the interburst interval decreases; at 24 weeks CA, the interburst interval is approximately 6–12 s, but by 30 weeks CA, it decreases to about 5–8 s. This continuously discontinuous EEG persists between 8 and 12 weeks CA; after this age, it can be divided into three stages; wake, active sleep (a precursor of REM sleep), and quiet sleep (a precursor of NREM sleep). Between 30 and 36 weeks CA, the EEG is more continuous in wake and active sleep but still very discontinuous in quiet sleep (with an interburst interval amplitude of >25 μV, "tracé discontinu"). Between 36 and 42 weeks, the activity becomes nearly continuous in active sleep and wake ("activité moyenne") and remains discontinuous in quiet sleep, but with higher amplitudes of the interburst interval than seen in tracé discontinue (>25 μV). The tracé alternant pattern ("tracé alternant", Fig. 18.14) gradually matures into the "continuous slow-wave sleep pattern" and complete continuity of the EEG background in all stages of sleep is generally achieved between 42 and 46 weeks CA.

Even after the neonatal period, there is a great deal of change in the electroencephalographic patterns until the adult patterns are reached. Drowsiness in the pediatric age group differs from the adult patterns in several ways. Before eight months of age, drowsiness is marked by a progressive slowing of EEG frequencies until delta waves predominate. After eight months, the onset of drowsiness is marked by long runs of continuous, generalized, high-voltage rhythmic theta or delta waves, which have been called hypnagogic hypersynchrony (see Chap. 24). Three types have been described in normal subjects [39]. In the most common type, the rhythmic slow waves have highest amplitude in the frontal and central regions. The continuous rhythmic slowing may persist for several minutes. Less commonly, amplitude is highest in the parieto-occipital regions. Finally, a paroxysmal type occurs in approximately 10 % of normal children. With this pattern, the alpha rhythm is gradually replaced by mixed frequencies. Diffuse bursts of 2- to 5-Hz slow waves, a few seconds in duration, then appear intermittently. Occasionally, random, poorly developed, and sharply contoured waveforms are noted amidst the slow waves. These may be random, superimposed alpha transients and should not be confused with epileptiform spike and wave. The first two types of hypnagogic hypersynchrony are rarely recorded after age 10. The paroxysmal type persists into the mid-teens or, rarely, into adulthood. In infancy and early childhood, 20- to 25-Hz beta is also a prominent feature of drowsiness. The beta rhythm may have maximum

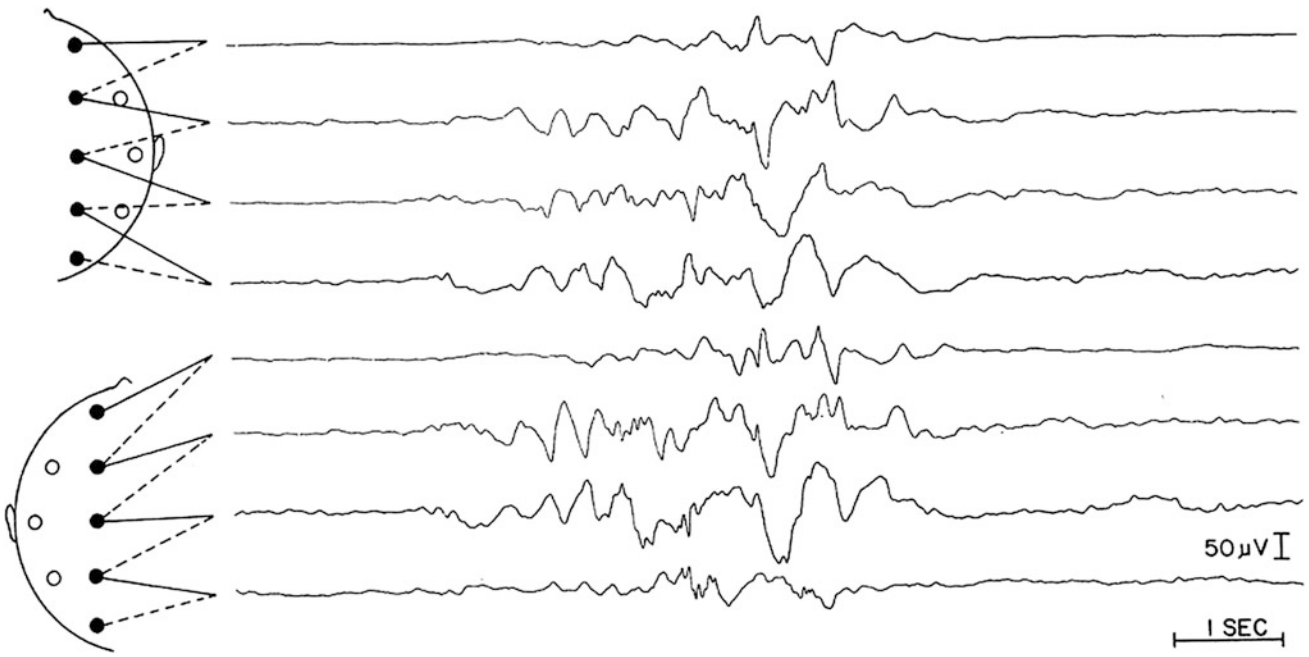

Fig. 18.14 Pattern of quiet sleep ("trace alternant") in a normal full-term infant, 4 days old. Reproduced with permission from: Fisch and Spehlmann's EEG Primer [70]

voltage anteriorly or posteriorly or have a diffuse distribution. The amplitude may reach 60 μV. This pattern appears at 6 months and is seen most frequently from 12 to 18 months. Prevalence decreases subsequently, and prominent beta rhythm during drowsiness is rarely seen after 7 years [40].

Vertex waves may be seen around three months, and K complexes appear at age six months. These potentials are rather blunt and may reach amplitudes exceeding 200 μV in infancy and early childhood. By age five years, both vertex waves and K complexes have an increasingly spiky configuration. Mild asymmetry is quite common. They may occur repetitively in brief bursts. Sleep spindles appear at approximately three months of age. Between three and nine months of age, spindles occur in wicket-like trains often exceeding several seconds. These potentials are common at this age, often occupying as much as 15 % of Stage N2 sleep. Asynchrony between the hemispheres is the rule, with only half of the trains demonstrating interhemispheric synchrony at six months. Interhemispheric synchrony increases to 70 % by 12 months and the duration and frequency of the spindle bursts gradually decrease. By two years of age, virtually all spindle trains are synchronous; however, spindles are much less frequent, occupying only 0.5 % of Stage II sleep. Spindles remain infrequent until approximately five years of age [41–43].

Stage N3 sleep is marked by slow activity, as in adults, but the amplitude of the slow activity is usually higher. An occipitofrontal gradient is often present with a very high amplitude, slower frequencies predominating posteriorly, and lower amplitude, faster frequencies predominating anteriorly. This gradient becomes less striking with age, so that by five years, the slow waves are distributed more diffusely.

EEG during REM sleep in infants and children is characterized by a greater amount of slow activity than in adults. The mature desynchronized EEG with scattered alpha emerges during the mid-teens. Neonates may have up to 50 % of sleep occupied by REM, and may often directly enter sleep through REM. The percentage of a normal night's sleep occupied by REM gradually decreases from 40 % at age 3–5 months to 30 % at age 12–24 months and then gradually assumes adult values by about six years. REM onset latency gradually lengthens over the first year of life as well [44, 45].

Abnormal EEG

While EEG abnormalities on PSG recordings are not very common, the polysomnographer must be familiar with the most frequently occurring findings of clinical significance. This section is not intended to be an exhaustive description of all possible EEG abnormalities but is meant to provide an introduction to the most frequently encountered findings. Readers are referred to several excellent volumes that deal with EEG abnormalities in depth [5, 46–48].

Slowing

Diffuse slowing of background activity (Fig. 18.15) is probably the most commonly recorded EEG abnormality. This may range from mild slowing, where the PDR is below the expected frequency, or the background may have excessive, diffuse theta and delta activity with a normal PDR. More moderate slowing occurs when there is no clear PDR or anteroposterior gradient, and the background is diffusely in the theta or delta ranges. The most severe slowing entails a nonreactive background, generally in the delta range. Specific patterns may have their own significance; for example, frontal intermittent rhythmic delta activity (FIRDA) is often seen with midline or diffuse lesions and triphasic waves (described in greater detail below) may be seen with a variety of toxic-metabolic encephalopathies. Before concluding that an EEG has excessive slowing of background frequencies, the polysomnographer must consider the patient's age and state of alertness. More diffuse theta is seen in normal children than is acceptable for adults. Frequency of background rhythms must be assessed while the patient is clearly awake. As noted earlier, both slowing of alpha rhythms and diffuse slower frequencies are commonly found in drowsiness in normal subjects. Consequently, the polysomnographer must be certain that the background frequencies are slow during wakefulness. Unfortunately, diffuse slowing of background frequencies is a very nonspecific pattern. It is commonly interpreted as being consistent with a variety of diffuse encephalopathies, including toxic, metabolic, and degenerative encephalopathies but is generally unable to distinguish between them.

Focal slowing (Fig. 18.16) refers to slow frequencies that predominate over one discrete region of the brain. Electrocerebral activity elsewhere is normal or generalized slowing is present but is relatively mild. A structural lesion must always be suspected when persistent focal slowing is recorded, although this may not always be reflected in brain imaging [49]. In epilepsy patients, this slowing may be due to an ongoing local ictal phenomenon (such as in patients with temporal intermittent rhythmic delta activity [TIRDA], see below) or may be a transient postictal finding.

Another important abnormality is background attenuation, where activity over one region or one hemisphere is of lower amplitude than the other. Any fluid collection between the cortex and the recording electrode attenuates the recorded EEG activity. Thus, subdural fluid collections and

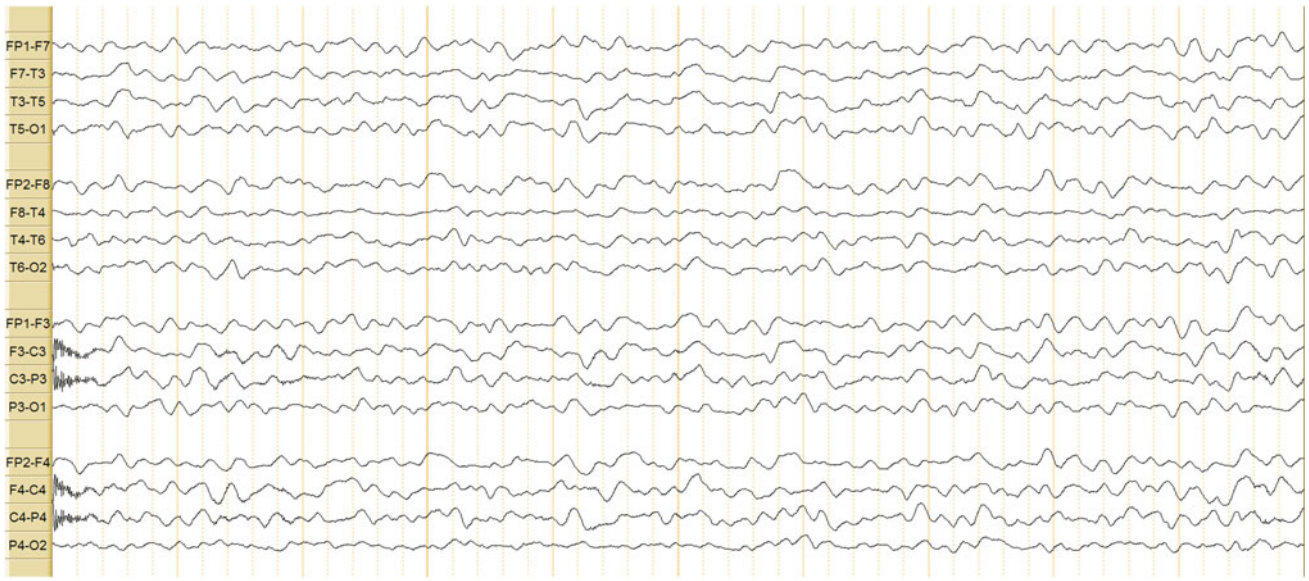

Fig. 18.15 10 s EEG epoch recorded from an 81-year-old woman with mild cognitive impairment. Note the slow, disorganized background and slow, ill-defined, and ill-sustained posterior dominant rhythm in the theta range (6–7 Hz). This is suggestive of a nonspecific toxic metabolic encephalopathy

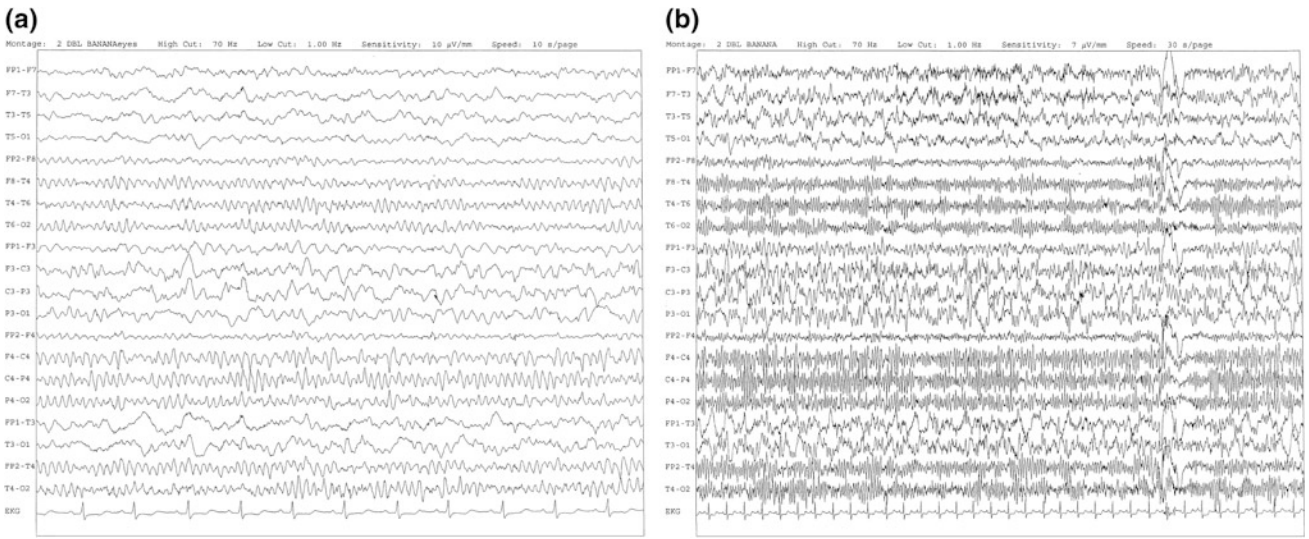

Fig. 18.16 **a** 10-s and **b** 30-s EEG epoch shows focal slowing at 3–6 Hz over the left temporoparietal region in an 85-year-old man with history of a stroke. Normal alpha rhythm at 10–11 Hz is noted on the right side. Reproduced with permission from: Chokroverty and Thomas [65]

subgaleal hematomas may result in a focal attenuation of background, although the cortex may not be damaged.

The converse situation exists when a section of skull is missing or the skull has a defect, which results in a breach rhythm. Without the attenuating effect of bone, local electrocerebral activity is of higher amplitude, more sharply contoured, and may display more fast frequencies than its counterpart in the other hemisphere. Such skull defects are generally a result of neurosurgical intervention to address an underlying brain lesion; hence, there is frequently slowing and possibly also sharp activity interspersed with breach rhythms. Determining the epileptogenic potential of such activity often poses a challenge to even the most experienced electroencephalographer.

Epileptiform Activity

EEGs cannot be interpreted in isolation; as the old adage goes, the clinician must treat the patient, not the EEG. Epilepsy is a clinical diagnosis. Therefore, history must be obtained from patients, relatives, witnesses, or medical personnel. The history must include descriptions of preictal, ictal, postictal, and interictal phenomena, family and drug histories, as well as history of any significant medical or surgical illnesses that might be responsible for triggering the seizures. A meticulous and thorough physical examination must be conducted to find any evidence of neurological or other medical disorders before ordering an EEG. EEG is the single most important diagnostic laboratory test for patients with suspected seizure disorder, when ordered appropriately in light of the patient's history and physical examination findings. Certain characteristic EEG waveforms correlate with a high percentage of patients with clinical seizures and therefore can be considered of potentially epileptogenic significance. These epileptiform patterns consist of spikes, sharp waves, spike and waves, sharp and slow-wave complexes, as well as evolving pattern of rhythmic focal activities, particularly in neonatal seizures. In addition, a pattern that correlates highly with complex partial seizure is temporal intermittent rhythmic delta activity (TIRDA) (Fig. 18.17). Another pattern that is considered a marker of the seizure onset zone is interictal scalp high-frequency oscillations (HFOs) consisting of gamma frequency activity (30–80 Hz), ripples (80–250 Hz), and fast ripples (250–1000 Hz), recorded noninvasively using amplifiers with appropriate filter settings (Fig. 18.18). Therefore, recording HFOs may help map epileptogenic zones.

Recognition of a spike or a sharp wave depends on the presence of certain characteristics [50]. A spike is defined as a waveform, which suddenly appears out of the background rhythm with a brief duration of 20–70 ms showing a field of distribution and is often followed by an after-going slow wave (Fig. 18.19a). It must also have a field, i.e., there must be some evidence of the area of cortical negativity over adjacent electrodes. A sharp wave fulfills all the criteria described for a spike except that the duration is 70–200 ms. Generally, spikes or sharp waves are surface negative (resulting in phase reversals in bipolar montages, see discussion above). The characteristic feature of a true epileptiform spike or sharp wave is a biphasic or triphasic appearance with a sharp ascending limb followed by a slow descending limb in contrast to augmented background rhythm of sharp contour, which is generally monophasic and has uniform ascending and descending limbs (Fig. 18.19b). The amplitude of a true epileptiform spike or sharp wave is at least 30 % higher than the background activity, and often there is a disturbance in the background rhythm in the neighboring region of the spikes or the sharp waves. Spike and waves, and sharp- and slow-wave complexes may be transient or may repeat for several seconds or longer, and in some patients these repeat in a rhythmic manner, such as may be seen in patients with absence seizure showing 3-Hz spike and wave complexes in the EEG (Fig. 44.1).

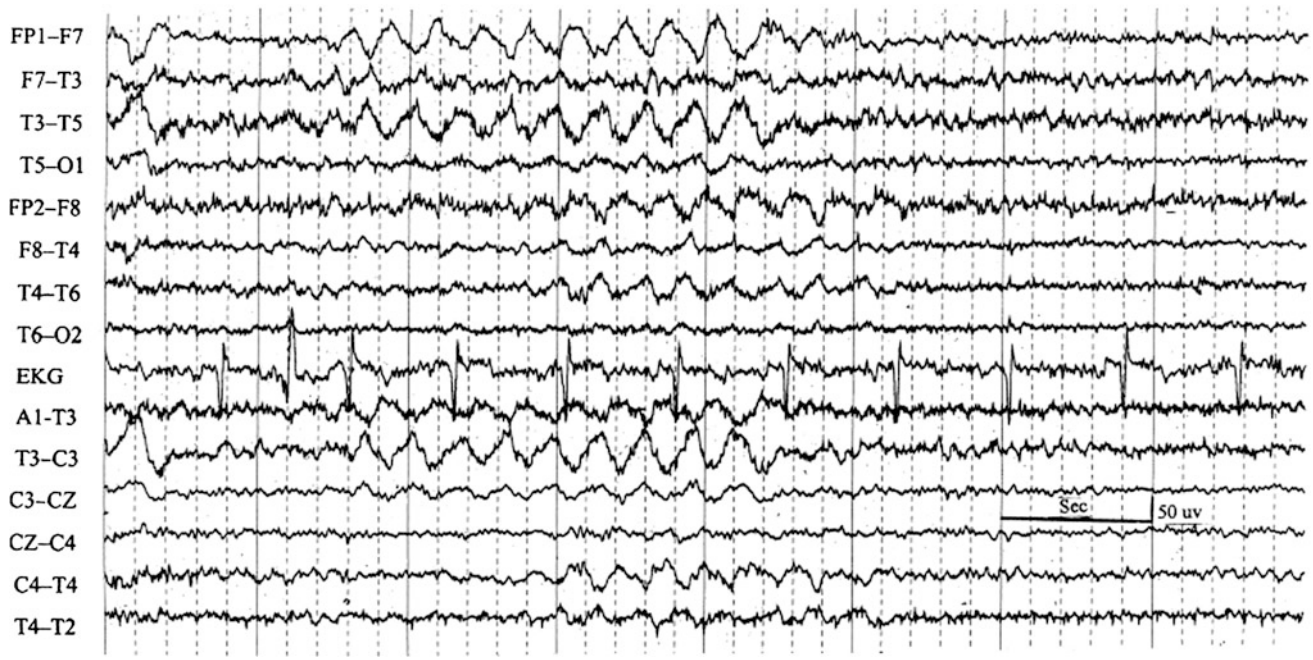

Fig. 18.17 10 s EEG epoch shows left temporal intermittent rhythmic delta activity (TIRDA) during wakefulness in a 30-year-old woman with partial complex seizures. Reproduced with permission from: Chokroverty and Thomas [65] (Figures 2–7 from Atlas 2nd edition)

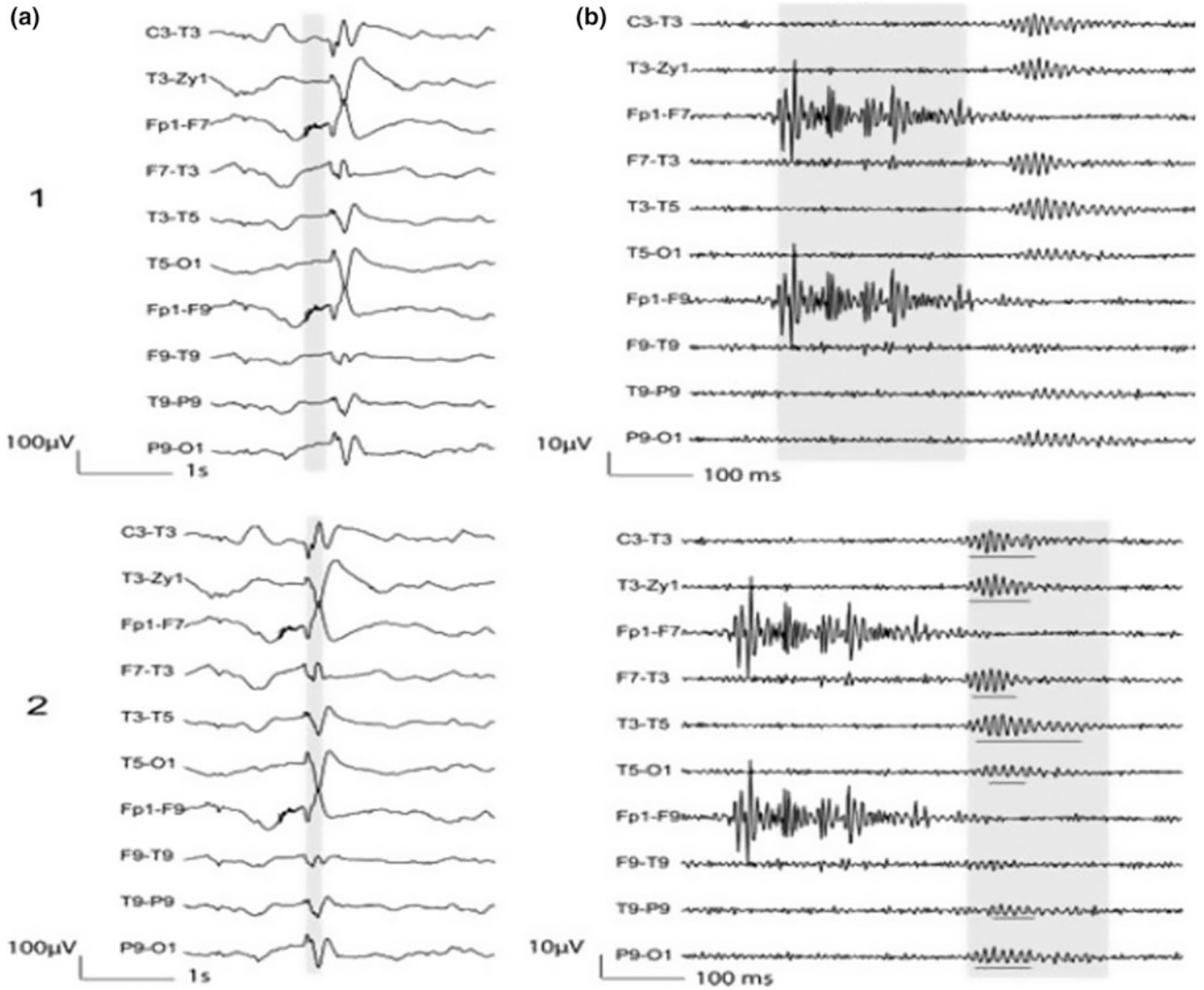

Fig. 18.18 *1* Short EMG burst, which could be mistaken for ripples but are actually artifactual oscillations. *2* Ripples co-occurring with sharp wave. **a** Raw EEG. **b** EEG filtered with high-pass filter of 80 Hz. Gray section in A is expanded in time and amplitude in B. Note that for this figure the calibration is different in the left and right part of the figure but is the same for the top and bottom parts. Ripple oscillations are underlined. The waveform morphology of nonartifactual fast oscillations is more rhythmic and regular in amplitude and frequency than artifactual oscillations. From Andrade-Valencia et al. [66]. Used with permission

A basic distinction is made between generalized and focal epileptiform discharges. Generalized epileptiform discharges indicate that the patient's seizure is likely to start simultaneously throughout the brain. An example is the aforementioned generalized 3-Hz spike and wave that is characteristic of petit mal absence seizures. Focal epileptiform discharges indicate that the patient's seizure is likely to start in a restricted area of the brain, although it may subsequently spread. An example is the anterior temporal sharp wave that is characteristic of complex partial seizures of temporal lobe origin (Fig. 18.20). This is an important distinction because the treatment and prognosis in these two epilepsy syndromes are very different.

It is important to distinguish between epileptiform activity, which portends a potential propensity toward seizures, and an actual electrographic seizure. Many electroencephalographers liken this distinction to the difference between the weather being cloudy (epileptiform activity on an EEG) and it actually raining (an electrographic seizure). When spikes, sharp waves, or rhythmic slow waves increase in frequency and rhythmicity and evolve in location and distribution, a seizure is recorded. If there is a clinical correlate to this finding, it is called a clinical seizure, otherwise it remains an electrographic or nonconvulsive seizure. It is therefore crucial that the technician be ever vigilant during the recording and carefully document any abnormal behavior

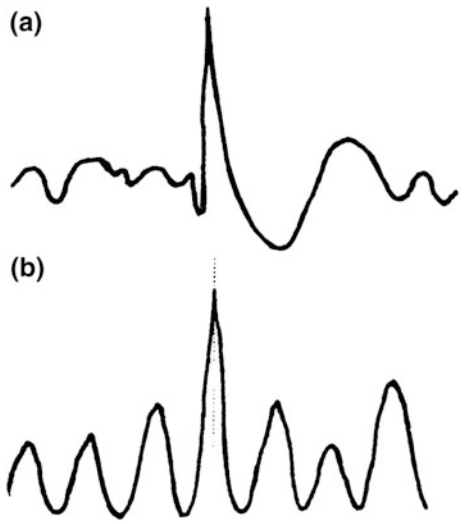

Fig. 18.19 Diagram of epileptic spike (**a**) and an augmented background sharp rhythm (**b**) (From Ajmone-Marsan [67], with permission)

on the patient's part. However, it is rare to observe the occurrence of a clinical seizure during an EEG recording (see Chap. 44). Therefore, a definitive statement about the diagnosis of epilepsy in a particular patient cannot be made even in the presence of the characteristic EEG signs of epilepsy. Approximately 90 % of adults with epileptiform discharges will have a history of seizures, and incidental epileptiform discharges are very uncommon in normal adults [51, 52].

In patients suspected of seizure disorder, it is advantageous to include activation procedures such as sleep, hyperventilation, and photic stimulation during routine EEG recording in the daytime in order to bring out the ictal or interictal epileptiform patterns. Special basal temporal electrodes (T1, T2 and sphenoidal electrodes) should be used in addition to the routine electrode placement in patients suspected of partial complex seizure. Many patients are referred to the sleep laboratory with suspected nocturnal seizures, and as described above, in such patients, the PSG study must include multiple EEG channels covering the parasagittal and temporal regions bilaterally.

Epileptiform Patterns in Sleep

Patients with focal or generalized seizures may sometimes present only during night. On the one hand, such nocturnal seizures may be mistaken for other motor disorders during sleep such as parasomnias. On the other hand, patients with a variety of sleep-related movement disorders (severe sleep apnea, periodic limb movements in sleep, hypnic jerks, confusional arousals, and night terrors) are misdiagnosed as having nocturnal seizures. It is, therefore, important for the sleep specialists to be familiar with the clinical and EEG patterns seen in primary generalized seizure (e.g., absence spells or generalized tonic–clonic seizures) and partial complex seizures of temporal or extratemporal (frontal) origin.

Patients with nocturnal frontal lobe epilepsy are often referred to the laboratory for PSG recording (see Chap. 44). The characteristic EEG pattern in the primary generalized epilepsy of the absence type is the presence of symmetrical and synchronous frontally dominant 3-Hz spike and wave discharges (Fig. 44.2) seen either as an ictal or as an interictal pattern. EEG immediately before and after this discharge remains normal. Patients with tonic–clonic seizures may show a sudden burst of spike and slow waves beginning at a rate of 4–6 Hz and then gradually slowing down and stopping before the postictal

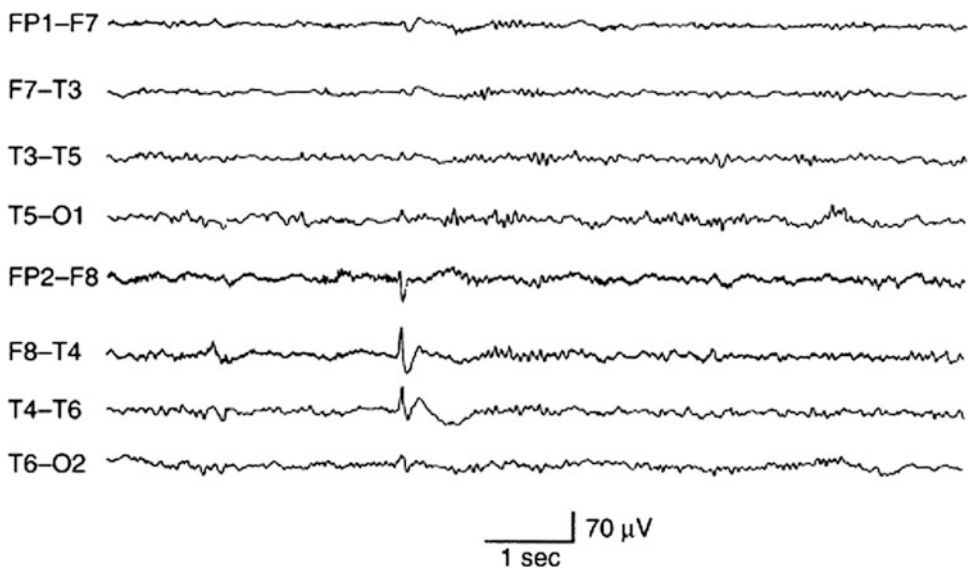

Fig. 18.20 Right temporal interictal epileptiform discharge in a 32-year-old patient with complex partial seizures. Calibration: *vertical bar* 70 µv, *horizontal bar* 1 s (Reproduced with permission from Emerson [71]

period. These discharges are seen in a bilaterally symmetrical and synchronous fashion. Postictal slow waves are followed by gradual recovery to the preictal normal background rhythm after several hours or sometimes after a day or two. Interictal EEG may show generalized synchronous and symmetrical 4- to 6-Hz spike- and slow-wave discharges or multiple spike and waves.

Some patients with generalized tonic–clonic and partial complex seizure may also have predominantly nocturnal seizures. It is well known that sleep deprivation can lower seizure threshold; indeed, sleep-deprived EEGs increase the yield of identifying epileptiform activity.

In addition, certain types of seizures are characteristically observed during sleep or at sleep–wake transition, and so it is important to differentiate nocturnal seizures from motor and behavioral parasomnias and other movement disorders persisting during sleep. Tonic seizures are typically activated by sleep, occur frequently during NREM sleep, and are never seen during REM sleep. A typical EEG shows interictal abnormality as slow spike and waves intermixed during sleep with trains of fast spikes. Benign focal epilepsy of childhood with centrotemporal spikes is characterized by the presence of centrotemporal or rolandic spikes or sharp waves (Fig. 44.7). Seizures generally resolve by the age of 15–20 years without any neurologic sequelae. Juvenile myoclonic epilepsy (Fig. 18.21) typically shows in the EEG synchronous and symmetrical multiple spikes and

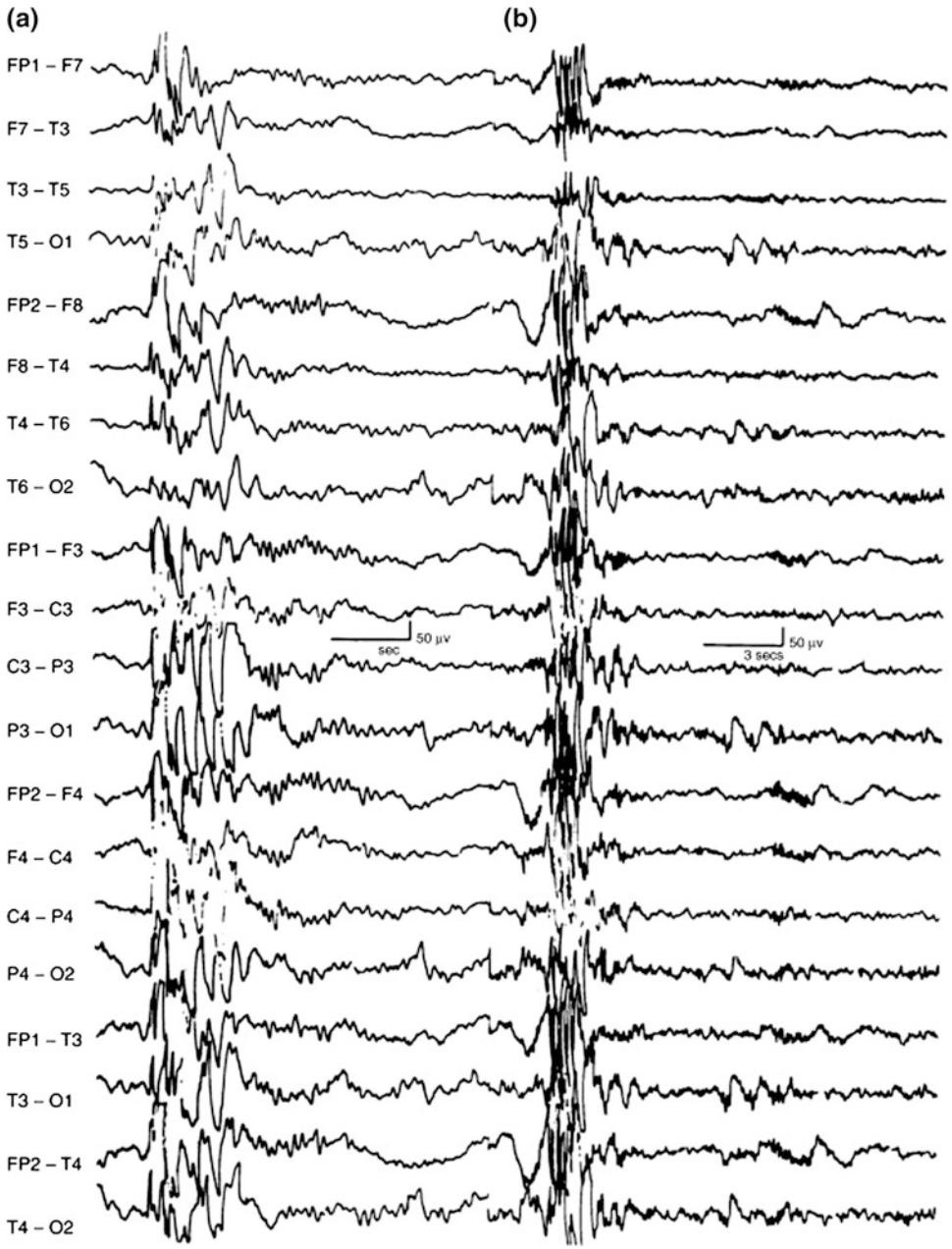

Fig. 18.21 Interictal generalized multiple spike and wave discharges in the EEG of a patient with juvenile myoclonic epilepsy. Note the recording at 30 mm/sec (10 s epoch, conventional EEG speed) on the *left* (**a**) and at 10 mm/s (30 s epoch, conventional polysomnogram speed) on the *right* (**b**) (From Chokroverty and Montagna [72]) (Figures 2–30 from Atlas 2nd ed)

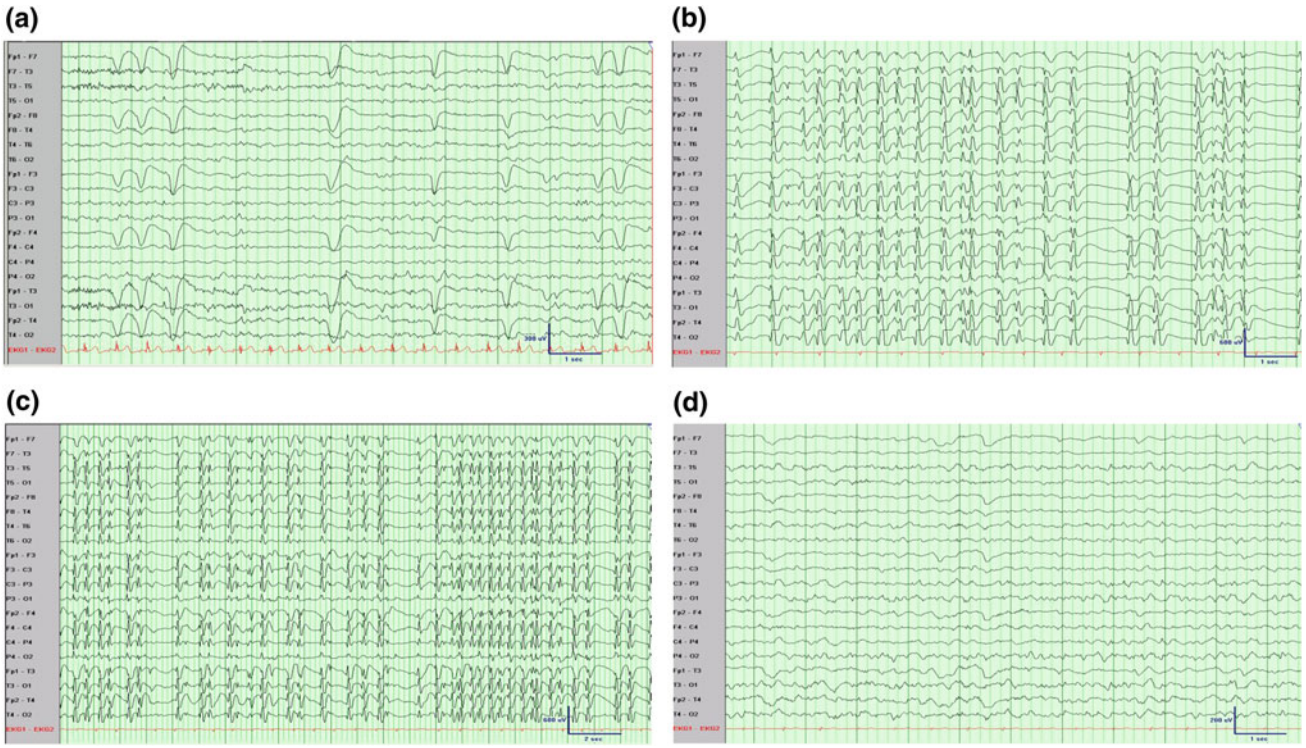

Fig. 18.22 EEG tracings from a 9–year-old boy with developmental delay and poor speech output and nocturnal events of uncertain etiology. **a**: 30 mm/s epoch of wakefulness showing eye blinks in the bilateral frontopolar leads with no evidence of epileptiform activity. **b**: 30 mm/s EEG epoch of Stage N3 sleep. The patient had 2–3.5 Hz continuous generalized spike and wave discharges with 1–2 s of electrocerebral decrement (continuos spike and wave in slow-wave sleep, CSWS). **c**: Same epoch as B, displayed at a speed of 10 mm/s (the usual speed at which polysomnograms are reviewed). **d**: 30 mm/s EEG epoch of rapid eye movement (REM) sleep in the same patient showing absence of epileptiform activity (Reproduced with permission from Neiman et al [68])

spike-wave discharges. The EEG in the entity of continuous spike and waves during NREM sleep consists of generalized 2- to 2.5-Hz spike and wave discharges occupying 85 % of slow-wave (CSWS) sleep and are suppressed during REM sleep (Fig. 18.22). This entity is generally seen in children and is associated with developmental regression; it may be mistaken for autism and illustrates the importance of capturing sleep even on daytime EEGs [53].

Chapter 44 discusses the relationship between clinical seizures and sleep in greater detail.

Nonepileptiform Patterns Mimicking Epileptiform Discharges

There are several nonepileptiform EEG patterns that may mimic epileptiform discharges but are not of epileptogenic significance. They are benign in nature, but the inexperienced electrencephalographer and polysomnographer may misread these completely normal variants as abnormal findings. Familiarity with them is the key to avoiding an erroneous report of epileptiform activity, which may lead to unnecessary further testing and unwarranted medication administration. Some commonly seen normal variants are described below.

Benign Sharp Transients Seen During Sleep and Wakefulness

A number of normal variants with sharply contoured morphology occur in sleep and wakefulness, and may perplex a polysomnographer unless they are identified correctly. However, they are all benign phenomena with no clinic significance.

Positive occipital sharp transients (POSTs) (Fig. 18.23) are diphasic or triphasic sharp waves with a predominant positive phase at the occipital electrodes and generally occur in drowsiness and early Stage N1. POSTs are noted synchronously over the two hemispheres and may occur singly or in runs. Occasional shifting amplitude asymmetry is noted in normal controls; however, persistent significant asymmetry should raise suspicion of a posterior lesion. Because, these potentials have a paroxysmal sharply contoured appearance, they may be confused with epileptiform discharges [54]

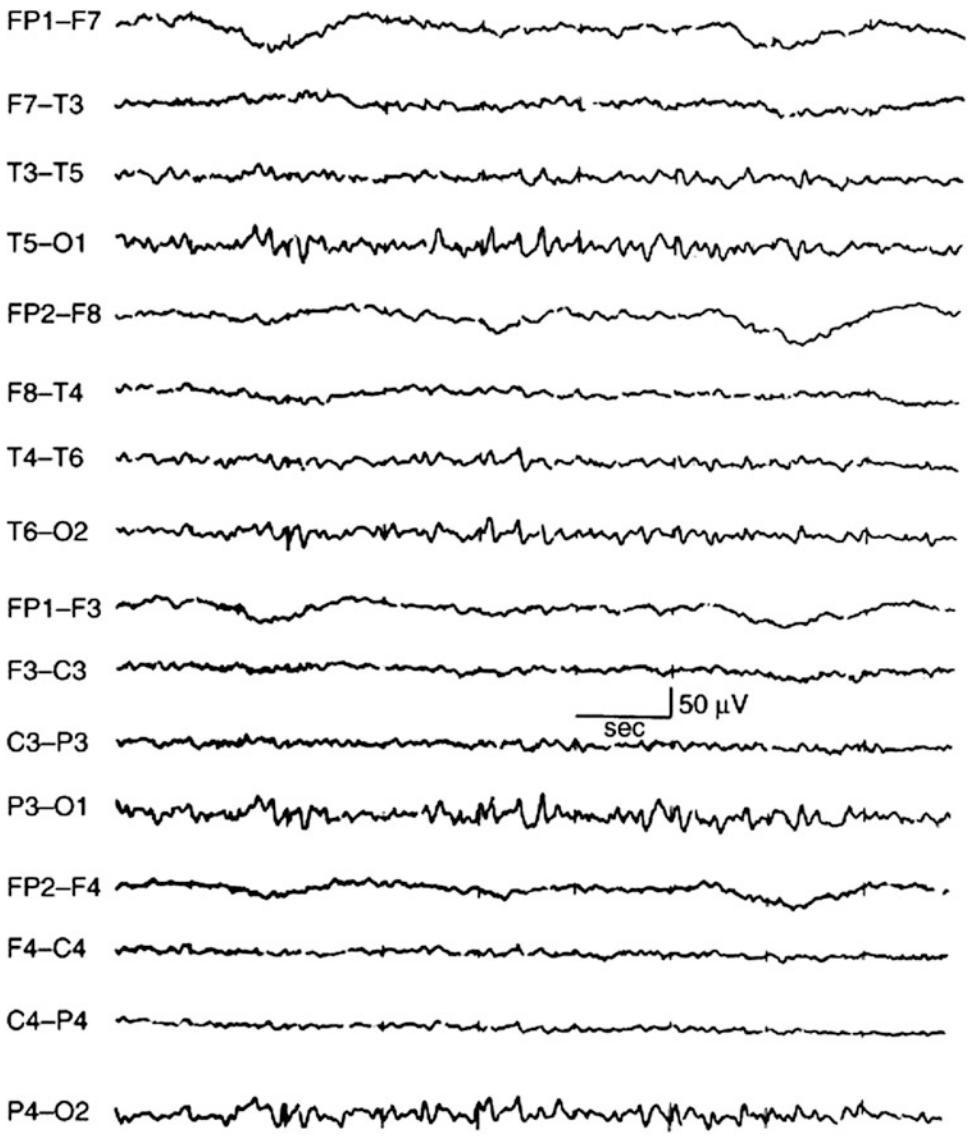

Fig. 18.23 **a** A 30-s epoch from nocturnal polysomnography recording. Positive occipital sharp transients of sleep (POSTs) are seen bilaterally in posterior temporal and occipital electrodes recorded during Stage II nonrapid eye movement sleep. **b** Same subject data as in A viewed at a 10-s epoch

Lambda waves (Fig. 18.24) are present in approximately 75 % of young adults and become somewhat less common as individuals age. Lambda waves assume a diphasic or triphasic waveform with the most prominent phase being positive at O1 or O2, morphologically similar to POSTs. The lambda wave is elicited by saccadic eye movements and appears to be an evoked response. It is present only during wakefulness with eyes open and scanning, in contradistinction to POSTs with which they may otherwise be confused.

Mu rhythms, seen in approximately 20 % of routine daytime EEGs, most commonly in young adults, consist of brief trains of 7–11 Hz waves over the central regions. The waves have a wicket or arciform shape (Fig. 18.25). Mu may occur synchronously or independently over the two hemispheres. This rhythm shows a characteristic reactivity. Active or passive movement of the contralateral limbs or even an intention to move the limb attenuates mu activity. Mu is seen during wakefulness and may become more prominent during stages N1 and N2. It typically disappears in slow-wave sleep and may reappear during REM sleep [55]. This has led to the conclusion that mu is an "ubiquitous rhythm of the sensorimotor cortex at rest."

Posterior slow waves of youth (Fig. 18.26) are found in the occipital regions bilaterally after 2 years in as many as 10 % of normal subjects. Prevalence is highest at approximately age 10 and gradually decreases afterwards. These waveforms rarely occupy more than 25 % of the record, and they do not significantly exceed amplitude of other background rhythms. They react to eye opening in the same manner as the alpha rhythm; these waves are in fact considered a variant of the alpha rhythm.

Benign epileptiform transients of sleep (BETS), also known as small sharp spikes (SSS) (Fig. 44.8), is seen in 5–24 % of normal subjects. These are spiky, often diphasic

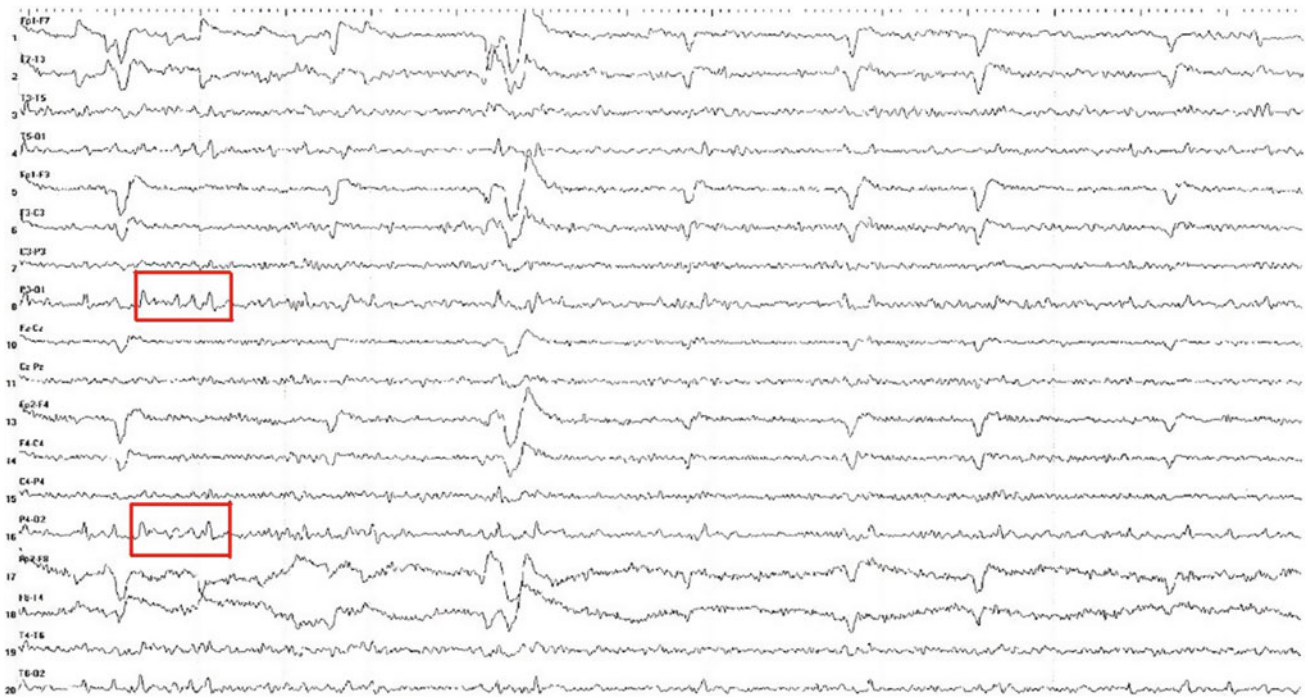

Fig. 18.24 10 s EEG epoch showing lambda waves (in *red box*) recorded from a 16-year-old female with a history of a syncopal spell. She was scanning ceiling tiles at the time of the recording. Note the surface positive, occipitally predominant activity occurring simultaneously with rapid eye movements recorded in the frontal channels. Reproduced with permission from: Chokroverty and Thomas [65]

transients with a broad field of distribution, usually involving both hemispheres. They typically shift from side to side and become less frequent during deeper sleep stages. Although BETS may superficially resemble epileptiform spikes, they are not associated with seizure disorders [56, 57].

The 6-Hz *spike and wave* (Fig. 18.27) may be noted in either the frontal or temporal regions. The spike component usually has a relatively low amplitude, whereas the following slow wave is more prominent. For this reason, it is also known as phantom spike and wave, with the "phantom" referring to the subtle spike component (perhaps less confusingly, it may be referred to as "wave-and-phantom spike.") Paroxysms of such activity rarely last longer than 3 s, have an evanescent quality, and are less common during deeper sleep. It occurs in two variants with descriptive acronyms, the WHAM (wake, high amplitude, anterior, men) and FOLD (female, occipital, low amplitude, drowsy). Despite their paroxysmal quality, they are not associated with epilepsy [58].

The *Ciganek rhythm* (Fig. 18.28) is a 4–7 Hz, midline, somewhat sharply contoured waveform seen in drowsiness and early NREM sleep [59], but occasionally in REM sleep as well. Its field is generally maximal at Cz and while it may have a waxing and waning amplitude, it generally does not evolve or spread to other locations. While in the past it was thought to have epileptogenic significance, it is now considered a normal variant.

Epileptiform-like Patterns Without Epileptogenic Significance

While the typical polysomnographer is unlikely to encounter most of the following patterns during a PSG, they all have specific clinical significance and are important to be able to identify.

Triphasic waves (Fig. 18.29) have an initial positive deflection and characteristic distribution. These are seen synchronously and symmetrically with frontal dominance of the amplitude with anteroposterior phase shift. Triphasic waves are not of epileptiform significance. The pattern has classically been described in hepatic encephalopathy and correlates with serum ammonia level. Triphasic waves may also be seen in other metabolic or toxic encephalopathies (e.g., renal or respiratory failure). Sometimes these are also seen in anoxic encephalopathies. Their presence suggests a rather severe degree of encephalopathy.

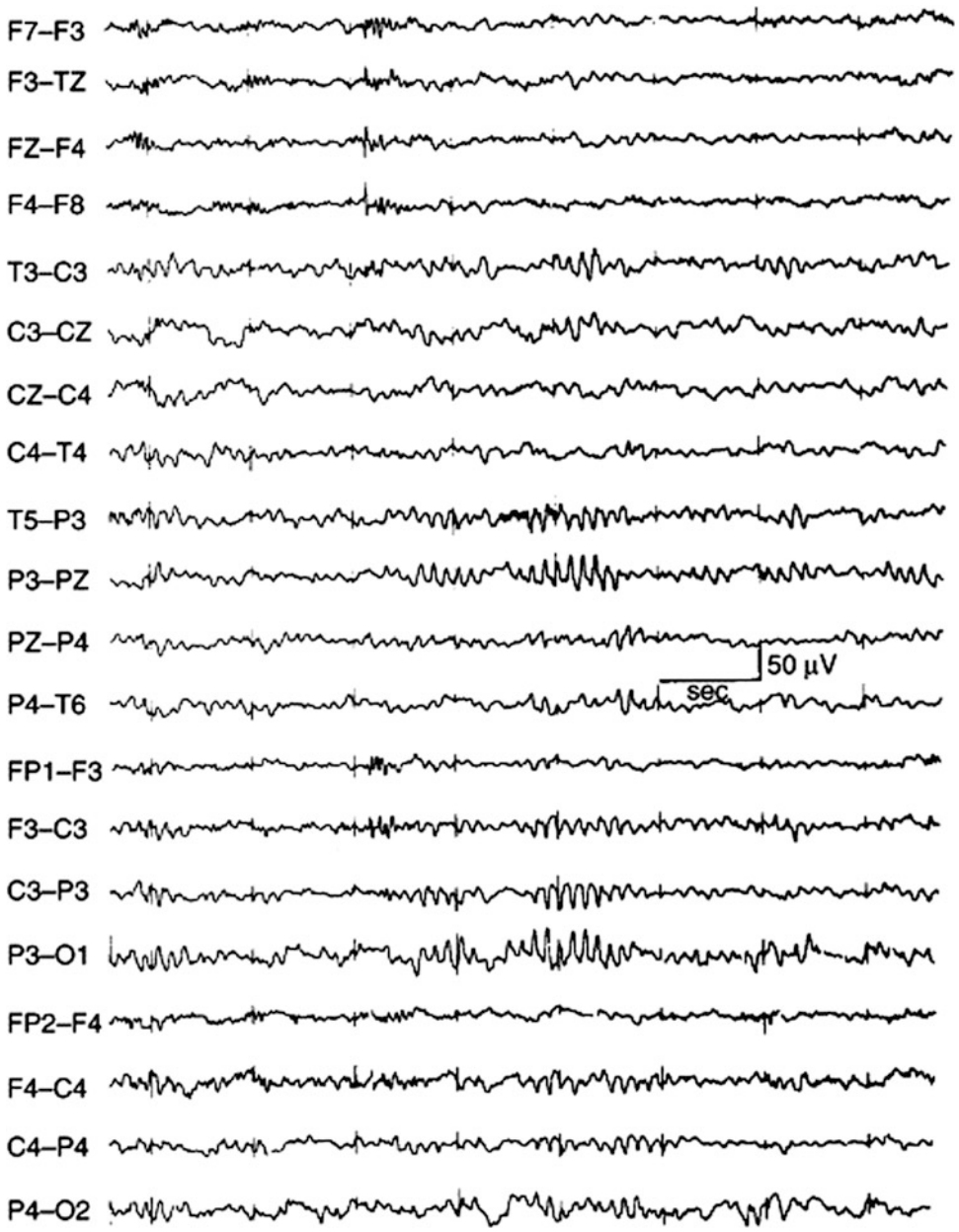

Fig. 18.25 Mu rhythm in the left parietal region (P3). Note phase reversal of the 7- to 8-Hz comb-like rhythm at P3 with spread of activity to C3

Periodic lateralized epileptiform discharges (PLEDs) are another important pattern to recognize. In this pattern, stereotyped sharply contoured discharges are recorded continuously over a given region (Fig. 18.30). They occur at regular intervals, usually every 1–2 s, and are thus labeled periodic. Background activity is usually significantly attenuated on the side with the discharges, and excessive slow frequencies are often seen bilaterally. This pattern is usually associated with an acute focal cerebral insult, most commonly an acute cerebral infarction, infection, anoxia, or other causes. Clinically, PLEDs are associated with obtundation, seizures, and focal neurologic deficits. Whether PLEDs themselves are ictal or interictal waveforms remains controversial. However, certain specific PLEDs patterns, known as PLEDs-plus, characterized by PLEDs with high-frequency, low-amplitude multispikes have a stronger

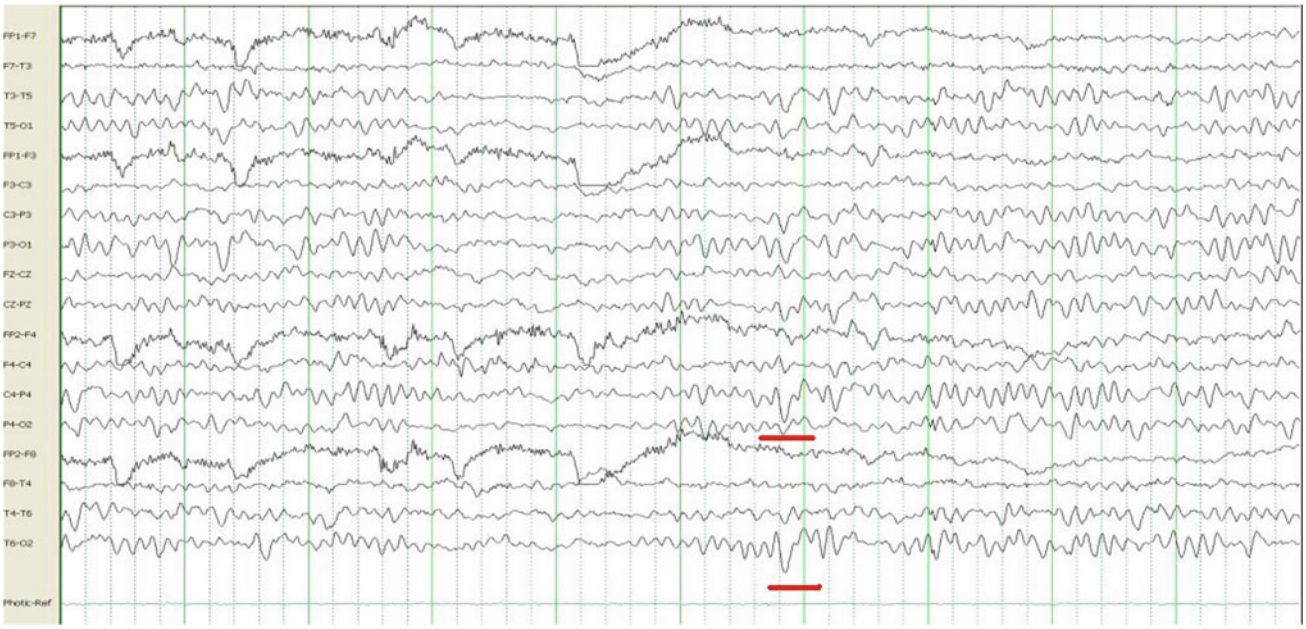

Fig. 18.26 A 15-year-old female patient with history of new onset of seizures. The EEG in wakefulness shows slow waves of youth (*underlined in red*) at 2 to 3 Hz superimposed intermittently on occipital alpha rhythm at 9 to 10 Hz bilaterally. This is a normal finding between ages 2 and 21 years of age, most commonly occurring between 8 and 14 years of age, and attenuates with eye opening. Reproduced with permission from: Chokroverty and Thomas [65]

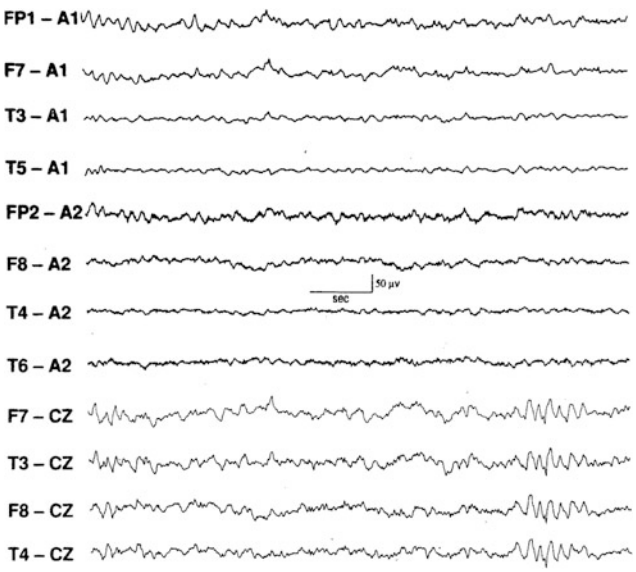

Fig. 18.27 Six-hertz spike and wave pattern seen in the last four channels. (From: Walczak T, Chokroverty S (2009). Electroencephalography, electromyography, and electro-oculography: General principles and basic technology in Chokroverty S (ed) Sleep Disorders medicine, ed3, Saunders/Elsevier, Philadelphia)

correlation with clinical seizures than simple PLEDs [60]. Of note, PLEDs can occur independently over the two hemispheres (known as BiPLEDs) or the discharges may be generalized (generalized periodic epileptiform discharges, GPEDs) [61–63, 64].

Artifacts

Given the relatively small voltages that the EEG, EOG, EMG, and ECG channels are intended to record, it is not surprising that artifacts from extraneous electrical activity, though not of clinical relevance, may obscure the biological signals of interest in these channels. Nevertheless, making the distinction between the signal of interest and artifact is a central task for the polysomnographer. Artifacts may come from the environment (50 or 60-Hz artifact, telephone or pager artifact, intravenous drip artifacts), the patient (ECG artifact in non-ECG channels, artifacts from deep brain stimulators, vagus nerve stimulators and pacemakers, movement, sweat and respiratory artifacts), or from the equipment (electrode artifacts and pops from

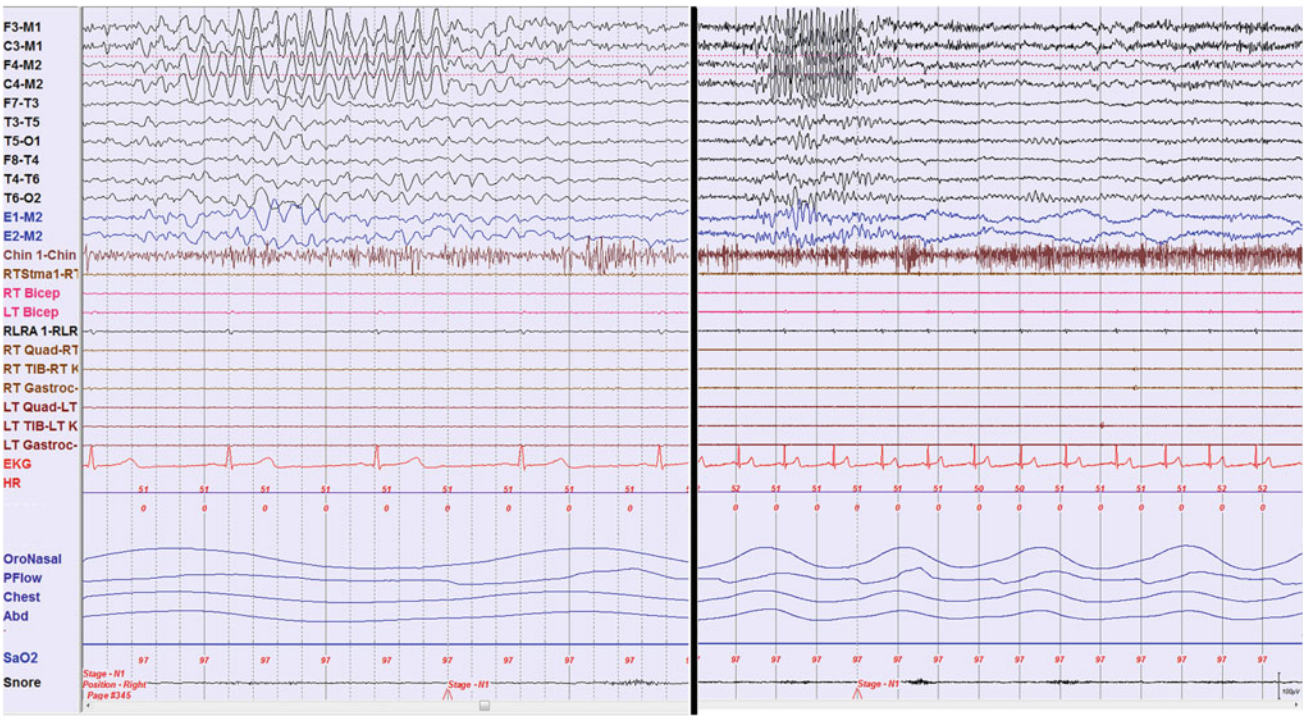

Fig. 18.28 10-s (*left*) and 30-s right epochs of Stage N1 sleep from the overnight PSG of a 35-year-old woman referred to the sleep laboratory for abnormal movements in sleep, later diagnosed to be intensified hypnic jerks. Note the occurrence of a burst of 6–7 Hz theta range slowing in the bilateral parasagittal leads (F3-M1, C3-M1; F4-M2, C4-M2), not evident in the bitemporal leads (F7-T3, T3-T5, T5-O1; F8-T4, T4-T6, T6-O2). This rhythm, known as a midline theta of drowsiness or Ciganek's rhythm, is a variant usually occurring in drowsiness or light sleep. It is considered to be benign but may be mistaken for epileptiform discharges. Chin1-Chin2, submental electromyogram (EMG); RT Stma1, right sternomastoideus EMG; RT Bicep; LT Bicep, right and left biceps brachii EMG; RLRA, right lateral rectus EMG; RT Quad; LT Quad, right and left quadratus femoris EMG; RTIB; LTIB, left and right tibilais anterior EMG; LGAST; RGAST, left and right gastrocnemius EMG; ECG, electrocardiogram; HR, heart rate; OroNasal, oronasal airflow; Pflow, nasal pressure transducer recording; SaO2, arterial oxygen saturation by finger oximetry. Also included is a snore channel

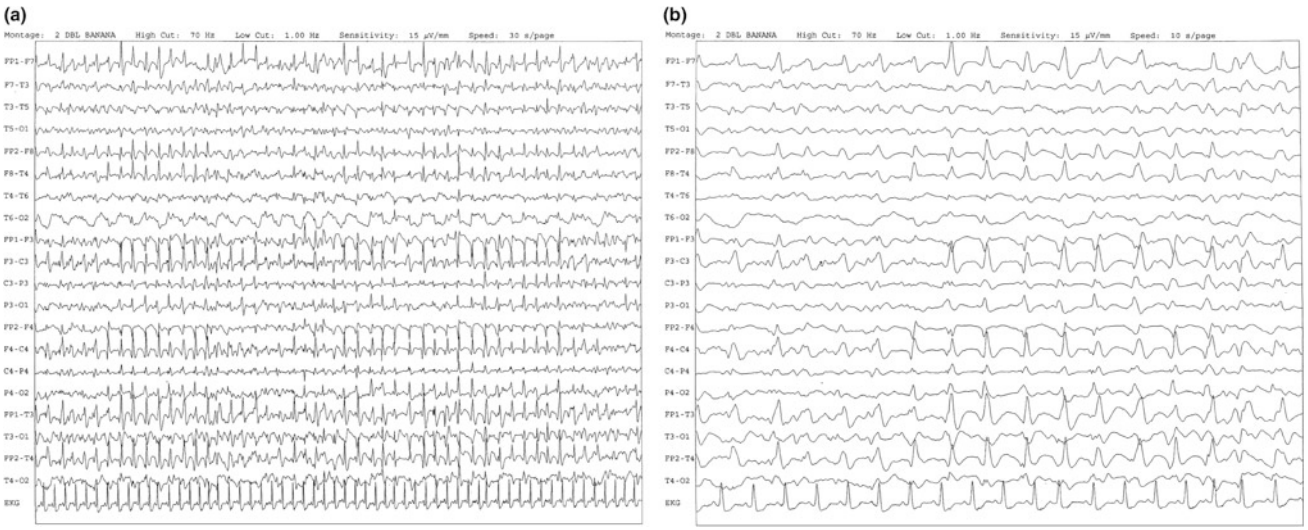

Fig. 18.29 **a** 30-s and **b** 10-s EEG epochs showing triphasic waves at 1–2 Hz recorded synchronously, with maximal amplitude frontally in a 67-year-old woman with a history of end-stage renal disease and hepatitis. Reproduced with permission from: Chokroverty and Thomas [65]

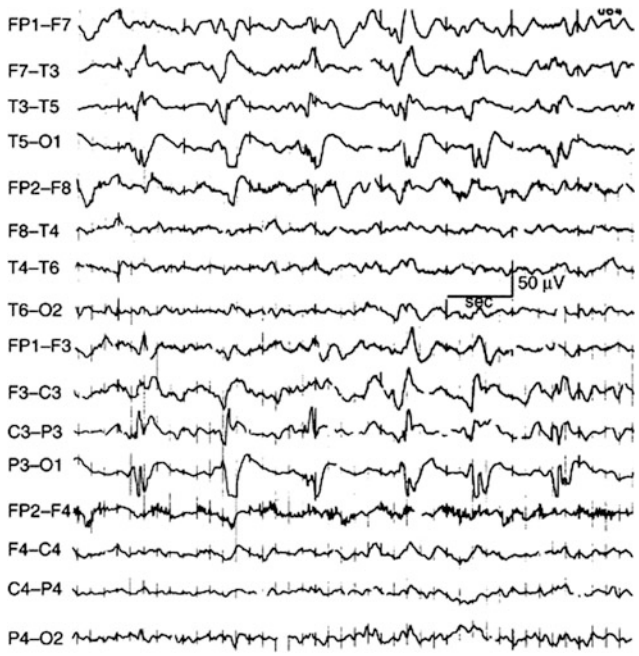

Fig. 18.30 Periodic lateralized epileptiform discharges at a rate of 0.8 per second arising from the left parietal and posterior temporal regions (P3, T5) in a 72-year-old woman with a history of confusion and falling episodes

improperly placed or loose electrodes or poor impedence). An ever-vigilant, alert, and experienced technician is the first and best defense against artifact. The technician must strive to eliminate the artifact during the recording; if this is not possible, the source of the artifact must be meticulously recorded and the interpreter must identify the artifact as such. Artifacts are dealt with in great detail in Chap. 17.

Summary

The EEG plays a central role in the interpretation of a PSG. While unfortunately, the limited number of inputs available on standard PSG equipment results in a suboptimal number of channels available for EEG recording, the use of multiple channels dedicated to the EEG allows the polysomnographer to better determine whether a suspicious waveform is artifact, a normal variant, or of clinical significance. Polysomnographers require a thorough knowledge of the fundamentals of EEG recording and interpretation. This includes the nature of physiological changes that generate EEG potentials, basics of electronics such as differential amplification, filters and sensitivities, and the ability to identify common artifacts and benign waveforms.

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Electrocardiography: Principles and Applications in Sleep Medicine

19

Daniel M. Shindler and John B. Kostis

A wealth of information is available about cardiac rate and rhythm disturbances during sleep. Twenty-four-hour ambulatory electrocardiography (ECG) has made it possible to study cardiac rhythm in both awake and sleeping subjects. For most practical purposes, it is possible to think about cardiac rhythm during sleep in the same way as during wakefulness, although the average heart rate is slower during sleep. As a result, escape-type arrhythmias may appear or become more frequent. One should first be familiar with the normal behavior of the heart and subsequently become familiar with a simple classification of cardiac arrhythmias.

Normal Cardiac Rhythm

The normal cardiac rhythm is defined as a normal sinus rhythm —that is, the cardiac rate is between 60 and 100 bpm and the cardiac impulse originates in the sinus node. This is best confirmed by identifying a normal-looking P wave that is followed by a normal and constant PR interval and is always succeeded by a single QRS complex. It is quite normal for cardiac cycle length (R–R interval) in a given patient to be somewhat variable. This is referred to as *sinus arrhythmia* (Fig. 19.1) [1–3]. The heart rate of children and infants is faster than the heart rate of adults. The rate of the sinus node is influenced by the autonomic nervous system.

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Cardiac Arrhythmias

Arrhythmias are due to disturbances of impulse formation, impulse conduction, or a combination of the two. Arrhythmias can be separated into two large groups. Those that originate in the sinus node, atria, or atrioventricular (AV) node are referred to as *supraventricular arrhythmias*; those that originate in the ventricles are classified as *ventricular arrhythmias*. Figures 19.2, 19.3, 19.4, 19.5, 19.6, 19.7, 19.8, 19.9, 19.10, 19.11, 19.12, 19.13, 19.14, 19.15, 19.16, 19.17, and 19.18 illustrate a variety of cardiac arrhythmias.

Supraventricular Arrhythmias

When the QRS complex is narrow, the arrhythmia is, with few exceptions, supraventricular. Unfortunately, when the QRS complex is wide, it is often impossible to determine conclusively whether an arrhythmia is supraventricular or ventricular. Inspection of the ECG is the first step in evaluating an arrhythmia. If the arrhythmia is considered potentially life threatening, a specialized electrophysiologic study may be required to further assess its significance.

Sinus Tachycardia

The most common rhythm disturbance (which may not be abnormal), sinus tachycardia, is an acceleration of the sinus heart rate above 100 bpm [4]. In most cases, sinus tachycardia does not exceed 180 bpm. Sinus tachycardia is best diagnosed by identifying P waves, determining that they are of normal morphology, subsequently establishing that the PR interval is normal and constant, and determining that each QRS complex is preceded by the P wave and each P wave is followed by a normal QRS. In the course of normal daily activity, the heart rate rises in a gradual fashion and subsides in a gradual fashion [5]. Sinus tachycardia can

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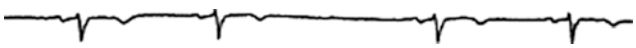

Fig. 19.1 Normal sinus rhythm with sinus arrhythmia

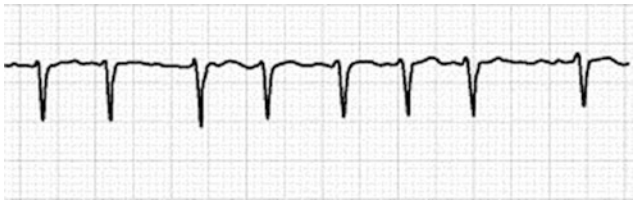

Fig. 19.2 Atrial fibrillation

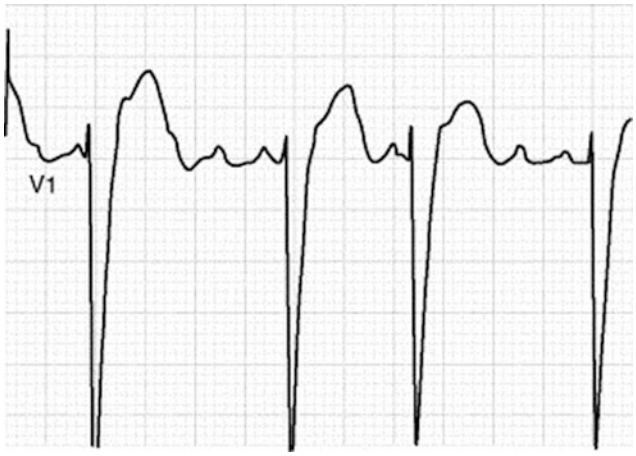

Fig. 19.3 Atrial flutter with variable ventricular response

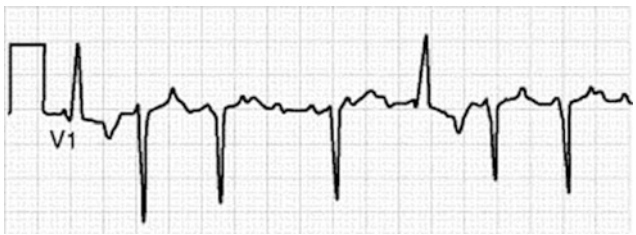

Fig. 19.4 Atrial flutter. The first and fifth QRS complexes are aberrantly conducted

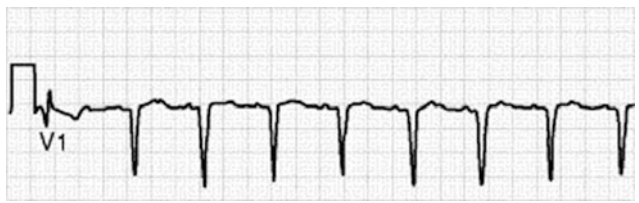

Fig. 19.5 Atrial tachycardia with 2:1 block

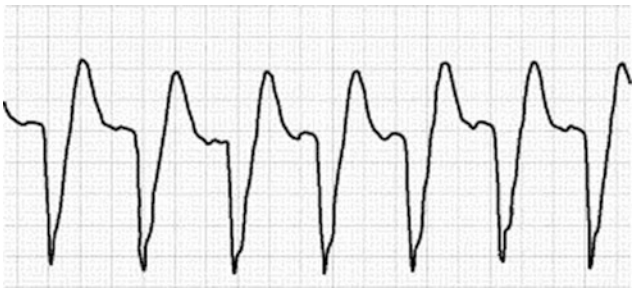

Fig. 19.6 Undetermined wide-complex rhythm, rate 100 bpm

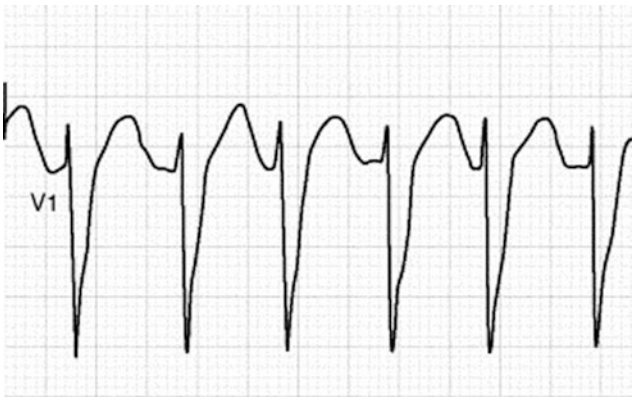

Fig. 19.7 Undetermined wide-complex tachycardia, rate 145 bpm

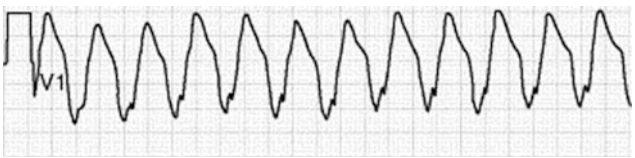

Fig. 19.8 Ventricular tachycardia

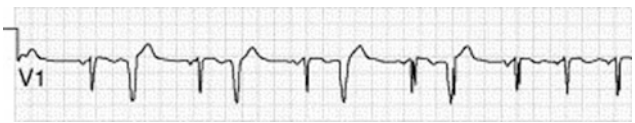

Fig. 19.9 Normal sinus rhythm. Premature ventricular contractions in bigeminy

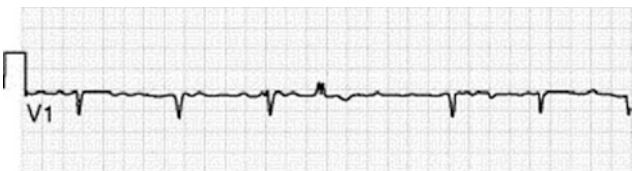

Fig. 19.10 Atrial fibrillation. Premature ventricular contraction

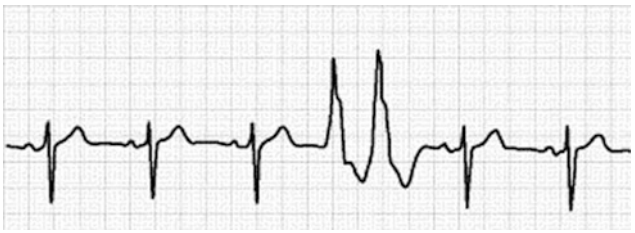

Fig. 19.11 Normal sinus rhythm. Premature ventricular couplet

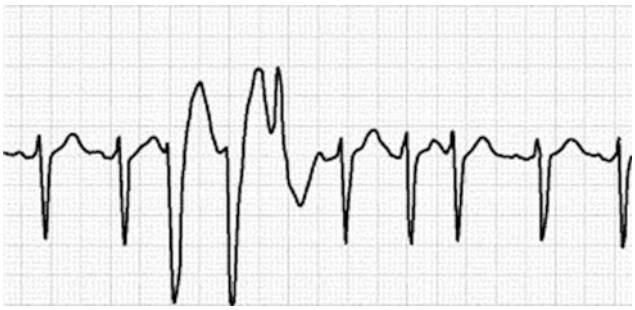

Fig. 19.12 Normal sinus rhythm. Three-beat multifocal ventricular tachycardia salvo. The eighth QRS complex is a premature atrial contraction

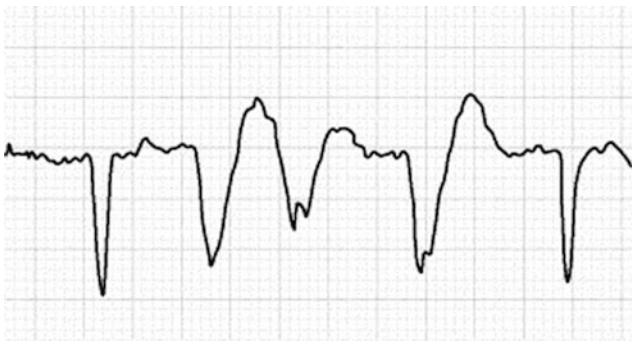

Fig. 19.13 Three-beat ventricular salvo resembling baseline artifact. Artifacts do not have T waves

occur during rapid eye movement (REM) sleep. Yet, patients suffering from REM sleep behavior disorder can have violent body movements without an increase in the heart rate due to the absence of autonomic arousal.

Sinus Bradycardia

The opposite boundary of normal heart rate is sinus bradycardia. Sinus bradycardia is defined as a rate slower than 60 bpm [6]. Again, it is manifested by a normal P-wave appearance, a normal and constant PR interval, and a normal relationship of the P wave to the QRS complex, with a 1:1 sequence similar to that of sinus tachycardia. One observational

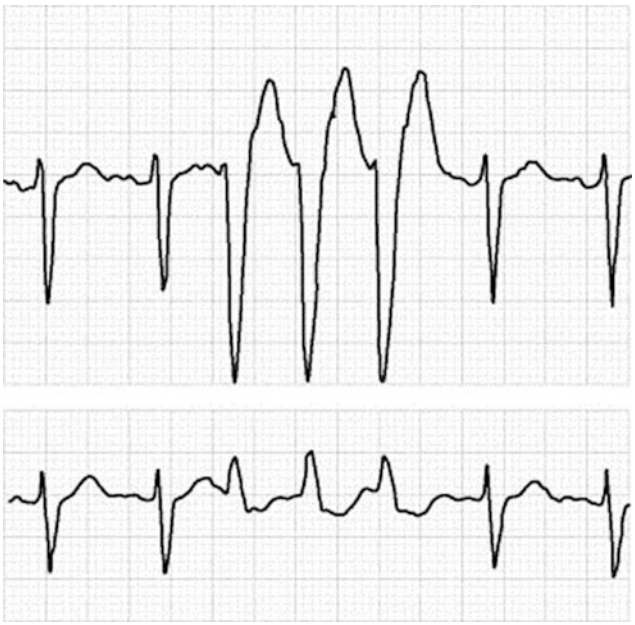

Fig. 19.14 Three-beat ventricular salvo demonstrated in two simultaneous leads

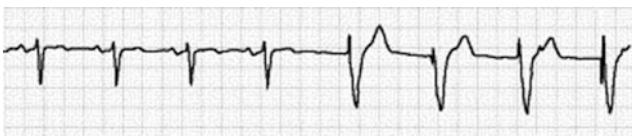

Fig. 19.15 Sinus rhythm with a demand pacemaker taking over in the last 4 beats. Note the disappearance of P waves

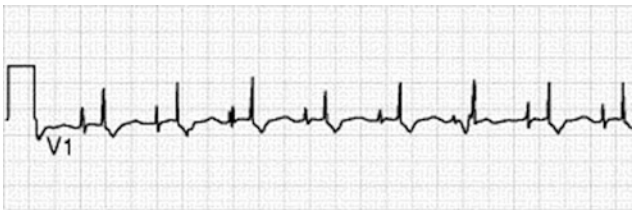

Fig. 19.16 AV sequential pacemaker. The sixth QRS complex is a native nonpaced premature beat. The pacemaker is programmed to deliver a ventricular pacing spike anyway

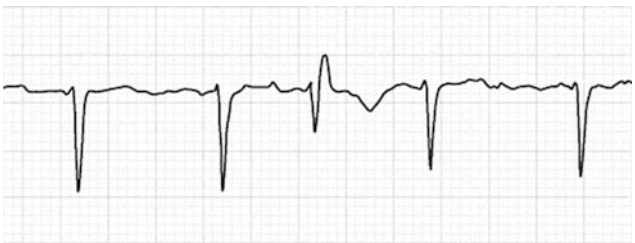

Fig. 19.17 Aberrant conduction

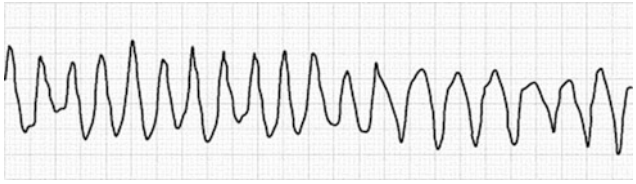

Fig. 19.18 Torsades de pointes

pitfall in the patient with sinus bradycardia is the fact that, at times, U waves become very prominent and can easily be confused with P waves. As a result, blocked premature atrial contractions can be misdiagnosed. Use of β blockers can slow the heart rate as well as cause nightmares and sleep disruption.

Sinus Arrhythmia

Sinus arrhythmia is especially easy to notice with slowing of the heart rate during sleep. The P-wave morphology usually does not change. If it does change, the changes are phasic and the P-waves do not appear retrograde. There should be a 10 % difference between the maximum and minimum cardiac cycle length. Atrioventricular conduction is normal. This is manifested as a PR interval greater than 120 ms. A shorter PR interval with an abnormal P wave would indicate that the beats are not of sinus origin. The variations in sinus cycle length may be phasic, with respiration becoming shorter with inspiration due to reflex inhibition of vagal tone. This form of sinus arrhythmia disappears with apnea.

Premature Atrial Contractions

Premature atrial contractions are observed frequently in normal subjects and patients with a variety of diseases. They are manifested as an interruption in the heart rhythm with a premature beat having a narrow QRS complex. Because the origin of the atrial impulse is ectopic, the appearance of the P wave is abnormal, denoting its abnormal early origin. There is quite a wide spectrum in the incidence and frequency of premature atrial contractions. Their nature is classified as follows: If the premature atrial contractions occur singly, they are classified according to their incidence per period of time. Therefore, an ambulatory ECG report commonly describes how many premature atrial contractions were observed in a given time, such as an hour, a minute, or 24 h, according to how common they are. When premature atrial contractions are frequent, it is customary to further describe their nature (cyclic or noncyclic) and rate. For example, when premature atrial contractions occur cyclically, they may show a bigeminal pattern.

Multifocal Atrial Tachycardia

A variant of frequent premature atrial contractions is tachycardia, which is called *multiform atrial tachycardia* or *chaotic atrial tachycardia* [7]. This is a rhythm disturbance with definite clinical significance. It is identified by an irregular heart rhythm with narrow QRS complexes and rates in excess of 100 bpm. As the name implies, it is multifocal: The atrial beats originate in multiple sites in the atria. Consequently, the appearance of the P waves varies with the point of origin. There is variability in both the P-wave morphology and the PR interval. Multifocal atrial tachycardia is an arrhythmia that may have significant consequences. It is particularly common in patients with significant lung disease. These same patients often suffer sleep disorders. When analyzing ECG recordings, multifocal atrial tachycardia should not be confused with atrial fibrillation.

Atrial Fibrillation

Atrial fibrillation is a very common rhythm disturbance that is important to diagnose, as the initial heart rate can be quite fast and drug therapy may be required to slow it down. Patients with chronic atrial fibrillation are at increased risk for thromboembolic phenomena and are therefore often admitted to the hospital for further management when this rhythm is diagnosed [8]. Management may be either rate control or attempted cardio version. Both approaches are typically accompanied by chronic antithrombotic therapy. The ECG hallmark of atrial fibrillation is a completely random and irregular heart rhythm with no reproducible R–R interval. Because the atria are fibrillating at a rate of 500 bpm, there are no P waves. The ECG baseline may appear irregular and erratic. This should not be confused with the variable P waves of chaotic atrial tachycardia or with U waves, as mentioned earlier. The ventricular rate in patients with atrial fibrillation tends to be fast when it first occurs. The rate may range around 150 bpm. A clue to underlying conduction system disease is a slow ventricular rate. In this case, caution needs to be exercised with therapeutic modalities, because of possible undesirable AV conduction problems [9, 10].

Atrial Flutter

A variant of atrial fibrillation is a rhythm disturbance known as *atrial flutter* [11]. Atrial flutter differs in that atrial activity can be diagnosed as occurring 300 times per minute. At this rate, the ECG hallmark is a characteristic sawtooth pattern at a rate of 300 bpm. The usual presentation of atrial flutter is an atrial rate of 300 bpm with some degree of block between the atria and ventricles (the usual block is 2:1). Therefore, it is quite typical to recognize atrial flutter by the presence of a sawtooth baseline with a ventricular response of 150 bpm. The therapeutic goal in atrial flutter (similar to atrial fibrillation) is to slow down the ventricular response when it is fast. Again, caution is exercised when the initial ventricular response (with no medication) is an unduly slow rate with a

conduction block of 4:1 or greater. Patients may benefit from radiofrequency catheter ablation.

Automatic Versus Re-entrant Tachycardia

The rhythm disturbances referred to earlier are classified as automatic rhythm disturbances. If properly diagnosed, they can be classified as disorders of cardiac automaticity. The warm-up phenomenon (gradual, nonabrupt increase in heart rate) is a hallmark of automatic tachycardia. Usually, an automatic tachycardia requires a search for its cause, which is then treated. For example, multifocal atrial tachycardia is typically seen in patients with lung disease, and improvement of hypoxemia often results in the return of the cardiac rhythm to normal. Sinus tachycardia frequently indicates a metabolic disturbance such as fever, thyrotoxicosis, or hypovolemia. Again, therapy of the cause is the proper approach rather than addressing the mechanism of the rhythm disturbance itself [12, 13]. Conversely, a group of tachycardias referred to as *re-entrant* are treated by addressing the mechanism of reentry. When this is corrected, the rhythm is restored to normal.

Paroxysmal Atrial Tachycardia

Paroxysmal atrial tachycardia is the classical re-entrant tachycardia treated with medications that interrupt the mechanism of reentry [14]. As the name implies, a paroxysmal atrial tachycardia begins abruptly. There is no warm-up phenomenon, and the heart rate instantly increases to between 140 and 180 bpm. It may cease spontaneously and, just as abruptly, return to sinus rhythm. It is quite common to observe these salvos of atrial tachycardia in patients, whether they are awake or asleep. When paroxysmal atrial tachycardia is persistent, it warrants treatment because of the unduly fast heart rate. Several maneuvers that increase vagal tone, such as a Valsalva maneuver or carotid sinus massage, can break the arrhythmia [15]. When these are ineffective, it becomes necessary to use medication. The calcium channel blocker verapamil was quite useful for this purpose. Subsequently, adenosine, an agent that causes complete but very transient AV block, has emerged as the modality of choice [16]. Long-term management consists of catheter ablation of the AV node.

Sick Sinus Syndrome

Various combinations of tachycardia with bradycardia may suggest the diagnosis of sick sinus syndrome. Ambulatory ECG monitoring may be required to demonstrate the presence of sinus node dysfunction [17–20]

Aberrant Supraventricular Conduction

A transient delay in intraventricular conduction can be seen in patients with supraventricular tachycardias. If the P waves are not clearly identifiable, the rhythm may be misdiagnosed as ventricular tachycardia (see *Ventricular Tachycardia* later). QRS complex morphology may be useful in making the correct diagnosis. The initial aberrant conduction occurs in the QRS complex, which terminates a short cardiac cycle immediately preceded by a long cardiac cycle [21, 22].

Ventricular Arrhythmias

The next group of rhythm disturbances, the ventricular arrhythmias, may be more hemodynamically significant and can be associated with clinically important heart disease. They can also be seen in normal patients.

Premature Ventricular Contractions

A very common rhythm disturbance often felt by patients is the premature ventricular contraction. It is most commonly an early beat that is easily recognized on the ECG as a wide QRS complex with abnormal repolarization [23]. The incidence on 24-h ECG monitoring can be reported according to how often this finding is present; therefore, premature ventricular contractions are reported as occurring a certain number of times per hour. If rare, they are classified by how many times they occur in 24 h; if very common, they may be classified in terms of occurrence per minute [24].

Ventricular Bigeminy

A very common rhythm disturbance is a sustained rhythm, especially at night, consisting of an alternating normally conducted QRS complex with a premature ventricular contraction followed by a pause and a resumption of the sequence. This is referred to as *ventricular bigeminy*. It is benign for most practical purposes, but it has some clinical implications. For example, a clinician taking a pulse may notice only the normally conducted beats. The pulse deficit might then result in a mistaken diagnosis of bradycardia.

Ventricular Tachycardia

The finding of three or more premature ventricular contractions in a row (at a heart rate faster than 100 bpm) is referred to as *ventricular tachycardia* [25], and it may be brief or sustained [26]. The most important distinction that needs to be made when ventricular tachycardia is suspected is the alternate diagnosis of supraventricular tachycardia with aberrant ventricular conduction. The diagnostic approach to this critical differential diagnosis is multifaceted. The diagnosis begins at the bedside. If the patient is hemodynamically decompensated, it is necessary to act rapidly [27, 28]. Multiple ECG leads should be used to identify P waves that mark atrial activity. Atrial P waves that are unrelated to ventricular QRS complexes make ventricular tachycardia more likely than aberrant conduction. The appearance of the QRS complex has been useful in the

recognition of a ventricular origin for tachycardia. Sustained ventricular tachycardia often degenerates into ventricular fibrillation, resulting in death [29].

Ventricular Fibrillation

Ventricular fibrillation is a lethal terminal dysrhythmia that requires immediate electrical defibrillation. There are no identifiable QRS complexes. It may begin on a T wave (this is referred to as *R on T*). It may also be seen in association with a unique ventricular tachyarrhythmia called *torsades de pointes*.

Torsades de Pointes

The morphology of torsades de pointes is unique. The points of the ventricular complexes vary in their height, appearing to turn around a central axis, the baseline of the ECG tracing. It is important to measure the QT interval. QT prolongation can be caused by electrolyte disturbances, antiarrhythmic drugs, or central nervous system or congenital disease [30–34].

Accelerated Idioventricular Rhythm

The law of the heart states that the fastest pacemaker is the one that governs the heart. Accelerated idioventricular rhythm (AIVR) is a slow ventricular rhythm that captures the heart because the sinus rate is even slower. The rate of AIVR is less than 100 bpm. It is usually faster than the typical 40-bpm ventricular escape rate (thus the term *accelerated*). This is typically an escape rhythm that should not be suppressed with antiarrhythmic agents such as lidocaine. AIVR is often short lived and has no hemodynamic consequences. In this setting, it does not require treatment. When AIVR is sustained and hypotension is observed, an agent such as atropine may be useful in overdriving the AIVR by accelerating the sinus node. The ECG diagnosis of AIVR consists of establishing the ventricular origin of the rhythm.

Brugada Syndrome

Patients with a structurally normal heart may have syncopal episodes and/or sudden cardiac death due to Brugada syndrome. This genetically determined syndrome is rare. There may be a family history of sudden death. Ventricular fibrillation may occur during sleep and may be related to nighttime bradycardia [35]. The ECG hallmark of the Brugada syndrome is a combination of right bundle branch block and ST-segment elevation in leads V_1 to V_3 (Fig. 19.19). This diagnostic ECG pattern can be evanescent and may not be present in patients at all times.

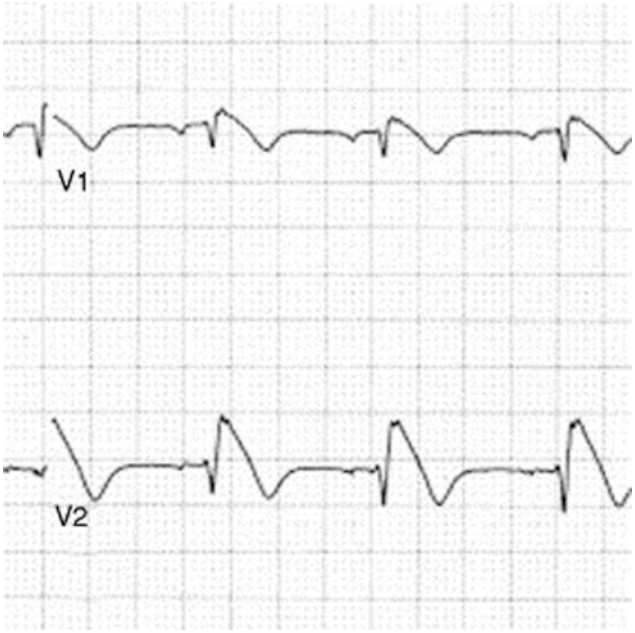

Fig. 19.19 Brugada syndrome: leads V1 and V2 show an rSR' QRS complex with ST-segment elevation in both leads

Pacemaker Rhythm

Pacemaker rhythms are identified by the pacemaker spike preceding the wide QRS complex. It is necessary to determine proper capture as well as proper sensing. Dual-chamber pacemakers are designed to restore the normal sequence of AV contraction. They are also associated with pacemaker-induced arrhythmias [36]. Some patients may have a pacemaker or defibrillator implanted to treat life-threatening ventricular arrhythmias [37, 38].

Intracardiac Recordings

Certain patients may be referred for electrophysiologic study to further evaluate their arrhythmia. The tracings obtained during those studies may demonstrate ECG information about the heart that is unobtainable from surface ECG studies. It is possible to record the electrical activity of the bundle of His. This may help decide which patients require a permanent pacemaker. The sinus node recovery time can be measured in patients with sick sinus syndrome. Ventricular arrhythmias can be induced to assess efficacy of antiarrhythmic therapy [39].

Signal-Averaged Electrocardiogram

It is possible to amplify the ECG complex by as much as 1000 times with the use of signal averaging. The signal-averaged ECG can demonstrate the presence of late potentials (high-frequency, low-amplitude signals). Their absence is associated with a more favorable prognosis after myocardial infarction.

Management of Arrhythmias Detected During Sleep

The sophisticated monitoring equipment available today permits detection of cardiac arrhythmias and conduction disturbances as they occur during sleep. Sustained ventricular arrhythmias require immediate attention. The patient needs to be awakened, and blood pressure and mental status must be determined. If the ventricular arrhythmia causes hypotension or the patient is unarousable, emergency measures may be required, but this is extremely rare. Nonsustained ventricular arrhythmias are a more common finding. Typically, by the time the patient is aroused, blood pressure is normal. The patient needs to be monitored, however, for recurrence of the arrhythmia. Conduction disturbances can also be detected. Sinus arrest is manifested by the disappearance of P waves and an area other than the sinus node taking over the cardiac rhythm. This can be a junctional, ectopic atrial, or ventricular rhythm. It is important to ascertain by ECG whether arrhythmias are, as mentioned, sustained or nonsustained. It is also worthwhile to determine whether a newly detected rhythm disturbance is a consequence of a conduction abnormality followed by an escape mechanism, rather than a premature mechanism for arrhythmia initiation such as a premature ventricular contraction. The hemodynamics, as measured by blood pressure, are the most important indicators of the significance of an arrhythmia as it is occurring. It is also important to take into account the underlying cardiac status of the particular patient in whom the arrhythmia is observed.

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Evaluation and Monitoring of Respiratory Function

20

Reena Mehra and Harneet K. Walia

Evaluation of Baseline Pulmonary Function and Physiology

With increasing recognition and awareness of sleep-disordered breathing (SDB), a high proportion of patients are referred to the sleep clinic for evaluation, many of whom have comorbid factors including those that are pulmonary specific. Although some patients may carry previously diagnosed or recognized pulmonary disorders, in many situations these remain undiagnosed, and therefore, there is an opportunity to utilize the sleep evaluation to uncover concomitant pulmonary disease either through clinical evaluation or via sleep testing. It is crucial to perform a comprehensive assessment of the patient's baseline pulmonary status by obtaining a thorough medical history and performing a complete physical examination geared toward pulmonary-based issues. Medical history should focus particularly on symptoms of dyspnea on exertion or at rest, cough, sputum production, stridor, and wheezing; extensive smoking history/illicit drug use; occupational exposures; and family history of pulmonary disorders/sleep apnea and other sleep disorders. Physical examination should include a strategic assessment of the airway (e.g., Friedman classification, nasal valve incompetence, nasal septum examination, tonsillar hypertrophy, retrognathia, micrognathia, thyromegaly, macroglossia), lung auscultation (including with forced expiration) and percussion, evaluation of clubbing/cyanosis, along with comprehensive evaluation of other organ systems. A resting baseline oxygen saturation, the so-called fifth vital sign [1] should also be obtained in the clinic setting, which allows the ability to detect baseline hypoxia prior to sleep testing and prepare accordingly. If clinical suspicion of impaired pulmonary function is suspected based on initial evaluation, then testing to assess the type and severity of limitation is warranted.

Testing of Baseline Respiratory Function and Physiology

Although the testing discussed in this section is not warranted in the routine evaluation of pulmonary disorders, if a provocative history of baseline pulmonary abnormality is elicited in the context of a sleep disorder evaluation, then further pulmonary disorder diagnostic workup is indicated.

Chest X-ray/CT Chest

Radiographic assessment of the lung fields may be helpful in the context of a concerning pulmonary symptoms or examination findings particularly in the context of a smoking history of greater than 20 pack years. Radiographic review of enlarged pulmonary arteries, reticulonodular densities, lung mass, mediastinal lymphadenopathy, and interstitial/alveolar processes can be made.

Spirometry/Pulmonary Function Testing

Spirometry

Pulmonary function testing allows for the ascertainment of lung physiology and mechanics. Spirometry, or the measuring of breath, is performed with flow-volume loops and assesses the mechanical properties of the respiratory system by measuring expiratory volumes and flow rates. This test requires the patient to make a maximal inspiratory and expiratory effort. The patient in a sitting position breathes into a mouthpiece, and nose clips are placed to prevent air leak. At least three tests of acceptable

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effort are performed to ensure reproducibility of results. Spirometric standards are derived from population-based epidemiologic data with the most commonly used standards from NHANES III to derive prediction equations for normative values based upon age, gender, and race/ethnicity [2]. The following are some of the measured values gleaned from spirometry:

Forced Vital Capacity (FVC): After a deep inhalation, this is the volume of air which can be forcibly and maximally exhaled out of the lungs until no more can be expired. FVC is expressed in liters.

Forced Expiratory Volume in One Second (FEV1): *After a deep inhalation, this is* the volume of air which can be forcibly exhaled from the lungs in the first second of a forced expiratory maneuver measured in liters.

FEV1/FVC: This is the ratio of FEV1 to FVC and indicates what percentage of the total FVC was expelled from the lungs during the first second of forced exhalation.

The general approach to interpretation of spirometry involves evaluation of the FEV1/FVC; a reduction is consistent with obstructive lung disease physiology, and to gauge the severity, the FEV1 percentage of predicted provides a sense of the degree of obstruction. If the FEV1/FVC is normal, then the patient either has normal or restrictive pulmonary physiology; in this context if the FVC is reduced, then this is suggestive of restrictive lung disease. Lung volumes and diffusion capacity may be helpful in the latter circumstance to ascertain severity grade and whether the restriction is intra or extrathoracic (Fig. 20.1).

The flow-volume loop is another aspect of data generated from spirometry characterized by a graphic illustration of inspiratory and expiratory flow (on the vertical axis) against volume (on the horizontal axis) during the performance of maximally forced inspiratory and expiratory maneuvers. Flow is plotted against volume to display a continuous loop from inspiration to expiration. The overall shape and the contour of the flow-volume loop are important in interpreting spirometric results (Fig. 20.2). In healthy subjects, maximal expiratory flow is highest at total lung capacity and progressively is reduced until residual volume is reached, while inspiratory flow is more even throughout the maximal effort of breathing in from residual volume to total lung capacity. In addition, the flow patterns are smooth during expiration or inspiration.

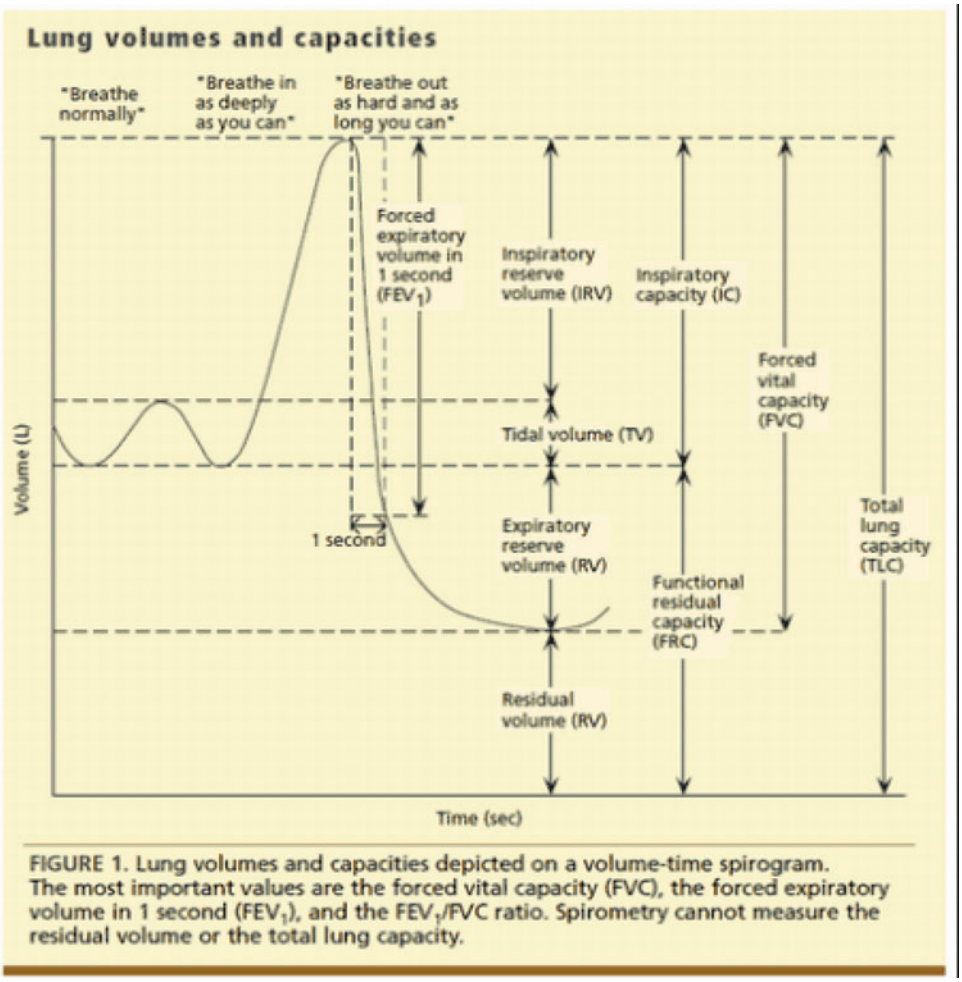

Fig. 20.1 This figure obtained from Cleveland Clinic Journal of Medicine with permission 2003 Oct; 70(10):866, 868, 871–873

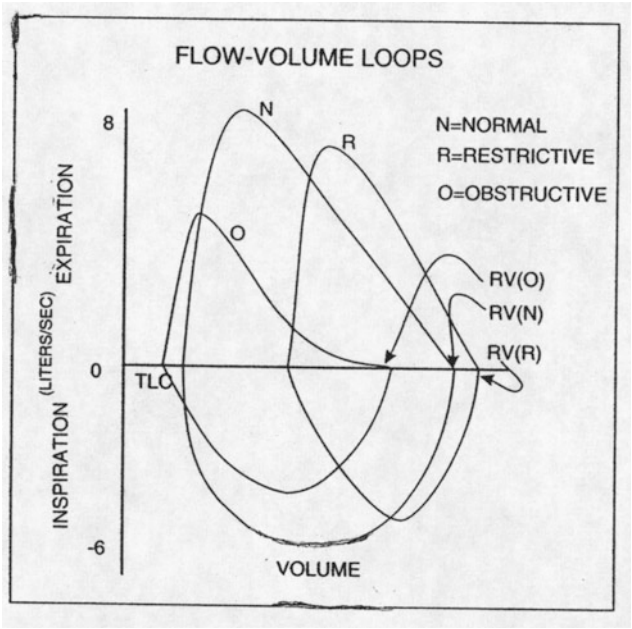

Fig. 20.2 Flow-volume loops

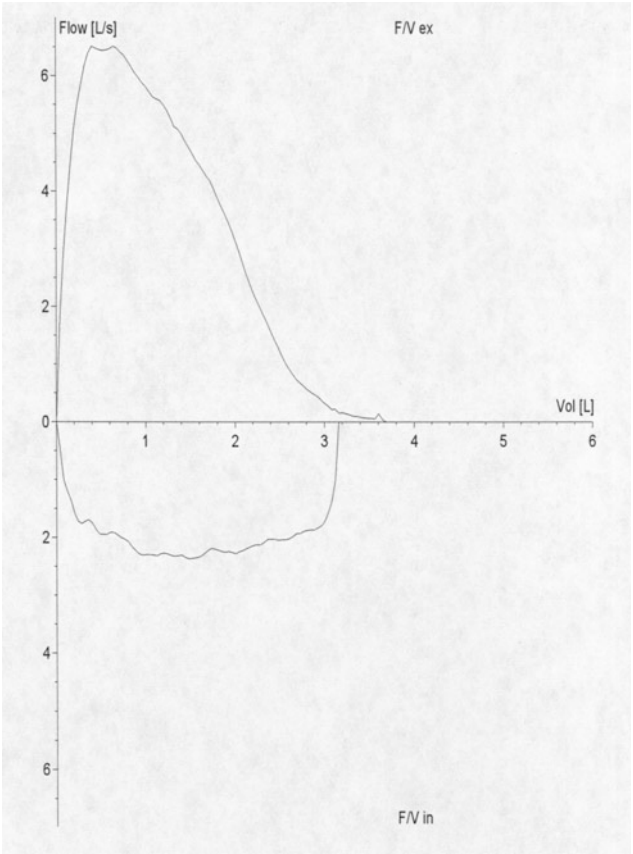

Fig. 20.3 Example of variable extrathoracic obstruction: note the "squaring" of the inspiratory limb of the flow-volume loop

Obstructive Lung Disease: Another feature is the proportion of flow between inspiration and expiration, especially at mid-lung volumes, halfway between residual volume and total lung capacity. At this point, expiratory flow is less than inspiratory flow in those diseases in which there is intrathoracic airway disease, such as asthma, chronic obstructive pulmonary disease (COPD), or tracheomalacia. Patients with airflow limitation due to obstructive lung disease often have a concave upward pattern on the expiratory portion of the flow-volume loop.

Restrictive Lung Disease: The characteristic flow-volume loop pattern of restrictive disease is a decrease in vital capacity combined with supernormal expiratory flows when corrected for lung volume. The resulting shape of the flow-volume curve is a tall appearance with a steep descending limb.

Fixed Airway Obstruction: If flows are equal and reduced, there is a possibility of a fixed upper airway obstruction, such as tracheal damage from prior surgery or airway tumor/foreign body.

Variable extrathoracic obstruction: If inspiratory flow exceeds expiratory flow at mid-lung volume, this physiology is one of a variable extrathoracic obstruction, seen in people with tracheal injury, vocal cord paralysis, and other conditions where the act of breathing in restricts the size and flow of inspiration, while breathing out opens the segment that has dynamic collapse during inspiration (Fig. 20.3).

Variable Intrathoracic Obstruction: Flow limitation is encountered during forced expiration, when the pleural pressure becomes positive relative to airway pressure, and the effect of any obstructive lesion becomes pronounced.

One feature of the loop that was thought to represent sleep apnea was a saw-tooth pattern on inspiration as well as on expiration believed to represent unstable upper airway structures (saw-tooth sign) [3] (Fig. 20.4). Although the precise mechanism may differ among individuals, fluttering on inspiration is not routinely seen in sleep apnea and can be present in those with motor disease like Parkinson's disease and may also be seen in normal patients due to artifact [4]. Reversibility of airways obstruction can be assessed with the use of bronchodilators. After spirometry is completed, the patient is given an inhaled bronchodilator and the test is repeated. The purpose of this is to assess whether a patient's pulmonary process is bronchodilator responsive by looking for improvement in the expired volumes and flow rates. In upper airway obstruction an increase in >12 % increase in the FEV1 (an absolute improvement in FEV1 of at least 200 ml) or the FVC after inhaling a beta agonist is considered a significant response. Spirometry is typically reported

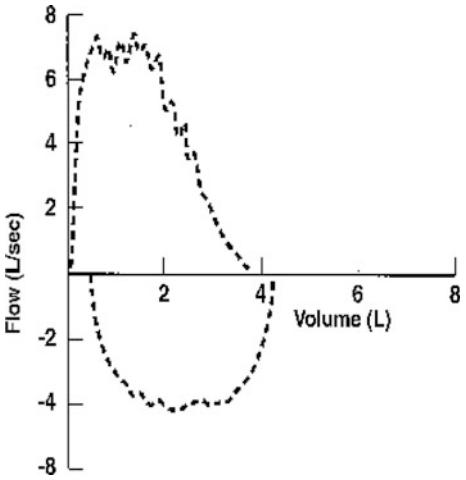

Fig. 20.4 Saw-tooth pattern of flow-volume loop: this finding may be observed in the setting of an individual at increased risk of sleep apnea or a patient with neuromuscular disease. Alternatively, this finding also may simply reflect artifact

in both absolute values and as a predicted percentage of normal. Normal values vary depending on sex, race, age, and height.

Lung Volumes

In contrast to spirometry, a dynamic test of airflow function, measurement of lung volumes is designed to collect values relating to the size of the lung as a gas-exchanging unit. These volumes are indirectly calculated from measures of a slow inspiration (or expiration) and a direct measure of thoracic gas volume (TGV) at functional residual capacity (FRC), with a subsequent derivation of a number of values. FRC is usually measured by a gas dilution technique or body plethysmography. Gas dilution techniques are based on a simple principle, are widely used, and provide a good measurement of all air in the lungs that communicates with the airways.

Body plethysmography is a second method of measuring lung volume that takes advantage of the principle of Boyle's law, which states that the volume of gas at a constant temperature varies inversely with the pressure applied to it. The primary advantage of body plethysmography is that it can measure the total volume of air in the chest, including gas trapped in bullae. Another advantage is that this test can be performed quickly. Drawbacks include the complexity of the equipment as well as the need for a patient to sit in a small enclosed space. From the FRC, the patient pants against a closed shutter to produce changes in the box pressure proportionate to the volume of air in the chest. The volume measured by this technique is referred to as TGV and represents the lung volume at which the shutter was closed, typically FRC.

After measurement of FRC, the patient would exhale fully and then take a large breath to total lung capacity. The difference between FRC and residual volume is called the expiratory reserve volume (ERV), and the difference between the total lung capacity and FRC is called the inspiratory capacity. The ERV is reduced in obesity where the chest wall mass makes for a smaller FRC (Fig. 20.1).

The interpretation of lung volumes is coordinated with that of spirometry to allow one to distinguish between obstructive lung physiology and a mixed picture (Fig. 20.2). An obstructed pattern may be seen most commonly if there is narrowing of the airways due to bronchial smooth muscle contraction (i.e., asthma), narrowing of the airways due to inflammation and swelling of bronchial mucosa and the hypertrophy and hyperplasia of bronchial glands (i.e., bronchitis).

In some patients, obstructive sleep apnea may co-exist with COPD, which has been coined the "overlap syndrome" given that this is a clinically distinct entity compared with each disease in isolation [5]. Patients with the overlap syndrome have been shown to have a higher frequency of breathing and lower tidal volume compared with patients with sleep apnea [6]. In COPD, the oxygen saturation falls approximately 2–4 % from the awake baseline value with minor fluctuations until a more substantial reduction is noted in REM sleep, and therefore, nocturnal oxygen desaturation is a commonplace finding in the setting of obstructive lung disease (Fig. 20.5). A more pronounced degree of hypoxia occurs in the setting of COPD due to starting on a steeper portion of the oxyhemoglobin curve, alveolar hypoventilation due to reduction in chemosensitivity and reduction in

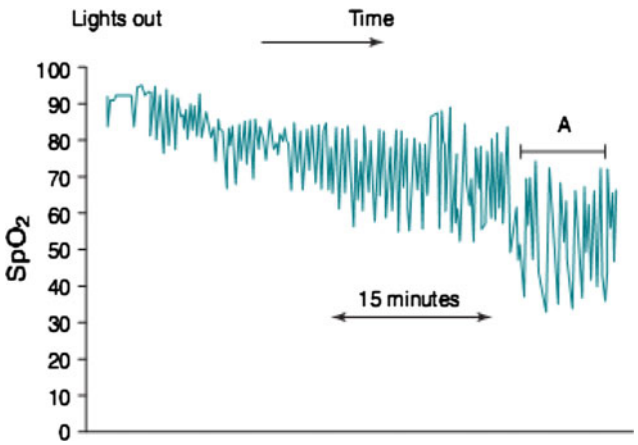

Fig. 20.5 In a patient with both snoring and moderate COPD, the baseline is reduced during sleep but the saw-tooth pattern is suggestive of obstructive sleep apnea. *A* period of REM sleep

end-expiratory lung volumes. The importance of the identification of overlap syndrome is highlighted by the observed association with increased risk of death and hospitalization because of COPD exacerbation [7]. Overlap syndrome has been associated with more pronounced sleep-related hypoxemia and hypercapnia compared with patients with COPD or OSA alone, which may explain the above findings [8]. The presence of OSA has also been demonstrated to result in increased COPD exacerbations and accelerated lung function decline [9].

Restriction can be applied to patients whose total lung capacity has been measured and found to be significantly reduced. Total lung capacity is the volume of air in the lungs when the patient has taken a full inspiration. There are a variety of restrictive disorders such as intrinsic lung disease (sarcoidosis, interstitial lung disease), extrinsic restrictive lung disorders (morbid obesity, kyphosis/scoliosis), and neuromuscular restrictive disorders (myasthenia gravis, muscular dystrophy, post-polio syndrome, amyotrophic lateral sclerosis). Although preliminary findings appear to support reduced REM sleep and increased sleep fragmentation, overall there are limited data characterizing relationships of sleep and sleep apnea with restrictive parenchymal lung disease [10].

Measurement of maximal inspiratory and expiratory pressures is indicated whenever there is an unexplained decrease in vital capacity or respiratory muscle weakness is suspected clinically. Maximal inspiratory pressure (MIP) is the maximal pressure that can be produced by the patient trying to inhale through a blocked mouthpiece. Maximal expiratory pressure (MEP) is the maximal pressure measured during forced expiration (with cheeks bulging) through a blocked mouthpiece after a full inhalation. Repeated measurements of MIP and MEP are useful in following the course of patients with neuromuscular disorders.

Diffusing Capacity

Diffusing capacity measures the features at work involving movement of oxygen from the alveolar surface through to the hemoglobin molecule. The clinical test diffusing capacity of the lung (DL) most commonly uses carbon monoxide (CO) as the tracer gas for measurement because of its high affinity for binding to the hemoglobin molecule. This property allows a better measurement of pure diffusion, such that the movement of the CO is in essence only dependent on the properties of the diffusion barrier and the amount of hemoglobin. The properties of oxygen and its relatively lower affinity for hemoglobin compared with CO also make it more perfusion dependent; thus, cardiac output may influence actual measurement of oxygen diffusion measurements.

Diffusing capacity for CO (DLCO) is the measure of CO transfer. DLCO is a measure of the interaction of alveolar surface area, alveolar capillary perfusion, the physical properties of the alveolar capillary interface, capillary volume, hemoglobin concentration, and the reaction rate of CO and hemoglobin. The most widely used and standardized technique is referred to as the single-breath breath-holding technique. This technique relies on a subject inhaling a known volume of test gas, the patient inhales the test gas and holds his or her breath for 10 s and then exhales to "wash out" mechanical and anatomic dead space. DLCO is calculated from the total volume of the lung, breath-hold time, and the initial and final alveolar concentrations of CO. Alveolar volume is estimated by the helium dilution and the initial alveolar concentration of CO. The driving pressure is assumed to be the initial alveolar pressure of CO.

Because the level of hemoglobin present in the blood and diffusing capacity are directly related, a correction for anemic patients (DLCOc) is used to further delineate whether a DLCO is decreased due to anemia or due to parenchymal or interface limitation. Diseases such as interstitial pulmonary fibrosis or any interstitial lung disease may make the DLCO abnormal long before spirometry or volume abnormalities are present. Low DLCO is not only an abnormality of restrictive interstitial lung disease but may also occur in the presence of emphysema. On the other end of the spectrum, alveolar hemorrhage or congested capillary beds may actually increase the DLCO. Similar to spirometry, predicted formulas have been established for DLCO and DLCO corrected for alveolar volume. It is important to note, however, that differences in race have been observed in normal subjects, and a race correction of 7 % is allowed for African American patients [11]. The diffusing capacity, if reduced, may be a reason for oxygen levels to be low even when there are relatively normal values on spirometry or lung volumes. Such a circumstance is found with pulmonary vascular disease [12]. To the extent that a reduced diffusing capacity affects oxygen levels, it can be one reason for excess hypoxemia during sleep, even in the absence of apneas or hypopneas.

Arterial Blood Gas

A sample of arterial blood is drawn anaerobically from a peripheral artery (typically radial, however, brachial, axillary, or femoral routes may be considered) via a single

percutaneous needle puncture, or from an indwelling arterial cannula or catheter for multiple samples. A resting arterial blood gas may be considered in the setting of hypoxia out of proportion to the degree of sleep-disordered breathing, thereby suggesting underlying possible cardiopulmonary disease or to obtain a sense of resting hypercapnia if underlying obesity hypoventilation, obstructive lung disease, or neuromuscular disease is known or suspected.

The arterial blood gas allows for the measurement of partial pressures of carbon dioxide ($PaCO_2$) and oxygen (PaO_2), acidity (pH), total hemoglobin (Hbtotal), oxyhemoglobin saturation (HbO_2), carboxyhemoglobin (COHb), and methemoglobin (MetHb). Refer to Table 20.1 for the approach to acid–base determination. Arterial blood gases permit another assessment of gas exchange and of ventilation. One can derive a value of the A–a gradient to determine a problem in gas exchange at the alveolar level:

$$P(A-a)O_2 = [FiO_2(P_B - P_{H_2O}) - PaCO_2/RQ] - PaO_2$$

- $P(A–a)O_2$ = Alveolar-Arterial O_2 Gradient. It is the difference between the amount of oxygen in the alveoli and the amount of oxygen dissolved in plasma.
- FiO_2 = Inspired Oxygen. It is the fraction of the inspired oxygen (0.21 at room air)
- P_B = Atmospheric Pressure of O_2
- P_{H_2O} = Partial Pressure of H_2O
- $PaCO_2$ = Partial Pressure of CO_2 in the Arterial Blood
- PaO_2 = Partial Pressure of O_2 in the Arterial Blood
- RQ: The Respiratory Quotient is the amount of CO_2 relative to the amount of O_2 consumed (in normal situations, this is approximately 0.8)

An increased A–a gradient would cause a reduction in arterial blood oxygen levels and be the result of a ventilation-perfusion mismatch (most common and most commonly observed in obstructive diseases such as COPD or asthma) or by an anatomic shunt (as in liver disease resulting in hepatopulmonary syndrome). A second pattern seen is a normal A–a gradient with the hypoxemia explained by hypoventilation of lung units, retention of carbon dioxide, and elevated arterial $PaCO_2$. Hypoxemia due to pure hypoventilation (e.g., in obesity hypoventilation syndrome, neuromuscular disease resulting in CNS depression and impaired neural conduction) corrects with increase in fraction of inspired oxygen. A process resulting in hypoxemia during wakefulness is likely to produce lower oxygen saturation levels during sleep as the latter is associated with a

Table 20.1 Determination of acid–base status

Step I. Determine primary acid–base status disorder	
(*A*) *Determine acidosis versus alkalosis*	
1. pH < 7.36: Acidosis	2. pH > 7.44: Alkalosis
(*B*) *Determine metabolic versus respiratory*	
1. Primary metabolic disorder (a) pH changes in same direction as bicarbonate, $PaCO_2$ (b) Metabolic acidosis (i) Serum pH decreased (ii) Serum bicarbonate and PaCO2 decreased (c) Metabolic alkalosis (i) Serum pH increased (ii) Serum bicarbonate and $PaCO_2$ increased	2. Primary respiratory disorder (a) pH changes in the opposite direction of bicarbonate, $PaCO_2$ (b) Respiratory acidosis (i) Serum pH decreased (ii) Serum bicarbonate and $PaCO_2$ increased (c) Respiratory alkalosis (i) Serum pH increased (ii) Serum bicarbonate and $PaCO_2$ decreased
Step II. Determine compensation	
(A) Metabolic acidosis: $PaCO_2$ decreases 1.2 mmHg per each 1 meq/L bicarbonate fall	*(A) Acute respiratory acidosis*: Bicarbonate increases 1 meq/L per 10 mmHg $PaCO_2$ rise
(B) Metabolic alkalosis: $PaCO_2$ increases 6 mmHg per 10 meq/L bicarbonate rise	*(B) Chronic respiratory acidosis*: Bicarbonate increases 4 meq/L per 10 mmHg $PaCO_2$ rise
	(C) Acute respiratory alkalosis: Bicarbonate decreases 2 meq/L per 10 mmHg $PaCO_2$ fall
	(D) Chronic respiratory alkalosis: Bicarbonate decreases 4 meq/L per 10 mmHg $PaCO_2$ fall

Normal range of values can vary among different laboratories. Normal pH is from 7.35 to 7.45, normal PCO_2 is 35–45 mm Hg, and normal HCO_3 is from 21 to 27 meq/L

reduction in the FRC and also reduced ventilation. Therefore, the presence of hypoxemia or hypoventilation in an awake resting arterial blood gas is predictive of greater hypoxemia during a sleep study.

Monitoring of Respiratory Function During Sleep

Updates have been put forth by the American Academy of Sleep Medicine (AASM) regarding scoring rules for respiratory events [13]. The goal of these updates was to revise the rules to reflect changes in our understanding of the predictiveness of various levels of hypoxia and flow reduction relative to adverse outcomes and also to address knowledge gaps in terms of specification of the sensor for detection of apnea and hypopnea during the positive airway pressure (PAP) titration given that PAP devices have the ability to output an analog or digital signal from the internal flow sensor. The updated rules also sought to overcome confusion caused by the endorsement of two hypopnea rules in the prior manual and to make more consistent the adult and pediatric respiratory event scoring rules. New evidence has emerged since 2007 showing the impact of the scoring rules in diagnosis of OSA [14, 15]. Below represents a description of the sensors that may be used for respiratory physiologic monitoring and also an overview of definitions recommended to be used for the scoring of respiratory events.

Airflow Monitoring

Most airflow sensors detect apneas reliably, but the detection and quantification of decreased flow needed to diagnose hypopneas depends on the type of sensor used. Hypopnea comprises the majority of obstructive respiratory events and therefore its measurement needs to be reliable.

The 2013 task force recommends thermistors, thermocouples, or polyvinylidene fluoride (PVDF) sensors for the detection of airflow. PVDF sensors have been included in the definition of thermal sensors for the detection of airflow given data demonstrating that the PVDF sum signal provides comparable detection of events independent of direct airflow monitoring with thermistry or nasal pressure. The PVDF sensor also performed as well as the pneumotachograph in the detection of the number of respiratory events [16, 17]. For identification of an apnea during the diagnostic study, the oronasal thermal airflow sensor is recommended to monitor airflow. If the oronasal sensor is not functioning or the signal is not reliable, then the use of nasal pressure transducer, respiratory inductance plethysmography (RIP) flow, or RIP sum is suggested. The nasal pressure signal is not the recommended sensor for apnea detection as the signal can show decreased amplitude during mouth breathing [18].

Pneumotachometer

This method of airflow monitoring provides a direct quantitative measurement of airflow or tidal volume and, however, requires connection to a sealed mask placed over the nose or mouth. It is considered the reference standard for obstructive apnea and hypopnea detection. Although its use provides a beneficial and accurate research tool, in the clinical setting this technique is somewhat cumbersome and therefore not standardly utilized. This method measures the flow rate of gases during breathing. The breath is passed through a short tube in which there is a fine mesh, which presents a small resistance to the flow. Flow (V′) is derived from the pressure difference over a small, fixed resistance, offered by a fine metal mesh. The pressure drop across the resistance relates linearly to flow at relatively low flows, when the flow pattern is laminar. Accurate measurements are best performed when the flow pattern is laminar and flow is linearly related to pressure drop.

Nasal Thermocouple/Thermistor

Oronasal thermocouple sensor assesses airflow via indirect semiquantitative assessment detecting increased temperature of expired air with only directional changes providing reliable results. Oronasal sensors can detect both nasal and oral airflow. Thermocouples are commonly used for temperature measurement as they are highly accurate and operate over a broad range of temperatures. Thermistors consist of an electronic component (semiconductor material) that exhibits a large change in resistance in proportion to a small change in temperature. In comparison with thermocouples, thermistors have a limited (smaller) temperature range; however, they are highly sensitive within this range. The resistance of these devices often changes in a nonlinear fashion and additional instruments are required to linearize the reading. In laboratory models that have compared thermistors and thermocouples to the pneumotachograph, the thermal sensors have been shown to be nonlinearly related to airflow, generally providing an overestimation of ventilation [19].

Intranasal Pressure/Transducer

This technique provides an indirect measurement of airflow by detecting pressure changes with an excellent response to airflow profile and is capable of detecting airflow limitation. Changing pressures require a transducer, which can respond to rapid changes. Nasal pressure transducers provide a significantly more sensitive measure of airflow than temperature-based sensors and many believe that the pressure transducers may provide a measure of upper airway resistance as inspiration and expiration provide transducer signal fluctuations similar to airflow [20, 21]. In one study, the nasal cannula/pressure transducer has been found to serve as a noninvasive reproducible detector of all events in SDB; in particular, it detects the same events as esophageal manometry (respiratory effort-related arousals, RERAs) with an intraclass correlation coefficient of 0.96 [22]. The nasal pressure transducer provides additional information for scoring hypopneas compared with themistry. If used for evaluation of sleep-related breathing disorders, the improved level of sensitivity offered by the nasal pressure transducer may lead to scoring of many more events than are typically scored with other methods of airflow detection. Nasal pressure monitoring is not recommended for patients who are predominantly mouth breathers or have nasal obstruction in which case airflow may be underestimated [23]. Square root linearization of nasal pressure more accurately approximates flow and greatly increases the accuracy for quantifying hypopneas and detecting flow limitation [24, 25]. Features of the signal such as flattening of the inspiratory portion of the waveform serve as a surrogate for flow limitation; however, reliable detection of flow limitation requires the use of a DC signal or an AC signal with an appropriately low frequency filter setting [26].

Respiratory Inductance Plethysmography

The literature supports that RIP is acceptable for the semiquantitative measurement of ventilation assessed by thoracic and abdominal pressure changes. The 2013 task force includes the available dual RIP belt signals, RIP sum signal (sum of the thorax and abdomen belt signals), and RIP flow (time derivative of the RIP sum signal) [13] unlike the previous manual, which did not clearly differentiate the utility of these RIP signal subtypes. With this technique, transducers are placed at the level of the nipples and at the umbilicus to monitor cross-sectional changes reflected by changes in inductance or resistance to change in flow of the transducers. The sum of the signals may provide an estimate of tidal volume and respiratory pattern during sleep [27]. Measurement inaccuracies may occur due to slippage (displacement of transducer bands) and position changes. RIP detects changes in the volume of the chest and abdomen during inspiration and expiration and, when properly calibrated, the sum of the two signals can provide an estimate of tidal volume [28]. However, calibration may be difficult to maintain throughout the night [29]. In uncalibrated RIP, deflections in the RIP sum signal allow detection of relative change in tidal volume compared with baseline breathing; however, when calibrated, it provides a more accurate estimate of tidal volume. RIP flow is the time derivative of the RIP sum signal and serves as a semiquantitative estimate of airflow in calibrated RIP [30, 31].

Snore Monitoring

The microphone is used to detect snoring during polysomnography (PSG), providing an output signal with easily identifiable waveforms. This tracing in conjunction with sleep technician comments may assist in the diagnosis of primary snoring when there is lacking evidence for SDB. The piezoelectric sensor or nasal pressure transducer can also be used for monitoring snoring. In addition, snoring may be detected as superimposed oscillations on the airflow waveform. Unfiltered nasal pressure signal, piezoelectric sensors, or acoustic sensors can be used to record the sound of the snoring. High-frequency oscillations may be seen in the nasal pressure signal but may not be observed on the PAP device flow signal.

Esophageal Balloon Manometry

The measurement of esophageal pressure with continuous overnight monitoring is the reference standard for measuring respiratory effort during PSG and, however, carries intrinsic practical issues that obviate its use clinically. Respiratory efforts are associated with changes in pleural pressure which can be accurately measured using esophageal manometry. This method is useful when distinguishing central versus obstructive apneas, and is useful for detecting RERAs in the setting of upper airway resistance syndrome during which there is increasingly more negative esophageal pressures immediately preceding an arousal, subsequent to which the esophageal pressure fairly rapidly returns to normal levels [32, 33].

Pulse Oximetry Monitoring

Pulse oximetry monitoring may be performed at baseline in the clinical setting and is recommended to be included in standard sleep study monitoring including portable sleep monitoring. Pulse oximetry may also be performed during

sleep to assess the residual degree of hypoxia after someone has been placed on treatment with PAP for sleep apnea in order to assess the need for concomitant supplemental oxygen. Although the AASM clinical guidelines and practice parameters do not specify the location of the probe (e.g., ear, finger, forehead), it is generally agreed that finger oximetry probes be utilized. In order to maximize ability to extract data in a meaningful way and to ensure capturing desaturations in synchrony with respiratory events, AASM guidelines recommend a maximum signal averaging time of ≤3 s at a heart rate of >80 beats per minute even in the setting of portable sleep monitoring [34].

The fundamental physical property that allows the measurement of arterial oxygen saturation is that blood changes color with saturation. Hemoglobin, in its reduced form or oxygenated state, absorbs light at wavelengths below approximately 630 nm, which includes the entire part of the visible spectrum aside from the red region. The opposite situation occurs in the near-infrared region (810–1000 nm), where hemoglobin absorbs more light when it is desaturated. Pulse oximeters usually are designed with two emitters (usually light-emitting diodes); one designed to emit light in the red region (~660 nm), and the other in the near-infrared region (~925 or 940 nm). In order to measure absorption of arterial blood only, without interference from venous blood, skin, bone, and to minimize scatter effect, a differential absorption is calculated by dividing the small change in intensity by the total intensity of the output light. Chromophores other than oxyhemoglobin and reduced hemoglobin, such as carboxyhemoglobin and methemoglobin, may cause falsely elevated readings for the arterial oxygen saturation. Of note, oximeters may be calibrated using functional or fractional oxygen saturation with the former reading slightly higher (1–3 %). Oximeters may be prone to artifact such as during states of poor perfusion, hypothermia, profound anemia, excessive patient motion (particularly at the probe site), and electrical noise and may also be affected by changes in heart rate and circulation time [35].

It is also important to note that while oxygen saturation from pulse oximetry allows a convenient and noninvasive means of assessing arterial oxygenation, it does not in and of itself allow for assessment of ventilation. Moreover, due to the sigmoidal shape of the oxyhemoglobin dissociation curve, a large reduction in arterial PO_2 will not result in a substantial decline in the oxygen saturation until the steeper portion of the curve is approached. Overall, pulse oximetry is easy to use, inexpensive, readily available, and noninvasive and permits continuous monitoring of oxygen saturation. Pulse oximetry sensitivity is improved with shorter sampling intervals, and minimal filtering in order to achieve the most rapid response. During scoring of sleep study data, the oxygen desaturation associated with the respiratory event is defined as drop in baseline SpO_2 preceding the event to the nadir in the SpO_2 following the event.

Carbon Dioxide Monitoring

Expired End-tidal CO_2 Monitoring

Arterial partial pressure of carbon dioxide is the gold standard method for determining hypoventilation; however, it is difficult to obtain. Therefore, other surrogate sensors are commonly used during PSG such as end-tidal CO_2 monitoring. This modality works by a drawing a stream of air from the nose or the mouth to a chamber in which a light is shone through the air (side stream method). The degree of absorption at a certain frequency of infrared light is proportional to the concentration of CO_2. Continuous measurement of CO_2 reflects the excretion pattern of carbon dioxide from the lung. Values for CO_2 are near or at zero on inspiration and show an abrupt rise until the end of expiration when there is a plateau in the CO_2 level. The end-expiratory value is correlated with arterial PCO_2 provided that there is complete gas emptying to FRC, and little effect of ventilation-perfusion mismatch. The arterial partial pressure of CO_2 and end-tidal CO_2 difference is usually 2–7 mmHg with overall trends of capnography CO_2 values underestimating the arterial PCO_2 values [36] and in general is higher in patients with lung disease [37].

End-tidal CO_2 monitoring may help in identifying hypoventilation in obesity hypoventilation syndrome, as well as COPD, congestive heart failure, and neurologic diseases that produce neuromuscular weakness. In addition, end-tidal CO_2 values can be helpful in assessing disorders of chronic hyperventilation, distinguishing pathophysiologic from psychogenic causes by the persistence or resolution of hypocapnia during sleep.

A limitation of end-tidal CO_2 monitoring includes the inability to accurately measure levels in the setting of continuous positive airway pressure (CPAP) or bilevel pressure therapy in order to assess response to treatment. The values are also inaccurate during application of supplemental oxygen as the supplemental oxygen dilutes the exhaled gas sample [38].

The value of capnography (breath-by-breath CO_2 measurements) is twofold as described below, but limited in scope compared with direct measures of airflow.

The first is that capnography may detect absence of expiratory airflow and signal an apnea. There are no established criteria, but an apnea event is considered to occur

when there is a failure for end-expiratory CO_2 to fall after expiration with subsequent decline in CO_2 over the next 10 s to values at or near zero. The end of the apnea is heralded by the occurrence of a rapid rise in CO_2 with expiration; the length of an event is from the peak of the last CO_2 rise to the peak of the next CO_2 rise if greater than 10 s. A cardiac oscillation in the capnography signal indicates a patent airway during a central apnea (but the frequency of this is only recorded at an anecdotal level of evidence). There can be expiratory puffs after an obstructed inspiratory effort, but again the frequency of this is only recorded at an anecdotal level of evidence. Second, capnography can be used to identify obstructive hypopneas. In this instance, there are persistent efforts characterized by asynchronous chest wall movements of the ribcage and abdomen with a rising end-tidal CO_2 over time. The frequency of this kind of pattern is only recorded at an anecdotal level of evidence.

Scoring of events from the CO_2 monitor should be directed at apneas, and to the extent possibly correlated with ribcage/abdominal movements and CO_2 fluctuation in synchrony with EKG (central event) or in synchrony with respiratory efforts (expiratory puffs signaling an obstructive event). The length of an event is from the peak of the last CO_2 rise to the peak of the next CO_2 rise, if greater than 10 s. Obstructive hypopneas would be detected by a series of breaths with asynchronous ribcage/abdominal motion associated with an increasing end-expiratory CO_2 level.

Transcutaneous CO_2 Monitoring

There are two methods that may be employed in transcutaneous CO_2 monitoring: the first uses a silver electrode which measures CO_2 that has diffused from the skin through a gas-permeable membrane into solution (response time less than one minute), and the other uses an infrared capnometer that analyzes CO_2 in the gas phase (response time more than 2 min).

Transcutaneous CO_2, unlike end-tidal CO_2, remains accurate with mouth breathing, supplemental oxygen, or mask ventilation. Transcutaneous CO_2 may overestimate the arterial CO_2. In a study involving severe obese individuals, the difference between arterial CO_2 and transcutaneous CO_2 was −1.4 mm Hg (SD 1.3 mm Hg) [39] and another study demonstrated consistent findings with $TcCO_2$ measurement serving as an overestimate of arterial PCO_2 values during hypercapnia [40]. End-tidal CO_2 and transcutaneous CO_2 are surrogates of $PaCO_2$ during diagnostic studies. It is important to carefully review the tracings to determine whether artifacts are present that may compromise the integrity of the data. If there is a discrepancy in the readings in reference to the clinical picture, recalibration of a change in the sensor site may be required [38, 41].

Classification and Scoring of Respiratory Events

Obstructive Apneas: As per the latest AASM recommendations [26], obstructive apneas are defined as a drop in the peak signal excursion (defined as ≥ 90 %) from pre-event baseline in the amplitude of a valid measure of breathing that is oronasal thermal sensor (diagnostic study) or an alternative apnea sensor (diagnostic study), PAP device flow (titration study) during sleep lasting at least 10 s associated with continued or increased thoracoabdominal respiratory effort throughout the entire period of absent airflow. Recommended airflow sensors include oronasal thermal sensor or PVDF sensor. Of note, based upon consensus and clinical evidence, it is recommended that the PAP device flow signal be used to score apneas or hypopneas during the PAP titration with the caveat that the magnitude of oral airflow if present is not accurately estimated by the PAP flow signal.

Baseline is described as the mean amplitude of stable breathing and oxygenation in the preceding two minutes prior to the event in individuals who have a stable breathing pattern during sleep or the mean amplitude of the three largest breaths in the two minutes preceding the onset of the event in individuals without a stable breathing pattern.

Central Apneas: A drop in the peak signal excursion (defined as ≥ 90 %) from pre-event baseline in the amplitude of a valid measure of breathing that is oronasal thermal sensor (diagnostic study) or an alternative apnea sensor (diagnostic study), PAP device flow (titration study) during sleep lasting at least 10 s associated with absent inspiratory effort throughout the entire period of absent airflow.

Mixed Apneas: A drop in the peak signal excursion (defined as ≥ 90 %) from pre-event baseline in the amplitude of a valid measure of breathing that is oronasal thermal sensor (diagnostic study) or an alternative apnea sensor (diagnostic study), PAP device flow (titration study) during sleep lasting at least 10 s is associated with absent inspiratory events in the initial portion of the event, followed by redemption of inspiratory effort in the second portion of the event.

Hypopneas: Hypopnea is scored as a respiratory event when all the following criteria are met: The peak signal excursions drop by $\geq$30 % of prevent baseline using nasal pressure (diagnostic study), PAP device flow (titration study), or an alternative hypopnea sensor (diagnostic study). (A) The duration of >30 % drop in signal excursion is $\geq$10 s. (B) There is a $\geq$3 % oxygen desaturation from pre-event baseline or the event is associated with an arousal. The

recommended airflow sensor for hypopnea detection is nasal pressure transducer with or without square root transformation.

There has been a change in the definition of the hypopnea scoring criteria from 2007 scoring manual. The basis for incorporation of the 3 % oxygen desaturation in reference to the hypopnea definition is based upon accrued data demonstrating associations of SDB defined by the apnea hypopnea index including hypopneas accompanied by ≥3 % oxygen desaturations with adverse cardiovascular outcomes. Analysis of Wisconsin Sleep Cohort and Sleep Heart Health Data showed that the use of the AHI incorporating hypopnea defined by ≥3 % oxygen desaturation criteria was as predictive of adverse outcomes as utilizing the AHI based on ≥4 % hypopnea oxygen desaturation criteria [42, 43]. Several epidemiologic studies have determined that SDB defined by the AHI utilizing the 3 % oxygen desaturation hypopnea rule is significantly associated with increased atrial fibrillation and ventricular arrhythmia [44] as well as insulin resistance [45]. Moreover, use of the 3 % hypopnea rule has been longitudinally associated with an increased risk of stroke [46]. The use of greater than 30 versus 50 % reduction in airflow to define hypopnea was based upon the logic that irrespective of a 30 % or a 50 % reduction in flow is the presence of a significant physiologic consequence, i.e. hypoxia or arousal.

Given the need for identification of central respiratory events to characterize degree of central SDB burden clinically, there are now guidelines providing the option of differentiating obstructive versus central hypopneas based upon polysomnogram-identified features as follows:

Obstructive Hypopnea is scored if **any** of the following criteria are met:

(a) Snoring during the event
(b) Increased inspiratory flattening of the nasal pressure or PAP device flow signal compared with baseline breathing
(c) Associated thoracoabdominal paradox occurs during the event but not during the pre-event breathing (Fig. 20.6).

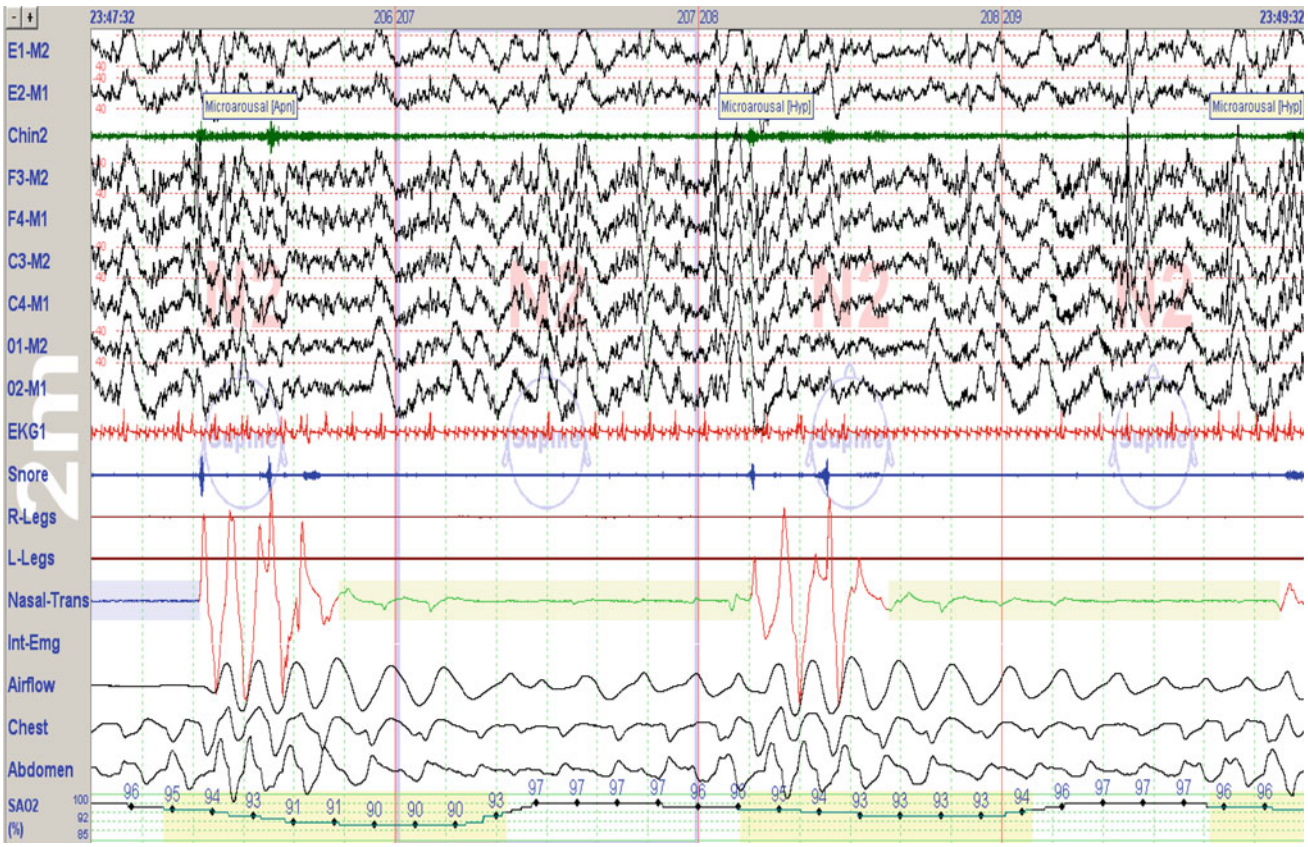

Fig. 20.6 Obstructive hypopneas: these events are associated with snoring, oxygen desaturation, and arousal accompanied by thoracoabdominal paradox

Central hypopneas can be scored if none of the following criteria are met:

(a) Snoring during the event
(b) Increased inspiratory flattening of the nasal pressure or PAP device flow signal compared with baseline breathing
(c) Associated thoracoabdominal paradox occurs during the event but not during pre-event breathing (Fig. 20.7)
(d) **Cheyne–Stokes Respirations**: Respiratory monitoring indicates at least three consecutive central apneas and/or central hypopneas separated by crescendo and decrescendo change in breathing pattern with cycle length of more than or equal to 40 s, and there are five or more central apneas or hypopneas per hour of sleep, associated with the crescendo/decrescendo breathing pattern recorded over ≥2 h of monitoring [26] (Fig. 20.8)
(e) **Sleep-Related Hypoventilation**: This is defined as one or both of the following: (1) an increase in arterial PCO_2 (surrogate) to a value ≥55 mm Hg for more >10 min and/or (2) there is ≥10 mm Hg increase in arterial PCO_2 (or surrogate) during sleep (in comparison with an awake supine value) to a value exceeding 50 mm Hg for >10 min [26] (Fig. 20.9)

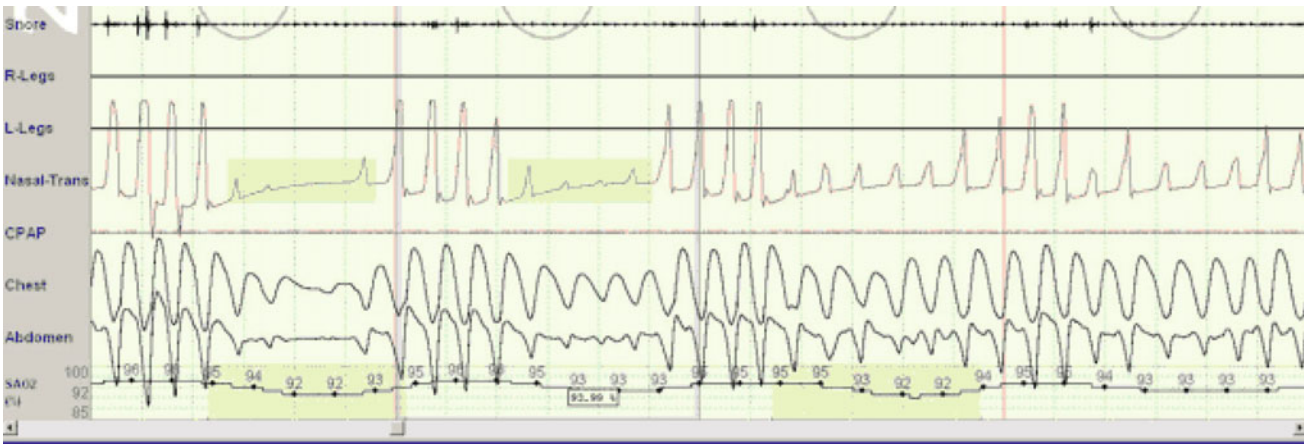

Fig. 20.7 Central hypopneas: these events are associated with absence of snoring, oxygen desaturation (albeit less substantive than that noted in obstructive events), and lack of thoracoabdominal paradox

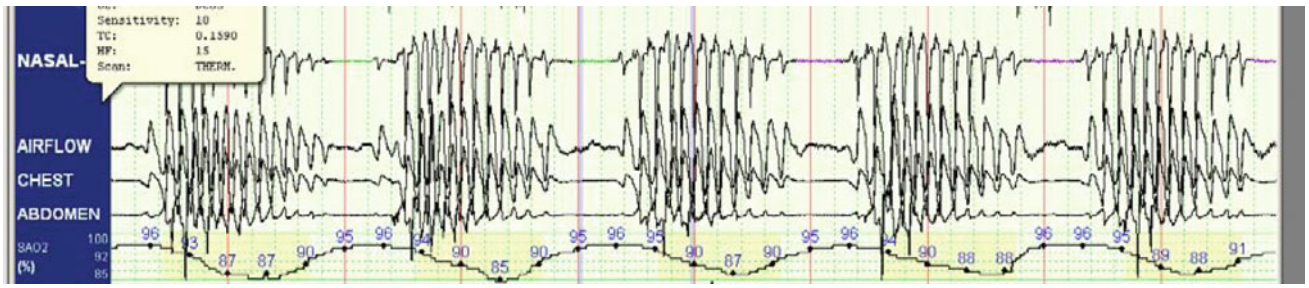

Fig. 20.8 Cheyne–Stokes respiration. Periodic breathing is characterized by crescendo-decrescendo change in breathing amplitude which separates at least three consecutive central apneas and/or central hypopneas

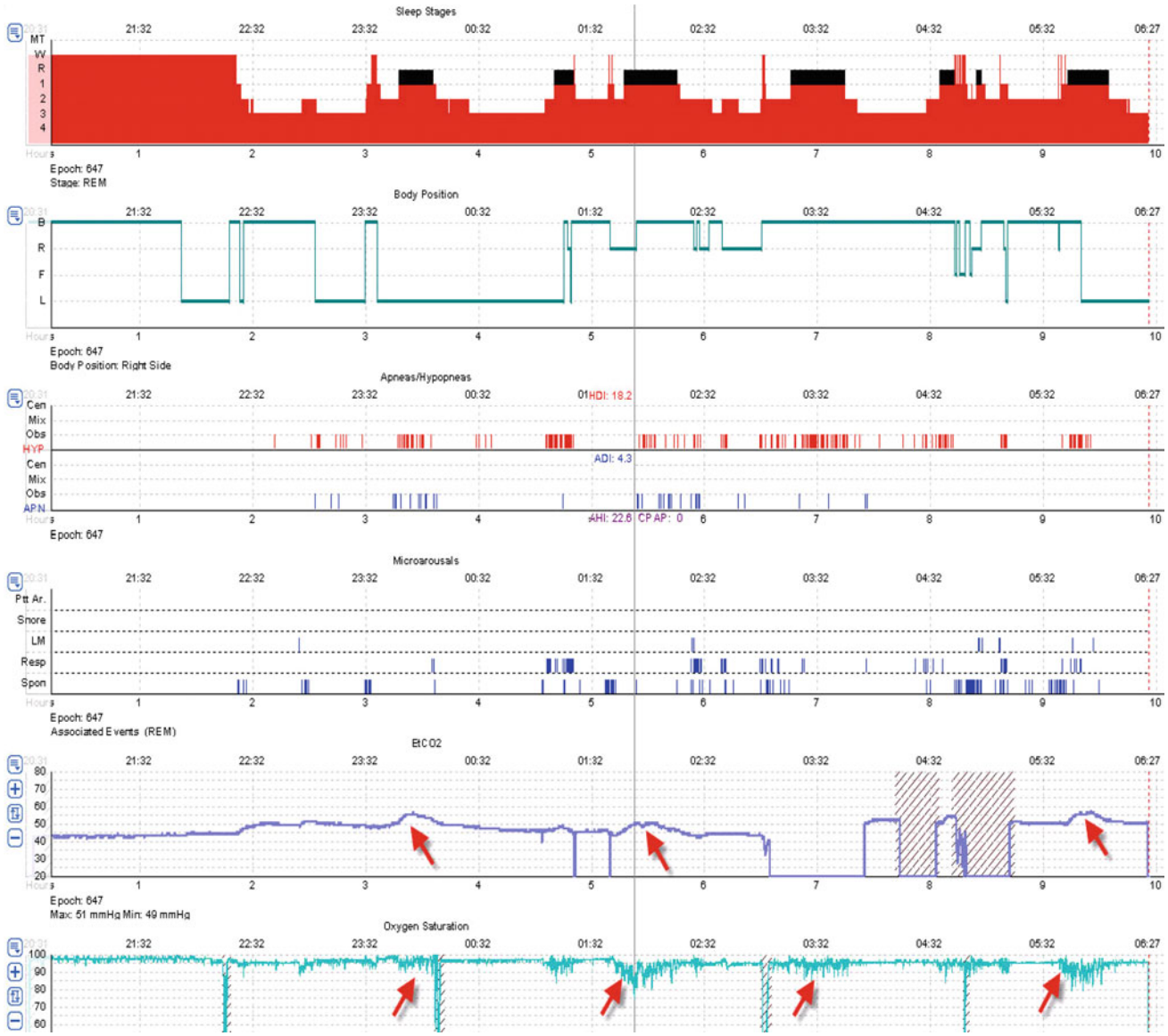

Fig. 20.9 Sleep-related hypoventilation. The *leftward slanting arrows* point toward the rise in CO_2 level with accompanying drop in oxygen saturation as indicated by the *rightward slanting arrows*. Note the increase in the CO_2 level with the sleep onset

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Neuroimaging in Normal and Abnormal Sleep

21

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Introduction

Functional neuroimaging is a powerful tool to explore regional brain activity in humans. It includes a variety of metabolic and hemodynamic techniques such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), and near-infrared spectroscopy. Neurophysiologic techniques such as electroencephalography (EEG) and magnetoencephalography (MEG) are not reviewed here.

Neuroimaging in patients suffering from sleep disorders may serve several purposes. First, it can help characterize the cerebral consequences of sleep disruption due to intrinsic sleep disorders and extrinsic environmental or medical causes. For instance, neuroimaging studies have shown that chronic sleep fragmentation in sleep-disordered patients [e.g., patients with obstructive sleep apnea syndrome (OSAS)] [1] or acute sleep deprivation in normal subjects [2–4] eventually leads to impaired cognitive functioning associated with significant changes in the underlying pattern of regional brain activity.

Second, neuroimaging may serve to better characterize the pathogenic mechanisms of sleep disorders, or at least their cerebral correlates [5]. This endeavor is hindered by the fact that, from the practical and methodological points of view, scanning patients during their sleep is not easy. However, alternative approaches are available, as the functional and structural consequences of these sleep disorders can also be assessed during wakefulness. For instance, voxel-based morphometry (VBM) analysis can be used to detect structural brain changes typical of specific sleep disorders. Likewise, cardiovascular regulation can be assessed by probing important reflexes (e.g., during the Valsalva maneuver).

Third, neuroimaging might help to establish the nosography of sleep disorders. For instance, neuroimaging could help classify different subtypes of insomnia in terms of their underlying characteristic patterns of regional brain activity, an approach that may prove complementary to clinical observation.

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This chapter reviews attempts made in these various directions. To set the stage for the study of sleep disorders, we first describe recent contributions of neuroimaging techniques to the functional neuroanatomy of normal sleep in humans.

Neuroimaging in Normal Human Sleep

Sleep profoundly impacts the activity of numerous physiologic systems (see, e.g., Kryger et al. [6]). PET, SPECT, or fMRI studies reviewed in this section have demonstrated that global and regional patterns of brain activity during sleep are remarkably different from those during wakefulness. These studies have also shown the persistence of brain responses to external stimuli during sleep, and plastic changes in brain activity related to previous waking experience.

Functional Neuroimaging of Normal Human Sleep

Noninvasive functional neuroimaging with PET brought an original description of the functional neuroanatomy of human sleep. These studies described a reproducible regional distribution of brain activity during sleep stages (rapid eye movement [REM] and non-REM [NREM] sleep) that largely differs from wakefulness, as expected from animal data. More recent data, using event-related fMRI, have also assessed the brain activity related to spontaneous neural events within sleep stages, such as sleep spindles.

NREM Sleep

In mammals, the neuronal activity observed during NREM sleep is sculpted by a cortical slow oscillation that alternates short bursts of firing ("up" states) and long periods of hyperpolarization ("down" states) [7]. Slow oscillations organize the synchronization of other NREM sleep rhythms (spindles and delta waves) [8] and should also have a major impact on regional cerebral blood flow (rCBF), which when averaged over time decreases in the areas where they prevail. Taking into account that PET measurements average cerebral activity over 45–90 s, decreases in cerebral blood flow (CBF) and cerebral glucose metabolism during NREM sleep are thought to underlie a change in firing pattern, reflected by the slow oscillation and characterized by synchronized bursting activity followed by long hyperpolarization periods [8]. Accordingly, as compared to wakefulness, the average cerebral metabolism and global blood flow levels begin to decrease in light (stage 1 and stage 2) NREM sleep [9–11], and reach their nadir in deep (stage 3) NREM sleep, also named slow-wave sleep (SWS) [12, 13].

In animals, the cascade of events that generates NREM sleep oscillations by thalamo-neocortical networks is induced by a decreased firing in the activating structures of the brainstem tegmentum [7]. In agreement with animal data, humans' PET studies show that brainstem blood flow is decreased during light NREM sleep [14] as well as during SWS [14–17]. During light NREM sleep, the pontine tegmentum appears specifically deactivated, whereas the mesencephalon seems to retain an activity that is not significantly different from wakefulness [14]. In SWS, both pontine and mesencephalic tegmenta are deactivated [16].

The thalamus occupies a central position in the generation of NREM sleep rhythms, due to the intrinsic oscillating properties of its neurons and the intrathalamic and thalamo-corticothalamic connectivity. As expected, in humans, regional activity decreases have been found in the thalamus during both light and deep NREM sleep in PET [14–16] and block-design fMRI [16] studies; rCBF decreases in the thalamus have also been evidenced in proportion to the power density of the EEG signal in the spindle and delta frequency range [18] (see Dang-Vu et al. [19] for a critical discussion of these findings).

The role of the cortex in the generation of NREM sleep oscillations is equally important but not yet fully understood [20], especially at the neuronal level. Electroencephalographic power density maps have revealed a relatively typical predominance of the delta frequency band in the frontal regions, whereas sigma power predominated over the vertex [21]. Human PET data similarly showed that the pattern of cortical deactivation was not homogeneously distributed throughout the cortex. As compared to wakefulness, the least active areas in SWS were observed in various associative cortices of the frontal (in particular the dorsolateral and orbital prefrontal cortex) and parietal, and to a lesser extent in the temporal and insular cortices [14, 15, 16, 22]. In contrast, the primary cortices were the least deactivated cortical areas [15]. Finally, a meta-analysis of our own data [19] showed a linear (inverse) relationship between EEG spectral power within the delta frequency band and rCBF in ventromedial prefrontal regions during NREM sleep in non-sleep-deprived normal subjects. This result suggests an important role of medial prefrontal cortices in the modulation of delta waves.

The reasons for this heterogeneous cortical distribution remain unclear. One hypothesis is that, since polymodal association cortices are the most active cerebral areas during wakefulness, and because sleep intensity is homeostatically related to prior waking activity at the regional level [23], these cortices might be more profoundly influenced by SWS rhythms than primary cortices [8].

The predominance of rCBF decreases in prefrontal regions may be functionally important since these cortical

regions are involved in mood regulation and in various cognitive functions (e.g., planning or probability matching) [24] that help adaptation of individual behaviors. Studies of the deleterious effects of sleep deprivation on human cognition also pointed to a high sensitivity of these association cortices to sleep deprivation (see later).

The previous functional brain imaging studies have compared periods or "blocks" of brain activity averaged over several tens of seconds or minutes between NREM sleep and wakefulness. Because hyperpolarization phases may predominate over these periods, the resulting picture emerging from these studies is decreasing brain activity during NREM sleep in the areas where slow oscillations are most prevalent. While NREM sleep is consistently characterized by a global and regional net decrease of brain activity over several seconds or minutes, the concept of NREM sleep as a stage of brain quiescence is not accurate, as we know from animal studies that NREM sleep is also characterized by transient bursts of neuronal discharge ("up" states) organized by NREM sleep oscillations. We conducted an event-related fMRI study during NREM sleep in normal non-sleep-deprived human volunteers and showed that the occurrence of the phasic sleep spindles was associated with increases of brain activity in a specific set of cortical and subcortical structures, including the thalamus, paralimbic areas, and superior temporal gyri [25]. Moreover, beyond this general activation pattern, we also demonstrated that slow and fast spindles could be differentiated in terms of their macroscopic hemodynamic responses: slow spindles were specifically associated with activation of the superior temporal gyrus, and fast spindles preferentially recruited hippocampal and sensorimotor cortical areas. Besides bringing further evidence that spindles can be divided in two biologically distinct subtypes, this study demonstrates that NREM sleep cannot be reduced to a state of sustained brain deactivation but is characterized by phasic increases in brain activity triggered by NREM sleep oscillations, such as spindles, in agreement with animal data.

Further support for this notion was obtained from another study from our group, this one evaluating brain activation in response to slow waves during NREM sleep [26]. Compared with baseline activation during deep sleep, slow waves were associated with significant activation in the inferior frontal gyrus, parahippocampal gyrus, precuneus, posterior cingulate cortex, brain stem (pons), and cerebellum. Higher amplitude slow waves (>140 μV) were more consistently associated with parahippocampal and brainstem activation [26]. This specificity of slow-wave regional recruitment, particularly in parahippocampal and prefrontal regions, may subserve a role of slow waves in sleep-dependent memory consolidation. In addition, the activation of pontine structures with slow waves suggests a change of firing rate—from a tonic to a phasic mode—in specific brainstem nuclei during NREM sleep, in agreement with recent animal data [27].

REM Sleep

REM sleep is characterized by desynchronized neuronal activity [28, 29] and, correspondingly, by high cerebral energy requirements [12] and blood flow [13, 30]. In this active but sleeping brain, some areas are particularly active, even more than during wakefulness, while others have lower than average regional activity.

PET studies have shown significant rCBF increases during REM sleep in the pontine tegmentum, thalamic nuclei, limbic and paralimbic areas, amygdaloid complexes [31, 32], hippocampal formation [15, 32], anterior cingulate cortex [15, 31, 32], and orbitofrontal and insular cortices [32] (Fig. 21.1). Posterior cortices in temporo-occipital areas were also found to be activated [15], although less consistently. In contrast, the inferior and middle dorsolateral prefrontal gyri, the inferior parietal cortex, and the posterior cingulate cortex and precuneus were the least active brain regions [15, 31].

Regional brain activity in subcortical mesopontine and thalamic regions during human REM sleep [14, 31] is in keeping with our current understanding of sleep generation in animals. REM sleep is generated by neuronal populations of the mesopontine reticular formation that activates the thalamic nuclei, which in turn activate the cortex [28].

Functional connectivity between remote brain areas is also modified during human REM sleep. The functional relationship between striate and extrastriate cortices, usually excitatory, is reversed during REM sleep [15, 33]. Likewise, the functional relationship between the amygdala and the temporal and occipital cortices is different during REM sleep than during wakefulness or NREM sleep [34]. This pattern suggests that functional interactions between neuronal populations are different during REM sleep than during wakefulness. A recent resting-state fMRI study demonstrated that REM sleep connectivity is also different from NREM sleep connectivity, specifically in the set of brain areas known as the default-mode network [35]. The default-mode network consists of regions activated when the brain is not engaged in externally oriented behavior [36]. The functional connectivity within the default-mode network is diminished in NREM sleep, but in REM sleep, it is comparable to that in wakefulness [35]. Moreover, in REM sleep, the higher-order association cortices (encompassing the default-mode network) engage in a rapid oscillatory fluctuation of anticorrelated activation with the sensorimotor areas [35]. These characteristic patterns of activation may underlie neuroplastic and phenomenal aspects of REM sleep.

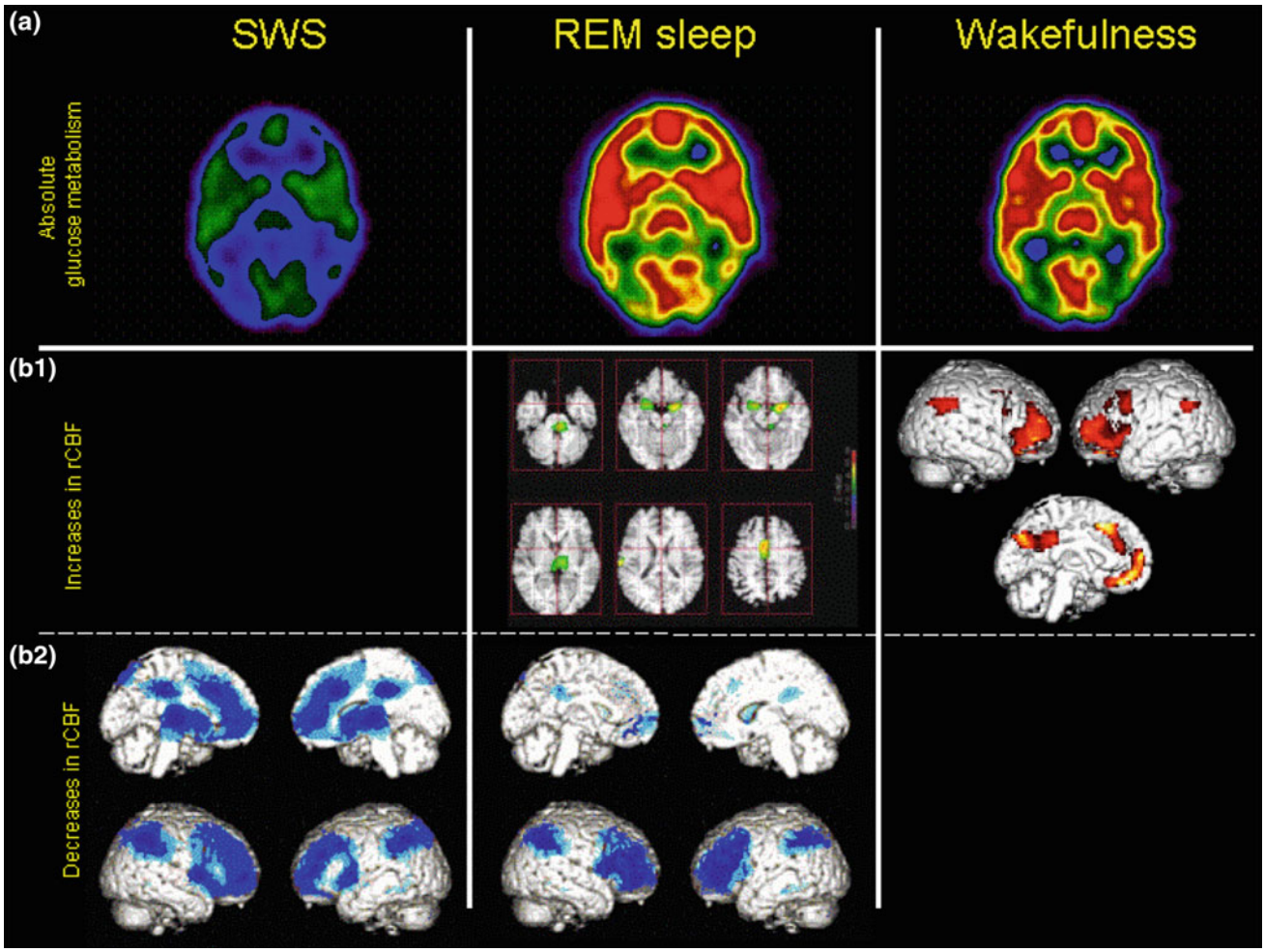

Fig. 21.1 Cerebral glucose metabolism (*CGM*) and regional cerebral blood flow (*CBF*) during deep NREM sleep (*first column*), REM sleep (*second column*), and wakefulness (*third column*). Row **a** CGM quantified in the same individual at 1-week interval, using FDG and PET. The three images are displayed at the same brain level using the same color scale. The average CGM during deep NREM sleep (versus wakefulness) is significantly decreased. During REM sleep, the CGM is as high as during wakefulness. Row **b1** Distribution of the *highest* regional brain activity, as assessed by CBF measurement using PET, during wakefulness and REM sleep. The most active regions during *wakefulness* are located in the polymodal associative cortices in the prefrontal and parietal lobes (both on the medial wall and convexity). During REM sleep, the most active areas are located in the pontine tegmentum, thalami, amygdaloid complexes, and anterior cingulate cortex. Other data (not shown) have shown a large activity in the occipital cortices, insula, and hippocampus [15]. Row **b2** Distribution of the *lowest* regional brain activity, as assessed by CBF measurement using PET, during NREM and REM sleep. In both sleep stages, the least active regions are located in the polymodal associative cortices in the prefrontal and parietal lobes (convexity). During NREM sleep, the brainstem and thalami are also particularly deactivated

Pontine waves, or ponto-geniculo-occipital (PGO) waves, are also primary features of REM sleep. In rats, the generator of the pontine waves projects to a set of brain areas shown to be active in human REM sleep: the occipital cortex, the entorhinal cortex, the hippocampus, and the amygdala as well as brainstem structures participating in the generation of REM sleep [37]. Although most easily recorded in the pons [38], the lateral geniculate bodies [39], and the occipital cortex in cats [40], PGO waves are also observed in many parts of the brain, including limbic areas (amygdala, hippocampus, cingulate gyrus) [41]. Several observations suggest that PGO waves also occur during human sleep. In epileptic patients, direct intracerebral recordings in the striate cortex showed monophasic or diphasic potentials during REM sleep, isolated or in bursts [42]. In normal subjects, surface EEG revealed transient occipital and/or parietal potentials time-locked to the REMs [43]. Source dipoles of MEG signal were localized in the brainstem, thalamus, hippocampus, and occipital cortex during REM sleep [44, 45]. Using PET, we showed that the rCBF in the lateral geniculate bodies and the occipital cortex is tightly coupled to spontaneous eye movements during REM sleep, but not during wakefulness [46]. This finding has been confirmed by fMRI studies [47, 48]. Although fully conclusive

components are still awaited, these elements support the hypothesis that PGO-like activities participate in shaping the distribution of regional brain activity during human REM sleep.

Many subjective aspects of dreams may be related to changes in brain activation during REM sleep [49], as evidenced by a series of PET studies. Increased perfusion in the occipital and temporal lobes, in the absence of afferent sensory input, may relate to the visual and auditory experiences that characterize dreams [33]. Indeed, lesions in the occipital cortex are associated with suppressed visual mentation during dreams. Increased perfusion in the motor and premotor areas during REM sleep may relate to movement perception in dreams [8, 15]. These intended movements are not physically enacted because efferent motor signals are suppressed in REM sleep by muscle atonia. This suppression can be inhibited by pontomedullary lesion, as has been shown in cats. Lesioned cats then engage in coordinated movement during REM sleep, ostensibly acting out their dreams. Similar behavior is also observed in humans with REM sleep behavior disorder (RBD) (see section below). The amygdala is particularly active during REM sleep [15, 31], perhaps underlying the potent emotions experienced in dreams. Regional deactivations during REM sleep are also related to certain elements of dreams. The lateral prefrontal cortex, an area involved in the monitoring of complex cognitive processes during waking, shows marked hypoperfusion during REM sleep [8]. Accordingly, dreams are often characterized by a bizarreness and incoherence of which the dreamer is unaware. The failure to coherently access episodic memory during dreams is also attributable to lateral prefrontal deactivation. In contrast, the medial prefrontal cortex remains activated in REM sleep. The representation of others' minds, known as theory of mind, is a function thought to be subserved by this area, and indeed, dreams contain characters with thoughts, emotions, and intentions of their own. However, the delimitation of the dreamer's mind is less distinct. Dreamers commonly move between first-person and third-person perspectives over the course of a dream. The inability to differentiate first- and third-person perspective may be associated with decreased perfusion in the inferior parietal cortex [50].

Recently, Dresler et al. [51, 52] were able to image lucid dreaming, a rare and intriguing feature of REM sleep. Unlike in normal dreams, lucid dreamers can gain awareness of the fact that they are dreaming, can access long-term memory stores, and can willingly control the events of their dream. Moreover, lucid dreamers can, to a slight extent, control their real eye and hand movements while maintaining polysomnographic sleep. By instructing the dreamer to provide gestural signals at the onset of a lucid dream, researchers determined that several areas normally deactivated in normal dreaming become activated during lucid dreaming, including the dorsolateral prefrontal cortex [51]. In a related experiment, Dresler et al. [52] asked participants to perform a pretrained motor task during lucid dreaming. They found that similar areas were activated during the dreamed mentation of a motor task and during its execution in wakefulness. It should be noted that both of these studies are limited by very small samples of 1 or 2 participants, owing to the rarity of lucid dreaming.

Brain Reactivity to External Stimulation During Sleep

Electrophysiologic studies have demonstrated that sleep is not a state of complete unresponsiveness to external stimuli (e.g., Perrin et al. [53]). Early studies have shown that external stimuli can induce an autonomic or electrophysiologic response during human sleep, in particular after a relevant or meaningful stimulus presentation [54]. Available PET and fMRI data globally suggest that the processing of external stimuli can proceed beyond the primary cortices during NREM sleep. However, the mechanisms by which salient stimuli can recruit associative cerebral areas during sleep remain unclear. A pioneering fMRI study found that, during NREM sleep as during wakefulness, several areas continue to be activated by external auditory stimulation: the thalamic nuclei, the auditory cortices, and the caudate nucleus [55]. Moreover, the left amygdala and the left prefrontal cortex were found to be more activated by subjects' own names than by pure tones, suggesting the persistence during sleep of specific responses for meaningful or emotionally laden stimuli.

Other groups observed that auditory stimulation induced a decreased response in the auditory cortex [56, 57]. Intriguingly, visual stimulation during SWS in adults elicited a decrease in activity in the occipital cortex [58]. This decrease was more rostral and dorsal compared to the relative rCBF increase along the calcarine sulcus found during visual stimulation in the awake state. The origin of this negative blood oxygenation level is still unclear [59]. One fMRI study investigated responsiveness to sounds during REM sleep, and detected auditory cortex activation during tonic but not phasic REM sleep. The non-responsiveness observed in phasic REM sleep was interpreted as a state of functional isolation [60].

Processing of external stimuli during sleep may be dependent on spontaneous brain activity, such as sleep spindles. In order to explore this interaction, we conducted an EEG/fMRI study involving the presentation of pure tones

to participants sleeping in the scanner [61]. When comparing blood-oxygen-level-dependent (BOLD) activation from tones presented during and outside of sleep spindles, we found a stark difference in global activation. Whereas tones played outside of spindles elicited activation in the thalamus and auditory cortex, replicating earlier results [55], tones played during spindles produced no significant activation, save for a small area in the brainstem [61]. These results show that sleep spindles effectively hinder the transmission of external auditory stimulation to the cortex during NREM sleep. This finding may explain variable susceptibility to noise disturbance during sleep, within and between subjects. Indeed, in another study, sleep stability in the presence of auditory disturbance was correlated with spindle density [62]. The "noise-canceling" function of sleep spindles is also consistent with its hypothesized role in sleep-dependent memory consolidation, in that it may contribute to brain functional isolation necessary for endogenous information processing in the absence of contaminating inputs. In support of this notion, hippocampal connectivity with neocortical areas was increased during sleep spindles, suggesting information transfer akin to systems consolidation [63]. In the same EEG/fMRI study, we also investigated the interaction between incoming auditory stimulation and K-complexes. It was found that sound-induced K-complexes were associated with increasing activation in the auditory cortex [61]. This finding suggests that K-complexes reflect a facilitated processing of sensory information at the cortical level during NREM sleep. Finally, in a complementary study, we examined the effect of slow-wave phase on the processing of auditory stimulation in NREM sleep [64]. We found a larger activation of the superior temporal gyrus with sounds presented during the up state of the slow wave compared to those presented during the down state. Therefore, the processing of sensory stimulation during NREM sleep is closely regulated by the underlying state of neural synchronization and firing, as reflected by slow waves and spindles.

Sleep and Brain Plasticity

Evidence accumulates suggesting that sleep participates in the consolidation of recent memory traces [65]. Accordingly, PET studies have shown that waking experience influences regional brain activity during subsequent REM and NREM sleep. Several brain areas, activated during procedural motor sequence learning (using a serial reaction time task) during wakefulness, have been found to be significantly more activated during subsequent REM sleep in subjects previously trained on the task than in non-trained subjects [66]. Furthermore, this effect is not observed in subjects trained to a task with similar practice requirements but devoid of any sequential content [67]. These findings speak against use-dependent changes in regional brain activations. Additionally, functional coupling between learning-related areas was found to be enhanced during post-training REM sleep [68]. Another PET study demonstrated that hippocampal and parahippocampal areas, which are activated during a spatial memory task, can be reactivated during post-training NREM sleep and that the amount of hippocampal activity during SWS positively correlated with overnight improvement in the memory for spatial locations [69]. Collectively, these findings suggest that reactivations of regional activity and modifications of functional connectivity during post-training sleep reflect the off-line processing of recent memory, which eventually leads to improved performance the next day. Moreover, these results are in line with behavioral data suggesting that NREM sleep and REM sleep differentially modulate the consolidation of declarative and non-declarative memories, respectively [70, 71]. However, they do not rule out an alternative hypothesis that natural succession of NREM sleep and REM sleep is also mandatory for memory consolidation.

Functional MRI studies demonstrated that sleep deprivation hinders the plastic changes that normally would occur during post-training sleep [72]. In this study, the effects of normal sleep or sleep deprivation on learning-dependent changes in regional brain activity were assessed after the subjects were trained on a pursuit task, in which they had to hold a joystick position as close as possible to a moving target, whose trajectory was predictable on the horizontal axis but not on the vertical axis. The time on target was used as the behavioral performance parameter. In the first group, subjects were totally sleep-deprived during the first post-training night, while in the second group, they were allowed to sleep. Both groups were then retested after 2 more nights of normal sleep in order to recover a similar state of arousal across the two groups and between the training and retest sessions. The fMRI scanning session was recorded during the retest, while subjects were exposed to the previously learned trajectory and also to a new one in which the predictable axis was vertical. Behavioral results showed that the time on target was larger for the learned trajectory than for the new one in both groups during the retest and that this performance gain was greater in the sleeping group than in the sleep deprivation group. The fMRI data showed a significant effect of learning, irrespective of the group, in two regions: the left supplementary eye field and the right dentate nucleus. A region of the right superior temporal sulcus, close to regions coding for motion processing (biologic motion, smooth pursuit, etc.), was found to be more active for the learned than for the new trajectory, and more so in the sleeping group than in the sleep deprivation group. The functional connectivity also showed that the dentate nucleus was more closely linked to the superior temporal sulcus, and the

supplementary eye field to the frontal eye field, for the learned than for the new trajectory, and more so in the sleeping group. Moreover, interactions between the temporal cortex and cerebellum, as well as between the frontal eye field and the supplementary eye field, are both known to be implicated in the standard pursuit eye movement pathways [73]. These results therefore suggest that the performance on the pursuit task relies on the subject's ability to learn the motion characteristics of trajectory in order to program optimal motor pursuit execution. Sleep deprivation during the first post-training night would disturb the slow processes that lead to the acquisition of this procedural skill and alter related changes in functional connectivity that were reinforced in subjects allowed to sleep [72].

Orban et al. [74] used fMRI in order to map regional cerebral activity during place-finding navigation in a virtual town, immediately after learning and 3 days later, in subjects either allowed regular sleep (RS) or totally sleep-deprived (SD) on the first post-training night. Results showed that, at immediate and delayed retrieval, place-finding navigation elicited increased brain activity in an extended hippocampo-neocortical network in both RS and SD subjects. Moreover, behavioral performance was equivalent between groups. However, striatal navigation-related activity increased more at delayed retrieval in RS than in SD subjects. Furthermore, correlations between striatal response and behavioral performance, as well as functional connectivity between the striatum and the hippocampus, were modulated by post-training sleep. Overall, these data suggest that brain activity is restructured during sleep in such a way that navigation in the virtual environment, initially related to a hippocampus-dependent spatial strategy, becomes progressively contingent in part on a response-based strategy mediated by the striatum. Interestingly, both neural strategies eventually relate to equivalent performance levels, indicating that covert reorganization of brain patterns underlying navigation after sleep is not necessarily accompanied by overt changes in behavior [74]. Further studies have also evidenced a reorganization of brain activity when post-training sleep is allowed both for neutral [75] and emotional [76] verbal material, as well as for visual face-to-location associations [77]. In addition, exposure to an odor during SWS that had been presented as context during prior learning improved the retention of hippocampus-dependent declarative memories and elicited a significant hippocampal activation during SWS [78]. In a similar experiment using sounds to cue object-location memory, it was also shown that functional connectivity between the parahippocampal region and the visual cortices was enhanced upon sound presentation during SWS [79].

In addition, EEG and MEG studies have provided robust evidence for the "sleep and memory consolidation" hypothesis by focusing on more specific sleep features and mechanisms that are regarded as important for different types of memory, including sleep spindles [80–83], slow waves [84], or the actual number of rapid eye movements [85]. For instance, sleep homeostasis has a local synaptic component, which can be triggered by a learning task involving specific brain regions. The local increase in slow-wave activity after learning correlated with improved performance of the task after sleep [84]. Moreover, the induction of slow oscillation-like potential fields by transcranial application of slowly oscillating potentials (0.75 Hz) during early nocturnal NREM sleep (i.e., a period of emerging SWS) enhanced the retention of hippocampus-dependent declarative memories in healthy humans. This stimulation induced an immediate increase in SWS, cortical slow oscillations, and slow spindle activity in the frontal cortex [86].

Sleep spindles appear to play a central role in NREM sleep-dependent memory consolidation. Specifically, spindles appear to organize the concerted reactivation of neocortical areas involved in a memory with its hippocampal trace. In this way, spindles are believed to facilitate the transfer of newly consolidated memories from the hippocampus to the neocortex. Accordingly, Bergmann et al. [87] demonstrated in an EEG-fMRI study that sleep spindles were temporally coupled with concurrent activation in the hippocampus and neocortical areas relevant to a previously learned declarative memory task. Notably, this spindle-hippocampo-neocortical synchrony was greater after declarative learning than after a visuomotor control task and was correlated with performance on the declarative task. Furthermore, the magnitude of hippocampo-neocortical activation was proportional to variations in spindle amplitude. The key role of sleep spindles in memory consolidation is consistent with its aforementioned ability to block out external stimulation during NREM sleep [61].

Alertness, Performance, and Sleep Deprivation

Sleep deprivation or fragmentation is increasingly common in industrialized societies (noisy environments, shift work). Likewise, many sleep disorders are common in the general population (e.g., insomnia, anxiety disorders). The considerable proportion of vehicle accidents related to sleep loss is now viewed as a serious concern for public health [88]. The impact of sleep deprivation on cognition and brain functions has been assessed mainly in healthy subjects. By comparison, studies on the consequences of sleep disorders on behavior and cerebral activity remain scarce.

Cognitive Challenges

Sleep deprivation is known to alter alertness and performance in a series of cognitive tasks. Several neuroimaging studies have tried to determine the underlying patterns of cerebral activity during different cognitive tasks. The cerebral responses to sleep deprivation seem to depend on the type of task and also on its level of difficulty. Both decreases and increases in responses were reported. The former were interpreted as metabolic impairments related to sleep deprivation, whereas the latter were viewed as compensatory responses.

An early PET study with [^{18}F]2-fluoro-2-deoxy-D-glucose (^{18}FDG) investigated the effect of total sleep deprivation (about 32 h) on brain metabolism [89]. Although global brain metabolism was not affected by sleep deprivation, regional glucose metabolism significantly decreased in the thalamus, basal ganglia, and cerebellum. A significant reorganization of regional activity was observed after sleep deprivation, with relative decreases in the cerebral metabolic rate of glucose (CMRglu) within the temporal lobes and relative increases in the visual cortex [89]. Additionally, sleep deprivation significantly reduced performance in an attentional continuous performance test, and this decrease was significantly correlated with reduced metabolic rate in thalamic, basal ganglia, and limbic regions [89].

One study showed that, even after as little as 24 h of continuous wakefulness, significant decreases in global CMRglu are observed with ^{18}FDG PET [2]. When subjects performed a sleep deprivation-sensitive serial addition/subtraction task (which combines arithmetic processing and working memory), significant decreases in absolute regional CMRglu were found in several cortical and subcortical structures, whereas no areas of the brain showed any significant increase in regional metabolism. Alertness and cognitive performance scores declined in parallel with deactivations in the thalamus and in the prefrontal and posterior parietal cortices [2].

The same group of researchers characterized the cerebral effects of 24, 48, and 72 h of sleep deprivation during the same task performance in 17 healthy subjects using correlations with performance measures outside of the scanner and metabolism during resting state assessed by ^{18}FDG PET [90]. Results showed that absolute CMRglu and relative regional CMRglu decreased further at 48 and 72 h of sleep deprivation primarily in the prefrontal and parietal cortices and in the thalamus, the same areas that showed decreases at 24 h of sleep deprivation. The authors proposed that the decreases in CMRglu induced in the prefrontal-thalamic network by sleep deprivation underlie the progressive impairment in cognitive performance and alertness and the progression toward sleep onset. In contrast, increased activity in visual and motor areas would reflect voluntary attempts to remain awake and perform despite a continuing decline in prefrontal-thalamic network activity [90].

In these PET CMRglu studies, metabolism during resting state was correlated with performance measures obtained outside of the scanner. However, a different picture emerges when subjects are scanned during task performance using fMRI.

Drummond and colleagues used fMRI on normal subjects while those subjects performed different cognitive tasks after a normal night of sleep or following 35 h of sleep deprivation. In a first report [4], the study used a serial subtraction task. Bilateral activations in the prefrontal, parietal, and premotor cortices were found during task practice after a normal night of sleep, whereas activity in these regions declined markedly after sleep deprivation, mainly in the prefrontal cortex [4], which is in agreement with the hypothesis of prefrontal cortex vulnerability to sleep deprivation [91]. Likewise, Mu et al. [92] found reduced activations in several frontal and parietal regions (left dorsolateral prefrontal cortex, right ventrolateral prefrontal cortex, supplementary motor area, Broca's area, and bilateral posterior parietal cortices) during practice of the Sternberg working memory task after 30 h of sleep deprivation compared to normal sleep. However, a very different pattern emerged when using other types of tasks. For example, the effects of 35 h of continuous wakefulness on cerebral activation during verbal learning (memorizing a list of words) were also investigated using fMRI [93]. The authors found that the prefrontal cortex and parietal lobes were more activated during verbal learning after 1 night of sleep deprivation than after normal sleep. In addition, increased subjective sleepiness in SD subjects correlated significantly with the amount of prefrontal cortex activation, while stronger parietal lobe activation was linked to less impairment in the free recall of words. Neurobehavioral (fMRI) effects of 24 h of continuous wakefulness were assessed using two verbal working memory tasks of different difficulty levels, known to induce responses in frontal-parietal networks in normal, non-sleep-deprived conditions. After sleep deprivation, activity was reduced in the medial parietal, anterior medial frontal, and posterior cingulate regions in both tasks, and disproportionately greater activation of the left dorsolateral prefrontal cortex and bilateral thalamus was observed when additional manipulation of information in working memory was required [94] (see also [95]). It has been suggested that these results reflect dynamic, compensatory changes in cerebral activation during verbal learning after sleep deprivation [93]. Compensatory mechanisms may lead to stronger responses within regions typically underlying task performance, as well as to activation in regions that do not show significant responses to task demands in the well-rested condition [96]. Indeed, the thalamus was also found to be

hyperactivated in sleep deprivation during a visual attention task, in the absence of performance deficits [97]. In another fMRI study, performance on a higher-order attention task was unaltered by sleep deprivation, while greater thalamic activation was recruited in the SD group [98]. The thalamus may thus play an important role in cognitive compensation in SD states.

These data suggest that decreases in regional brain activity could contribute to cognitive impairment after sleep deprivation and that increased prefrontal and thalamic activation may represent compensatory adaptation. In a similar attempt to better understand how sleep deprivation might interact with task difficulty, an fMRI study found stronger correlation between difficulty in a logical reasoning task and increased activity in the bilateral inferior parietal lobes, bilateral temporal cortex, and left inferior and dorsolateral prefrontal cortex following 35 h of continuous wakefulness than after normal sleep [96]. In a second study by the same group, the effects of normal sleep and 36 h of total sleep deprivation were assessed by fMRI during a verbal learning task with two levels of difficulty (easy and difficult words) [99]. A set of regions showed increased response to difficult words after sleep deprivation compared with normal sleep (inferior frontal gyrus, dorsolateral prefrontal cortex, and inferior parietal lobe, bilaterally). While better free recall performance on the difficult words following sleep deprivation was positively related to activation within the left inferior and superior parietal lobes and left inferior frontal gyrus, it was negatively related to activation within the right inferior frontal gyrus. Consequently, the performance relationships are thought to be both beneficial (as a compensatory function) and deleterious (as an interference with task performance), depending on the brain regions implicated. In addition, these studies suggest that increased recruitment of compensatory brain regions is yoked to rising task difficulty.

The default-mode network appears to be compromised by sleep deprivation. Disengagement of these brain regions is thought to be necessary for optimal externally oriented cognitive performance, and disturbances in default-mode function are observed in mental disorders [100]. According to a few recent studies, typical task-related default-mode network suppression was disrupted after sleep deprivation [101] and functional connectivity between default-mode areas was compromised [102, 103]. Furthermore, the anti-correlation between the default-mode network and its externally oriented counterpart was weakened in the SD condition [102].

Other cognitive domains seem to be impaired by sleep deprivation. For instance, competent decision making was impaired after sleep deprivation, which induced a modulation of activation in the nucleus accumbens and insula, brain regions associated with risky decision making and emotional processing [104]. Likewise, SD healthy adults were more likely to adopt risky strategies in a gambling task, and this change correlated with ventromedial prefrontal activation and anterior insular deactivation [105]. Furthermore, the ventromedial prefrontal and ventral striatum showed greater activation during wins, and the anterior cingulate displayed smaller deactivation during losses. These data indicate that the pursuit of gain is amplified in sleep deprivation, while losses are perceived more optimistically. Another fMRI study deprived participants of REM sleep only or NREM sleep only and evaluated emotional reactivity in a visual emotional reactivity task [106]. They found emotional reactivity to be enhanced in the REM-deprived group only, concurrently with increased activity in occipital and temporal areas, compared to NREM-deprived controls. The authors conclude that emotional reactivity is modulated by REM sleep.

Since prefrontal cortex functioning appears to be affected by sleep loss, processes mediated by this region should be altered after sleep deprivation (e.g., attention, emotion, motivation, feeding, and olfaction). In order to assess the effects of sleep deprivation on olfaction, which is mediated by the orbitofrontal cortex, a region known to have decreased activity after sleep deprivation [2], Killgore and McBride [107] studied 38 healthy subjects at rest and after 24 h of sleep deprivation. Relative to rested baseline performance, SD subjects showed a significant decline in the ability to identify specific odors on the Smell Identification Test. In relation to effects on feeding, an fMRI study examined BOLD response to the presentation of images of food items after a night of sleep deprivation [108]. Activation of the anterior cingulate cortex in response to food was increased in sleep-deprived participants with respect to non-sleep-deprived controls, independent of prescan blood-glucose levels. Moreover, this activation correlated significantly with increased post-scan hunger ratings. Sleep deprivation thus seems to enhance hedonic response to food stimuli.

Changes in dopamine neurotransmission may underlie the cognitive challenges observed in sleep deprivation. Dopamine's involvement in sleep/wake regulation remains unclear, but degeneration of dopamine pathways is associated with sleep disorders such as REM sleep behavior disorder and excessive daytime sleepiness in Parkinson's disease (PD) [109, 110]. In a series of studies, Volkow et al. [111–113] studied the effect of sleep deprivation on dopamine using PET with ^{11}C-raclopride, a dopamine D_2/D_3 receptor radioligand. They found dopamine receptor occupancy to be increased in the ventral striatum. Furthermore, this increase does not seem to be due to changes in dopamine transporter (DAT) density [114]. Increases in dopaminergic activity were associated with worse performance on a visual attention task, concurrent with BOLD changes in known dopamine-modulated areas (smaller

deactivation of anterior cingulate cortex and insula) as well as in other areas (greater deactivation of inferior occipital cortex and cerebellum) [112]. These findings suggest that striatal dopamine hyperactivity may interfere with attentional processes, or instead, may represent a compensatory mechanism in order to maintain arousal after sleep deprivation.

Personal Vulnerability to Sleep Deprivation

People may be differently affected by the same sleep-depriving environmental conditions. Studies suggest that brain responses to sleep deprivation for a given task are modulated by individual vulnerability to sleep deprivation [115]. For example, in one fMRI study, subjects were divided into two groups, a sleep deprivation-resilient group and a sleep deprivation-vulnerable group, according to their performance on a working memory task after sleep deprivation. In the sleep deprivation-resilient group, significant activations were found in several cortical areas (left dorsolateral prefrontal cortex, left ventrolateral prefrontal cortex, left supplementary motor area, and left posterior parietal cortex) during practice of the working memory task after sleep deprivation. By contrast, in the sleep deprivation-vulnerable group, only the left dorsolateral prefrontal cortex was activated after sleep deprivation. The patterns of brain activation after sleep deprivation may therefore differ as a function of the subjects' individual vulnerability to sleep deprivation [115]. The same group conducted another fMRI study on fatigue vulnerability in military pilots. Pilots were scanned during the working memory task under non-sleep-deprived conditions, and individual fatigue vulnerability was quantified using performance on a flight simulation during 37 h of continuous wakefulness. Analyses revealed that global cortical activation during the working memory task was positively correlated with fatigue resistance in flight-simulator performance. The authors therefore proposed that baseline fMRI activation during the working memory task may provide a good index of individual fatigue susceptibility [116].

Individual differences in the effect of sleep deprivation on working memory performance were assessed by fMRI in 26 healthy volunteers, in a rested condition and after 24 and 36 h of sustained wakefulness [117]. In both sleep deprivation conditions, task-related activation was significantly decreased with respect to the rested condition in the superior parietal regions and left thalamus. There was also an inverse correlation between activation of left parietal and left frontal regions during the rested condition, and individual decline in working memory performance from the rested condition to the 24-h sleep deprivation condition. In this way, frontoparietal activation in the rested state may distinguish individual cognitive vulnerability to sleep deprivation. Similarly, another fMRI study showed that lower task-related activation of the ventral prefrontal cortex during rested wakefulness was predictive of greater individual ability to maintain inhibitory efficiency in a go/no-go task [118]. Low-vulnerability individuals also showed reduced activation in this region as well as in the right insula after sleep deprivation, compared to highly vulnerable individuals.

In addition to functional imaging, structural neuroimaging techniques were also used to investigate interindividual differences in responses to sleep deprivation. For instance, studies of white matter anatomy with fractional anisotropy (FA) may provide one such physiologic marker of vulnerability to sleep deprivation [119]. In that study, West Point cadets first completed a simple visual-motor task before and after 24-h sleep deprivation and their change in performance was assessed. Taking these change scores as indices of sleep deprivation vulnerability, cadets were separated into a more vulnerable and a less vulnerable group by median split. They were then scanned with MRI using diffusion tensor imaging (DTI), and FA was calculated for each cadet as an indicator of fiber number, density, and myelination in white matter tracts. FA values were significantly greater in the low-vulnerability group than in the high-vulnerability group, predominantly in ascending and longitudinal pathways of the right hemisphere and the genu of the corpus callosum. Furthermore, greater FA values correlated significantly with smaller decreases in the performance on the task. These findings are consistent with those of aging studies linking greater white matter integrity to improved cognitive performance [120].

Sleep Deprivation in Depression

Sleep deprivation has profound effects on brain metabolism in both normal and depressed subjects. When used therapeutically (i.e., wake therapy), sleep deprivation relieves acute depressive symptoms in 60 % of patients. In depressed patients responding favorably to sleep deprivation, ^{18}FDG PET [121–123], technetium-99m–labeled hexamethylene-propyleneamine oxime (^{99m}Tc-HMPAO) SPECT [124, 125], and fMRI [126] revealed greater baseline brain activity during wakefulness in responders than in non-responders in the anterior cingulate cortex and/or the nearby mesial frontal cortex. This activity was significantly decreased after sleep deprivation. A similar profile of brain metabolism was observed with ^{18}FDG PET in elderly depressed patients, including normalization after total sleep deprivation associated with antidepressant treatment [127]. Moreover, the normalization of anterior cingulate metabolism persisted even after recovery sleep. However, these results were not replicated with placebo control [128].

MRI spectroscopic studies have shown glutamate [129, 130] and serotonin [131] levels to be globally increased after sleep deprivation in depressed patients. These neurotransmitters may then underlie the antidepressant effect of sleep

deprivation. This is consistent, in the case of serotonin, with the widespread use of selective serotonin reuptake inhibitors as antidepressants. With PET and SPECT, it was also shown that sleep deprivation responders exhibit a significant decrease in relative basal ganglia D_2 receptor occupancy after sleep deprivation, as compared to non-responders [132]. Sleep deprivation also resulted in lower binding of ^{11}C-raclopride, a D_2/D_3 receptor radioligand, in the striatum and thalamus of healthy subjects [111]. These results suggest that the antidepressant benefits of sleep deprivation are correlated with enhanced endogenous dopamine release in responders, although a later study suggests DAT downregulation may instead be responsible for observed increases in dopamine receptor occupancy [113]. Nonetheless, these results corroborate previous hypotheses about the role of dopaminergic response in the therapeutic action of sleep deprivation and indirectly support a dopamine hypothesis of depression [132]. In relation to this hypothesis, sleep-deprived healthy subjects reacted more intensely to pleasure-evoking stimuli in dopaminergic mesolimbic brain networks associated with reward [133]. In addition, gains produced higher ventromedial prefrontal and ventrostriatal activation in healthy subjects, and losses produced less anterior cingulate deactivation [105]. Together, these findings suggest that the antidepressant effect of sleep deprivation may operate through reward-enhancing increases in dopaminergic activity.

^{31}Phosphorous magnetic resonance spectroscopy (^{31}P-MRS) has also been applied to healthy SD participants to understand the metabolic and bioenergetic changes that may underlie the antidepressant effect of wake therapy. Within-subject designs with healthy participants showed no change in phosphate brain chemistry after a night of sleep deprivation [134, 135], although one study found elevated β-nucleoside triphosphate and reduced phospholipid catabolism after a subsequent recovery night [134]. In a sample of depressed women, higher baseline levels of choline compounds in the pons were associated with the improvement in mood after sleep deprivation, indicating a role of pontine choline metabolism in the antidepressant response to sleep deprivation [136]. Further studies are needed scanning both depressed patients and healthy controls before and after sleep deprivation.

Sleep deprivation data suggest a tight link between mood alteration and activity in limbic and paralimbic structures. The data suggest that anterior cingulate hyperactivity in depressed patients during wakefulness may hinder further increases during REM sleep. Hence, sleep deprivation may alleviate depression symptoms by decreasing abnormally elevated activity in the anterior cingulate cortex during wakefulness. However, further studies are needed to understand the causes and consequences of these mesial frontal metabolic disturbances.

Instrumental Manipulation of Sleep Deprivation Effects

Repetitive transcranial magnetic stimulation (rTMS) can be used to artificially stimulate cortical brain areas, enabling true experimental designs in human neuropsychology. Luber et al. [137] used rTMS to artificially relieve impairments in working memory performance from sleep deprivation. Fifteen participants were first scanned with fMRI before and after sleep deprivation, while completing a working memory task. The brain areas that showed deactivation under sleep deprivation were then used as guides for rTMS application after a second night of sleep deprivation, two weeks later. Of the three identified sites, stimulation of the upper middle occipital site produced improvements in performance, whereas no improvement was accrued from the other sites or from sham rTMS. Furthermore, the degree of performance enhancement was directly proportional to the magnitude of each participant's sleep-deprivation-induced deactivations. Hence, cognitive deficits from sleep deprivation can be corrected with rTMS by targeting the affected brain area. The authors replicated these findings in a recent experiment [138].

Summary

There is a marked heterogeneity in the functional findings relating to the cognitive effects of sleep deprivation. Deficits in cognitive function after sleep deprivation have been correlated with both activations and deactivations in several brain regions. Hypotheses explaining these findings range from compensatory mechanisms in order to maintain cognitive function, to homeostatic pressure diverting energy from certain regions, resulting in cognitive deficits. These hypotheses remain speculative. The wide range of tasks employed in these studies may in part explain the variability in results. Nonetheless, some interesting markers of individual vulnerability to sleep deprivation have been identified, including white matter integrity. In addition, the study of the therapeutic effect of sleep deprivation in depression has yielded some promising findings, particularly in relation to the dopaminergic system. Lastly, sleep deprivation effects can seemingly be rectified by the targeted use of rTMS.

Neuroimaging in Sleep Disorders

Sleep may be disrupted in a number of conditions ranging from medical diseases (e.g., endocrine disorders, chronic pain, brain lesions, and sleep apnea) and psychiatric disorders (e.g., anxiety, depression, and schizophrenia) to environmental situations (e.g., jet lag, shift work, and noisy environment).

In this section, we consider several primary sleep disorders (narcolepsy, periodic limb movement disorder, idiopathic insomnia, recurrent hypersomnia, and obstructive sleep apnea) as well as specific parasomnia syndromes

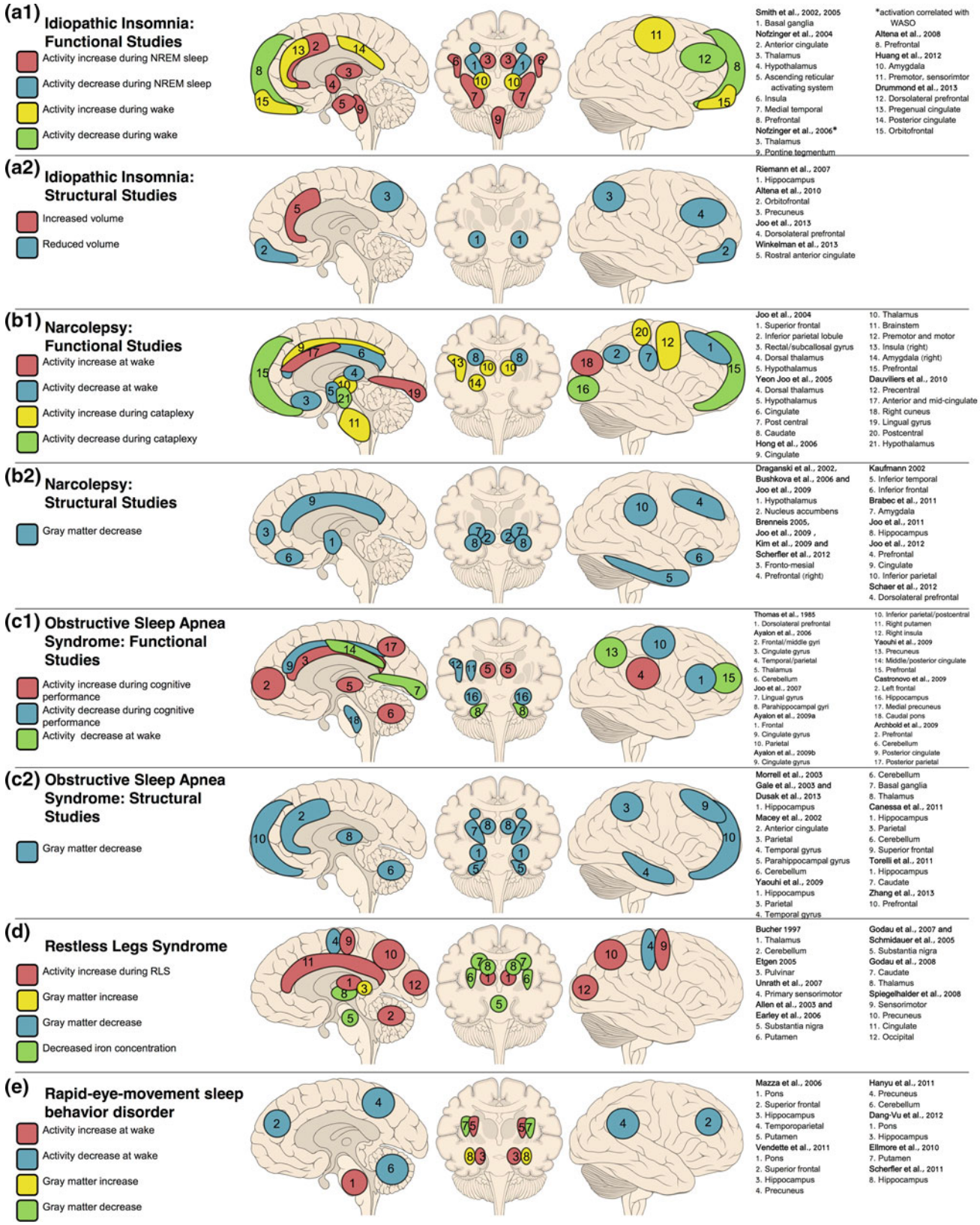
(a1) Idiopathic Insomnia: Functional Studies
Activity increase during NREM sleep
Activity decrease during NREM sleep
Activity increase during wake
Activity decrease during wake
Smith et al., 2002, 2005
1. Basal ganglia
Nofzinger et al., 2004
2. Anterior cingulate
3. Thalamus
4. Hypothalamus
5. Ascending reticular activating system
6. Insula
7. Medial temporal
8. Prefrontal
Nofzinger et al., 2006*
3. Thalamus
9. Pontine tegmentum
*activation correlated with WASO
Altena et al., 2008
8. Prefrontal
Huang et al., 2012
10. Amygdala
11. Premotor, sensorimtor
Drummond et al., 2013
12. Dorsolateral prefrontal
13. Pregenual cingulate
14. Posterior cingulate
15. Orbitofrontal
(a2) Idiopathic Insomnia: Structural Studies
Increased volume
Reduced volume
Riemann et al., 2007
1. Hippocampus
Altena et al., 2010
2. Orbitofrontal
3. Precuneus
Joo et al., 2013
4. Dorsolateral prefrontal
Winkelman et al., 2013
5. Rostral anterior cingulate
(b1) Narcolepsy: Functional Studies
Activity increase at wake
Activity decrease at wake
Activity increase during cataplexy
Activity decrease during cataplexy
Joo et al., 2004
1. Superior frontal
2. Inferior parietal lobule
3. Rectal/subcallosal gyrus
4. Dorsal thalamus
5. Hypothalamus
Yeon Joo et al., 2005
4. Dorsal thalamus
5. Hypothalamus
6. Cingulate
7. Post central
8. Caudate
Hong et al., 2006
9. Cingulate
10. Thalamus
11. Brainstem
12. Premotor and motor
13. Insula (right)
14. Amygdala (right)
15. Prefrontal
Dauvilliers et al., 2010
12. Precentral
17. Anterior and mid-cingulate
18. Right cuneus
19. Lingual gyrus
20. Postcentral
21. Hypothalamus
(b2) Narcolepsy: Structural Studies
Gray matter decrease
Draganski et al., 2002,
Bushkova et al., 2006 and
Joo et al., 2009
1. Hypothalamus
2. Nucleus accumbens
Brenneis 2005,
Joo et al., 2009 ,
Kim et al., 2009 and
Scherfler et al., 2012
3. Fronto-mesial
4. Prefrontal (right)
Kaufmann 2002
5. Inferior temporal
6. Inferior frontal
Brabec et al., 2011
7. Amygdala
Joo et al., 2011
8. Hippocampus
Joo et al., 2012
4. Prefrontal
9. Cingulate
10. Inferior parietal
Schaer et al., 2012
4. Dorsolateral prefrontal
(c1) Obstructive Sleep Apnea Syndrome: Functional Studies
Activity increase during cognitive performance
Activity decrease during cognitive performance
Activity decrease at wake
Thomas et al., 1985
1. Dorsolateral prefrontal
Ayalon et al., 2006
2. Frontal/middle gyri
3. Cingulate gyrus
4. Temporal/parietal
5. Thalamus
6. Cerebellum
Joo et al., 2007
7. Lingual gyrus
8. Parahippocampal gyri
Ayalon et al., 2009a
1. Frontal
9. Cingulate gyrus
10. Parietal
Ayalon et al., 2009b
9. Cingulate gyrus
10. Inferior parietal/postcentral
11. Right putamen
12. Right insula
Yaouhi et al., 2009
13. Precuneus
14. Middle/posterior cingulate
15. Prefrontal
Castronovo et al., 2009
2. Left frontal
16. Hippocampus
17. Medial precuneus
18. Caudal pons
Archbold et al., 2009
2. Prefrontal
6. Cerebellum
9. Posterior cingulate
17. Posterior parietal
(c2) Obstructive Sleep Apnea Syndrome: Structural Studies
Gray matter decrease
Morrell et al., 2003
Gale et al., 2003 and
Dusak et al., 2013
1. Hippocampus
Macey et al., 2002
2. Anterior cingulate
3. Parietal
4. Temporal gyrus
5. Parahippocampal gyrus
6. Cerebellum
Yaouhi et al., 2009
1. Hippocampus
3. Parietal
4. Temporal gyrus
6. Cerebellum
7. Basal ganglia
8. Thalamus
Canessa et al., 2011
1. Hippocampus
3. Parietal
6. Cerebellum
9. Superior frontal
Torelli et al., 2011
1. Hippocampus
7. Caudate
Zhang et al., 2013
10. Prefrontal
(d) Restless Legs Syndrome
Activity increase during RLS
Gray matter increase
Gray matter decrease
Decreased iron concentration
Bucher 1997
1. Thalamus
2. Cerebellum
Etgen 2005
3. Pulvinar
Unrath et al., 2007
4. Primary sensorimotor
Allen et al., 2003 and
Earley et al., 2006
5. Substantia nigra
6. Putamen
Godau et al., 2007 and
Schmidauer et al., 2005
5. Substantia nigra
Godau et al., 2008
7. Caudate
8. Thalamus
Spiegelhalder et al., 2008
9. Sensorimotor
10. Precuneus
11. Cingulate
12. Occipital
(e) Rapid-eye-movement sleep behavior disorder
Activity increase at wake
Activity decrease at wake
Gray matter increase
Gray matter decrease
Mazza et al., 2006
1. Pons
2. Superior frontal
3. Hippocampus
4. Temporoparietal
5. Putamen
Vendette et al., 2011
1. Pons
2. Superior frontal
3. Hippocampus
4. Precuneus
Hanyu et al., 2011
4. Precuneus
6. Cerebellum
Dang-Vu et al., 2012
1. Pons
3. Hippocampus
Ellmore et al., 2010
7. Putamen
Scherfler et al., 2011
8. Hippocampus

Fig. 21.2 Findings from PET, SPECT, fMRI and MRI studies in sleep disorders. **a1** Brain areas showing metabolic changes in idiopathic insomnia. Most studies show hypermetabolism in cortical and subcortical areas during NREM sleep, as well as smaller decreases in metabolism in the transition from wake to sleep. These results are consistent with the hyperarousal theory of insomnia. During wake, insomnia patients show decreased prefrontal activity. **a2** Neuroanatomical alterations in idiopathic insomnia. While many studies found no anatomic changes in insomnia patients, some reported cortical gray matter loss or changes in hippocampal or rostral anterior cingulate volume. **b1** Areas showing functional abnormalities in narcolepsy. All metabolic and hemodynamic changes are shown during wake, and one study imaged hypoperfusions during a cataplectic episode. Abnormalities in narcoleptics were reliably observed in the hypothalamus, consistent with a hypocretinergic dysfunction. **b2** Neuroanatomical alterations in narcolepsy. Hypothalamic gray matter loss may relate to hypocretinergic dysfunction. Limbic and neocortical alterations may underlie mood disturbances in narcoleptic patients. **c1** Functional studies on OSAS have focused mainly on activity changes during cognitive tasks and have mostly detected deactivations. A few resting-state studies using PET and SPECT have found decreases in activity during resting wakefulness. **c2** Neuroanatomical alterations in OSAS. Gray matter loss in the hippocampus, parietal, and prefrontal cortices may underlie various neuropsychological deficits observed in OSAS, only some of which seem to be reversible by CPAP. **d** Brain areas showing structural or functional changes in RLS. Iron deficiencies in several areas, notably the SN, may contribute to RLS, possibly via dysregulation of the closely associated dopaminergic system. These changes may in turn sensitize sensorimotor pain sensation. **e** Areas showing functional and structural abnormalities in RBD. Changes have most consistently been shown in the pons, hippocampus, and superior frontal cortex. Adapted from Desseilles et al. [5], and from illustrations by Patrick J. Lynch and C. Carl Jaffe.

(sleepwalking and RBD). We do not review sleep disorders due to disturbances from external environmental sources.

Idiopathic Insomnia

Idiopathic insomnia is a lifelong inability to obtain adequate sleep that is presumably due to an abnormality in the neurologic control of sleep–wake regulation systems [139]. This disorder is thought to reflect an imbalance between the arousal system and the various sleep-inducing and sleep-maintaining systems. Neuroanatomic, neurophysiologic, or neurochemical dysfunctions or lesions within the sleep–wake systems are suspected in some of these patients [139].

Theoretically, either hyperactivity within the arousal system or hypoactivity within the sleep system may cause idiopathic insomnia, but hyperarousal is believed to be the final common pathway of the disorder [139]. Increased arousal might be of a physiologic, cognitive, or affective nature; it is likely that these categories overlap [6, 140], since several studies have reported increased alertness on the Multiple Sleep Latency Test, increased heart rate during the sleep period, increased anxiety on rating scales, and increased tension during wakefulness [140–142]. In addition, poor sleep leads to altered mood and motivation, decreased attention and vigilance, low levels of energy and concentration, and increased daytime fatigue [139].

Quantitative EEG recordings suggest an overall cortical hyperarousal in insomnia [143]. However, hyperarousal in primary insomnia was also found to be associated with greater increase in beta/gamma activity at sleep onset, followed by a decline of high-frequency EEG activity leading to a period of hypoarousal [143]. This could explain why some neuroimaging studies showed a cortical hyperarousal pattern in insomnia while others reported a decrease in cortical functions. In the latter case, decreased metabolism might originate from time-window coincidence of the cortical hypoarousal period to neuroimaging acquisition and therefore does not discard the hyperaousal hypothesis of primary insomnia.

Only a few studies tried to characterize the functional neuroanatomy of idiopathic insomnia disorder during sleep (referred to as primary insomnia in these reports) (Fig. 21.2a1). rCBF was estimated using ^{99m}Tc-HMPAO, a gamma-emitting radionuclide imaging agent used in the evaluation of rCBF, in five insomniacs and four normal sleepers. Patients with insomnia showed major rCBF decrease in the basal ganglia, medial frontal cortex, occipital cortex, and parietal cortex. These results suggest that idiopathic insomnia is associated with an abnormal pattern of regional brain activity during NREM sleep that particularly involves a dysfunction in the basal ganglia [144]. Four of the insomnia patients from the Smith et al. study [144] were rescanned after they had been treated with cognitive behavioral therapy [145]. After this treatment, sleep latency was reduced by at least 43 % and there was a global 24 % increase in CBF, with significant increases in the basal ganglia. Smith and collaborators proposed that such increase in brain activity might reflect the normalization of sleep homeostatic processes.

^{18}FDG PET was used to measure regional CMRglu of 7 patients with idiopathic insomnia and 20 healthy age- and gender-matched subjects during waking and NREM sleep [146]. Insomniac patients showed increased global CMRglu during sleep as compared to healthy subjects, suggesting an overall cortical hyperarousal in insomnia. Moreover, insomniac patients had a smaller decline, compared to healthy subjects, in relative CMRglu from waking to sleep states in the ascending reticular activating system, hypothalamus, thalamus, insular cortex, amygdala, hippocampus, anterior cingulate, and medial prefrontal cortices (Fig. 21.3). During wakefulness, reduced relative metabolism, as compared to healthy subjects, was found in the prefrontal cortex bilaterally, in the left temporal, parietal, and occipital cortices, and in the thalamus, hypothalamus, and

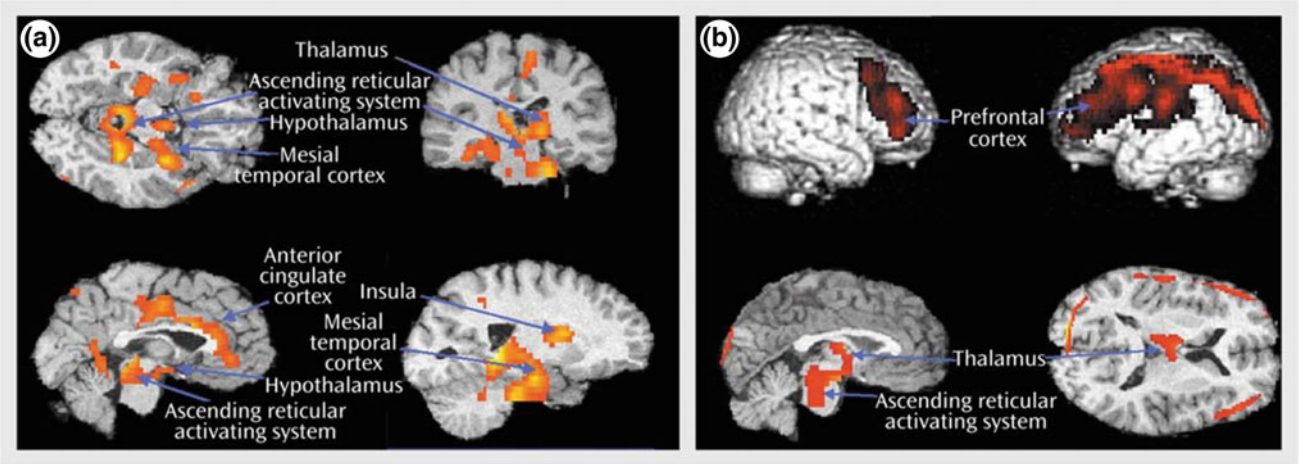

Fig. 21.3 CMRglu assessed by ^{18}FDG PET in insomniacs (versus healthy subjects) during waking and NREM sleep. **a** Brain structures that did not show decreased cerebral metabolic rate of glucose (CMRglu) from waking to sleep states in patients with idiopathic insomnia. **b** Brain structures where relative metabolism while awake was higher in healthy subjects than in patients with insomnia. Differences in all regions shown reached statistical significance ($p < 0.05$), corrected at the cluster level (Reproduced with permission from Nofzinger et al. [146]. Copyright 2004, American Psychiatric Association)

brainstem reticular formation. These findings confirm that regional brain activity does not normally progress from waking to sleep states in patients with insomnia. Additionally, it was proposed that daytime fatigue resulting from inefficient sleep may be reflected by decreased activity in the prefrontal cortex [146]. In another ^{18}FDG PET study by the same group [147] examining 15 insomniac patients, CMRglu in the pontine tegmentum and thalamo-cortical networks during NREM sleep was found to be significantly correlated with self-reported wake time after sleep onset (WASO), based on a 7-day sleep diary. Hence, elevated cortical arousal during sleep is associated with insomnia symptom severity, lending support to the hyperarousal theory of insomnia.

Additional studies have imaged idiopathic insomniacs during wakefulness, using fMRI (Fig. 21.2a1). In a first study [148], 21-year-old adult insomnia patients showed reduced medial and inferior prefrontal activation during the completion of a verbal fluency task, compared to 12 age-matched controls. In a second phase of the study after 8 weeks of non-pharmacological therapy, insomnia patients showed partial recovery of activation in these areas. These results corroborated similar findings by Nofzinger et al. [146] indicating prefrontal hypoactivation during wakefulness in insomnia. Another recent fMRI study [149] imaged 25 idiopathic insomnia patients and 25 age- and sex-matched controls during the performance of a working memory task. Interestingly, insomniacs failed both to recruit typical task-specific brain areas and to deactivate irrelevant, default-mode network regions. The authors suggested that the observed alteration in task-specific activation reflects compromised cognitive processing in insomnia, even though task performance in insomniacs was not different from controls. They attributed this to a masking effect of high perfectionism, a trait associated with insomnia.

Insomnia has been associated with high emotional reactivity [150]. An fMRI study investigated resting-state functional connectivity in the emotional system of 10 idiopathic insomnia patients and 10 matched controls [151]. Abnormalities were detected in functional connectivity between the amygdala and several cortical and subcortical areas in insomnia patients. While decreased connectivity was found for the striatum, insula, and thalamus, elevated connectivity was observed between the amygdala and the premotor cortex, sensorimotor cortex, a pathway associated with threat response. Increased motor activation is consistent with global cortical hyperarousal in insomnia.

Some recent efforts have been made to identify structural brain alterations in idiopathic insomnia, with the use of magnetic resonance imaging (MRI) (Fig. 21.2a2). While an early study found reduced hippocampal volumes in idiopathic insomnia patients compared to controls [152], subsequent studies were unable to replicate the finding [153–156]. One study found significant negative correlations between hippocampal volume and insomnia duration, as well as with a polysomnography-based index of arousal [154]. Consistent with these findings, significant inverse correlations have been reported between hippocampal volume and actigraphic WASO and sleep efficiency [153]. In one retrospective study, rostral anterior cingulate volumes were significantly greater in insomniacs [157]. The role of the anterior cingulate in insomnia is corroborated by earlier

findings in insomniacs of attenuated deactivation in this area during the transition from waking to sleep [146], and of reduced levels of inhibitory neurotransmitters in this area [158]. Additional structural studies have inspected small-scale brain modifications using VBM. VBM is a neuroimaging analysis technique that allows the investigation of focal differences in tissue composition (gray and white matter) based on high-resolution MRI scans. Prefrontal gray matter concentrations were smaller in insomniacs than in good sleepers, specifically in the orbitofrontal [156, 159] and dorsolateral prefrontal cortices [159], but these findings were not replicated in a later study [155].

Magnetic resonance spectroscopy (MRS) has been applied to the study of idiopathic insomnia. According to proton MRS (^{1}H-MRS) studies, relative concentrations of gamma-aminobutyric acid (GABA) appear to be reduced in insomniacs relative to good sleepers, globally (single-voxel) [160] and locally, in the occipital and anterior cingulate [158], although another study found occipital GABA levels to be increased instead [161]. This latter study also detected a significant inverse correlation between global GABA levels and polysomnography-based WASO. A ^{31}P-MRS study investigating gray and white matter phosphocreatine levels found this cell metabolite in lower concentrations in the gray matter of insomniac patients relative to controls, indicating a possible increase in cortical energy demand in insomnia [162].

Together, neuroimaging studies of insomnia tend to support hyperarousal theory. Diminished inhibition in the transition from waking to sleep [146], increased connectivity in the emotional and threat response systems [151], decreased ability to inhibit irrelevant cognitive processes [149], depletion of inhibitory neurotransmission [158, 160], and increased cortical energy demands [162] all are consistent with an incapacity to modulate cortical arousal across the sleep–wake cycle. In addition, evidence of reduced hippocampal volume [152], reduced prefrontal gray matter concentrations [156, 159], and increased rostral anterior cingulate volume [157] provide possible neural correlates of cognitive and emotional dysfunctions experienced in insomnia. Still, these findings require replication in larger, clinically homogeneous samples.

Narcolepsy

Narcolepsy is a disorder characterized by excessive sleepiness that is typically associated with several manifestations of so-called dissociated or isolated REM sleep features, such as muscle atonia (i.e., cataplexy), sleep paralysis, and hallucinations [139, 163]. Human narcolepsy has been found to be associated with reduction in or loss of the hypothalamic peptide hypocretin (also called orexin) implicated in arousal systems [164–167].

Anatomic Neuroimaging Studies of Narcolepsy

Structural abnormalities in narcolepsy have been examined extensively (Fig. 21.2b2). The pontine tegmentum controls transitions between sleep states and was therefore first proposed as a possible main site of anatomic or functional impairments in narcolepsy. While Plazzi and coworkers had reported pontine tegmentum abnormalities in three narcoleptic patients [167], two other structural MRI studies [168, 169] found no pontine abnormalities (except in 2 of 12 patients who had long-standing hypertension [169]. The MRI abnormalities found in Plazzi et al.'s study could reflect non-specific age-related pontine vascular changes rather than a narcolepsy-related phenomenon [167].

VBM has been employed to find evidence for hypothalamic abnormalities in narcoleptic patients, reporting equivocal results. An early study found no structural change in brains of patients with hypocretin-deficient narcolepsy [170]. Subsequent studies did find cortical gray matter reduction predominantly in frontal brain regions [171–174], as well as in inferior temporal regions [175]. Interestingly, relative global gray matter loss was independent of disease duration or medication history, and there were no significant subcortical gray matter alterations [175]. Significant gray matter concentration decreases were found in the hypothalamus, cerebellum (vermis), superior temporal gyrus, and right nucleus accumbens in 29 narcoleptic patients relative to unaffected healthy controls [176] (Fig. 21.4). Given the widespread projection sites of hypocretin, the decreases in gray matter could thus reflect secondary neuronal losses due to the destruction of specific hypocretin projections. The results of this study were later corroborated by two other VBM studies [171, 177]. More recent MRI studies in narcolepsy with cataplexy identified volumetric decreases in the bilateral hippocampus [178] and amygdala [179]. Notably, amygdalar deficits may underlie emotional dysregulation in narcolepsy.

Anatomic alterations have also been described using MRI cortical thickness measurements. A localized thinning of the cortex was detected in the prefrontal, cingulate, inferior parietal, and temporal areas in narcoleptic-cataplectic individuals [180]. Another study measured increased cortical volume and thickness in the dorsolateral prefrontal cortex of narcoleptic patients [181]. Furthermore, early-onset narcoleptic patients exhibited thinner cortex than late-onset narcoleptics in the precentral gyrus, inferior parietal cortex, and temporal regions. These results were interpreted as reflecting distinct pathological subtypes [181].

Recent studies have used DTI to detect alterations in fiber tract integrity, based on water diffusion in the brain. Using FA and mean diffusivity measures, it was shown that white matter tracts were disrupted in frontal, temporal, and anterior cingulate regions in narcolepsy [173]. Another DTI study found similar results, in addition to white matter

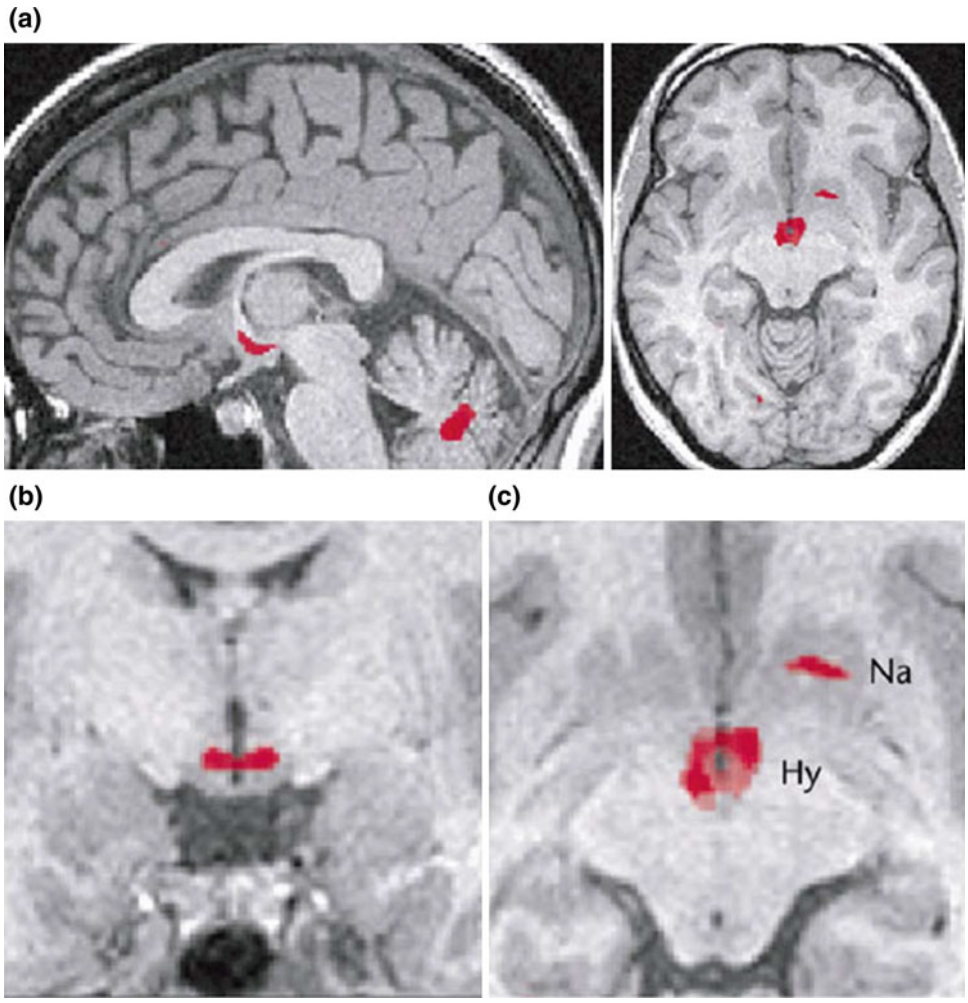

Fig. 21.4 Statistical parametric maps demonstrating the structural difference in *gray* matter between narcolepsy patients and healthy control subjects. Differences are shown superimposed in *red* on a normalized image of a healthy control subject. The *left panel* in A is the *left side* of the brain. A significant decrease in *gray* matter concentration was found in the hypothalamus (Hy) (**a**–**c**) and in the area of the *right* nucleus accumbens (Na) (**a** and **c**) (Reproduced with permission from Draganski et al. [176]. Copyright 2002, Nature Publishing Group)

abnormalities in the pons, right hypothalamus and left mesencephalon, consistent with a dysfunction in the hypothalamic hypocretin system in narcolepsy [182].

Proton MRS was also used to assess the *N*-acetylaspartate (NAA) and creatinine plus phosphocreatinine (Cr + PCr) content in specific brain areas of narcoleptic patients. A reduced NAA/Cr + PCr ratio indicates reduced neuronal function, which could reflect neuronal loss (i.e., fewer neurons) but could also be due to reduced activity of existing neurons. An analysis of spectral peak area ratios revealed a decrease in the NAA/Cr + PCr ratio in the hypothalamus [183] and the ventral pontine areas [184] of narcoleptic patients compared with control subjects. These results may indicate structural damage to these areas in narcolepsy.

Several factors can explain equivocal results across structural neuroimaging studies, such as inhomogeneous patient groups, history of treatment, or, for VBM, prestatistical image processing and limited sensitivity of this technique. VBM studies with larger samples of drug-naive patients are required to identify reliable structural abnormalities in narcolepsy.

Functional Neuroimaging Studies of Narcolepsy

A number of studies have examined brain metabolic differences in narcoleptic patients in the waking state (Fig. 21.2 b1). Early functional observations using ^{133}Xe inhalation showed that, during wakefulness, CBF in the brainstem was lower in narcoleptic patients than in normal subjects. However, after sleep onset (3 of 13 cases in REM sleep), the CBF increased in all regions, particularly in temporoparietal regions. This pattern was supposedly attributed to dreaming activity, in line with prior reports showing increased regional blood flow in temporoparietal areas during visual dreaming and hypnagogic hallucinations [185, 186].

A ^{99m}Tc-HMPAO SPECT study in six narcoleptic patients found similar HMPAO uptake in the waking state and REM sleep [187], suggesting a similar overall cortical activity. Data analysis using regions of interest additionally indicated an activation of parietal regions during REM sleep [187]. The latter result is intriguing given the parietal deactivation usually observed by PET studies during normal REM sleep [8]. Further studies during REM sleep are needed to confirm these results in a larger population.

Two ^{18}FDG PET studies were conducted in the waking state to examine differences in narcoleptic brain activation. In the first study, a sample of 24 narcoleptic patients had reduced CMRglu in the bilateral posterior hypothalami, mediodorsal thalamic nuclei, and frontal and parietal cortices, compared to controls [188]. The second study instead found a CMRglu increase in the cingulate and visual association cortices in 21 narcoleptic patients also suffering from cataplexy [189]. A SPECT study revealed hypoperfusion during wakefulness in several areas including the bilateral anterior hypothalami, caudate nuclei, pulvinar, parahippocampal gyri, cingulate gyri, and prefrontal cortices [190].

There are very few data describing the neural correlates of cataplexy in narcoleptic patients (Fig. 21.2b1). One SPECT study was conducted on two patients during a cataplexy episode compared to REM sleep or a baseline waking period [191]. During cataplexy, perfusion increased in limbic areas (including the amygdala) and the basal ganglia, thalami, premotor cortices, sensorimotor cortices, and brain stem, whereas perfusion decreased in the prefrontal cortex and occipital lobe. Increased cingulate and amygdala activity may relate to concomitant emotional processing that is usually reported as a powerful trigger of cataplexy. However, such hyperperfusion in the pons, thalami, and amygdaloid complexes was not found in two subsequent studies [189, 192]. A more recent PET study imaged two patients during a cataplectic attack and found a large decrease in glucose metabolism in the hypothalamus, as well as increased metabolism in pre-postcentral gyri and somatosensory cortex [189].

Based on the clinical observation that cataplexy episodes are often triggered by positive emotions (e.g., hearing or telling jokes), an fMRI study was performed on narcoleptic patients and controls while they watched sequences of humorous pictures [193]. Group comparisons revealed that humorous pictures elicited reduced hypothalamic response together with enhanced amygdala response in the narcoleptic patients. These results suggest that hypothalamic hypocretin activity physiologically modulates the processing of emotional inputs within the amygdala and that suprapontine mechanisms of cataplexy might involve a dysfunction of hypothalamic–amygdala interactions triggered by positive emotions [193, 194]. Another fMRI study examined amygdalar response to emotional stimuli, by pairing visual stimuli with painful electric shock. Whereas healthy controls showed enhancement of amygdalar response to conditioned aversive stimuli, no such enhancement was observed in narcoleptic subjects [195]. In addition to this abnormal emotional circuitry, abnormal reward circuitry was evident in another report by the same group [196].

Neurotransmission in Narcolepsy

Given the role of acetylcholine as an important neurotransmitter in the generation of REM sleep [28, 197], it was hypothesized that disturbances in the cholinergic system might underlie narcolepsy. However, a PET study with ^{11}C-*N*-methyl-4-piperidylbenzilate found no evidence for a change in muscarinic cholinergic receptors in narcoleptic patients [198].

Likewise, the dopamine system has been probed by PET and SPECT in narcoleptic patients because increased dopamine D_2 receptor binding was shown in the brains of deceased narcoleptic patients [199, 200]. The results from these neuroimaging studies remain mostly inconsistent. One SPECT study showed elevated D_2 receptor binding in the striatal dopaminergic system, correlating with the frequency of cataplectic and sleep attacks in seven patients with narcolepsy [201]. However, other PET [202–204] or SPECT [205, 206] ligand studies did not find such change in D_2 receptor binding. A potential explanation for this discrepancy might be related to the drug treatment of narcoleptic patients. Indeed, considerable increase in the uptake of ^{11}C-raclopride, a specific D_2 receptor ligand, was observed in the putamens of narcoleptic subjects older than 31 years who underwent various regimens of prolonged treatment [207]. Likewise, despite the fact that the binding of iodobenzamide (IBZM, a highly selective CNS dopamine D_2 receptor ligand), was similar in narcoleptic patients and normal controls, treatment by stimulants and/or antidepressants for 3 months significantly changed ligand uptake in four of five patients [206]. Therefore, elevated postmortem dopamine binding might be due to the long-term effect of prior treatment rather than intrinsic modifications.

Brain Response to Drug Probe in Narcolepsy

The effects of stimulant drugs on cerebral function in narcoleptic patients were assessed using functional imaging. The effect of amphetamines was evaluated using fMRI in two patients with narcoleptic syndrome [208]. The extent of the brain response to auditory and visual stimulation decreased after amphetamine administration in normal subjects. The reverse pattern was observed in the narcoleptic patients. These findings remain difficult to interpret, and larger samples of patients should be studied.

Modafinil is a wakefulness-promoting psychostimulant used to treat narcoleptic patients. Two fMRI studies have evaluated its effect on brain perfusion responses. A first study found that normal subjects showed larger brain responses to a multiplexed visual and auditory stimulation paradigm at 10:00 A.M. than at 3:00 P.M. in visual areas, but not in auditory areas, suggesting time-of-day influences [209]. Surprisingly, the reverse pattern of activity was

observed in a group of 12 narcoleptic patients, with greater perfusion at 3:00 P.M. than 10:00 A.M.. Critically, modafinil administration did not modify the average level of activity either in normal subjects or in narcoleptics ($n = 8$), but post-drug activity level was inversely proportional to the predrug activity level. These findings are not easy to interpret but might suggest that modafinil can modulate brain activation in response to external stimuli. The second fMRI study tested the effect of modafinil on brain activation during a working memory task in healthy subjects, following a night of sleep deprivation. Modafinil at once improved working memory performance and enhanced activation in the executive network, specifically in the prefrontal and anterior cingulate cortices [210].

The metabolic effect of modafinil was studied in healthy individuals using ^{99m}Tc-ethylcysteinate dimer (^{99m}Tc-ECD) SPECT before and after the administration of the stimulant or a placebo [211]. Modafinil increased wakefulness and rCBF to areas in the brain associated with arousal, emotions and executive function, including the prefrontal, insular, cingulate, middle/inferior temporal and parahippocampal cortices and the pons. An ^{18}FDG PET study imaged baseline CMRglu in awake patients and controls before and after treatment with modafinil. Decreased CMRglu was observed in the brainstem, hypothalamus, thalamus, and mesio-temporal areas in narcoleptics compared to controls. When comparing pre- and post-treatment conditions in narcoleptic patients, an increase in CMRglu was found in the left hippocampus post-modafinil [212]. A second ^{18}FDG PET study compared CMRglu levels in 14 narcolepsy-cataplexy patients treated with psychostimulants and anticataplectics, and 7 narcolepsy-cataplexy patients that were not treated with drugs. Treated narcoleptic had higher levels of CMRglu in their cerebellum and primary sensory motor cortex. However, these results were hard to interpret due to sample heterogeneity [189].

Summary

Structural and functional neuroimaging studies in narcolepsy with cataplexy show remarkable convergence. Primarily, the hypothalamus displays consistent abnormalities in narcoleptic patients, both structural and functional. Hypothalamic involvement in narcoleptic psychopathology is consistent with the characteristic loss of hypocretinergic neurons in this disorder. The limbic system also shows abnormal responding, including the amygdala, which may reflect emotional dysregulation seen in the disorder and triggering cataplectic episodes. Structural abnormalities were equally found in the hippocampus and various cortical areas, perhaps underlying dysfunctions in cognitive processing. Sparse imaging data acquired during cataplexy itself suggest a possible role of the hypothalamus and somatosensory cortex. As for treatment response, modafinil seems to alter metabolism in a variety of areas, but none have stood out from the few studies to date. Despite recent breakthroughs in the pathophysiology of narcolepsy, more studies using state-of-the-art technology of acquisition and analysis of functional neuroimaging data are needed to better characterize the functional organization of the narcoleptic brain during wakefulness and sleep.

Recurrent Hypersomnia

Recurrent hypersomnia is a disorder characterized by recurrent episodes of hypersomnia that typically occur weeks or months apart [139]. One SPECT study in a 24-year-old male with recurrent hypersomnia showed decreased blood flow in the left thalamus during the hypersomnolent period, but failed to report any abnormal activation during recovery or remission periods [213]. This case report neuroimaging study provides only limited information about possible pathophysiologic mechanisms of this disorder. By contrast, other clinical and electrophysiologic studies clearly point toward a hypothalamic rather than a thalamic dysfunction [214, 215].

A typical form of recurrent hypersomnia, KLS, is characterized by periodic hypersomnia as well as behavioral and cognitive abnormalities, mainly in male adolescents [216]. Neuroimaging studies of KLS patients have revealed normal brain anatomy [216–218]; however, functional abnormalities were observed in SPECT. In an early SPECT study with ^{99m}Tc-ECD, unilateral hypoperfusion of both thalami was found in a sample of 27 KLS patients. These hypoperfusions consistently occurred during the symptomatic period [218] and were confirmed in later studies using both SPECT and ^{1}H-MRS [219–221]. During asymptomatic periods, perfusion of thalami returned to normal levels in all subjects, while other abnormalities in hypoperfusion persisted, mainly in the temporal lobe [218]. Other studies corroborated that hypoperfusion of the temporal lobe persists in asymptomatic patients [220]. Hypoperfusion of both thalami and basal ganglia [217, 220], as well as the frontal [222–224] and temporal lobe [216, 218, 220, 222, 225, 226], may provide insight to the pathophysiology of KLS, but the roles of the brain structures are not yet clear.

Obstructive Sleep Apnea Syndrome (OSAS)

OSAS is characterized by repetitive episodes of upper airway obstruction that occur during sleep, usually associated with a reduction in blood oxygen saturation [139]. Population-based epidemiologic studies have revealed a high prevalence (1–5 % of adult men) of OSAS. They also associate OSAS with significant morbidity, such as hypertension, cardiovascular disease, stroke, and motor vehicle accidents [227]. OSAS may lead to functional and structural brain alterations. Functional alterations such as sleep

fragmentation are often associated with neuropsychological deficits that can be reversible after treatment of OSAS. Structural alterations may indicate irreversible consequences on brain integrity and suggest permanent cognitive impairment, although this proposal remains a matter of debate in the literature, especially given recent structural imaging data showing a reversibility after treatment [228].

The pathophysiology of OSAS is complex and not yet completely understood. Several studies suggest that OSAS across all age groups is due to a combination of both anatomic airway narrowing and abnormal upper airway neuromotor tone. Notwithstanding the known anatomic factors, such as craniofacial anomalies, obesity, and adenotonsillar hypertrophy, that contribute to OSAS, clear anatomic contributing factors cannot always be identified [139]. This suggests that alterations in upper airway neuromuscular tone also play an important role in the etiology of OSAS [229]. The pathophysiology of OSAS also includes enhanced chemoreflex sensitivity and an exaggerated sympathetic response during hypoxemic episodes [230].

Apnea episodes in OSAS patients have considerable hemodynamic consequences, which are mediated by a complex cascade of physiologic events. Repetitive episodes of apnea trigger marked fluctuations in both blood pressure and heart rate, with consequent effects on the estimates of cardiovascular variability [6]. Several important regulatory mechanisms in cardiovascular homeostasis seem to be impaired in OSAS patients. Specific chemoreceptors seem to be implicated in the pathophysiology of OSAS [231]. For instance, the ventilatory response to carbon dioxide is elevated in OSAS patients [231] due to an elevation of the partial pressure of carbon dioxide that delimits carbon dioxide ventilatory recruitment threshold. An altered autonomic balance has been suggested as one possible pathogenic factor. This autonomic dysfunction has been thought to be implicated in the subsequent development of cardiovascular diseases in patients with OSAS.

Functional Neuroimaging Studies of OSAS

Several fMRI studies have been conducted in OSAS patients to characterize the neural correlates of integrated afferent airway signals with autonomic outflow and airway motor response [232–234]. For instance, altered response after a Valsalva maneuver involves cerebellar, limbic, and motor area deactivation. Enhanced sympathetic outflow after a forehead cold pressor challenge results in both diminished response in the thalamus, hippocampus, and insula, and exaggerated response in the cingulate cortex, cerebellum, and frontal cortex. Mandibular advancement led to decreased fMRI response in the left cingulate gyrus and the bilateral prefrontal cortices in 12 healthy subjects during induced respiratory stress [235]. Simultaneously, the subjective effects of this treatment were assessed by a visual analog scale that confirmed successful reduction of respiratory stress.

OSAS has been associated with distinctive cognitive alterations in various domains. Both hypoxemia and fragmented sleep are proposed as the main factor leading to neurocognitive impairments during wakefulness [236–243]. Several studies emphasized the deterioration of executive functions in OSAS patients, including the inability to initiate new mental processes [244, 245] and deficits in working memory [244, 246], analysis and synthesis [244, 246], contextual memory [247], selective attention [248], and continuous attention [248]. A meta-analysis showed that untreated patients with OSAS had a negligible impairment of intellectual and verbal functioning but a substantial impairment of vigilance and executive functioning [249].

A number of functional imaging studies of OSAS patients have used fMRI to evaluate BOLD contrasts during performance on cognitive tasks (Fig. 21.2c1). Generally, these studies have found deactivations in various regions [250–254], while some instead showed increases in activation [255] or mixed results [252, 256, 257]. For example, Ayalon et al. [253] compared 14 OSAS patients with 14 healthy controls on a sustained attention task and found task-related reductions in activation in OSAS patients across parietal, cingulate, and frontal regions typically recruited in attention tasks. Archbold et al. [256] found that OSAS severity correlated with increased activation of the right parietal lobe during a working memory task, in a sample of 9 treatment-naïve male OSAS patients. Deactivations are consistent with OSAS-related structural deterioration (described below), whereas activation increases may represent compensatory recruitment. More recent studies have focused on resting-state functional connectivity changes and have found regional reductions in connectivity in the medial and dorsolateral prefrontal cortices, which make up part of the default-mode network [258, 259]. Concordantly, default-mode network deactivation was compromised in OSAS patients during a visuospatial N-back task, in parallel with performance deficits [252, 260].

Aside from fMRI studies during cognitive performance, functional correlates of OSAS have also been studied during restful wakefulness, using PET and SPECT. A ^{99m}Tc-ECD SPECT study observed decreased baseline rCBF in the parahippocampal and lingual gyri of OSAS patients compared to healthy volunteers [261]. Using ^{18}FDG PET, another group found reduced CMRglu in the prefrontal, parieto-occipital, and cingulate gyri of OSAS patients, compared to healthy controls [262].

Long-term consequences of OSAS have been rarely assessed after nasal continuous positive airway pressure (CPAP) treatment. An early ^{99m}Tc-HMPAO SPECT study in 14 adult OSAS patients reported a marked frontal hyperperfusion in 5 patients [263]. In contrast, regional analysis showed reduced perfusion in the left parietal region. All these changes were reversed by effective CPAP therapy, suggesting that the main deleterious effects of OSAS on

brain activity are reversible. According to the authors, there might be an apnea-associated effect of local vascular autoregulation mechanisms acting to compensate systemic blood flow alterations or blood gas changes in OSAS. Similar findings were obtained in an fMRI study, where hyperactivation of prefrontal and hippocampal areas was reversed with 3 months of CPAP treatment [257]. In a recent study, 2 months of CPAP treatment improved task-related default-mode network deactivation, concomitantly with improvements in behavioral performance [260].

Anatomic Neuroimaging Studies of OSAS

Structural modifications of brain morphology in OSAS have been studied extensively in several modalities (Fig. 21.2c2). In an early study, structural changes were assessed using VBM in 21 patients with OSAS and in 21 control subjects [264]. Gray matter loss was apparent in patients with OSAS in multiple brain sites involved in motor regulation of the upper airway as well as in various cognitive functions, including the frontal and parietal cortices, temporal lobes, anterior cingulate, hippocampus, and cerebellum. Additional VBM studies found gray matter loss in similar regions, mainly in the prefrontal, anterior cingulate, parietal, and hippocampus [228, 258, 262, 265, 266, 267, 268]. These anatomic changes were often [228, 266, 267] but not always [262] associated with cognitive deficits, notably memory impairment. Female gender [269] and depressive symptoms [270] were associated with exacerbated neural damage and neurocognitive symptoms from OSAS. Another MRI study compared both neuroanatomical and neuropsychological effects of hypoxia in patients with either carbon monoxide poisoning or OSAS and found a hippocampal atrophy in both groups [266]. Of note, a linear relationship between hippocampal volume and memory performance selectively in the OSAS group was found for a subset of tests (the delayed recall or the Rey-Osterrieth Complex Figure Design and Trail 6 of the Rey Auditory Verbal Learning Test among others). Moreover, hippocampal volume was related to performance on nonverbal information processing (Wechsler Adult Intelligence Scale–Revised Block Design) in both groups. In a more recent study, hippocampal volume was also negatively correlated with excessive daytime sleepiness [268]. Further investigation will be necessary to better delineate the specificity and contribution of hippocampal atrophy in OSAS. A set of interesting correlations between indices of OSAS severity and prefrontal cortex changes were observed with MRI. Apnea–hypopnea index was negatively correlated with frontal gray matter volumes [228]. Also in the frontal regions, prolonged arterial oxygen desaturation correlated with gray matter decreases [228], deactivations during working memory tasks [251, 252], and decreased cortical connectivity [259]. In one of these studies, 3 months of CPAP treatment in 17 treatment-naïve OSAS patients resulted in the recovery of gray matter concentrations in the hippocampus and frontal regions, alongside significant improvements in neurocognitive performance [228]. These findings underline the effectiveness of CPAP treatment in both physiologic and cognitive recovery from OSAS-related neural damage.

Single-voxel ^{1}H-MRS has also been used to assess whether OSAS can induce axonal loss or dysfunction, or myelin metabolism impairment. An early study using this technique showed that the NAA/Cr ratio in cerebral white matter was significantly lower in patients with moderate to severe OSAS than in patients with mild OSAS and healthy subjects [271]. A series of studies followed which compared OSAS patients to controls and found significantly lower NAA/Cr [272, 273], NAA/choline (Cho) [273, 274], and Cho/Cr [275] ratios in frontal white matter, as well as greater Cho/Cr ratios in the thalamus [273] and temporal regions [272]. In addition, apnea–hypopnea index was negatively correlated with NAA/Cr ratios [272]. These findings may explain some of the deficits in executive function associated with OSAS. Consistent with the VBM results noted previously, decreases in absolute and relative creatine-containing compounds in the left hippocampal area correlated with increased OSAS severity [274, 276, 277, 278] and worse neurocognitive performance [277]. Together, VBM and spectroscopy studies point to an atrophy and/or dysfunction of hippocampal regions in OSAS. In a ^{1}H-MRS study of the effects of CPAP on OSAS severity, NAA in the parieto-occipital cortex was significantly lower in 14 OSAS patients than in controls, but this reduction persisted after CPAP therapy despite clinical, neuropsychological, and neurophysiologic normalization [279]. Accordingly, a later MRS study found no significant differences in creatine-containing compounds after 6 months of CPAP treatment [274].

Summary

Altogether, these findings suggest that neuropsychological deficits in OSAS might relate to various alterations in the prefrontal cortex, hippocampus, and parietal cortex. In particular, volumetric decreases may provide a useful biomarker of OSAS severity [280]. Reduced functional connectivity of the default-mode network may also relate to cognitive deficits in OSAS. Even if abnormal brain activations and even structural changes seem reversible under CPAP, several studies have suggested that not all neuropsychological impairments disappear after the treatment [245, 281, 282]. Although the basic pathophysiologic mechanisms of OSAS are not completely understood, a dysregulation in autonomic control seems to play an important role [232–234].

Restless Legs Syndrome and Periodic Limb Movements

Periodic limb movements (PLM) during sleep and restless legs syndrome (RLS) are distinct but overlapping disorders. RLS is typified by an irresistible urge to move the legs (and less often, the arms), especially during sleep onset. The compulsion is associated with relentless feelings of discomfort from deep inside the limbs [283, 284]. PLM is characterized by periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep [284]. While these movements disturbed sleep and can result in awakening, patients are mostly unaware of the movements or even that their sleep has been disturbed. Diagnosis requires a polysomnographic recording along with a complaint such as "unrefreshing" sleep [284, 285].

RLS and PLM commonly co-occur. However, PLM is non-specific, occurring in isolation in healthy individuals or comorbid with other sleep disorders such as narcolepsy, RBD, and sleep apnea [285]. Given their close association, few neuroimaging studies have investigated PLM alone and instead RLS and PLM are most often considered in concert. The present section will first cover neuroimaging studies focused on RLS (Fig. 21.2d) and will end by covering the few studies of PLM alone.

Restless Legs Syndrome

An early ^{18}FDG PET study found no differences in glucose metabolism between six RLS patients and six age-matched controls, albeit when measured outside the symptomatic period [286]. An fMRI study also attempted to localize some cerebral generators of leg discomfort and PLM in RLS [287]. During RLS leg discomfort, the study showed a bilateral activation of the cerebellum and contralateral activation of the thalamus in patients. A later fMRI study examined brain activation in concert with electromyography measures of tonic activity in the legs, in 7 RLS patients [288]. Tonic activity was inversely correlated with reported discomfort in the legs and with cerebellar activation and positively correlated with activation in the sensorimotor cortex, cingulate gyrus, precuneus, and occipital cortex.

An inhibition of descending inhibitory pathways implicating dopaminergic, adrenergic, and opiate systems is thought to be involved in RLS pathogenesis [289]. Patients' condition worsens when dopamine antagonists are given [290], whereas dopaminergic drugs have been shown to relieve RLS [291–293].

Dopamine research in RLS has centered mainly on the striatum, probing both presynaptic DAT and postsynaptic D_2 receptor occupancy. Striatal DAT can be taken as a measure of dopaminergic neuron density in the substantia nigra (SN). Some PET studies found reduced presynaptic dopamine activity in the striatum of RLS patients compared to controls, using either ^{11}C-methylphenidate [294] or ^{18}F-dopa [295, 296], although an early study using ^{18}F-dopa found no such difference in a small sample [297]. Additionally, some SPECT studies found no change in DAT in RLS compared to controls, using ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl) tropane (^{123}I-β-CIT) [298, 299] or ^{123}I-N-(3-iodopropen-2-yl)-2β-carbomethoxy-3β -(4-chlorophenyl) tropane (^{123}I-IPT) [300, 301]. Variable pharmacokinetic properties of radioligands may contribute to explain the discrepancy in these findings. DAT binding seems independent of clinical severity and time of day [294]. An additional SPECT study employed SPECT with ^{123}I-β-CIT and ^{123}I-IBZM, and contrarily to previous presynaptic dopamine studies, DAT density showed an increase in the striatum, as well as the caudate and posterior putamen [302]. The authors concluded that DAT dysregulation may be responsible for RLS pathogenesis, rather than DAT upregulation or downregulation specifically.

Results of postsynaptic D_2 receptor binding studies are also ambivalent. Among SPECT studies using ^{123}I-IBZM, some found no difference [300, 303, 304], and others detected a reduction in striatal D_2 receptor binding in RLS patients compared to controls [298, 305, 306, 307, 308]. In one of these studies, treating patients with dopamine replacement therapy increased the IBZM binding and improved sleep quality in these patients [305]. Two PET studies with ^{11}C-raclopride found conflicting results, with one showing an increase [295] and the other a decrease [309] in striatal D_2 receptor binding. Different pharmacological histories may explain this discrepancy; only the latter study used drug-naïve patients. Indeed, it has been shown that chronic drug treatment can downregulate D_2 receptors, thus decreasing ligand binding [310]. Another study using ^{11}C-FLB457 found increased binding potential in the striatum as well as in the insula, thalamus, and anterior cingulate cortex, all of which are components of the medial nociceptive system [309]. Upregulation of D_2 receptors in this area may be the consequence of endogenous dopamine depletion. Similar to presynaptic dopamine findings, clinical severity, and time of day had no effect on D_2 binding potential. [309]. A recent PET study using ^{11}C-raclopride found that RLS patients had reduced D_2 receptor binding potential in the putamen and caudate but not ventral striatum [311]. Altogether, pre- and postsynaptic dopamine studies remain inconclusive.

The role of dopamine in RLS pathophysiology may be better understood by taking into account studies implicating the cerebral metabolism of iron [312] (Fig. 21.2d). Iron and the dopaminergic system are linked since iron is an important cofactor for tyrosine hydroxylase, the step-limiting enzyme in dopamine synthesis, and also plays a major role

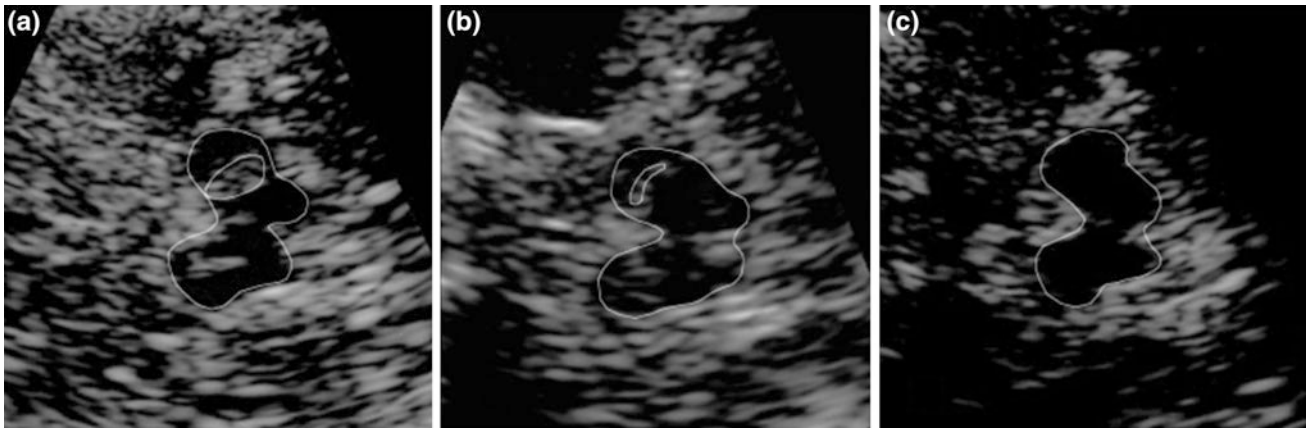

Fig. 21.5 Transcranial ultrasound images (axial plane) in three patients. **a** Patient with Parkinson's disease (PD). **b** Control subject. **c** Patient with restless legs syndrome (RLS). Midbrain is *encircled* and areas of hyperechogenicity are *encircled* in (**a**) and (**b**). There is a progression of decreased echogenicity from PD to healthy control to RLS (Reproduced with permission from Schmidauer et al. [319]. Copyright 2005, American Neurological Association)

in the functioning of postsynaptic D_2 receptors [6]. Notably, increased iron concentrations in the midbrain are a reliable biomarker in PD [313, 314]. Consistent with a link between the dopaminergic system and iron, Allen et al. [315] found decreased regional iron concentrations in the SN and putamens of five patients with RLS, both in proportion to RLS severity. In addition, Earley et al. [316] found diminished iron concentration across 10 brain regions in early-onset RLS patients but not in late-onset RLS patients when compared to controls. Transcranial ultrasound has also been used to measure decreased iron levels in the SN, capitalizing on iron's echogenic effect [317–319]. Of note, midbrain iron concentrations in RLS patients were significantly reduced relative to control subjects and showed an even more pronounced reduction relative to PD patients (Fig. 21.5) [319]. Iron depletion was also found in other areas than the SN, such as the thalamus and caudate, suggesting RLS is a multiregional disorder [317].

Opioid receptor agonists improve RLS symptoms [320], consistent with RLS as a disorder of the nociceptive system. This effect may be mediated by dopamine and may not necessarily reflect a endogenous opioids deficiency [321]. In support of this, one PET study examined opioids in RLS, using ^{11}C-diprenorphine (a non-selective opioid receptor ligand), and found no differences between patients and controls, although some correlations were detected between RLS severity or pain scores and decreased opioid binding in several brain areas [322]. These decreases in opioid receptor availability likely result from the endogenous release of opioids in response to RLS-related pain and discomfort.

Structural cerebral abnormalities have been reported in patients with idiopathic RLS [323]. High-resolution T1-weighted MRI of 51 patients and 51 controls analyzed using VBM revealed a bilateral gray matter increase in the pulvinar in patients with idiopathic RLS. These authors suggest that changes in thalamic structures are either involved in the pathogenesis of RLS or may reflect a consequence of chronic increase in afferent input of behaviorally relevant information. A number of VBM and DTI studies followed. Two studies by a same research group found gray matter decreases in the primary sensorimotor cortex using VBM (63 RLS patients, 40 controls) [324] and white matter alterations near this area and near the thalamus, using DTI (45 patients, 30 controls) [325]. These changes may, however, have been due to patient pharmacological treatment history. Indeed, four subsequent studies examining unmedicated patients detected no neuroanatomical differences using VBM [326–329] and DTI [329], except for a slight gray matter increase in the orbitofrontal gyrus and hippocampus [328]. However, these studies had possessed lower power due to smaller samples (from 15 to 20 patients). A recent multimodal study using ^{1}H-MRS found a significant reduction of *N*-acetylaspartate concentration and *N*-acetylaspartate to creatine ratio in the medial thalamus in RLS patients versus controls [330]. These results lend support to a role of thalamic dysfunction in RLS pathophysiology, although concurrent fMRI and DTI in this same study did not reveal thalamic alterations. It remains unclear whether RLS is associated with any consistent neuroanatomical changes.

A recent ^{1}H-MRS study demonstrated that thalamic glutamate/glutamine (Glx)/Cr levels were augmented in RLS patients, with respect to controls [331]. Furthermore, correlations were observed between Glx/Cr and WASO, a sleep variable related to RLS, but no correlation was found with PLM rate. This is interesting given that dopamine, to the contrary, has been correlated strongly with PLMs and not with WASO. The authors propose two dichotomous systems involved in RLS pathology, namely a glutamatergic arousal system and a dopaminergic motor system. Hence, the

glutamatergic system may be an important target for further pathophysiologic studies of RLS.

Periodic Limb Movements

A few studies have focused specifically on PLM. An fMRI study combining PLM and sensory leg discomfort showed activity in the cerebellum and thalamus with additional activation in the red nuclei and brainstem close to the reticular formation [287]. Notably, when subjects were asked to voluntarily imitate PLM, there was no activation in the brainstem, but rather additional activation in the globus pallidus and motor cortex. These results suggest an involuntary mechanism of induction and a subcortical origin for PLM.

Dopaminergic transmission has been studied in relation to PLM. Presynaptic dopamine transmission was measured in 11 patients with PD using SPECT with ^{123}I-β-CIT [308]. Patients with PD showed a large decrease in striatal binding relative to controls, as predicted. A negative correlation was detected between the number of polysomnography-based PLMs and striatal dopamine binding values. This indicates a potential role of presynaptic dopamine deficiency in PD-induced PLM. A few studies found reduced D_2 receptor occupancy in the striatum of PLM patients using SPECT and ^{123}I-IBZM [306, 307]. Dopamine replacement therapy can reverse this pattern and restore sleep quality [305].

Summary

Studies on RLS seem to indicate iron depletion in several brain regions, especially in the SN, which may interact with dopamine metabolism to unbalance the sensorimotor control of pain. Functional studies on opioids and glutamate are few, but may shed further light on the disorder. Meanwhile, structural studies have not revealed any consistent changes in brain structure in RLS. The thalamus stands out as a potentially important area in RLS pathology, having shown functional and structural abnormalities. Further research into RLS and PLM brain activation during sleep is needed to better understand these disorders.

Sleepwalking

Sleepwalking, also known as somnambulism, is an arousal parasomnia consisting of a series of complex behaviors that result in large movements during sleep [332]. It is perceived as a dissociation state whereby most of the brain exhibits non-REM sleep patterns, except motor-related areas. One

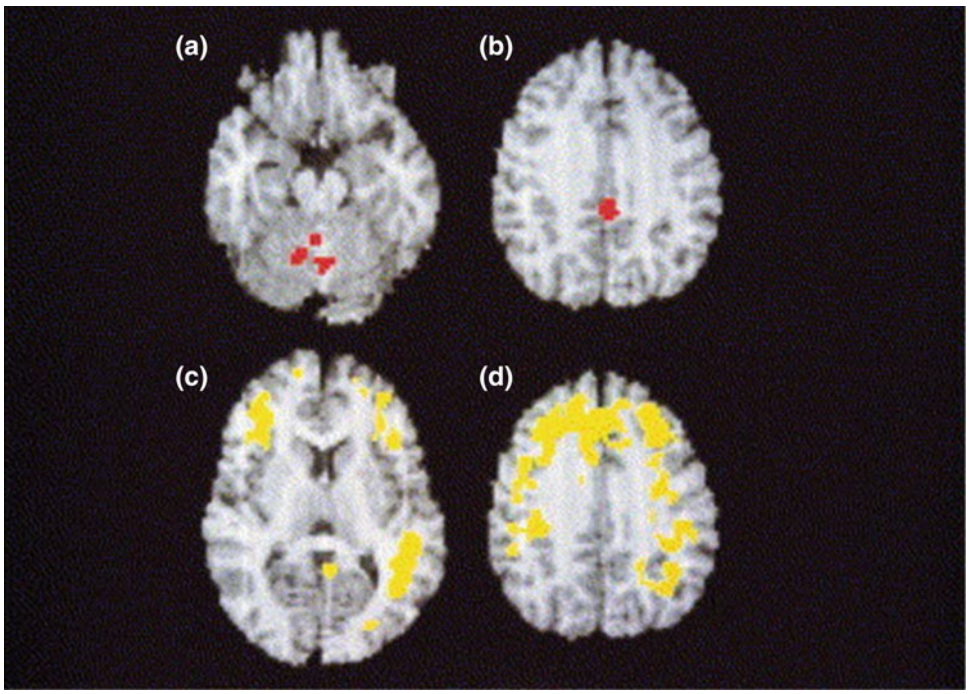

Fig. 21.6 SPECT findings during sleepwalking after integration into the appropriate anatomic magnetic resonance image. The highest increases of regional CBF (>25 %) during sleepwalking compared with quiet stage 3–4 NREM sleep are found in the anterior cerebellum (i.e., vermis) (**a**), and in the posterior cingulate cortex (**b**). However, as compared to data from normal volunteers during wakefulness, large areas of frontal and parietal association cortices remain deactivated during sleepwalking, as shown in the corresponding parametric maps. Note the inclusion of the dorsolateral prefrontal cortex (**c**), mesial frontal cortex (**d**), and left angular gyrus (**e**) within these areas (Reproduced with permission from Bassetti et al. [333]. Copyright 2000, The Lancet)

16-year-old male subject was studied during sleepwalking using ^{99m}Tc-ECD SPECT [333]. Compared to awake normal volunteers (n = 24), a decrease in rCBF in the frontoparietal associative cortices was found. Additionally, the posterior cingulate cortex showed increased rCBF during the sleepwalking episode, with respect to the patient's baseline activity. These results suggest that this state dissociation arose from combined activation of thalamo-cingulate pathways and persisting deactivation of other thalamo-cortical arousal systems (Fig. 21.6). Since only one patient has ever been studied while sleepwalking, further studies with larger sample sizes are needed to confirm these findings.

REM Sleep Behavior Disorder

This condition, initially described by Schenck et al. [334], is characterized by brisk movements of the body associated with dream mentation during REM sleep that usually disturbs sleep continuity. During the nocturnal spells, patients behave as if they were acting out their dream, in the absence of muscle atonia [139]. This disease may be idiopathic (up to 20 %) but mostly associated with neurodegenerative disorders. A sizeable proportion of patients with RBD will develop extrapyramidal disorders [335–337], Lewy body dementia (LBD) [338], and multiple system atrophy (MSA) [339, 340]. More recently, a strong association between RBD and α-synucleinopathies has been observed, with the parasomnia often preceding the clinical onset of the neurodegenerative disease [338]. It is notable that, an early experimental model of RBD in the cat has shown that lesions in the mesopontine tegmentum can lead to the disappearance of muscle atonia during REM sleep together with dream-enactment behavior [341].

Functional Neuroimaging Studies of RBD

Changes in perfusion to various brain regions have been shown in a number of studies (Fig. 21.2e). A SPECT study in 8 RBD patients during waking rest showed decreased activity in the frontal and temporoparietal cortices but found increased activity in the pons, putamen, and right hippocampus [342]. These results have been verified in later studies with larger sample sizes [343, 344]. In another SPECT study, 24 idiopathic RBD patients showed decreased rCBF in cerebellar, parietal, occipital, and limbic regions [345].

A recent longitudinal study followed 20 idiopathic RBD patients over an average period of 3 years. At the study's outset, patients were scanned during wakefulness with ^{99m}Tc-ECD SPECT. After the three-year period, 10 of the patients had developed PD or LBD. Regression analysis revealed that hyperperfusion in the hippocampus predicted

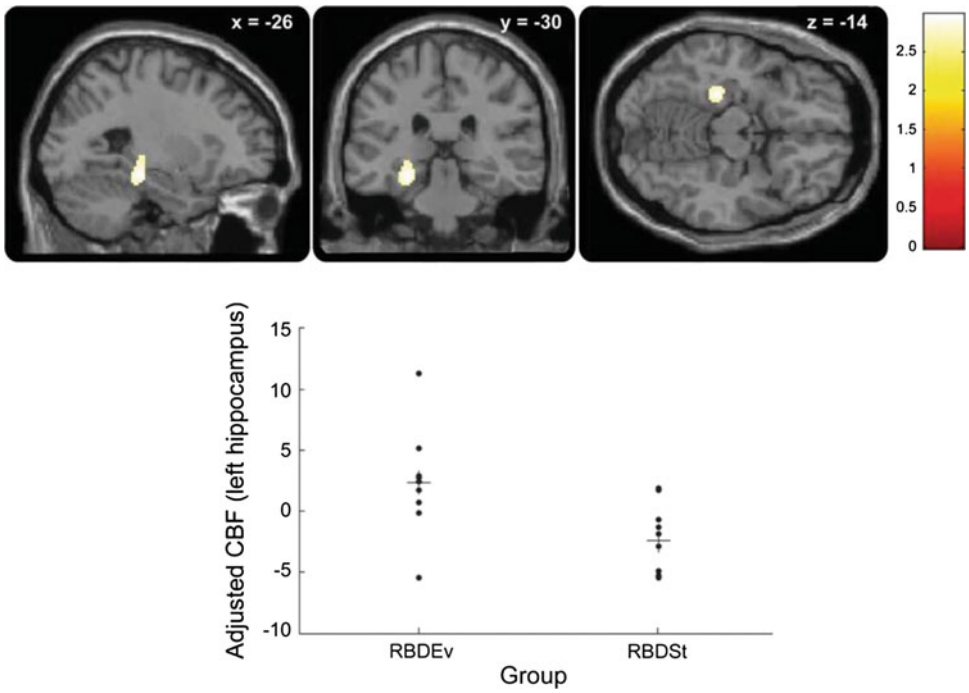

Fig. 21.7 Hippocampal hyperperfusion in REM sleep behavior disorder patients who did (RBDEv) and did not (RBDSt) develop synucleinopathy. Peak hypoperfusion of the left hippocampus at study outset is shown in sagittal, coronal, and transverse sections (p< 0.05 corrected). The range of t values for this contrast is shown in the *color scale* on the *right*. The coordinates are given at the *top right* corner of each panel. *Below*, the plot displays the adjusted regional cerebral blood flow in the left hippocampus, showing distinct distributions for RBDEv and RBDSt groups. Each subject is represented by a *black dot*. *Horizontal bars* represent group means (Reproduced with permission from Dang-Vu et al. [344]. Copyright 2012, American Academy of Neurology)

the subsequent development of LBD or PD in RBD patients (Fig. 21.7) [344]. Hippocampal perfusion across RBD patients was also correlated with motor and color vision scores, which are markers of neurodegeneration. This demonstrates the involvement of hippocampal perfusion as a consistent biomarker of the neurodegenerative evolution in RBD. Studies of brain perfusion with SPECT thus provide useful prognostic tools predicting the onset of neurodegenerative diseases in RBD patients.

One ^{99m}Tc-ECD SPECT study was able to capture an episode of RBD in an MSA patient [346]. Notably, perfusion to the supplementary motor area increased compared to wakefulness, while no such pattern was found during REM sleep in two healthy controls. However, REM sleep outside the episode was not imaged in the MSA patient, thus limiting conclusions about the specificity of supplementary motor area activation to dream enactment in RBD. Replication in larger samples, along with baseline REM sleep assessment, may determine whether this area plays a role in RBD pathophysiology.

Neurotransmission in RBD

Findings of RBD comorbidity with dopaminergic disorders, such as PD and LBD [344], have driven forward research into the nigrostriatal dopaminergic system in RBD patients. Presynaptic DAT densities have been probed in two SPECT studies with the DAT ligand ^{123}IPT [109, 347]. Together, they trace a spectrum of decreasing striatal DAT density from healthy subjects, to subclinical RBD patients showing muscle atonia with no dream enactment, to full-blown RBD patients, and finally to PD patients, who showed the lowest presynaptic DAT density. A similar spectrum was described by a third SPECT study using another presynaptic DAT ligand, ^{123}I-2β carbomethoxy-3 (4-iodophenyl)-*N*-(3-fluoropropyl)-nortropane (^{123}I-FP-CIT) [348]. In contrast, four more studies using this ligand reported striatal DAT decreases in only a minority of RBD patients (2 out of 11 [349], 2 out of 5 [350] and 3 out of 14 [348]). PET studies have also found striatal DAT decreases in RBD, using ^{11}C-dihydrotetrabenazine (^{11}C-DTBZ), an in vivo marker for dopaminergic nerve terminals. Significant reductions in striatal ^{11}C-DTBZ binding characterized 6 elderly subjects with chronic idiopathic RBD, as compared to 19 age-matched controls, particularly in the posterior putamen [351].

Two longitudinal ^{123}I-FP-CIT SPECT studies, from the same research group, examined the relationship between striatal DAT and incident neurodegenerative disease over the course of several years [352, 353]. The first study followed 43 idiopathic RBD patients and 18 controls [352]. At the outset, 40 % of RBD patients showed reduced striatal DAT. Patients were followed up 2.5 years later and 8 of them had developed a neurodegenerative disorder (PD, LBD, or MSA). Six of these eight patients had shown reduced striatal DAT at the outset of the study. This measure may then provide a useful tool early on for identifying RBD patients at high risk for developing neurodegenerative disease. The second longitudinal study followed 44 idiopathic RBD patients over the course of 7 years [353]. At follow-up, 82 % of patients had developed a neurodegenerative disease. The 4 patients showing no sign of disease had reduced striatal DAT at follow-up, placing them at high risk of developing a neurodegenerative disease later on. Both studies buttressed the association between RBD and reduced presynaptic DAT in the SN, and provided additional evidence that idiopathic RBD presents an early stage of neurodegeneration. The deterioration of presynaptic dopamine dysfunction was monitored in a longitudinal case report of a 73-year-old male suffering from RBD over 3.5 years. ^{11}C-CFT with PET was used to show a significant decrease (about 4–6 % per year) in dopamine binding in the striatum, similar to decreases observed in PD [354]. It remains to be shown whether these dopaminergic alterations play a causal role in the pathophysiology of RBD or reflect functional consequences and adaptations to the pathologic conditions.

Lastly, postsynaptic D_2 receptor density was also assessed in RBD in two previously cited ^{123}I-IBZM SPECT studies from the same group [109, 347]. There were no significant differences detected between RBD, PD, and healthy control groups, indicating that postsynaptic dopaminergic function is unaltered in RBD.

Anatomic Neuroimaging Studies of RBD

Neuroanatomical abnormalities in RBD have been revealed by structural neuroimaging (Fig. 21.2e). One study, employing MRI and VBM, demonstrated decreased bilateral putamen volumes in RBD patients compared to healthy controls, as well as in comparison with patients with early PD [355]. A later study conducted through DTI whole-brain scans showed white matter microstructural changes in 12 patients with idiopathic RBD compared with age-matched healthy controls [356]. These significant changes occurred in multiple brain regions known to be involved in REM sleep regulation. Notably, changes were found in the pons. A combined DTI-VBM study [357] found white matter decreases in the pontine region, as well as significant bilateral gray matter increase in the hippocampus of RBD patients. Structural alterations in the pons and hippocampus are in accord with findings from functional studies described above [342, 344, 358, 359].

In addition, an increased Cho/Cr ratio in the brain stem suggesting local neural abnormalities was revealed by ^{1}H-MRS in a 69-year-old man with idiopathic RBD as compared with healthy adults [360]. In contrast, one ^{1}H-MRS study, conducted in 15 patients with idiopathic RBD and 15 matched control subjects, failed to reveal any difference in metabolic peaks of NAA/Cr, Cho/Cr, and myoinositol/creatine ratios in the pontine tegmentum and the midbrain [361]. Similarly, a ^{1}H-MRS study examining pontine metabolic ratios in 15 PD patients with RBD and 15 PD patients without RBD detected no group difference [362]. Whether

idiopathic RBD involves mesopontine neuronal loss or ^{1}H-MRS–detectable metabolic disturbances therefore remains unsettled.

Transcranial ultrasound has been employed to measure SN iron levels in RBD based on midbrain echogenicity. Since increased nigral iron concentrations are a reliable biomarker of PD, as evidenced by ultrasound hyperechogenicity, Iranzo et al. hypothesized that transcranial ultrasound measures of nigral iron in RBD may predict the later onset of PD and other synucleinopathies. In their aforementioned longitudinal study [352], they measured nigral iron levels in 39 idiopathic RBD patients and 149 controls, and found hyperechogenicity in 36 % of RBD patients and 11 % of controls. Two and a half years later, 8 of 43 RBD patients had developed synucleinopathies, 5 of which had shown hyperechogenicity at the study's outset. In combination with DAT concentration measures from ^{123}I-FP-CIT SPECT, this study was able to use transcranial ultrasound to predict the conversion from idiopathic RBD to synucleinopathy with 100 % sensitivity and 55 % specificity. Similar to the decreasing DAT spectrum described earlier, this study provides evidence for a spectrum of increasing iron concentrations in the SN, from normal levels, to RBD, and ending in synucleinopathy.

Summary

Structural and functional neuroimaging studies in RBD agree with involvement of the pons in the pathophysiology of RBD. In addition, presynaptic dopamine dysfunction in nigrostriatal pathways seems related to the progression of RBD severity, with subclinical RBD showing the least reduction in DAT density, followed by a greater reduction in manifest RBD, and the greatest reduction in neurodegenerative disease, particularly in synucleinopathies (PD, LBD, and MSA). Whether dopaminergic dysfunction is a cause or consequence of RBD remains unclear. Similar to the spectrum of decreasing striatal DAT density, transcranial ultrasound data suggest a spectrum of increasing iron concentrations in the SN from normal levels, to RBD, and ending in synucleinopathy. Early biomarkers seem available to identify RBD patients at high risk of developing a synucleinopathy, using transcranial ultrasound of the SN combined with SPECT assessing presynaptic striatal DAT density or hippocampal hyperperfusion. Future studies would do well to investigate hippocampal involvement in RBD, as well as provide additional functional data during sleep, particularly during RBD dream-enactment episodes.

Conclusions

The relatively new field of neuroimaging has already yielded valuable insights into disorders of sleep. Functional anomalies in brain activation in insomnia patients support hyperarousal theory, whereas structural alterations in the hippocampus, rACC and prefrontal cortex may underlie cognitive and emotional deficits in insomnia. Hypothalamic abnormalities in narcolepsy, both functional and structural, are consistent with a dysfunction of the hypocretinergic system. Altered response of the limbic system and anatomic alterations of the hippocampus and cortical areas may relate to emotional dysregulation in narcolepsy. Thalamic hypoperfusion pervades the few recurrent hypersomnia studies. A dysregulation of autonomic control seems to underlie OSAS, and cognitive deficits may be reflected in structural alterations of the prefrontal cortex, parietal cortex, hippocampus, and white matter tracts. Functional alterations also occur in OSAS, notably in the reduced connectivity of the default-mode network. While functional and structural changes seem partially reversible by CPAP, some cognitive deficits may be more permanent. Turning to movement disorders, RLS may be due to an imbalance in the sensorimotor control of pain, which itself may be due to dopaminergic dysfunction and iron depletion in the SN. The single case report of a sleepwalking episode showed prefrontal hypoperfusion and posterior cingulate hyperperfusion. Lastly, RBD seems to be related to pontine abnormalities, as evidenced by structural and functional studies. Presynaptic dopamine dysfunction in the striatum is also a reliable feature of RBD, correlating with the degradation from subclinical RBD, through full-blown RBD, and eventually to synucleinopathy. Neuroimaging may provide a valuable tool in identifying RBD patients at greatest risk of neurodegenerative disease, by relying on biomarkers such as DAT density, nigral hyperechogenicity, and hippocampal hyperperfusion.

Functional neuroimaging provides unprecedented possibilities to explore brain function during normal and pathologic sleep. Nevertheless, neuroimaging in sleep is still in its infancy, at present mostly restricted to research purposes. A major research effort should be developed in order to better characterize pathophysiologic mechanisms of sleep disorders, teasing apart functional causes from consequences. These efforts should benefit from advanced multimodal neuroimaging and improved experimental designs.

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Multiple Sleep Latency Test

22

Thomas Roth and Timothy A. Roehrs

Introduction

Daytime sleepiness as a consequence of inadequate sleep the previous night is a common experience for most adults. Because of the universality of the acute experience of daytime sleepiness, it is typically minimized as a health problem within the general population; in a 1997 Gallup Poll of Americans, only 6 % of those reporting impairing sleepiness considered it medically serious [1]. Although minimized by laypeople, increasingly chronic excessive daytime sleepiness is recognized as an important and significant symptom in medicine and public health. Furthermore, excessive daytime sleepiness can and should be distinguished from fatigue, tiredness, and lassitude, although many patients may not make such distinctions themselves unless they are carefully queried.

Representative surveys of the populations of industrialized countries have found that between 11 and 32 % of respondents report that sleepiness interferes with activities almost daily [1–5]. Sleepiness is associated with a number of medical, behavioral, and pharmacologic causes, and, regardless of its cause, has serious social and medical consequences. Nearly half of the patients with excessive sleepiness seen at sleep disorders centers report automobile accidents; more than half report occupational accidents, some life threatening; many have lost jobs because of their sleepiness; and the impact of sleepiness has a disruptive effect on family life [6]. Information on traffic and industrial accidents in the general population suggests a link between sleepiness and life-threatening events. For example, the highest rate of self-reported automobile accidents occurs between 2 and 6 am, which is remarkable because fewer automobiles are on the road during these hours [7]. A population-based study related Department of Motor Vehicle (DMV)-verified automobile accidents to excessive sleepiness as measured by the MSLT and a commonly used subjective sleepiness questionnaire, the Epworth Sleepiness Scale (ESS) [8]. Those with the lowest MSLT scores had the highest accident rates, while the ESS was not predictive (see discussion below). Shift workers, a particularly sleepy subpopulation, have the poorest job performance and the highest rate of industrial accidents among all workers [9].

Problems in assessing sleepiness became evident during early research on the daytime consequences of sleep loss before the clinical significance of sleepiness was recognized. Sleep loss compromises daytime functions. Virtually all individuals experience dysphoria and reduced performance when they do not sleep adequately. The majority of performance tasks are insensitive to the effects of sleep loss [10], but long and monotonous tasks are reliably sensitive to the changes in the quantity and quality of nocturnal sleep. Using various measures of mood, including factor analytic scales, the most consistent and systematic response to sleep loss is increased sleepiness. Among the various subjective measures of sleepiness, the Stanford Sleepiness Scale (SSS) is the best validated [11]. Yet clinicians have found that patients may rate themselves alert on the SSS even as they are falling asleep [12]. The likely reason for such discrepancies is that subjective daytime sleepiness has multiple dimensions [13].

Normal and pathologic variations in daytime sleepiness and alertness can now be directly assessed and quantified by the multiple sleep latency test (MSLT), a test of the rapidity with which a subject falls asleep in a standardized, sleep-conducive setting, repeated at 2-h intervals throughout the day. The MSLT uses standard sleep recording methods to document both the rate of sleep onset and the appearance of rapid eye movement (REM) episodes at sleep onset. Other procedures that have been used to quantify sleepiness and alertness (but because of a variety of shortcomings are not

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widely used), including pupillometry, subjective rating scales, and tests of vigilance or reaction time, are all correlated to some extent with the MSLT. The MSLT has become the standard method in clinical sleep disorders medicine for documenting the complaints of excessive daytime sleepiness and to document treatment success. It is also used to document sleep-onset REM periods, a diagnostic sign of narcolepsy. The American Academy of Sleep Medicine has indicated that the MSLT should be used as part of an evaluation of suspected narcolepsy and may be helpful in the evaluation of suspected idiopathic hypersomnia [14]. Since the development of the MSLT by Carskadon and Dement [15] in the late 1970s, enormous progress has been made in the scientific investigation and understanding of both normal and pathologic variations in sleepiness and alertness. The original R–K method of recording and scoring has recently been slightly modified (see Chap. 6).

Multiple Sleep Latency Test Methods

Recording Montage

General and specific technical guidelines for the administration of the MSLT have been published [16]. Briefly, the guidelines require that the standard Rechtschaffen and Kales (R-K) recording montage be used in performing the MSLT [16]. The montage includes the referential electroencephalogram (EEG) from a central (C3 or C4) placement, two horizontal referential electrooculograms (EOGs) from right and left outer canthi, and a mental or submental electromyogram. Also helpful in the determination of sleep onset is a referential occipital EEG lead, which shows alpha activity in relaxed wakefulness with eyes closed and is followed by a characteristic change to mixed-frequency EEG activity at the onset of sleep. An EOG recording with filters set to allow visualization of slow rolling eye movements (e.g., 250 ms) is another sign of sleep onset.

General Procedures

As indicated in the guidelines, to ensure a reliable and valid MSLT, a number of general procedures are necessary [16]. A 1- or 2-week sleep diary recorded before the test that includes information on usual bedtime, time of arising, napping, and drug use (i.e., caffeine, alcohol, and illicit and licit drugs) is very helpful. Deviations from the subject's habitual sleep behavior should be noted, because sleep time accumulated or lost over the week before an MSLT can significantly affect the result. Some controversy has arisen regarding what defines adequate sleep prior to the MSLT [17, 18]. The critical point is that the sleep prior to the MSLT represents a patient's habitual sleep at home. Central nervous system (CNS)-active drugs, as well as their discontinuation, can alter sleep and REM latencies and therefore should be discontinued sufficiently well in advance of the test. The sleep of the night preceding an MSLT should be documented with a standard nocturnal sleep recording. This nocturnal sleep recording should be scheduled to coincide with the timing and amount of the subject's usual sleep, as revealed in the diary.

The reliability of the MSLT is based on multiple determinations of sleep latency, as the studies discussed in the following sections have shown. Consequently, as indicated in the guidelines, four or five tests of sleep latency at 2-h intervals throughout the day should be conducted [16]. Testing should be initiated from 1.5 to 3 h after the nocturnal sleep period has been terminated, typically at 9:30 or 10:00 AM. The MSLT should be conducted in a sleep-conducive environment that is quiet, dark, and controlled at a comfortable temperature. Any potentially arousing stimuli should be removed from the test area.

Specific Procedures

The following procedures are specified by the guidelines for conducting the MSLT [16]. After arising from nocturnal sleep, the subject should toilet, dress in street clothes, and eat the usual breakfast (avoiding caffeinated beverages). Between the latency tests, the subject should be kept out of the bed and monitored by technical staff to assure that no napping occurs. A small retrospective study of patients being evaluated for excessive daytime sleepiness monitored the patients telemetrically between tests and brief inadvertent napping did occur [19]. But, the naps occurred among the sleepiest patients and did not alter the clinical results appreciably. Preparations before each latency test include smoking cessation 30 min before lights out, bedtime preparation (removing shoes and restrictive clothes such as belts or neckties) at 10 min before lights out, all electrode connections and calibrations completed at 5 min before lights out, and the instructions to relax and fall asleep given 5 s before lights out.

Ending a Test

According to the guidelines, if sleep does not occur, each test is concluded 20 min after lights out [16]. For the clinical version of the MSLT, in which the occurrence of REM sleep is at question, the test is concluded 15 min after the first 30-s epoch of sleep. In a research version of the MSLT, the test is concluded after three consecutive 30-s epochs of stage I sleep or one 30-s epoch of another sleep stage. When the

recording is equivocal, it is safer to allow clearer signs of sleep (i.e., spindles and K-complexes) to emerge rather than to terminate the test prematurely.

Scoring and Interpretation

Criteria for scoring sleep onset differ from criteria for test termination [16]. There has been some confusion in the MSLT literature in this regard. Furthermore, it should be noted that the MSLT sleep latency criteria differ from the typical definition of nocturnal sleep onset (stage II sleep or 10 continuous minutes of sleep) in much of the all-night sleep literature. MSLT sleep latency is the elapsed time in minutes from lights out to the first 30-s epoch scored as sleep. According to the scoring criteria of Rechtschaffen and Kales [20], this implies that 16 s of sleep (i.e., >50 % on a given epoch of the recording) is sufficient to score a sleep onset. REM sleep latency in a clinical test is scored as minutes from sleep onset (as defined earlier) to the first epoch of REM sleep.

Average sleep latency (in minutes) for the four or five latency tests is the parameter typically used to express the level of sleepiness. In some of the clinical literature, the MSLT result is expressed as a median sleep latency or a sleepiness index, which is merely the average latency subtracted from 100 and multiplied by 100 % (and corrected if fewer than five tests are conducted). In population studies, survival analyzes have been used to examine the predictors of sleep onset during the MSLT [21]. The occurrence of REM sleep within 15 min of sleep onset is generally defined as a sleep-onset REM period (SOREMP), and the frequency of such SOREMPs is also tabulated.

Sources of Error

The level of sleepiness (defined as the average sleep latency) observed on the MSLT is affected by the sleep of the previous night and weeks. Any deviation from the subject's habitual sleep schedule (as revealed in the sleep diary) and sleep quality (as seen in the nocturnal sleep recording and the individual's estimate of its consistency with usual sleep) is likely to overestimate or underestimate the usual level of daytime sleepiness. Similarly, the timing of the nocturnal sleep and daytime MSLT assessment relative to the subject's circadian phase is a potential source of error, that is, an issue in studying shift and night workers. Out-of-phase sleep is likely to be disturbed and associated with shorter MSLT latencies. Moreover, sleep latency itself varies as a function of circadian phase.

Sedating or alerting effects of drugs or discontinuation of long-term drug use can also be a source of error in documenting sleepiness. For some patients, a urine drug screen may be necessary to confirm the absence of drugs. A noisy, bright, or stimulating test environment invalidates the MSLT result. In addition, stimulating activity immediately prior to a latency test will increase sleep latency on the subsequent test [22]. Instructions given to the subject at the initiation of the test are also important. Subjects should be aware that they are to close their eyes, lie still, and allow sleep to occur. Excessive tossing and turning are to be avoided. It should be recognized that the instruction "relax and fall asleep" may be emotionally loaded for patients with insomnia. This issue is discussed under the Determinants of Sleepiness section.

Finally, a "last test" effect might be observed (this has not yet been systematically studied). In anticipation of going home for the day, subjects may remain awake for the 20 min of the last latency test. This last test effect could elevate the average sleep latency for the day. It can be avoided by scheduling other non-arousing activities after the last latency test. Patient-feedback sessions with the clinician either before or after the last test can be disruptive to that test and should be avoided.

REM sleep can occur on latency tests of the MSLT as a result of a number of factors. Many drugs suppress REM sleep, and discontinuing them increases the likelihood of SOREMPs on an MSLT. For example, a study of cocaine addicts found an average of 2.8 SOREMPs on five-test MSLTs conducted on the first two days after discontinuing the cocaine use [23]. By days 13 and 14 of discontinuation, the average number had dropped to 0.2 SOREMPs. The circadian-phase timing of the MSLT is also important with respect to the occurrence of REM sleep. REM sleep can occur on early morning latency tests in a person who is a late-morning sleeper. Excessive disturbance of the sleep of the previous night also has the potential to result in REM sleep on early morning latency tests. For example, it has been suggested that apnea patients with highly fragmented sleep may have more SOREMPs than the general population. SOREMPs should be re-evaluated in patients suspected of narcolepsy, but who show apneas in the nocturnal sleep recording. It is rare for sleep restriction the week previous to an MSLT to alter REM occurrence on the MSLT.

Reliability and Validity

Reliability

Several studies of the reliability of the MSLT have been conducted. In healthy controls who maintained consistent sleep–wake schedules, the test–retest reliability of a four-test MSLT was 0.97 over a 4- to 14-month test–retest interval [24]. The test–retest interval ($\sim$6 months vs. >6 months)

and the level of sleepiness (average latency of ~5 min vs. 2 min) did not affect this MSLT reliability. The *number* of latency tests did alter MSLT reliability: The coefficient dropped to 0.85 for three tests and 0.65 for two tests. Another study of patients with insomnia over an interval of 3–90 weeks found a test–retest correlation of 0.65 on a five-test MSLT [25].

There has also been interest in the test–retest reliability of SOREMPs in patients with narcolepsy. The current criteria require two or more SOREMPs out of five possible sleep onsets. In the only one study done to date, 28 of 30 patients had two or more SOREMPs when retested ($K = 0.93$, $P < 0.05$). Of particular interest is the finding that the REM latency on SOREMPs during the initial evaluation was also correlated with that during retesting ($r == 0.64$, $P < 0.02$) [26].

Strength of test–retest reliability for mean sleep latency and SOREMPs on the MSLT is dependent on test–retest scoring reliability. Several studies have demonstrated strong scoring reliability in clinical populations. The intra-rater scoring reliability for mean sleep latency on MSLTs from 200 patients was 0.87, and the inter-rater coefficient was 0.90 [27]. The intra-rater and inter-rater scoring reliabilities for one or more SOREMPs were 0.78 and 0.91, respectively.

Validity

The MSLT measures the speed of falling asleep on repeated tests conducted in a sleep-conducive setting, as described above. The validity of the MSLT as a measure of sleepiness rests on its response characteristics to known determinants of sleepiness, which are discussed in the following section. Additionally, in evaluating its validity, the parametric limits of average sleep latency as measured on the MSLT must be discussed. The first issue is the two anchors of the scale. By scoring definition (i.e., sleep onset is scored in 30 s epochs) one cannot fall asleep in less than 30 s, often referred to as a "floor" effect. Thus, a brief <15 s attention lapse or micro-sleep, which emerges in continuous performance assessments of excessively sleepy individuals [28], is not scored on the MSLT. Similarly, by the standard MSLT procedure, the test is terminated after 20 min of continuous wake. Thus, average sleep latencies can be no longer than 20 min, which has been referred to as a "ceiling" effect. Consequently, alerting drug effects in non-sleepy individuals can be difficult to detect, although as discussed below studies have shown alerting drug effects in volunteers whose basal average sleep latency is within a standard deviation of population norms.

Secondly, the linearity of average sleep latency across the 0.5–20 min range of the MSLT cannot be assumed, an issue that has received little investigation. A study in healthy controls compared the alerting effects of caffeine 0, 75, and 150 mg after 8 h or 5 h time-in-bed (TIB) the previous night [29]. Average sleep latency was increased by 2 min with 75 mg and 4 min with 150 mg regardless of the placebo baseline, which was 6 min and 10 min, respectively, for the 5 and 8 h TIBs. On the other hand, in patients with excessive sleepiness and MSLT scores of <6 min, an increase due to treatment in average sleep latency from 2 to 6 min may be quite different than that from 6 to 10 min.

The validity and clinical utility of the MSLT were recently reviewed [30]. It was concluded that average sleep latency and multiple SOREMPs "do not discriminate well between patients with sleep disorders and normal populations." As the next section indicates, a number of factors cause sleepiness and multiple SOREMPs in both patients and controls. Furthermore, the excessive sleepiness of a given patient may have multiple causes. Thus, the MSLT would not be expected to have good diagnostic specificity. As to sensitivity, the review suggested that most patients with complaints of excessive sleepiness do show short average sleep latencies, although establishing the limits of normal and pathological is complex (see the section on Norms).

Determinants of Daytime Sleepiness

Quantity and Continuity of Sleep

A number of different causes of sleepiness have been identified. The degree of daytime sleepiness is directly related to the amount of nocturnal sleep. Habitual bedtime is predictive of median sleep latency on the MSLT with short bedtimes predictive of short latencies [31]. Partial or total sleep deprivation in normal subjects is followed by increased sleepiness the following day, which can reach pathologic levels [32]. Furthermore, modest sleep deprivation (as little as 1 h per night) accumulates over time to progressively increase daytime sleepiness, again to pathologic levels [33]. In normal young adults, however, increased sleep time extending TIB beyond the usual 7 or 8 h per night produces increased alertness (i.e., reduction in sleepiness) [34]. Daytime sleepiness also relates to the quality and continuity of a previous night's sleep. Sleep in patients with a number of sleep disorders is punctuated by frequent, brief arousals of 3–15 s duration. The arousals typically do not result in awakening, as judged by Rechtschaffen and Kales sleep staging criteria [20] or by behavioral indicators, and the arousals recur in some conditions as often as one to four times per minute. The arousing stimulus differs in various disorders and can be identified in some cases (e.g., apneas, leg movements, and pain). The critical point is that the arousals generally do not result in shorter sleep, but rather in fragmented or discontinuous sleep, and this fragmentation produces daytime sleepiness [35].

Correlational evidence suggests a relationship between sleep fragmentation and daytime sleepiness. Fragmentation, as indexed by the number of brief EEG arousals, number of shifts from other sleep stages to stage 1 sleep or wake, and the percentage of stage 1 sleep, correlates with excessive sleepiness in various patient groups [35]. Fragmentation of the sleep of healthy controls has been produced by inducing 3–15 s arousals with an auditory stimulus. Studies have shown that subjects aroused at various intervals during the night demonstrate the performance decrements and increased sleepiness on the following day [36–39] and that fragmented sleep is non-recuperative [40].

CNS Acting Drugs

CNS-depressant drugs, as might be expected, increase sleepiness. The benzodiazepine hypnotics hasten sleep onset at bedtime and shorten the latency to return to sleep after an awakening during the night, as demonstrated in a number of objective studies [41, 42]. If taken at bedtime, long-acting benzodiazepines continue to shorten sleep latency on the MSLT the next day [43]. Ethanol administered at bedtime and during the day reduces sleep latency as measured by the MSLT [44, 45]. One of the most commonly reported side effects associated with the use of H_1 antihistamines is daytime sleepiness, and studies with objective measurement of sleepiness have confirmed the effect [46, 47].

CNS-stimulant drugs reduce sleepiness. In healthy volunteers, caffeine, 75–300 mg, compared to placebo increased average sleep latency on the MSLT by 2–4 min during a simulated night shift or during the day after 4 h TIB the previous night [48]. Even after a night of "normal" sleep, average sleep latency was increased from 10.7 to 17.8 min by caffeine 400 mg t.i.d. [49]. Methylphenidate 20 mg in healthy volunteers increased average sleep latency after both 8 and 0 h TIBs, and methylphenidate 10 mg similarly increased average sleep latency after both 8 and 4 h TIBs [50, 51]. In patients with narcolepsy, methylphenidate 60 mg increased average sleep latency [52]. Finally, in three studies of patients with excessive sleepiness associated with narcolepsy, sleep apnea, and muscular dystrophy modafinil as well as armodafinil increased average sleep latency [53–55].

Sleep Disorders

Disorders of the CNS are assumed to be another determinant of daytime sleepiness. A deficiency in the hypothalamic hypocretin system is the putative cause of excessive sleepiness in patients with narcolepsy [56]. Another sleep disorder associated with excessive sleepiness and thought to be due to an unknown disorder of the CNS is idiopathic CNS hypersomnolence [57]. In both conditions, excessive sleepiness has been well documented, although the pathophysiology for idiopathic CNS hypersomnolence has not been definitively established.

Several case series have presented MSLT results in patients with complaints of excessive daytime sleepiness [58, 59]. These series have clearly shown that patients experiencing difficulties with excessive sleepiness show MSLT average sleep latencies of 8 min or less, although questions regarding the degree to which their diagnoses were based on the MSLT result have to be raised [26]. As noted above in the validity discussion, short average sleep latencies on the MSLT do not differentiate controls from patients (norms and deviations from the norm in healthy adults are discussed later). On the other hand, multiple SOREMPs are infrequent (i.e., rates of 5–10 % in population-based [60, 61]) in normal individuals, whereas the occurrence of two or more is considered suggestive of narcolepsy [26]. Furthermore, the data have shown that the differences in the severity of some sleep disorders are reflected in different levels of sleepiness on the MSLT. For example, patients with obstructive sleep apnea syndrome who have 40 or more apneas per hour of nocturnal sleep usually have average sleep latencies of 5 min or less, whereas those with fewer apneas per hour (20–40) have average latencies of 5–8 min and sometimes higher.

Among sleep disorders associated with excessive daytime sleepiness, a differentiation in the levels of sleepiness and the frequency of SOREMPs can be seen. Patients with chronic insufficient sleep usually have a more moderate level of sleepiness (5–8 min) than do patients with narcolepsy or severe obstructive sleep apnea syndrome (no more than 5 min) [26]. Among sleep disorders patients, only those with narcolepsy show two or more SOREMPs. Shift work disorder (SWD) patients complain of insomnia, sleepiness, or both and those with specific excessive sleepiness complaints compared to insomnia complaints and shift workers without SWD showed significantly lower MSLT scores that are in the pathologic range [62].

The relationship between nocturnal sleep and daytime sleepiness (i.e., MSLT scores) in insomnia patients appears to be the reverse of that in healthy controls. Insomnia patients do not generally complain of daytime sleepiness as the consequence of their perceived inadequate nocturnal sleep. Often the complaint is fatigue, tiredness, and dysphoria. In fact, some data suggest that insomnia patients may be "hyperalert." Although showing shortened and fragmented nocturnal sleep compared to age-matched, healthy controls, a majority of insomnia patients have unusually high average sleep latencies (i.e., $\geq$ 15 min) [63]. Most think of the MSLT as a measure of sleepiness, but elevations in the MSLT latency, particularly associated with short sleep, may also have clinical significance. A large study of the MSLT in

insomnia found MSLT latencies of ≥15 min (1 min above the population mean) in the majority of insomnia patients, and these high latencies were reliable across eight months [64]. In addition, the high MSLT latencies were associated with elevated urinary norepinephrine levels [65]. An interesting question is what is the MSLT in other disorders of arousal (e.g., generalized anxiety disorder, post-traumatic stress disorder, and mania).

Evaluation of Therapeutic Interventions

A number of studies have shown that the MSLT levels in various sleep disorders are improved after appropriate therapeutic intervention. Two current treatments for obstructive sleep apnea syndrome are continuous positive airway pressure (CPAP) and uvulopalatopharyngoplasty (UPPP). CPAP provides a pneumatic splint of the airway, eliminating the upper airway obstructions and thus the brief arousals that fragment sleep. This improved sleep is associated with normalization of the MSLT [66, 67], and the duration of nightly use predicts the degree of sleepiness on the MSLT [66, 67]. UPPP, a surgical treatment aimed at removing excess upper airway tissue and thus establishing a patent airway, is less consistently successful. In those patients who benefit from the surgery, apneas are reduced, sleep is improved, and the MSLT level of sleepiness is normalized [68]; but in patients whose apnea does not improve, the MSLT result remains at presurgery levels, even though patients perceive a subjective improvement in alertness. This once again indicates the inaccuracy of subjective assessments of sleepiness and alertness.

Modifications of the Multiple Sleep Latency Test

The basic MSLT procedure has been modified in various ways, with no clear improvement. The first such modification was a change in the instructions to "try and stay awake" while lying in bed in a quiet, dark room [69]. The instruction does produce longer sleep latencies, but the change did not increase sensitivity of the MSLT [69]. A subsequent variation, the maintenance of wakefulness test (MWT), instructs the subject to stay awake while seated in a chair [70]. Again, longer sleep latencies result from the change, but improvement in sensitivity over the MSLT has not been documented. Finally, the modified assessment of sleepiness test (MAST) has been offered as an alternative to the MSLT [71]. It consists of three standard sleep latency tests (with a "try to sleep" instruction) alternating with two tests of the subject's ability to remain awake while seated in a chair reading a book. As indicated above, MSLT reliability begins to decline as the number of tests is reduced; this is also found with the MAST. Improved sensitivity has not been established for the MAST.

The intent of the MSLT modifications is to measure a subject's ability to remain awake. It is argued that, clinically, the patient's problem is remaining awake (which adds a certain face validity to the instruction to remain awake). The ability to stay awake is a function of many factors that can momentarily override the underlying physiologic state, including the motivation to remain awake, the presence of competing motives, the environment, and the time of day. Consequently, the ability to maintain wakefulness varies significantly between individuals and hour to hour within an individual. No single laboratory test is generalizable to the variety of circumstances under which wakefulness is to be maintained. The MSLT attempts to remove the confounding factors and measure the underlying physiologic state, thus defining the patient's maximal risk.

Correlations among the standard MSLTs and these modified versions of the MSLT and also with two widely used subjective measures of sleepiness, the ESS and the Sleep-Wake Activity Inventory, are relatively weak [72, 73]. This has led some to argue that there are different types of or dimensions to sleepiness. A more parsimonious and valid explanation, however, is that the methodologies differ in sensitivity. Another more plausible explanation is that rather than different kinds of sleepiness, there are different levels of ability to detect sleepiness, different environmental demands for alertness, and different abilities to counteract sleepiness. Additional constructs have utility and become meaningful when the same variable affects the constructs in different ways. This has not been demonstrated for the various versions of the MSLT.

Multiple Sleep Latency Test Norms

Enough data on the MSLT have now been collected to describe the range of values. The previously described 2005 review of the MSLT calculated a weighted mean across a total of 27 studies that presented control or healthy normal data [14]. Across studies the mean daily sleep latency for studies presenting four-test MSLT data was 10.4 ± 4.3 min and for those studies presenting five-test MSLT data it was 11.6 ± 5.2 min. These studies selected their participants as healthy controls. From a representative US population-based sample of 1648 adults, 157 randomly chosen volunteers with a 68 % response rate underwent a five-test MSLT conducted on the day after an 8.5 h overnight polysomnogram [74]. The population mean daily sleep latency was 11.3 ± 4.5 min. These data, both selected and unselected, suggest that the population mean for a five-test MSLT is about 11 min with an approximate 5 min standard deviation.

Clinically, evidence of pathologic sleepiness is considered to be an average daily sleep latency of 5 min or less. An

average latency of 6–8 min is considered borderline pathologic and latencies of 9 min and greater are considered normal. In the samples of healthy, normal individuals, some have latencies in the pathologic range (not more than 5 min) [75]. These normative data (in a statistical sense) do not help in differentiating controls without complaints from sleep disorders patients with excessive sleepiness. What appears to be the critical difference is that the sleepiness in the controls is not persistent. With adequate sleep over a number of nights, the average daily sleep latency increases, reaching the population norm (see the discussion of sleep time determinants of daytime sleepiness). In the latest American Academy of Sleep Medicine, practice parameters of pathological sleepiness are considered to be a mean sleep latency of 8 min or less; an average sleep latency of 10 min or more is considered normal; latencies between these two means are considered borderline pathologic [76].

A final issue is the degree to which average sleep latency changes as a function of age. In several reports of healthy, non-complaining adults using a four-test MSLT, younger subjects aged 21–35 years had an average daily sleep latency of 10 min, adults aged 30–49 years had an average latency of 11–12 min, and subjects aged 50–59 years had an average latency of 9 min [77]. For the older subjects, nocturnal sleep efficiency was lower than that of the other age groups, and periodic leg movements during sleep were observed in 50 % of the sample. In the 2005 MSLT review, just the opposite age effect on MSLT values was found. With age average, daily sleep latency increased. The difference probably relates to the fact that those participants were selected for their normal nocturnal sleep. Finally, preadolescent children rarely fall asleep on a sleep latency test, and hence the average sleep latencies are close to 20 min [78].

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Maintenance of Wakefulness Test

23

Cathy Goldstein and Ronald Chervin

Introduction

Excessive daytime sleepiness is defined as the inability to maintain alertness during the day, resulting in unintentional intrusion of drowsiness or sleep into the major waking period [1]. Excessive daytime sleepiness can impair performance and increase propensity for accidents [2, 3]. Public safety becomes a concern as almost one-third of survey respondents report sleepiness that interferes with their daily activities at least a few days a month [4]. In fact, 36 % of drivers polled report nodding off or falling asleep while operating a motor vehicle [4]. Historically, sleepiness has been implicated in disasters such as the nuclear accidents at Chernobyl and Three Mile Island, and the Exxon Valdez oil spill. Sleep disorders such as obstructive sleep apnea, narcolepsy, or circadian rhythm alteration may be the source of sleepiness. However, the symptom often results from sleep deprivation and may be associated with certain medical conditions or pharmacotherapy.

Multiple measures exist to quantify excessive daytime sleepiness. The Epworth Sleepiness Scale (ESS) is one of the most commonly used subjective assessments [5–7]. Factors apart from the ability to maintain alertness may impact the score on subjective scales, which therefore must be interpreted carefully [5]. Objective tools to assess sleepiness include the multiple sleep latency test (MSLT) and maintenance of wakefulness test (MWT). The Oxford Sleep Resistance (OSLER) Test and pupillometry also objectively evaluate sleepiness but are not typically used in clinical settings [8, 9]. The MWT, the subject of this chapter, seeks to assess an individual's ability to remain awake in an environment lacking stimulation, whereas the MSLT focuses on an individual's propensity to fall asleep.

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The American Academy of Sleep Medicine (AASM) cites two specific situations in which the MWT may be beneficial [10]. The MWT is indicated to evaluate sleepiness when failure to maintain wakefulness may threaten the safety of the individual or public [10]. For example, the MWT may provide valuable data for patients employed in public transportation or aviation. However, mean sleep latency values that fall into normal ranges by no means guarantee optimal alertness and performance in a real-life environment. Limitations of the MWT will be discussed later in this chapter. The second indication for the MWT is to assess treatment response of patients who receive therapy for excessive daytime sleepiness [10].

History and Development

The need for improved objective testing to assess sleepiness became evident in the late 1970s when inconsistencies were seen in subjective sleepiness ratings among patients whose sleepiness did not result from acute sleep deprivation [11]. For example, some patients with chronic sleepiness described themselves as alert on the Stanford Sleepiness Scale, while they were visibly falling asleep [11]. Although performance testing and pupillography were available, performance testing was confounded by motivation, fatigue, and skill. Furthermore, neither test could reveal sleep-onset rapid eye movement (REM) periods which are the polysomnographic hallmark of narcolepsy [12]. The MSLT was developed in 1977 and recorded electroencephalogram (EEG), electro-oculogram (EOG), and electromyogram (EMG) to determine latency to sleep onset and distinguish sleep stages [13]. As the MSLT became widely used for the assessment of physiological sleep tendency, investigators began to use the test to assess treatment response [5]. Mean sleep latency, as measured by the MSLT, did not demonstrate improvements in line with reduced sleepiness reported by patients [14]. In this setting, the MWT was developed in

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1982 to measure the ability to remain awake as opposed to the MSLT's measure of the propensity to fall asleep [15].

The MWT recorded EEG, EOG, and EMG during five 20-min trials in which subjects remained in a chair in a dark room and were instructed "to stay awake as long as possible" [15]. This instruction was the most important difference from the MSLT, in which subjects were instructed to try to fall asleep. Sleep onset was defined as three consecutive epochs of stage N1 sleep or one epoch of any other sleep stage [15]. If no sleep occurred by minute twenty, the trial was concluded. If the patient did fall asleep prior to minute twenty, the trial was terminated after either 10 min of continuous sleep or when the patient awoke spontaneously after minute twenty (even if sleep duration was less than 10 min) [15]. Of note, in patients with untreated narcolepsy, mean sleep latency increased by threefold when it was derived from the MWT as opposed to the MSLT [15]. This is an extension of the previous work by Hartse, which demonstrated an increase in mean sleep latency on the MSLT simply by changing the instructions from "try to sleep" to "try to stay awake" [16]. These findings highlight the different physiological tendencies measured by the MSLT and MWT.

In the initial investigation by Mitler et al., contrary to the findings in patients with narcolepsy, control subjects displayed no difference between mean sleep latency derived from the MSLT and mean sleep latency derived from the MWT [15]. This may reflect a "ceiling effect" of the 20-min MWT protocol such that many of the control subjects could easily remain awake for the entire 20 min trial [15]. In subsequent studies, extending the MWT trials to 40 min diminished the "ceiling effect" [10, 13, 17, 18]. Both the 20- and 40-min protocols were used prior to the American Academy of Sleep Medicine's (AASM) practice parameter for clinical use of the MSLT and the MWT [10]. Normative data vary based on the protocol used as average mean sleep latencies in healthy subjects are much shorter when derived from the 20-min as opposed to 40-min protocols [18]. The AASM now recommends the 40-min nap trial MWT to standardize the test and minimize the "ceiling effect" [10].

Protocol

The 2005 practice parameters for use of the MSLT and MWT made recommendations on how to conduct the MWT [10]. The MWT should consist of four 40-min trials with the first trial one and a half to three hours after the patient's usual wake time, and at two-hour intervals thereafter. During these trials, central (C3-A2, C4-A1) and occipital (O1-A2, O2-A1) EEG derivations, bilateral EOG, chin EMG, and electrocardiogram should be recorded. The environment should be shielded from external light; however, a light should be situated behind the patient's head such that an illuminance of 0.10–0.13 lx is achieved at the cornea. The patient should be seated in bed, in a semi-recumbent position, with a bolster pillow to support the head and back. Room temperature may be adjusted for the patient's comfort. A light meal should be offered one hour before the first trial and immediately after the noontime trial. Biocalibrations prior to each trial should include eye opening, eye closure, lateral eye movement, blinking, and teeth clenching. The following instructions should be given to the patient at the start of each trial: "Please sit still and remain awake as long as possible. Look directly ahead of you, and do not look directly at the light." Slapping the face, singing, and other extraordinary measures to promote wakefulness are not permitted. If sleep occurs, the trial is terminated after either three consecutive epochs of stage one sleep or one epoch of any other sleep stage. If no sleep occurs, the trial is concluded after 40 min. The technician should document the following parameters for each trial: start and stop times, sleep latency, total sleep time, and sleep stages recorded. Mean sleep latency should be calculated. Recording sleep logs or conducting an overnight polysomnogram prior to the MWT is at the discretion of the ordering sleep physician based on the clinical scenario. In addition, the clinician may make his/her own determination in regard to the use of medications, caffeine, and tobacco prior to and during the MWT. Drug screening on the morning of the test should be considered [10]. Table 23.1 highlights the differences between the MWT and MSLT protocols.

Interpretation

Mean sleep latency is determined from the MWT by calculating the average sleep-onset latency from all four trials. Like the MSLT and overnight polysomnogram, sleep onset is defined as the start of the first thirty-second epoch scored as sleep [19]. Normative data guide interpretation of mean sleep latency. In 64 healthy controls, when defining sleep onset as at least ten seconds of sleep or the first epoch scored as sleep, mean sleep latency was 32.6 $\pm$ 9.9 min and 42 % of subjects remained awake for the entirety of all four 40-min trials of the MWT [20]. When a more stringent definition of sleep onset was used (three continuous epochs of N1 sleep, or one epoch of another sleep stage), mean sleep latency was 35.2 $\pm$ 7.9 min and 59 % of subjects remained awake for the entirety of all four trials [20]. Additionally, 97.5 % of normal subjects had a mean sleep latency $\geq$ 8 min [10]. Based on these data and a subsequent investigation in normal controls, the AASM recommends interpretation of mean sleep latency less than 8 min as abnormal and mean sleep latency between 8 and 40 min as a

Table 23.1 Protocols for conducting the maintenance of wakefulness test and multiple sleep latency test

	Maintenance of wakefulness test	Multiple sleep latency test
Overnight polysomnogram required prior to test	No	Yes
Recording montage	EEG (C3-A2,C4-A1,01-A2,02-A1), EOG (left and right), EMG (submetal), EKG	EEG (C3-A2,C4-A1,01-A2,02-A1), EOG (left and right), EMG (submetal), EKG
Environment	Seated in bed in a dimly lit room	Lying down in a dark quiet room
Patient instructions	Please sit still and remain awake for as long as possible. Look directly ahead of you, and do not look directly at the light	Please lie quietly, assume a comfortable position, keep your eyes closed, and try to go to sleep
Nap trials	4	5
Sleep-onset latency	The start of the first epoch of sleep	The start of the first epoch of sleep
Trial terminated	40 min if no sleep occurs or after 3 consecutive epochs of N1 sleep or 1 epoch of any other sleep stage	20 min if no sleep occurs or 15 min after the first epoch of sleep
Mean sleep latency of controls[a]	30.4 ± 11.2 min	11.6 ± 5.2 min

[a]Pooled from literature describing normative data. Adapted from Littner et al. [10]

value of uncertain significance [21, 10]. Remaining awake for the full 40 min on each trial provides the greatest objective evidence to support an individual's ability to maintain alertness [10].

Mean sleep latency may be affected by multiple factors. A significant, positive correlation between age and mean sleep latency is seen with the 40-min but not 20-min MWT protocol. This suggests that the ability to remain awake after the first 20 min of an MWT trial may be age-dependent [20]. Furthermore, medications, caffeine, prior total sleep time, sleep fragmentation, circadian phase, anxiety, depression, and motivation have all been shown to affect MWT results [22–35]. Even playing background music can increase mean sleep latency on the MWT [36]. Contrary to what may be expected, napping between MWT trials did not significantly impact the results in one investigation [37].

Special Populations

At this time, the MWT is not recommended in the pediatric population secondary to lack of data in this group including undefined normative values. However, a recent study did demonstrate that the MWT may be beneficial in assessing treatment responses of pediatric patients with narcolepsy [38]. The MWT has been evaluated in other specific patient populations, for example, patients with retinitis pigmentosa, myotonic dystrophy, and more extensively individuals with Parkinson's disease [22, 39, 40, 41]. The MWT may be a valuable assessment tool in patients with Parkinson's disease, particularly to assess the ability to maintain alertness in the setting of dopaminergic medication use [22, 41].

Utility for Specific Indications

The MWT is recommended as a tool to assess treatment response in individuals receiving therapy for hypersomnolence. The magnitude of change that represents adequate treatment is not defined, but the direction of change may be valuable when combined with clinical assessment [10]. Studies of patients with narcolepsy, idiopathic hypersomnia, obstructive sleep apnea, and shift work disorder have shown varying degrees of increased mean sleep latency on the MWT after treatment.

Additionally, the MWT may be used to evaluate individuals in whom impaired alertness could create risk to personal or public safety [10]. Studies have used driving simulators to investigate the relationship of mean sleep latency with performance, and their results are as follows. Subjects with disorders that cause hypersomnolence demonstrate significant negative correlations between mean sleep latency and the following measures of driving impairment: lane-position variability, crash frequency, inappropriate line crossing, and standard deviation from the center of the road [42–44]. Some studies have shown the greatest driving impairments in those with mean sleep latencies below 19 min [42]. Conversely, untreated obstructive sleep apnea patients with mean sleep latencies above 30 minutes perform similar to healthy controls on measures of vehicle control and vigilance [43]. Notably, in one investigation, driving simulator performance showed significant improvements when obstructive sleep apnea was treated with continuous positive airway pressure (CPAP) [45]. However, this did not correlate with increases in mean sleep latency [45]. Furthermore, in a group of subjects

undergoing partial sleep loss, only those who were also impaired by alcohol demonstrated a significant inverse correlation between simulator car crashes and mean sleep latency on the MWT [46]. Mean sleep latencies derived from the MWT show correlations with simulated driving performance that are superior to the MSLT [43, 44].

Significant limitations arise in evaluation of sleepiness in real drivers on actual roadways. A study that did examine actual highway driving showed a significant increase in inappropriate line crossings among very sleepy (mean sleep latency 0–19 min) and sleepy (mean sleep latency 20–33 min) untreated obstructive sleep apnea patients, as compared to alert patients and controls (mean sleep latency > 33 min) (Fig. 23.1, [47]. However, line crossings may not necessarily translate directly to automobile crashes. Another study found that drivers who had been in a motor vehicle accident, in comparison with those who had not, did not show significantly different MWT results [48]. Due to the paucity of data that address real-life fitness for operating a motor vehicle, the MWT is not generally required for commercial vehicle drivers with sleep disorders [49]. Furthermore, in contrast to the MWT findings on simulated driving performance, mean sleep latency derived from the MSLT has been associated with motor vehicle accidents, as demonstrated by an increased risk of car crashes in individuals with mean sleep latencies less than or equal to 5 min on MSLT [50].

Data on performance in aviators are scarce, but two pilots with hypersomnolence and short sleep latencies on MSLTs were successfully returned to duty after they demonstrated the ability to stay awake on all naps of the MWT [51]. Currently, the Federal Aviation Administration (FAA) does employ the MWT to ensure alertness in pilots with obstructive sleep apnea (www.faa.gov).

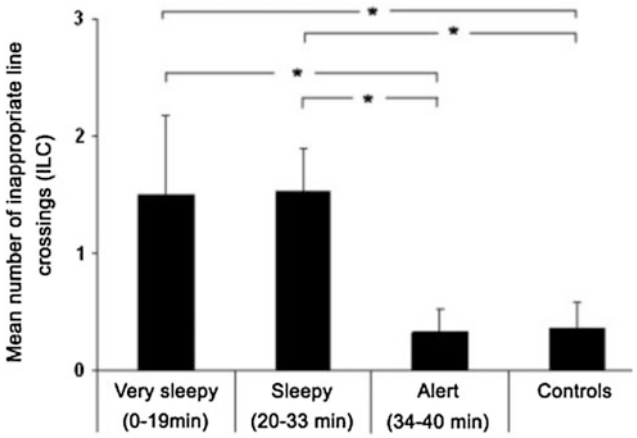

Fig. 23.1 Mean number of inappropriate line crossings (ILCs) during real driving (mean ± standard error) in the three mean sleep latency groups on the maintenance of wakefulness test (MWT) and in healthy control subjects. *$p < 0.05$. Reprinted from Philip et al. [47]. Copyright 2008 American Neurological Association. Reprinted with permission

Limitations

In addition to limitations in assessment of safety and performance, the MWT has other shortcomings. Compared to MSLT, less validity data exist for the MWT and clinicians tend to have less experience with this test. Although highly sensitive to sleepiness produced by acute, severe sleep deprivation, the linear relationship of mean sleep latency with sleep loss is attenuated in the setting of less severe, more chronic sleep deprivation [24]. Also, microsleep episodes, which are associated with performance decrements, are not typically reported in the interpretation of the MWT [52]. The MWT is not designed to aid in the diagnosis of narcolepsy. Sleep-onset REM periods are significantly decreased on the MWT compared to the MSLT, and use of the MWT in patients with suspected narcolepsy would lead to false-negative results [53]. The range of mean sleep latencies in the category of unclear clinical significance (between 8 and 40 min) is large, with the potential for overlap of normal individuals, those with sleep disorders, and patients with treated and untreated conditions. Furthermore, the ability to remain awake for all trials on the MWT may not reflect alertness in real-life situations where confounding factors such as prior sleep duration and circadian phase contribute to sleepiness, and motivation to stay awake may differ from that experienced during a laboratory test. For the MWT, as with the MSLT, the lack of prospective data to show prediction of future crashes and morbidity remains a significant limitation and area for further research.

Summary

The maintenance of wakefulness test is a tool designed to assess the ability to sustain alertness rather than the tendency to the fall asleep. This test may be beneficial to evaluate response to therapy in individuals with hypersomnolence. In addition, the maintenance of wakefulness test may provide valuable information when performed in patients whose occupations require constant alertness to ensure safety. However, like all diagnostic modalities, careful clinical correlation is required with interpretation of this test as results that fall into normal ranges may not guarantee alertness under other conditions.

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Scoring of Normal Sleep and Arousals

24

Raman K. Malhotra and Alon Y. Avidan

Abbreviations

LOC	Left electrooculogram
ROC	Right electrooculogram
Chin	Chin electromyogram
EKG	Electrocardiogram
LAT	Left anterior tibialis surface electromyogram
RAT	Right anterior tibialis surface electromyogram
SNORE	Snore sensor
N/O	Nasal and oral airflow
THOR	Thoracic respiratory effort
ABD	Abdominal respiratory effort
NPRE	Nasal pressure recording effort
SpO2	Pulse oximetry

Introduction to Sleep Stage Scoring

Continuous recordings of electroencephalographic (EEG), electrooculographic (EOG), and electromyographic (EMG) activity are required to classify the different stages of sleep and wakefulness. The original Rechtschaffen and Kales sleep scoring manual of 1968 [1], commonly known as the "R and K" rules, was used until 2007 at which point the American Academy of Sleep Medicine (AASM) created a new scoring manual known as the *AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications* [2]. Each scoring rule and subsequent revision is formed by consensus based on extensive literature review and analysis. At this time, the AASM scoring manual is updated continuously and is accessed online in its most updated version [3]. The *Rechtschaffen and Kales* method divides sleep into five distinct stages: non-rapid eye movement (non-REM) stages 1, 2, 3, and 4 and stage REM sleep. The most recent AASM scoring manual recognizes four sleep stages: stage N1 (formerly stage 1 sleep), stage N2 (formerly stage 2 sleep), stage N3 (formerly stages 3 and 4 sleep), and stage R sleep (formerly stage REM sleep). Sleep stages do not exist as single distinct entities, but should be viewed as gradual transition of a waveform. The scoring rules were devised to allow for standardization between sleep laboratories and offer a conceptual simplicity rather than a rigid structure.

The original version of this chapter was revised: For detailed information please see Erratum. The erratum to this chapter is available at https://doi.org/10.1007/978-1-4939-6578-6_59

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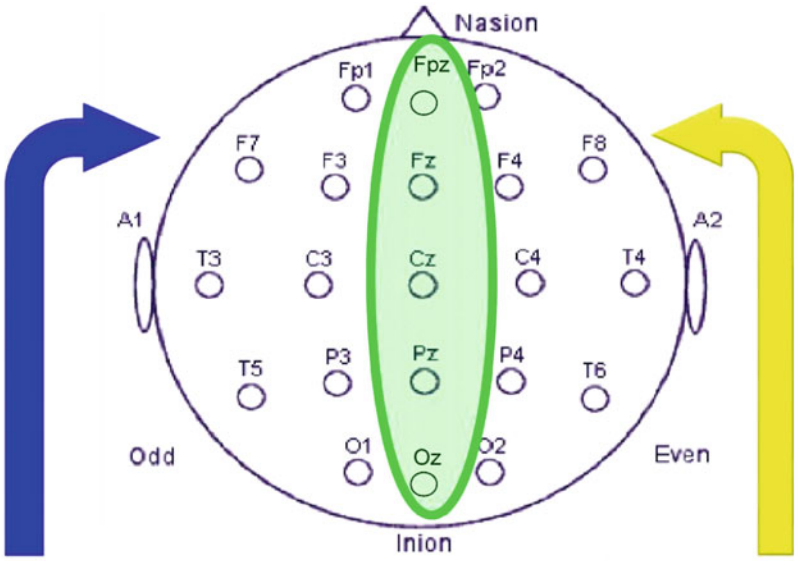


Brain Area	Left	Midline	Right
Frontal Pole	Fp1	Fpz	Fp2
Frontal	F3	Fz	F4
Inferior Frontal	F7		F8
Anterior Temporal	T1 or F9		T2 or F10
Mid-Temporal	T3		T4
Posterior Temporal	T5		T6
Central	C3	Cz	C4
Parietal	P3	Pz	P4
Occipital	O1	(Oz)	O2

Fig. 24.1 10–20 electrode placement. The 10–20 system assigns a number to further specify the location in the left or right hemisphere. Location "z" is used to indicate that the location of the electrode is in the midline or "zero" meaning that it is neither left hemisphere nor right hemisphere. The electrode placed at Cz is said to be the "Vertex" meaning that it is the mid central or at the top of the head. Fpz and Oz are used in achieving the other measurements and can be used as additional electrode placements for localization of activity. Fpz may be used as the location of the COM (common) or ground electrode placement. Copyrighted to Alon Y. Avidan, MD, MPH

Technical Specifications

Electroencephalogram (EEG) is recorded using the International 10–20 recording system as depicted in Fig. 24.1. The recommended derivations are F4-M1, C4-M1, and O2-M1 as demonstrated in Fig. 24.2. Backup electrodes should be placed at F3, C3, and O1 (all referenced to M2). An alternative acceptable derivation is Fz-Cz, Cz-Oz, and C4-M1 with backup electrodes at Fpz, C3, and O1. EEG recording criterion includes a minimum paper speed of 10 mm/sec. One page equates 30 s and is defined as one epoch. Time constant (TC) is 0.4 s (or low frequency filter of 0.3 Hz). Electrode impedances should not exceed 5K Ω.

The electrooculogram (EOG) signals measure changes in the electric potential of the positive anterior aspect of the eye, the cornea, relative to the negative posterior aspect, the retina. The "Recommended" EOG derivations are E1-M2 and E2-M2 with E1 placed 1 cm below the outer canthus of the left eye and E2 placed 1 cm above the outer canthus of the right eye. An alternative "Acceptable" derivation is placing E1 1 cm below and lateral to the outer canthus of the left eye and E2 1 cm above and lateral the outer canthus of the right eye as demonstrated in Fig. 24.3. During any eye movement, the cornea moves toward one electrode, while the retina moves away. When the eye is not moving, the change in relative position is zero, and the eye leads do not record a signal. Slow rolling eye movements (SREM) occur during drowsiness and light sleep and are recorded as long gentle waves with the initial deflection lasting longer than 500 ms (Table 24.1). In contrast, rapid jerking eye

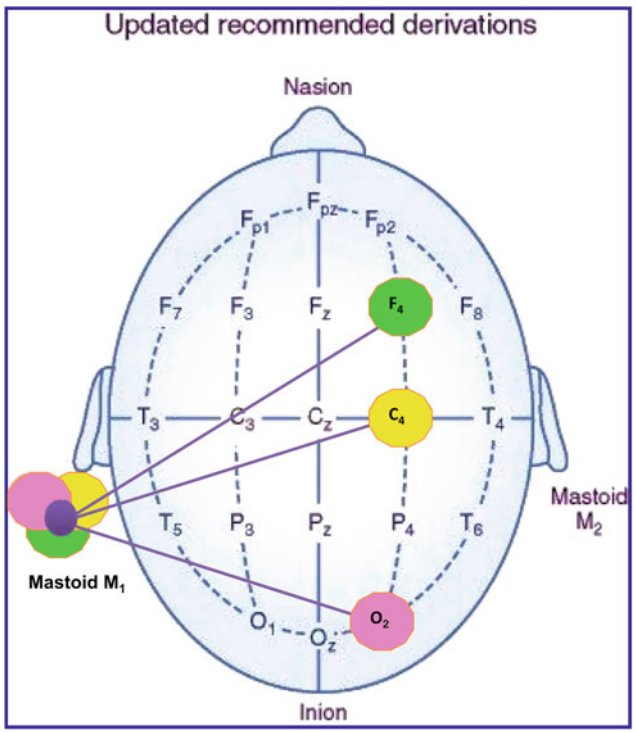


Fig. 24.2 Updated AASM-recommended derivations for recording the EEG. Electrode locations as recommended in 2007 by the American Academy of Sleep Medicine. Key: *Fp* frontopolar or prefrontal, *F* frontal, *C* central, *T* temporal, *P* parietal, *O* occipital, *A* ear or mastoid, *F3* left mid-frontal, *P3* left parietal, *T4* right temporal, *A1* right ear, and *Cz* vertex. Modified from Kryger [8]

movements are represented by sharply contoured fast waves with the initial deflection lasting less than 500 ms. Blinking of the eyes produces rapid vertical movements.

The electromyographic (EMG) signals are muscle twitch potentials, which are used in sleep studies to distinguish between sleep stages based on the fact that electromyographic activity progressively diminishes during deepening stages of sleep. Specifically, during rapid eye movement (REM) sleep, muscle activity is minimal. There are occasional intrusions of EMG artifact into the record, some of which may be expressed as yawns, swallows, and teeth grinding (bruxism). Three electrodes are placed to record chin EMG: (1) midline 1 cm above the inferior edge of the mandible, (2) 2 cm below the inferior edge of the mandible and 2 cm right of midline, and (3) 2 cm below the mandible and 2 cm left of the midline. The standard chin EMG derivation utilizes one electrode below the mandible referred to the electrode above the mandible.

Scoring Stages of Sleep

Epochs of polysomnography are broken into 30-second sequential epochs with a sleep stage assigned to each epoch based on scoring rules that will be discussed below. If two or more stages coexist during a single epoch, the stage occupying the greatest portion of the epoch will be assigned. When scoring a record for stage of sleep, it may be helpful to scroll through the entire record quickly to evaluate the quality of the recording. He or she should observe the specific shape of the features that represent the stages in that particular individual and to gain an overall picture of the cycles for that record. Specifically observe for sleep spindles, K complexes, slow waves, and rapid eye movements.

EEG cortical activity can be characterized by their specific frequencies. Frequency is defined as the number of times a repetitive wave recurs in a specific time period (typically one second). Frequency is noted as cycles per second (i.e., Hertz, Hz). EEG activity has been divided into four bands based on the frequency and amplitude of the waveform and are assigned Greek letters (alpha, beta, theta, and delta) and is summarized in Tables 24.1 and 24.2.

The following convention is used to define EEG frequencies as per the AASM scoring manual:

- Beta is greater than 13 Hz;
- Alpha is between 8 and 13 Hz;
- Theta is between 4 and less than 8 Hz; and
- Delta is the slowest activity at less than 4 Hz.

Beta activity originates from the frontal and central regions and can be present during wakefulness or drowsiness. Beta activity typically declines during deeper stages of sleep but may reemerge during REM sleep. Use of sedative hypnotics (such as benzodiazepines) may cause enhanced beta activity (termed pseudo-spindles or drug-spindles) as depicted in Fig. 24.4, with frequencies faster than true bona fide physiological spindle activity (Table 24.3).

Alpha activity, also known as the posterior dominant rhythm, originates in the parieto-occipital regions bilaterally and is normally symmetric over both cerebral hemispheres. The alpha rhythm is noted during quiet alertness with the eyes closed and disappears or decreases in amplitude when the eyes open (reactivity) (Fig. 24.5).

Stage Wake

Typically, the first several minutes of recording will consist of wake (W) stage. Stage W is scored when more than 50 % of the epoch has scorable alpha EEG activity over the occipital region. Submental EMG is relatively high tone and will reflect the high-amplitude muscle contractions and movement artifacts. The EOG channels will show eye blinks (0.5–2 Hz) (Fig. 24.6) or possibly reading eye movements if the eyes are open (Fig. 24.7). As the patient becomes drowsy, with the eyes closed, the EEG will show predominant alpha activity, while the EMG activity will become less prominent. The EOG channels may show slow rolling eye movements.

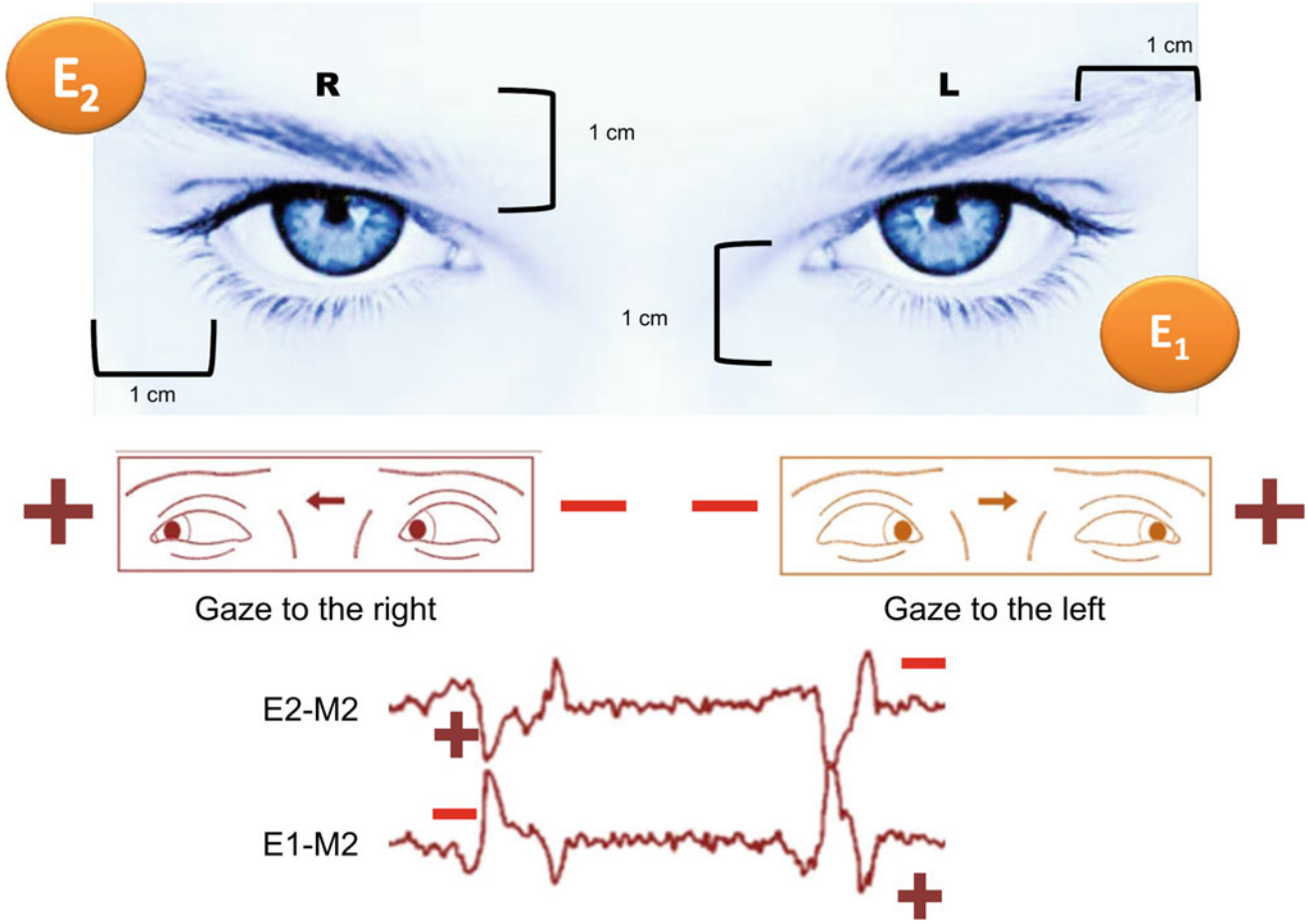
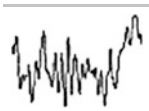
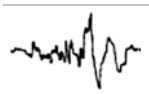


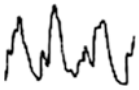
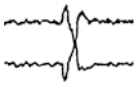
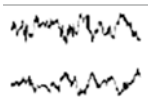
Fig. 24.3 Derivation of eye movements. *E1* Left outer canthus eye electrode (previously LOC). *E2* Right outer canthus eye electrode (previously ROC). *M1* Left mastoid electrode location. M2 Right mastoid electrode location. The eye can be envisioned like a battery with the positive pole at the cornea and the negative pole at the retina. The EOG consists of a bipolar linkage from the ROC electrode 1 cm lateral and 1 cm superior to one outer canthus to the LOC electrode 1 cm lateral and 1 cm inferior to the other outer canthus. The electrode toward which the eyes move becomes relatively positive, the other relatively negative. As the eyes move during sleep, they produce corresponding changes in the electrical field producing a correlating potential change in the EEG electrodes. This can be verified by noting corresponding movements in the EOG channels. From: Avidan and Barkoukis [9]. Copyrighted to Alon Y. Avidan, MD, MPH

Table 24.1 Key brain wave frequencies and landmarks used in sleep staging

Sample	Label	Definition
	Alpha activity	8–13 Hz rhythm, usually most prominent in occipital leads. Thought to be generated by cortex, possibly via dipole located in layers 4 and 5. Used as a marker for relaxed wakefulness and CNS arousals
	Theta activity	4–8 Hz waves, typically prominent in central and temporal leads. Sawtooth activity is a unique variant of theta activity (containing waveforms with a notched or *sawtooth-shaped* appearance) frequently seen during REM sleep
	Vertex sharp waves	Sharply contoured, negative-going bursts that stand out from the background activity and appear most often in central leads placed near the midline
	Sleep spindle	A phasic burst of 11–16 Hz activity, prominent in central scalp leads; typically last for 0.5–1.5 s. Spindles are a scalp representation of thalamocortical discharges; the name derives from their shape (which is spindle-like)
	K complex	Recently redefined in the AASM manual as an EEG event consisting of a well-delineated negative sharp wave immediately followed by a positive component standing out from the background EEG with total duration $\geq$0.5 s, usually maximal in amplitude over the frontal regions

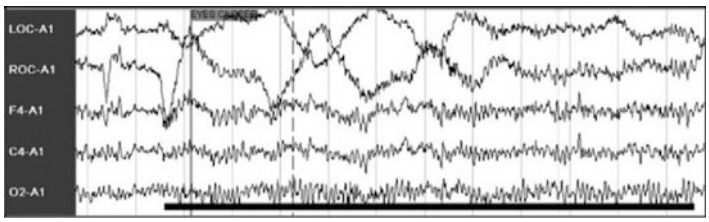
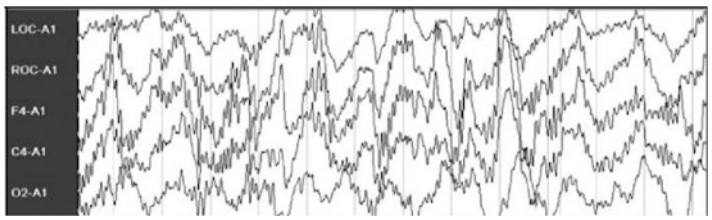
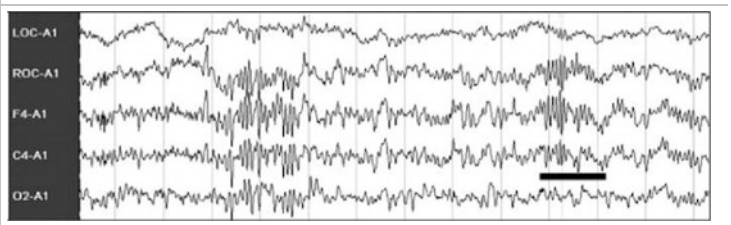
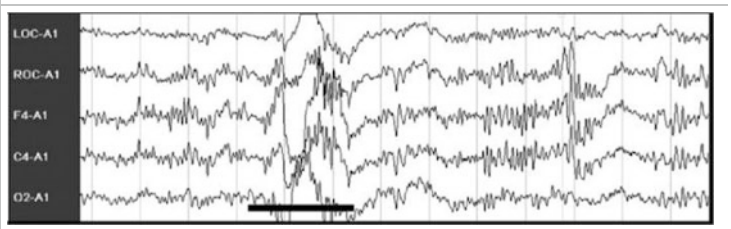
(continued)

Table 24.1 (continued)

Sample	Label	Definition
	Slow waves	High-amplitude ($\geq$75 μV) and low-frequency ($\leq$2 Hz) variants of delta (1–4 Hz) activity. Slow waves are the defining characteristics of stage N3 sleep
	REM	Rapid eye movements are conjugate saccades occurring during REM sleep correlated with the dreamer's attempt to look at the dream sensorium. They are sharply peaked with an initial deflection usually <1/2 s in duration
	SEM	Slow eye movements are conjugate, usually rhythmic, rolling eye movements with an initial deflection usually $\geq$1/2 s in duration

Modified from Kryger [8]

Table 24.2 Definitions and examples of sleep figures encountered on an EEG

EEG rhythm	Characteristics	Best seen	Examples
Posterior dominant rhythm (PDR)	8–13 Hz	Occipital	
Slow waves	0.5–2 Hz; amplitude $\geq$75 μV	Frontal	
Spindle	11–16 Hz; duration $\geq$0.5 s 8–12 Hz	Central	
K complex	Diphasic; large amplitude, duration $\geq$0.5 s	Frontal	

Please note that although all slow waves are in the delta frequency range, not all delta waves are slow waves

The patient may enter stage N1 sleep briefly for one or two epochs and then return to stage W. From stage W, patients typically proceed to stage N1, but infrequently they may enter REM sleep or stage N2 sleep directly, if the pressure to do so is high (reflecting a state of pathological sleep deprivation).

Stage N1 Sleep

Stage N1 sleep is scored if the alpha rhythm is attenuated or replaced by low-amplitude, mixed-frequency activity (4–7 Hz) for more than half of the epoch (Fig. 24.8). Some individuals

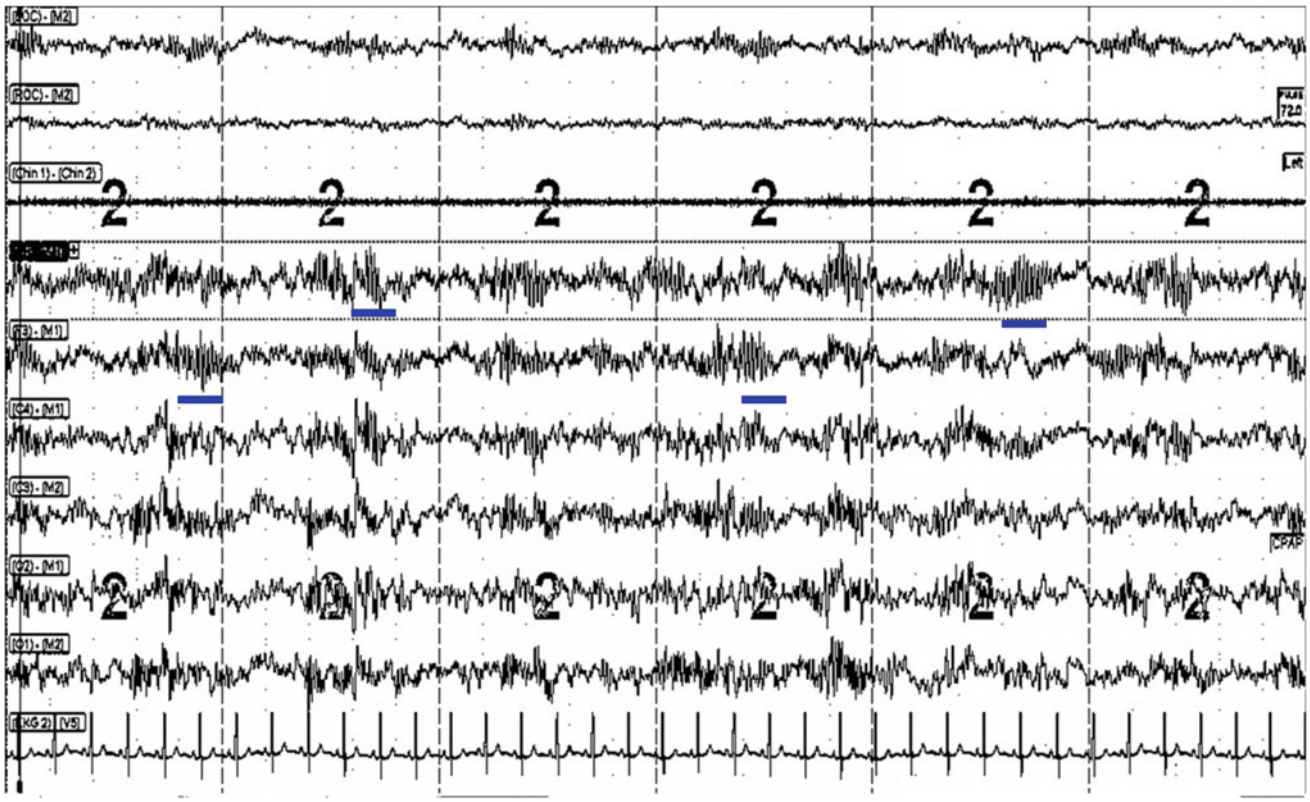


Fig. 24.4 This 30 s PSG epoch in a 45-year-old woman who takes nightly benzodiazepines. "Psuedospindles," or enhanced beta activity (identified by the *blue bars*), are noted during NREM sleep due to use of benzodiazepines

Table-24.3 Major differences between Rechtschafffen and Kales manual (R and K) and the AASM scoring manual from 2007

Differences	R and K manual	AASM scoring manual
EEG Electrodes	Score sleep stages using central (C3 and C4) leads	Score using frontal, central, and occipital leads
Major body movements	Movement time can be scored if more than half the epoch is obscured	No movement time staging exists
Slow wave sleep	Consists of both stage 3 and stage 4 sleep with delta wave amplitude measured using central leads	Only recognizes stage N3 sleep with delta wave amplitude measured using frontal leads
Terminology of stages	Stage 1, stage 2, stage 3, stage 4, and stage REM sleep	Stage N1, stage N2, stage N3, and stage R sleep
Reference electrode	Left and right ear or mastoid termed A1 or A2	Left and right mastoid termed M1 or M2
Scoring stage 2 (or N2) sleep	Three minute rule that states if greater than 3 min pass in between spindles or K complexes, then score stage 1 sleep	No 3 min rule exists

(approximately 10 %) do not generate an alpha rhythm upon eye closure and have similar occipital EEG activity during eye opening or closure. In these individuals, stage N1 is scored if there are vertex waves, slow rolling eye movements, or EEG activity in the range of 4–7 Hz (Fig. 24.9) with slowing of background frequencies by greater than or equal to 1 Hz from stage W. Vertex sharp waves (V waves) are sharply contoured waves lasting less than 500 ms that are maximal over the central regions (Fig. 24.9). Vertex sharp waves may be present but are not required to score stage N1. The EMG shows less activity than in wake, but the transition is gradual and of little assistance in scoring. In patients who have a background rhythm that is theta frequency due to a pathological state (encephalopathy, dementia, etc.), stage N1 sleep can be scored if there is further slowing of the background rhythm by greater than 1 Hz.

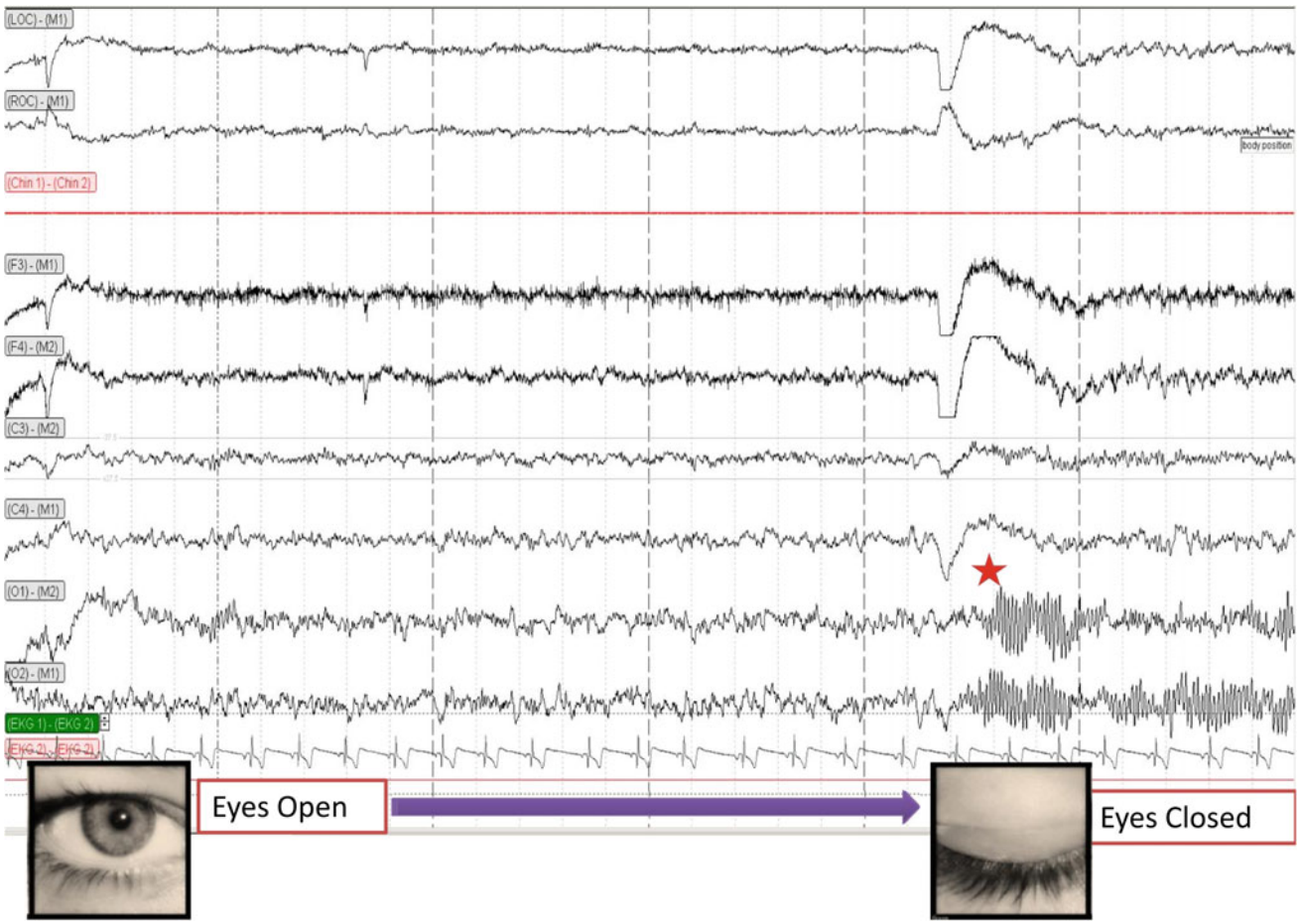


Fig. 24.5 This 30 s polysomnogram epoch showing the appearance of background alpha activity in the occipital leads when the patient is in quiet alertness and closes their eyes (*red star*). This rhythm is not apparent when the subject's eyes are open during the first portion of the epoch. Copyrighted to Raman K. Malhotra, MD

During stage N1 sleep, breathing becomes shallow, heart rate becomes regular, blood pressure falls, and the patient exhibits little or no body movement. The sleeper is still easily awakened and might even deny having slept. Many may have sleep starts during this stage of sleep.

Stage N2 Sleep

Stage N2 NREM sleep (Fig. 24.10) may also be termed *sigma, spindle*, or *intermediate sleep* and is classically demarcated by sleep spindles (red stars) along with K complexes (blue star). Stage N2 is an intermediate stage of sleep, but it also accounts for the bulk of a typical polysomnographic recording. It follows stage N1 sleep and initially lasts about 20 min. Stage N2 can begin to be scored if one or more K complexes (unassociated with arousal) or sleep spindle is noted during the first half of the epoch or the last half of the previous epoch (Fig. 24.11). K complexes are biphasic in morphology consisting of negative (upward deflection) sharp waves followed by a slower positive (downward deflection) component with a total duration of greater than 500 ms (Fig. 24.12). They characteristically stand out from the rest of the background and are seen maximal over the frontal leads, though no minimum amplitude criterion exists for K complexes [4]. K complexes may occur with or without stimuli such as a sudden sound and in this respect may represent a form of cortical evoked potential in a brain still minimally responsive to external stimuli. K complexes may be labeled as spontaneous if they arise from an unknown reason, indicating that their origin is of an endogenous brain activity. They may be labeled as evoked if they are clearly triggered by an external stimulus such as sound or noise. K-alpha complexes may be triggered by other entities such as periodic limb movements in sleep, an apneic event, or in association with an arousal (alpha EEG activity) immediately following the complex.

Sleep spindles are generated in the midline thalamic nuclei (reticular thalamic nucleus) and represent an inhibitory activity. Sleep spindles are characterized by 12–14 Hz

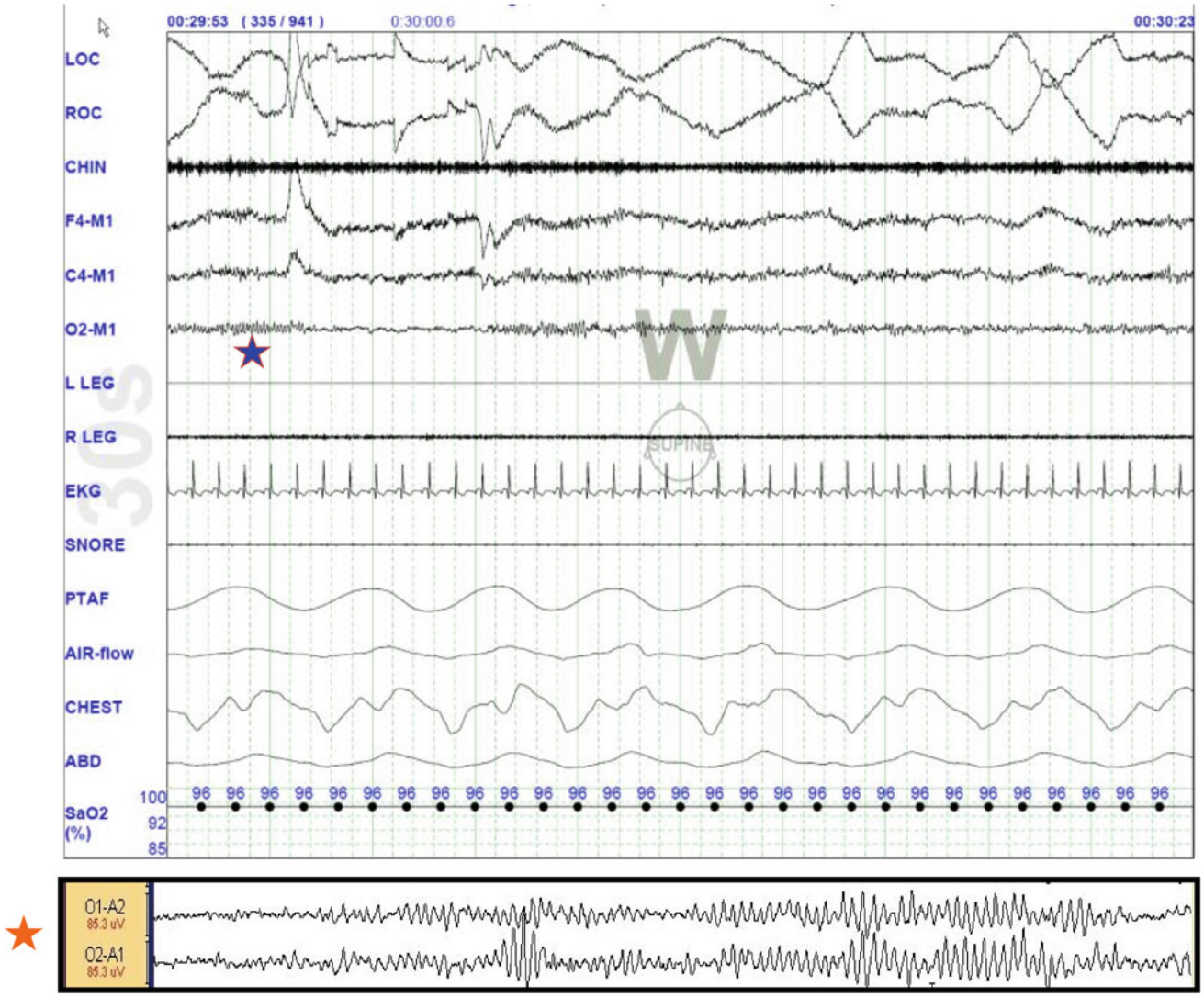


Fig. 24.6 This 30 s polysomnogram epoch demonstrates stage W with alpha rhythm noted in the occipital leads (*blue star*), increased chin EMG tone (CHIN electrode), and rapid eye movements of wakefulness (LOC, ROC). The lower panel demonstrates the prominent alpha activity (*orange star*) primarily seen in the occipital leads. Copyrighted to Alon Y. Avidan, MD, MPH

sinusoidal EEG activity in the central vertex region and must persist for at least 0.5 s (i.e., 6–7 small waves in 0.5 s), but rarely longer than 1 s (Figs. 24.13 and 24.14). Sleep spindles possess a high degree of synchrony and symmetry between the two hemispheres in patients older than one year of age. Although classically described as spindle shaped, they may be polymorphic and may attach as a tail to a K complex. As noted earlier, central nervous system (CNS) depressant drugs (such as benzodiazepines) often increase the frequency of the spindle activity leading to the presence of "pseudo-spindles" as shown in Fig. 24.4.

No specific criteria exist for EOG and EMG in this stage. Submental EMG activity is tonically low. There is typically no eye movement activity, though in some individuals [(i.e., patients on selective serotonin reuptake inhibitors (SSRI's)] slow eye movements may persist in this stage of sleep. Stage N2 is characterized by predominant theta activity (4–7 Hz EEG activity) and occasional quick bursts of faster activity. The EEG may show minimal alpha activity. Delta is only allowed to occur for less than 20 % of the epoch. The threshold triggering stage N3 sleep scoring is reached if 20 % of the epoch is comprised of delta activity.

Once meeting the criteria for N2 sleep, epochs can be continuously scored as stage N2 (even in the absence of K complexes or sleep spindles) assuming that there is not an arousal and the EEG continues to demonstrate low-amplitude, mixed-frequency activity (Fig. 24.15). For example, following an arousal from stage N2 sleep, an epoch would be scored stage N1 until a K complex or sleep spindle occurs again. Stage N2 scoring may end if the epoch meets criteria for wakefulness, stage N3, or stage R, or contains an arousal or a major body movement followed by slow eye movements.

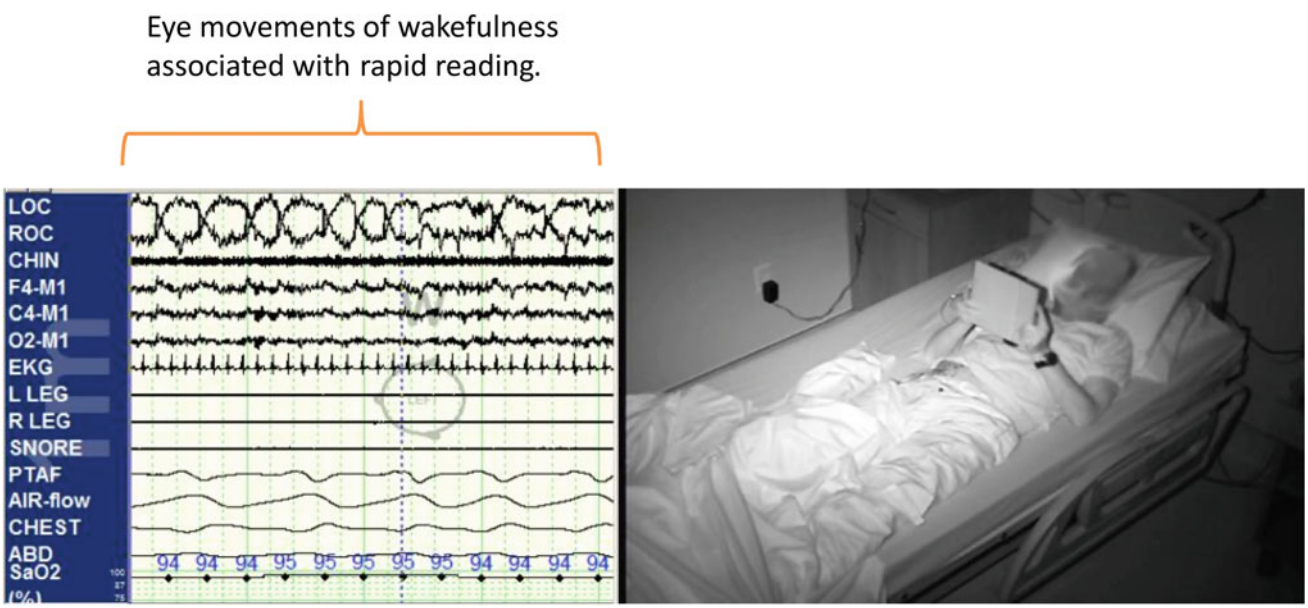


Fig. 24.7 This 60 s polysomnography epoch demonstrates stage W with alpha rhythm noted in the occipital leads, increased chin EMG tone (CHIN electrode), eye movements of wakefulness associated with rapid reading. Copyrighted to Alon Y. Avidan, MD, MPH

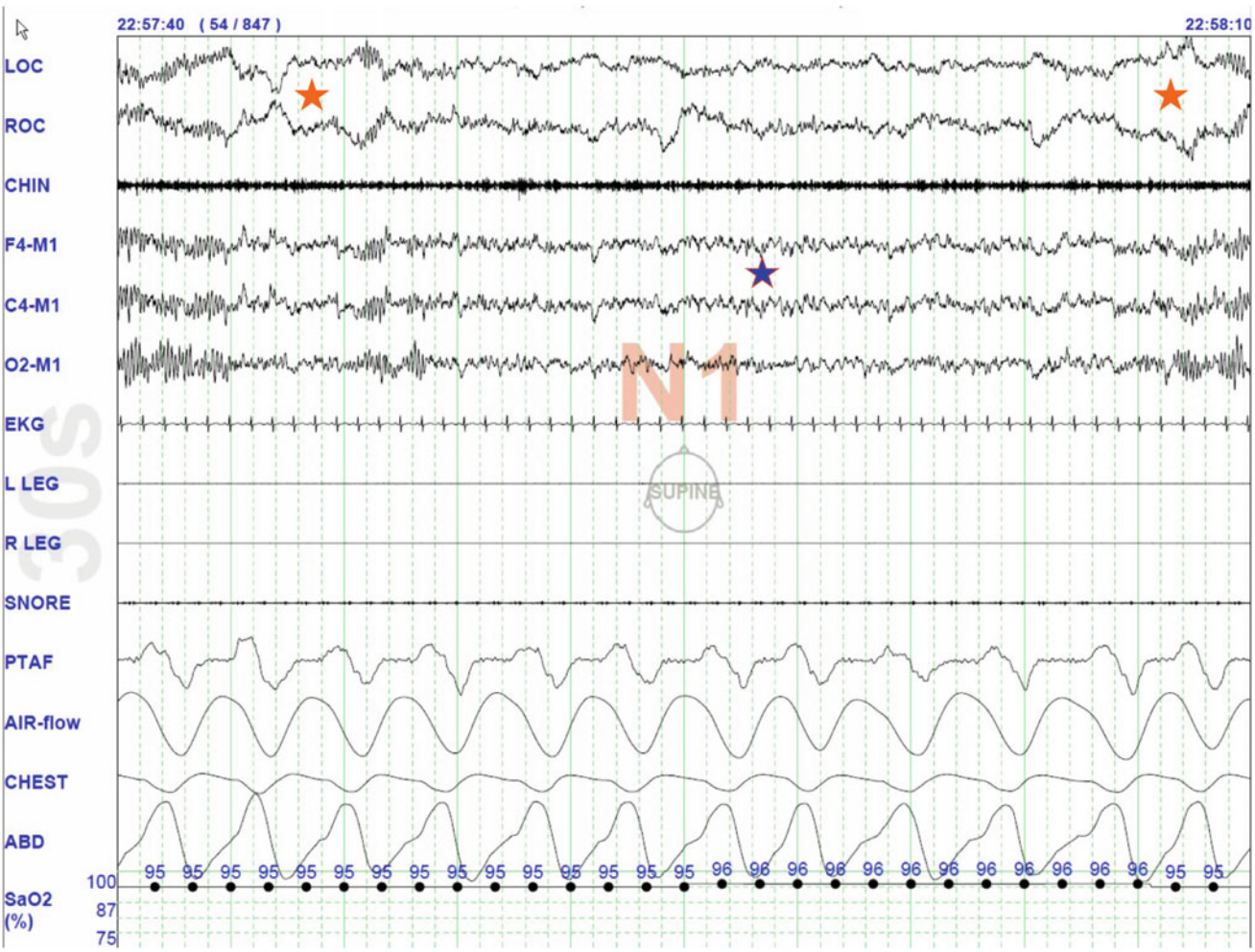


Fig. 24.8 Stage N1 sleep is characterized by the presence of low-voltage, mixed-frequency theta activity demarcated by the *blue star*. Slow rolling eye movements are evident (*orange star*) and so is a more substantial reduction in chin EMG tone (CHIN). Copyrighted to Alon Y. Avidan, MD, MPH

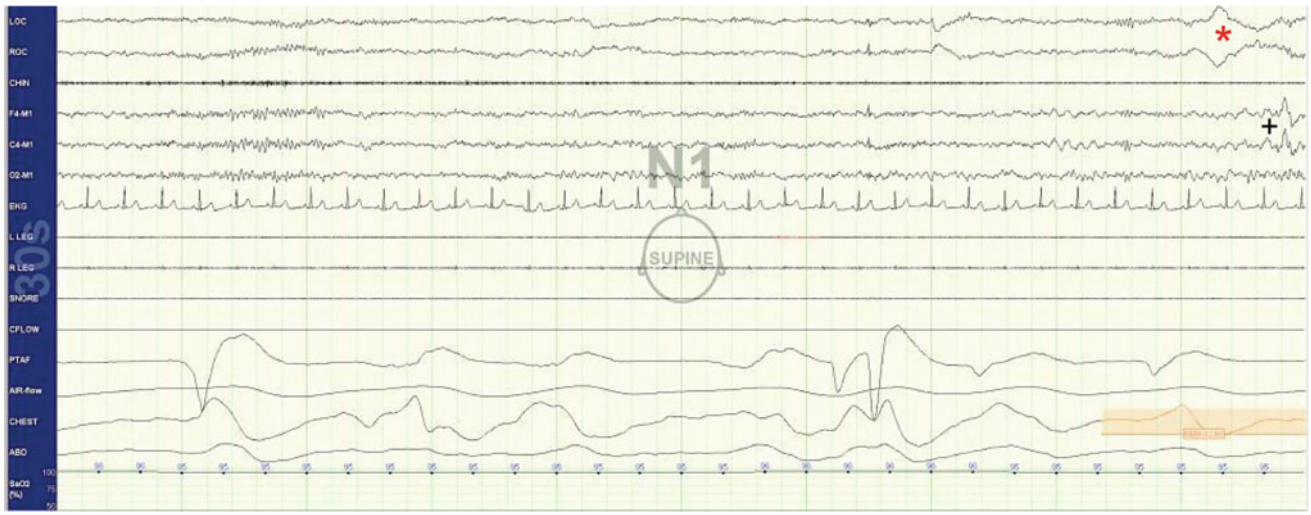


Fig. 24.9 This 30-s epoch is scored as stage N1 sleep as >50 % of the epoch is low-amplitude, mixed-frequency theta activity with some slow eye movements (*asterisk*) and a vertex sharp wave (*plus*) characteristic of stage N1 sleep

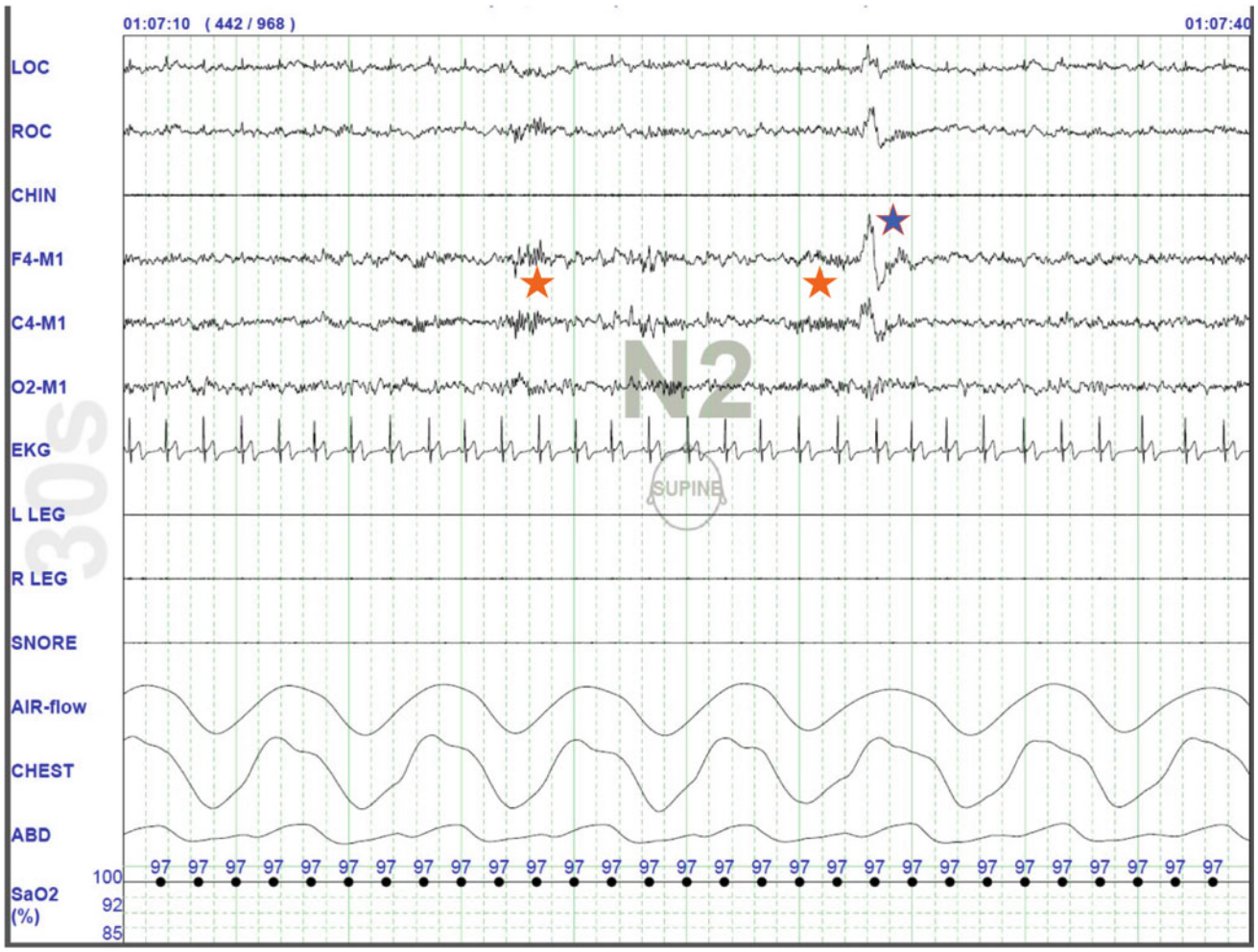


Fig. 24.10 This is a 30-s epoch designed to show the reader the classic characteristics of stage N2 sleep: sleep spindles (*red stars*) along with K complexes (*blue star*). K complexes are characteristic biphasic sharply negative followed by a slower positive deflection. K complexes have a duration criterion and must persist for at least 0.5 s. There is no minimum amplitude criterion for K complexes. Copyrighted to Alon Y. Avidan, MD, MPH

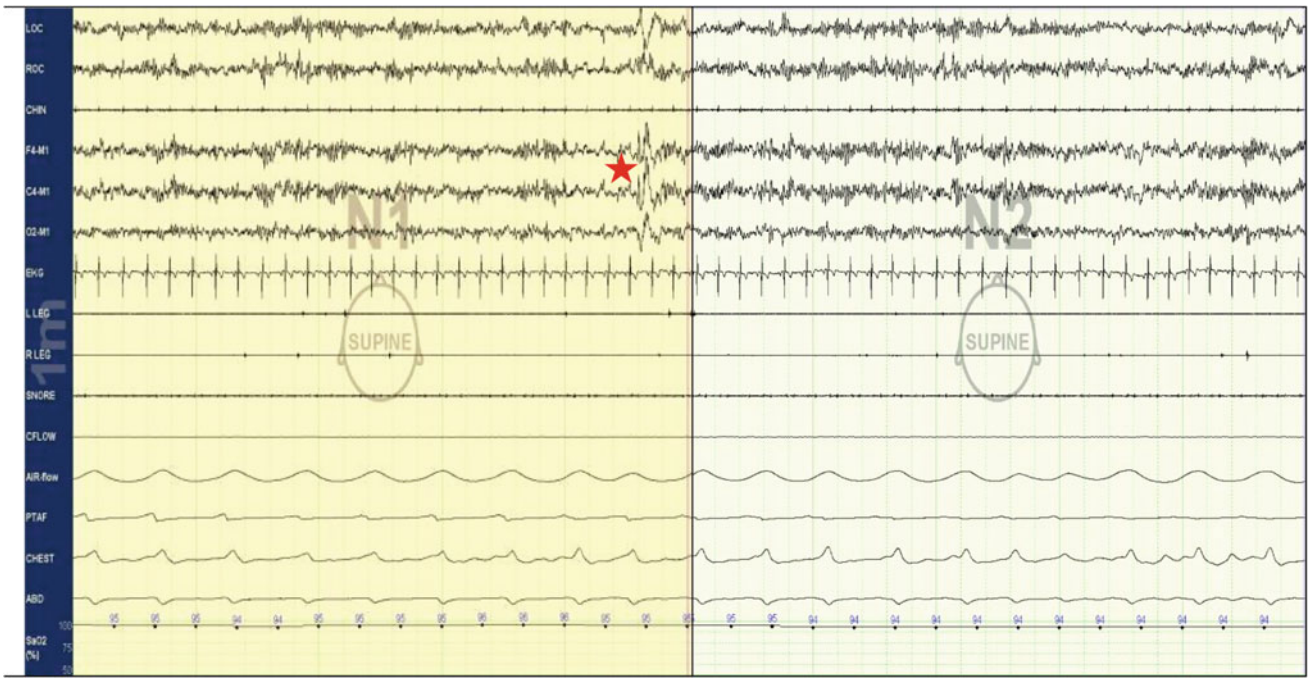


Fig. 24.11 Two consecutive 30 s PSG epochs demonstrating progression from stage N1 to stage N2. The first epoch is scored as stage N1 even with the presence of a K complex (*purple star*) because it occurs during the second half of the epoch. The following epoch is scored as stage N2

Stage N2 sleep is associated with a relative diminution of physiological bodily functions. Blood pressure, brain metabolism, gastrointestinal secretions, and cardiac activity are attenuated at this stage. The patient descends deeper into sleep, becoming more and more detached from the outside world and progressively more difficult to arouse.

Stage N3 Sleep

Stage N3 sleep may also be termed *deep sleep*, *slow-wave sleep (SWS),* or *delta sleep*. The updated AASM stage N3 is comprised of R & K stages 3 and 4 together and does not make a distinction between them as such distinction probably does not appear to serve clear clinical significance. This stage of sleep is marked by high-amplitude slow waves (0.5–2 Hz) with minimum amplitude of 75 microvolts as measured over the frontal regions. Slow-wave activity must be present for greater than or equal to 20 % of the epoch to be scored stage N3 sleep (Fig. 24.16). Both K complexes and sleep spindles may be seen in stage N3 sleep (Fig. 24.17). Pathological wave forms (epileptiform activity, slow waves in encephalopathy) are not counted as slow-wave activity of sleep, and sweat artifact (Fig. 24.18) must not be confused with stage N3. The sweat artifact is identified by high-amplitude slow frequency and may be sometimes confused and erroneously labeled as slow-wave sleep (stage N3). The most common electrodes affected by sweating are the EOG and anterior EEG electrodes [5]. The frequencies seen in sweat artifact are significantly slower, distinguishing them from stage N3 which is a distinguishing factor. Sweat artifact is also known as sway artifact or slow-wave artifact, the latter being a misnomer.

No specific criteria for EOG and EMG exist for stage N3 sleep, but in general, muscle tone is further decreased and there is no eye movement activity. This stage of sleep has the highest threshold for arousal and is associated with many parasomnias such as sleep terrors, sleepwalking, and confusional arousals. If the patient wakes up from stage N3 sleep, they may appear confused or disoriented. The patient may experience *sleep inertia* or *sleep drunkenness*, seeming unable to function normally for several minutes.

Stage REM Sleep

Stage R or rapid eye movement sleep may also be termed *paradoxical sleep* or *active sleep* (Fig. 24.19). REM sleep typically occurs about 90–120 min after sleep onset in adults. REM sleep typically occupies 20–25 % of overnight adult sleep. Stage R is characterized by relatively low-amplitude, mixed-frequency EEG theta waves, intermixed with some alpha waves, usually 1–2 Hz slower than wake. In addition, in order to score stage R, rapid eye movements and low chin EMG tone must be present. Sawtooth waves are frequently seen either during REM sleep or several seconds preceding scorable REM

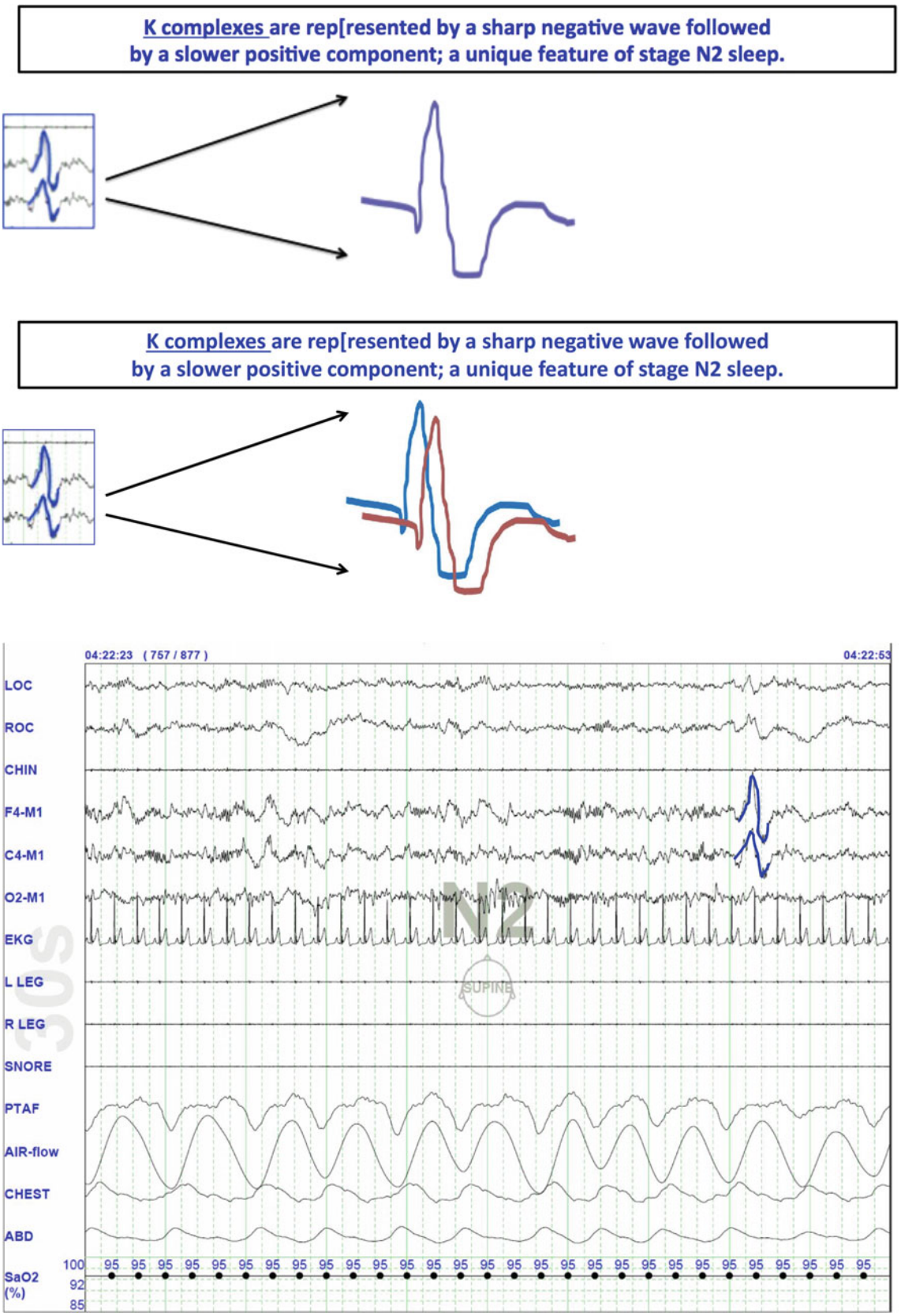


Fig. 24.12 K complexes are retraced in blue on this 30-s epoch with a negative (upward deflection) sharp waves followed by a slower positive (downward deflection) component with a total duration of greater than 500 ms. K complexes lack specific amplitude criteria. Copyrighted to Alon Y. Avidan, MD, MPH

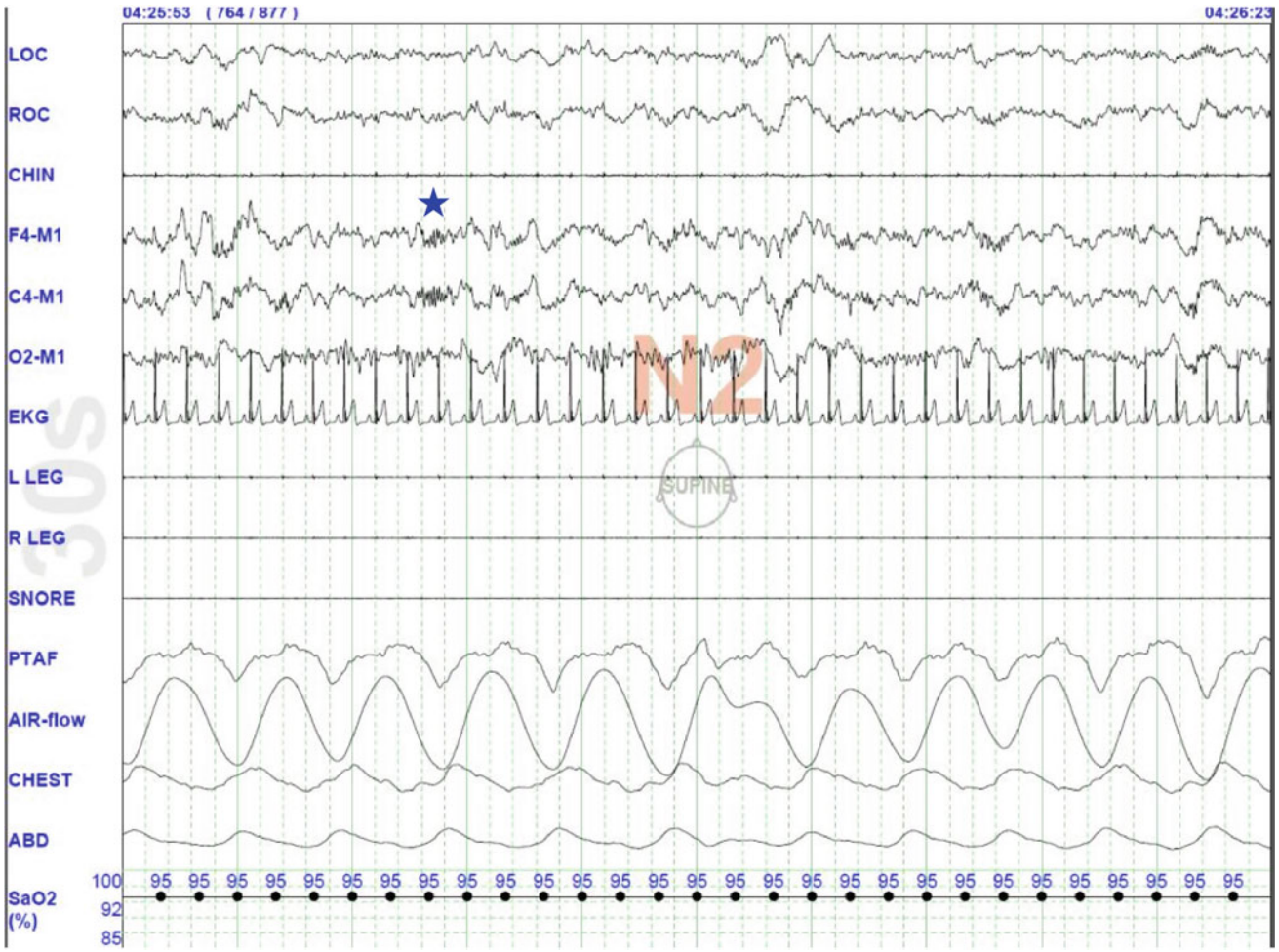


Fig. 24.13 This 30-s PSG epoch demonstrates a sleep spindle, as demarcated by the *blue star*, seen in stage N2 characterized by 12–14 Hz sinusoidal EEG activity in the central vertex region and must persist for at least 0.5 s. Copyrighted to Alon Y. Avidan, MD, MPH

sleep in which time they declare imminent entry into stage R. These are 2–6-Hz, sharply contoured triangular EEG patterns that are jagged-like in morphology and evenly formed, seen maximal in the central leads (Fig. 24.20). Rapid eye movements are conjugate, irregular, and sharply peaked eye movements with an initial deflection usually lasting <500 ms (red star, Fig. 24.21). Chin EMG tone should be at the lowest level of any sleep stage during stage R sleep (green arrows, Fig. 24.21). No specific amplitude criteria currently exist for this determination. Short, irregular bursts of EMG activity (less than 0.25 s), called transient muscle activity, may be seen in the chin, limb, EEG, or EOG leads usually in association with rapid eye movements (Fig. 24.22). Stage R should be continued to be scored for subsequent epochs even without rapid eye movements assuming the EEG shows low-amplitude, mixed-frequency activity without K complexes or sleep spindles, and the chin EMG tone remains low (Fig. 24.23).

REM sleep is sometimes divided into phasic (P) and tonic (T) components. P-REM sleep is characterized by phasic twitching in the EMG channel occurring concurrently with bursts of rapid eye movements. The phasic EMG twitchings in this stage are very short muscle twitches that may occur in the middle ear muscles, genioglossal muscle, and facial muscles and are associated with increased penile & clitoral tumescence. T-REM sleep generally consists of low-voltage activated EEG and is characterized by decreased or absent EMG activity, without obvious EOG activity. Unlike the progressive relaxation noted during the NREM sleep stages N1, N2, and N3, physiological activity during REM sleep is significantly higher. Blood pressure and pulse rate may increase dramatically or may show intermittent fluctuations. Breathing becomes irregular and brain oxygen consumption increases. Men exhibit penile erections, while women experience clitoral engorgement. The body seems to have abandoned its effort to regulate its temperature during the REM phase and resembles a state of poikilothermy, drifting gradually toward the temperature of the environment.

If patients are awakened from stage R sleep, they may often recall dreaming. Pathologically, short REM sleep latency may point to a state of acute or cumulative sleep deprivation, may be

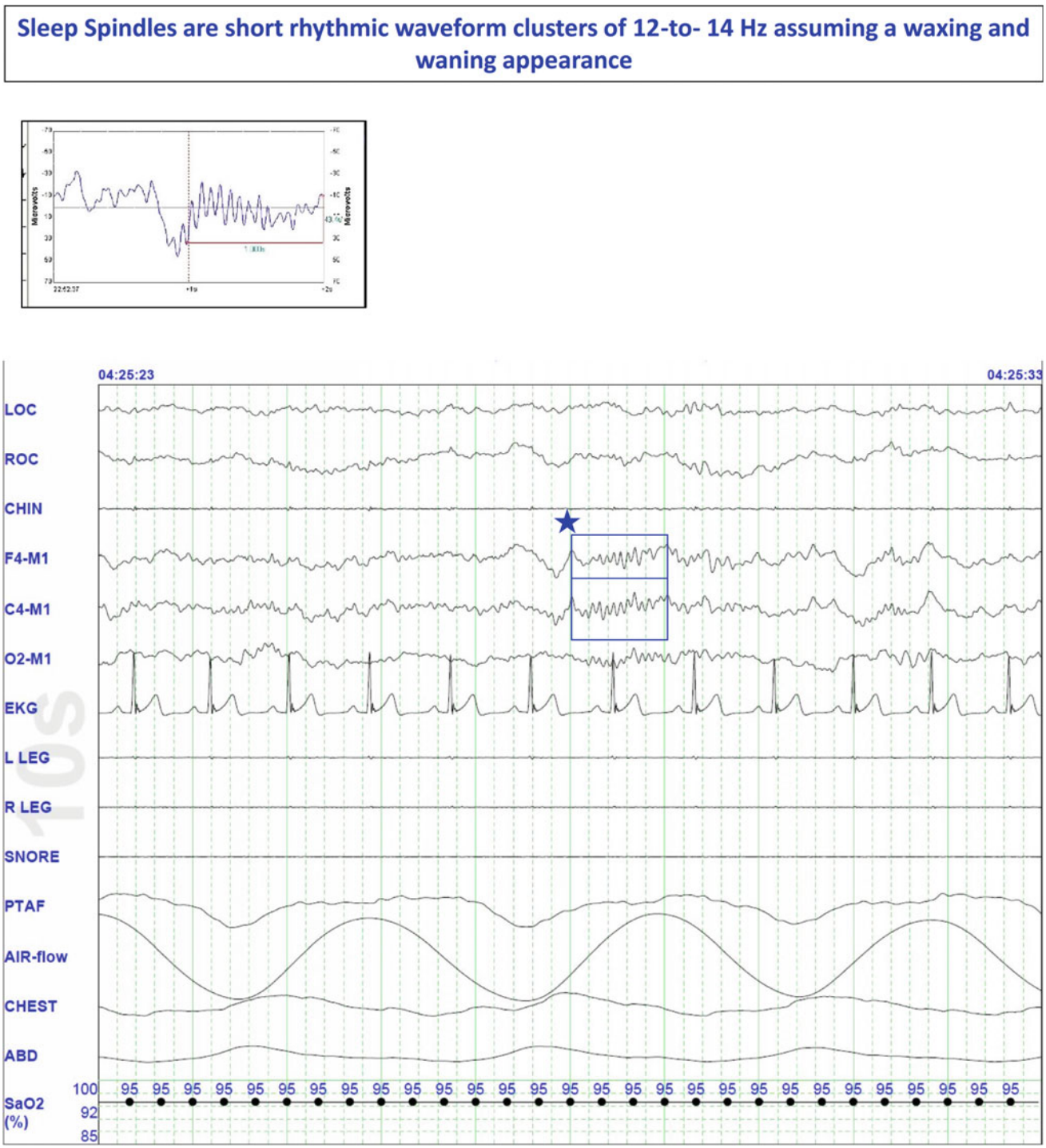


Fig. 24.14 This 10 s PSG epoch taken from the prior epoch demonstrates the sleep spindles within the *blue box* characterized by 12 Hz sinusoidal EEG activity in the central vertex region and must persist for at least 0.5 s. Copyrighted to Alon Y. Avidan, MD, MPH

caused by abrupt discontinuation of REM sleep–suppressing agents (such as antidepressants), narcolepsy-cataplexy syndrome, and may also suggest a major affective disorder. A variety of sleep disorders are strongly associated with REM sleep including a variety of parasomnias [REM sleep behavior disorder (RBD) and REM nightmares] (Fig. 24.24) and obstructive sleep apnea, which may be more pronounced during this sleep period (Fig. 24.25).

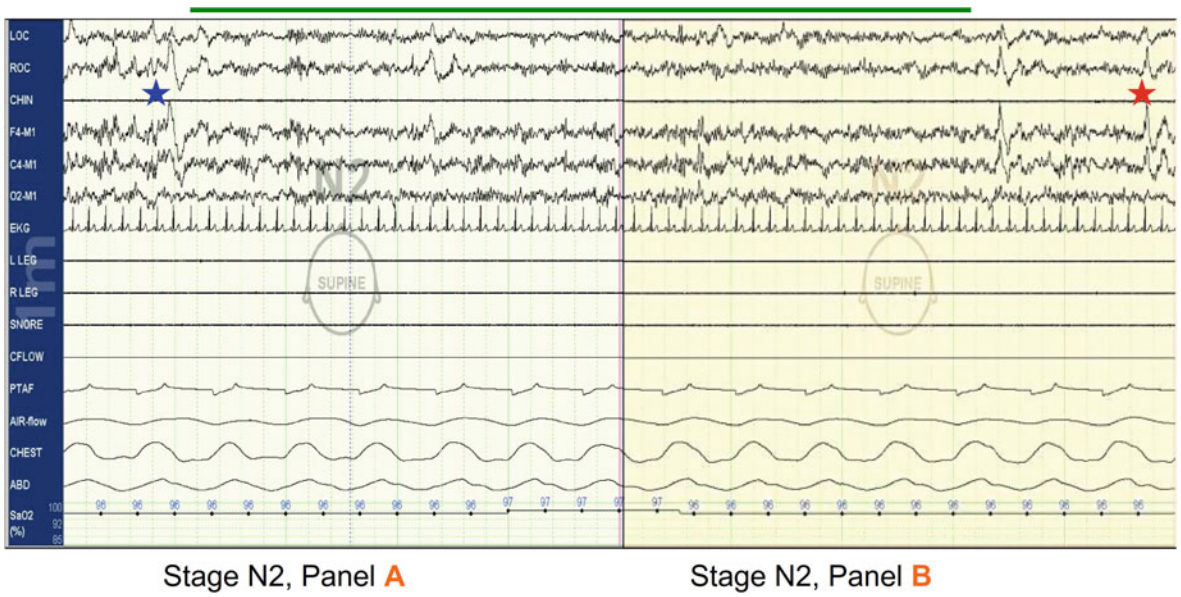


Fig. 24.15 These are two consecutive 30-s PSG fragments. The first epoch (*Panel A*) is scored stage N2 due to the K complex noted (*blue star*) during the first half of the epoch. The second epoch (*Panel B*) is also scored stage N2 sleep even though K complexes are only noted during the second half of the epoch (*red star*) as once an epoch meets criteria for N2 sleep, epochs can be continuously scored as stage N2 (even in the absence of K complexes or sleep spindles) assuming that there is not an arousal pattern and the EEG continues to demonstrate low-amplitude, mixed-frequency activity (the area under the *green bar*)

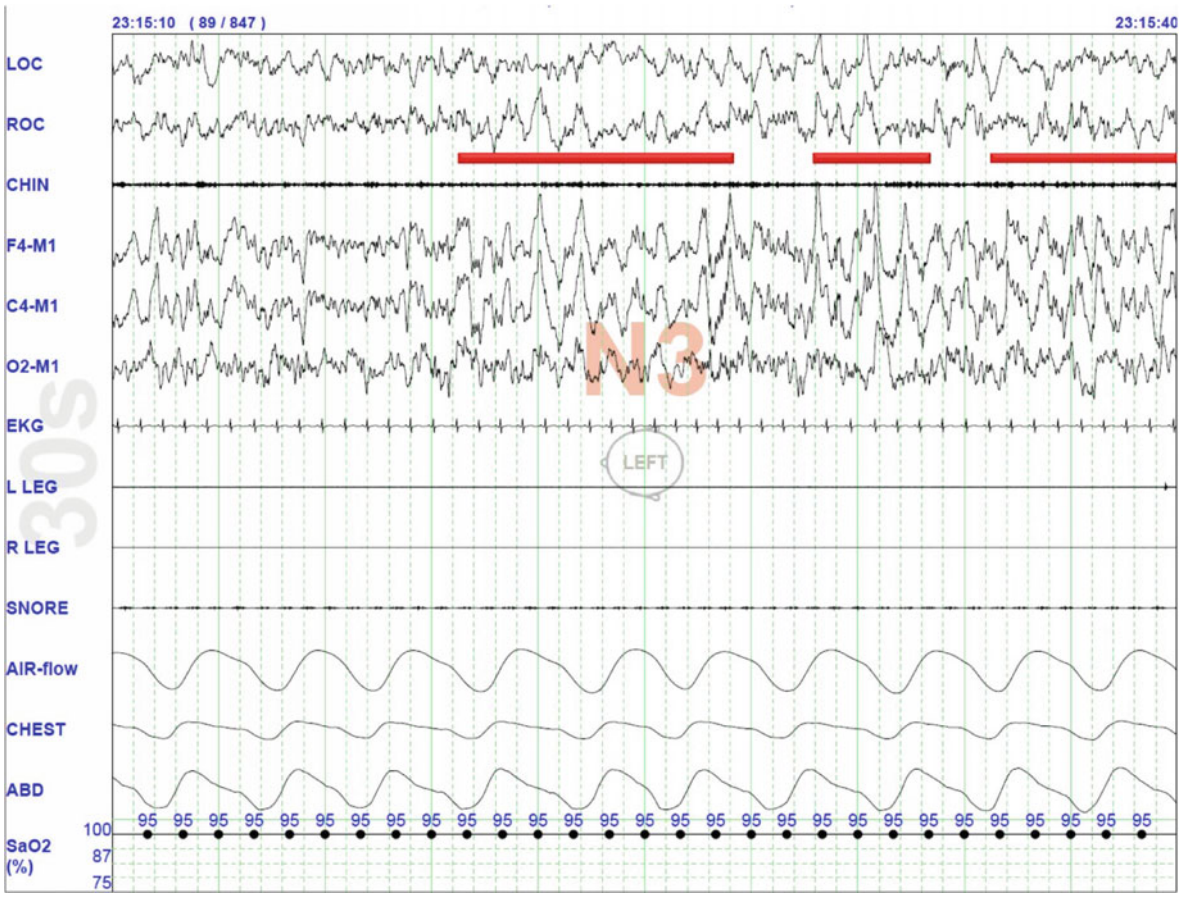


Fig. 24.16 This 30 s PSG epoch is scored as stage N3 sleep due to over 20 % of the epoch consisting of delta waves (0.5–2 Hz, depicted by the *red bars*) with minimum amplitude of 75 μV as measured over the frontal regions. Chin EMG tone is typically low, and there are no slow or rapid eye movements noted during this stage of sleep. Copyrighted to Alon Y. Avidan, MD, MPH

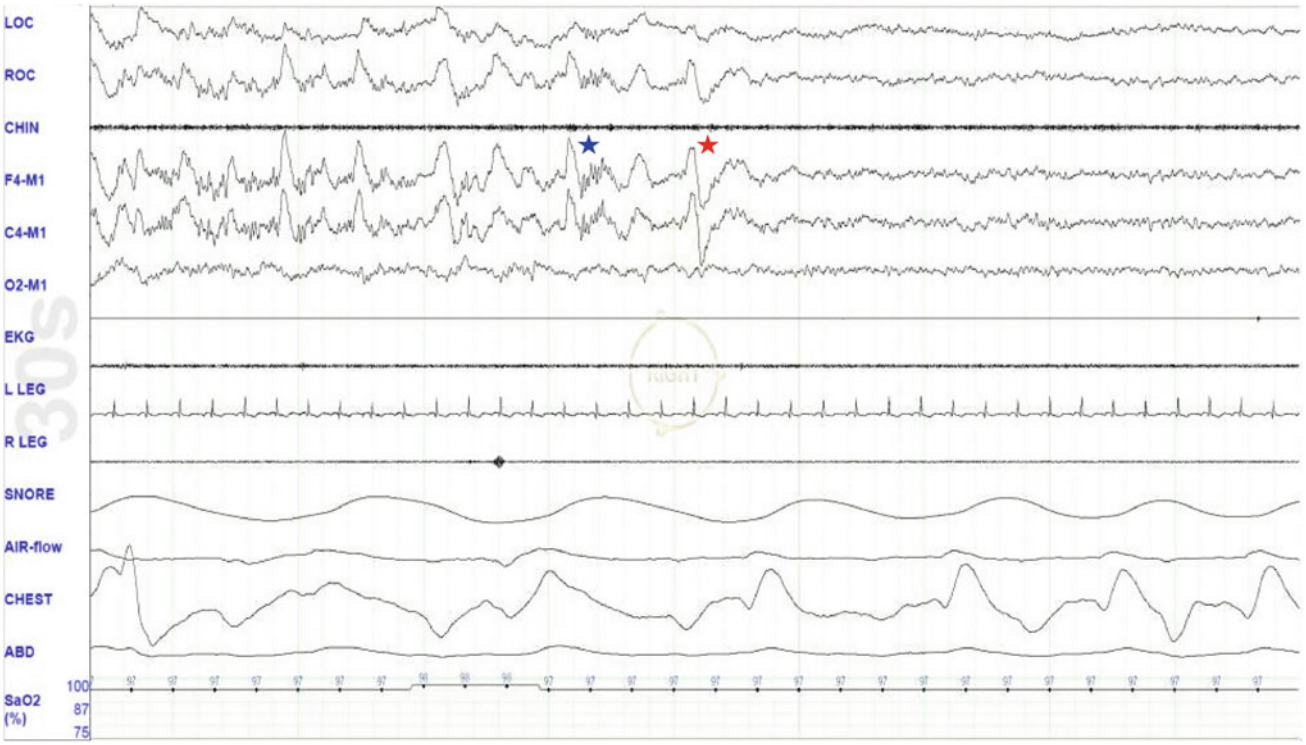


Fig. 24.17 This 30-s epoch is scored as stage N3 sleep due to over 20 % of the epoch containing delta slowing. Sleep spindles (*blue star*) and K complexes (*red star*) may be noted during stage N3 sleep. Copyrighted to Alon Y. Avidan, MD, MPH

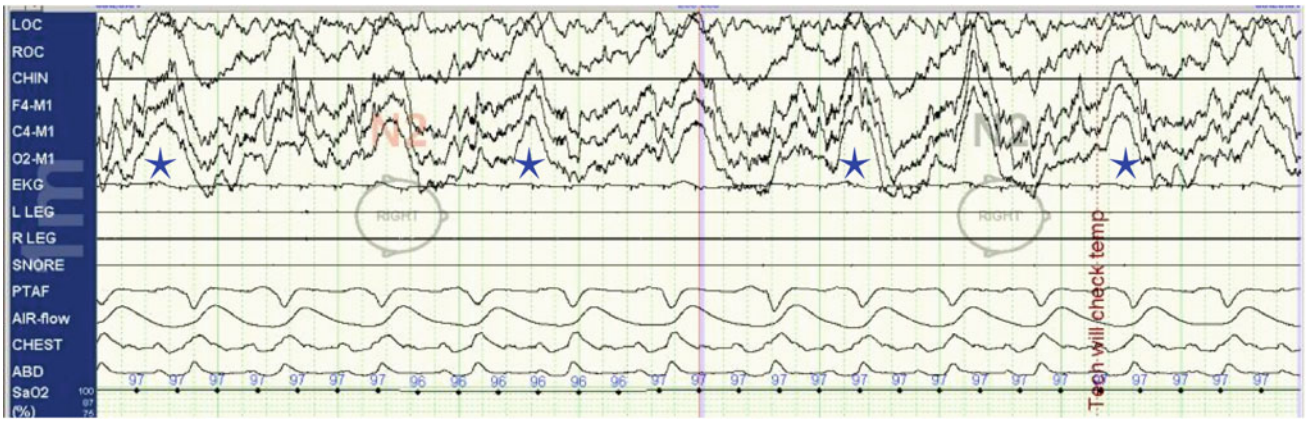


Fig. 24.18 This 60-s PSG epoch is correctly scored as stage N2 although there is evidence of high-amplitude slow-wave activity—sweat artifact—which may be confused as slow-wave sleep. Copyrighted to Alon Y. Avidan, MD, MPH

End Scoring Stage R Sleep

Stage R scoring should continue until there is a clear change to another sleep stage. Stage R ends if an epoch meets criteria for stage W or N3 sleep. In addition, a sustained increase in chin EMG tone with an absence of spindles or K complexes indicates the end of stage R and the beginning of stage N1 if the epoch meets criteria for stage N1 (Fig. 24.26). An arousal or major body movement followed by slow eye movements also indicates the termination of stage R and the beginning of N1. If the chin EMG tone returns to a low level and the epoch demonstrates an absence of slow eye movements, this would characterize the continuation of stage R (Fig. 24.27). If a K complex or sleep spindle appears in the first half of the epoch without any subsequent rapid eye movements, the epoch will be scored as stage N2 even if chin EMG tone remains low. If a sleep spindle or K complex appears in the second half of the

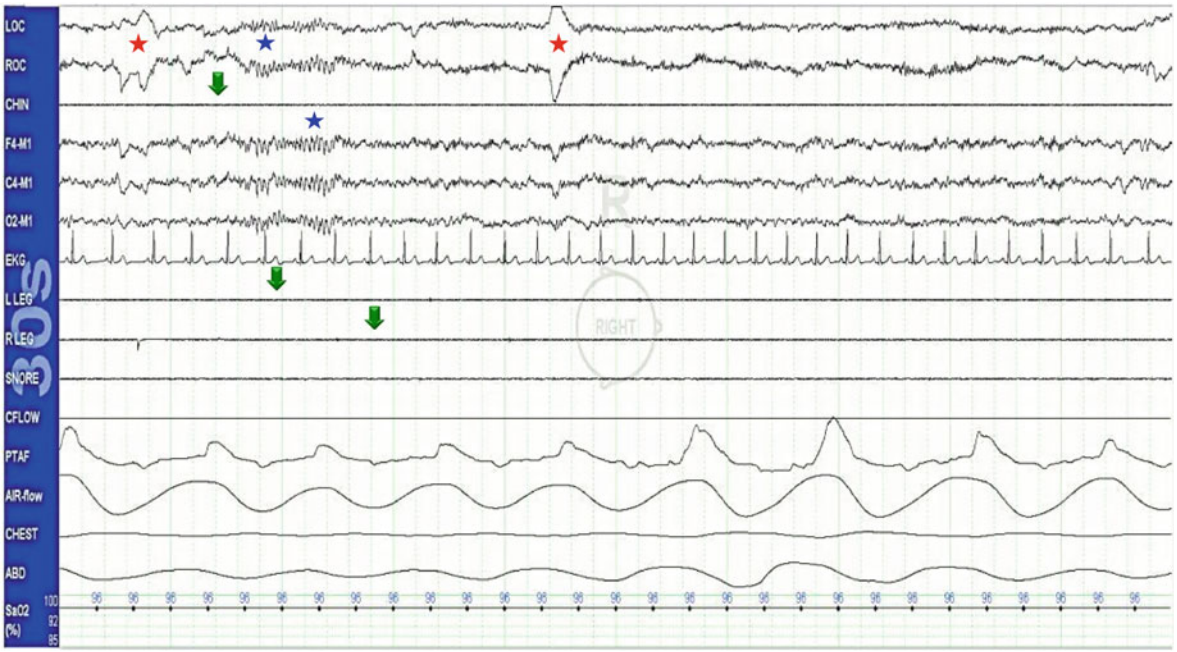


Fig. 24.19 This 30-s epoch demonstrates sawtooth waves (*blue stars*), rapid eye movements (*red stars*), and low chin EMG tone of stage R sleep (*green arrows*). Copyrighted to Alon Y. Avidan, MD, MPH

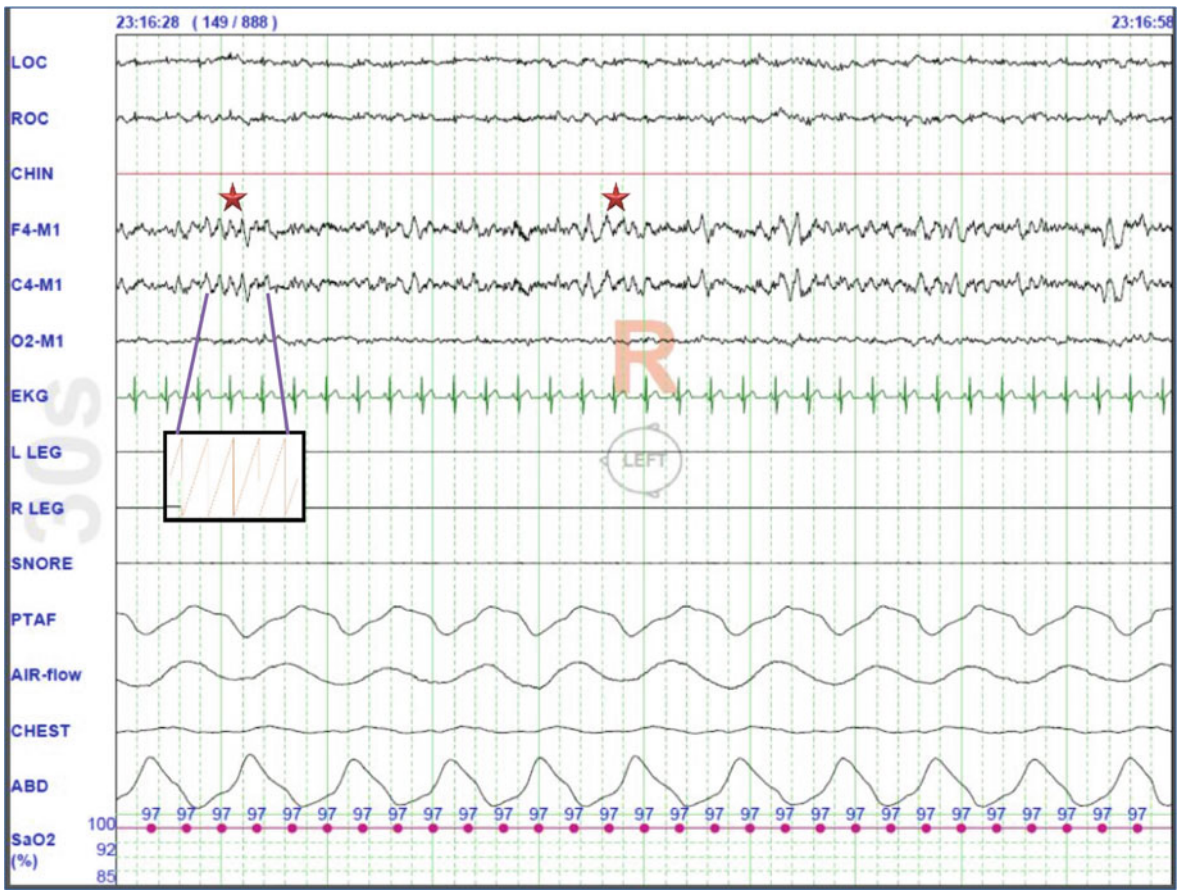


Fig. 24.20 This 30-s epoch demonstrates sawtooth waves (*blue stars*), depicting their characteristic frequency of 2–6 Hz, and sharply contoured triangular EEG jagged-like morphology (*box insert tracings*). Copyrighted to Alon Y. Avidan, MD, MPH

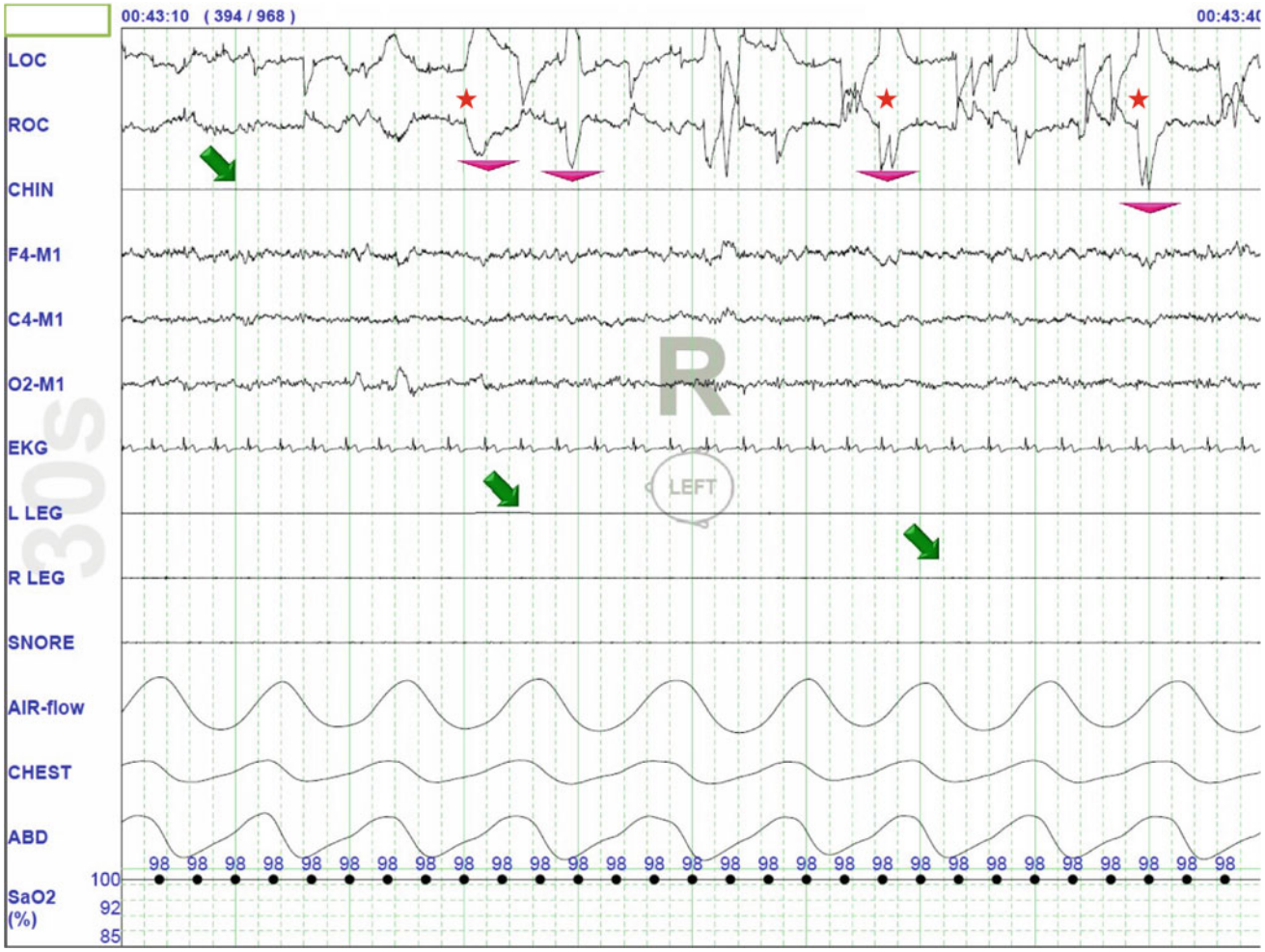


Fig. 24.21 This 30-s epoch demonstrates rapid eye movements (depicted by the *red stars* and highlighted *pink arrow heads*). There is also evidence of low chin EMG tone (*green arrows*). Copyrighted to Alon Y. Avidan, MD, MPH

epoch, then the epoch would still be scored R and the next epoch would be scored N2.

Transitions Between Stage N2 and Stage R

Scoring epochs between stage N2 and stage R can be challenging due to the occasional presence of K complexes and sleep spindles in epochs that otherwise look like stage R sleep. The first epoch after a decrease in chin EMG should be scored as stage R even if there are no rapid eye movements (Fig. 24.28, but K complexes and sleep spindles must be absent. If the record shows sleep spindles or K complexes, in the absence of rapid eye movements, the epoch will be scored as N2 sleep, even following a drop in chin EMG. Furthermore, an epoch with a K complex or spindle will be scored as stage R if either is followed by a rapid eye movement, while chin EMG tone is still low (Fig. 24.29).

Major Body Movements

Major body movement is movement and muscle artifact obscuring the EEG for more than half an epoch making determination of sleep stage difficult. In the updated AASM manual, if an epoch contains a major body movement, it can be scored as stage W if an alpha rhythm is present for any part of the epoch. If no alpha rhythm is noted, but stage W precedes or follows the epoch with a major body movement, it can be scored as stage W. The epoch can be scored the same stage as the epoch that follows it if there is no alpha rhythm present and stage W does not precede or follow the epoch.

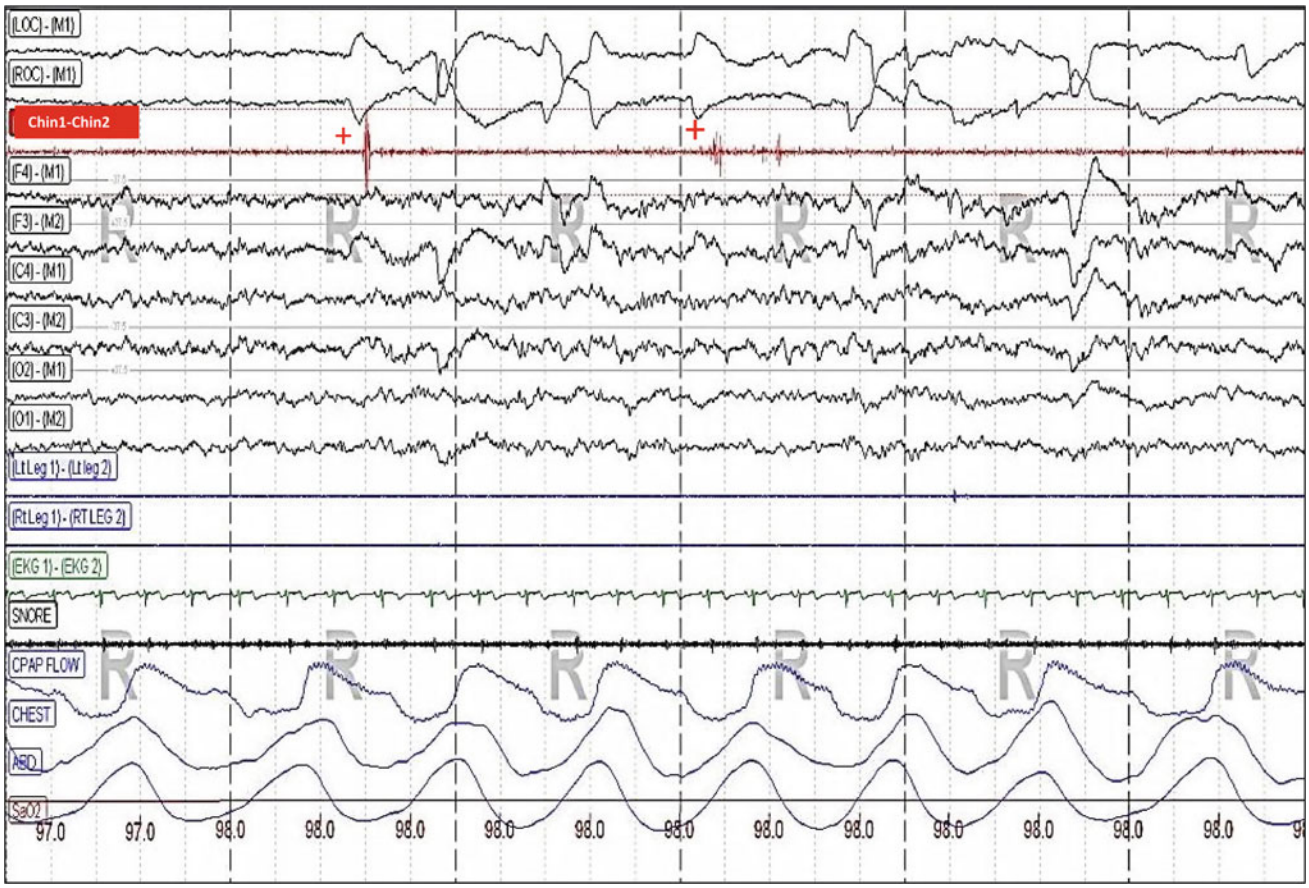


Fig. 24.22 This 30 s PSG epoch demonstrates transient muscle activity (*plus* in the chin EMG lead during REM sleep, short irregular bursts less than 0.25 s in duration, usually in association with rapid eye movements). Copyrighted to Raman K. Malhotra, MD

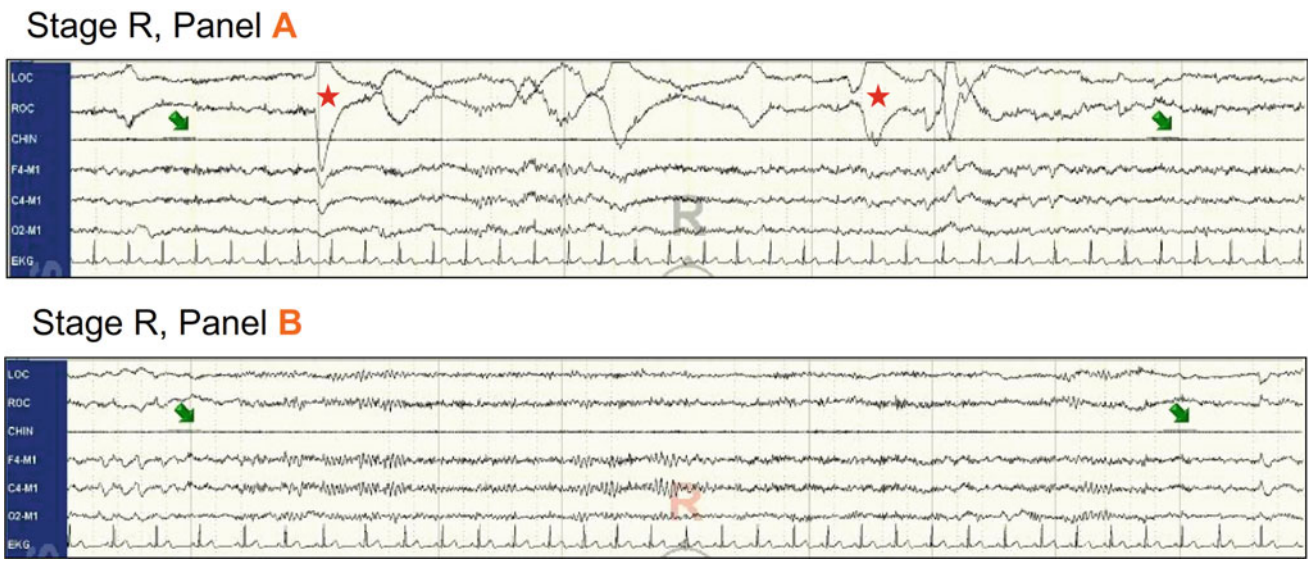


Fig. 24.23 Panel A: The first of two consecutive 30 s PSG epochs is scored as stage R due to low chin EMG tone (*green arrows*), low-amplitude, mixed-frequency EEG, and rapid eye movements (*red arrow*). Panel B: In the second epoch, Stage R should be continued to be even without a rapid eye movement since the EEG shows low-amplitude, mixed-frequency activity without K complexes or sleep spindles, and the chin EMG tone remains low (*green arrows*). Copyrighted to Alon Y. Avidan, MD, MPH

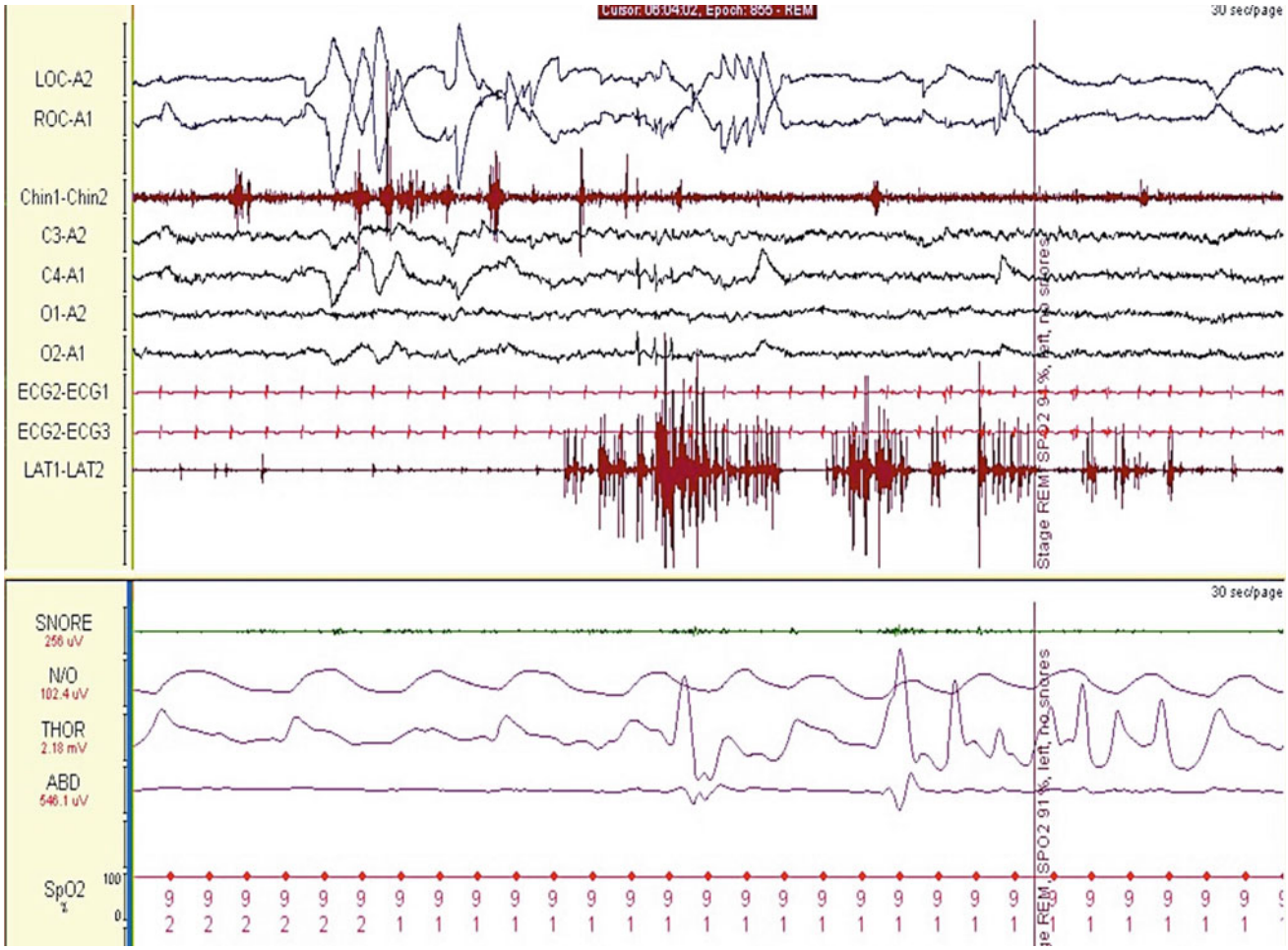


Fig. 24.24 A 30-s epoch from the diagnostic polysomnogram of an 75-year-old man who was referred to the sleep disorders clinic for evaluation of recurrent loud snoring and nocturnal awakenings and violent nighttime awakenings. Illustrated in this figure is a typical spell that this patient was experiencing. He was noted to yell, jump from bed, and have complex body movements. The *box* demonstrates the normal REM-associated muscle atonia in the left anterior tibialis muscle. Shown by the two arrows in the figure are abnormal EMG augmentations in the chin (*green arrow*) and limb (*blue arrow*) leads. Copyrighted to Alon Y. Avidan, MD, MPH

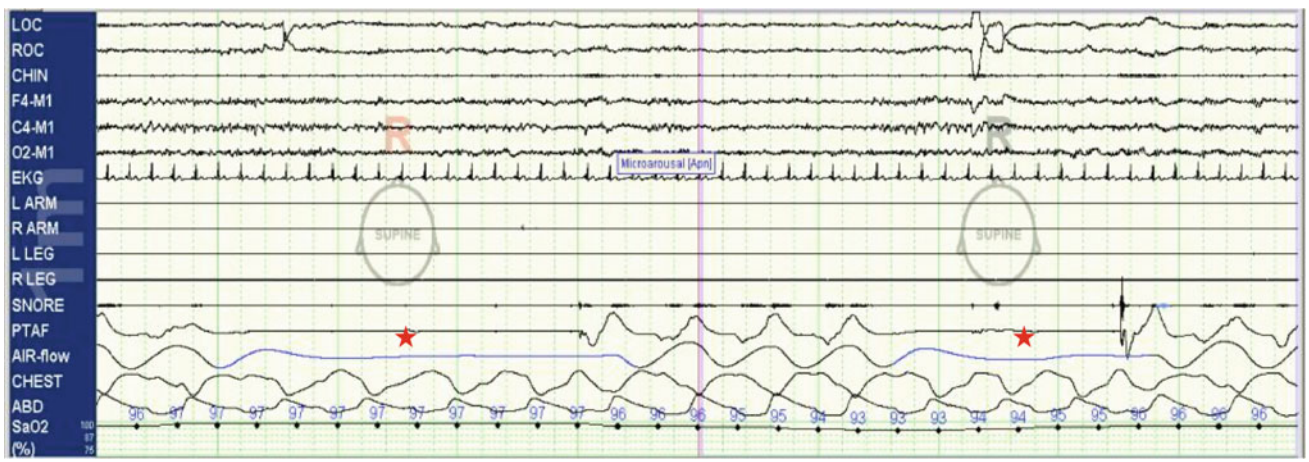


Fig. 24.25 A 60-s epoch from the diagnostic polysomnogram a patient with snoring and daytime sleepiness. Shown by the *red stars* are episodes of REM-related obstructive events, which the patient experienced exclusively during REM sleep. Copyrighted to Alon Y. Avidan, MD, MPH

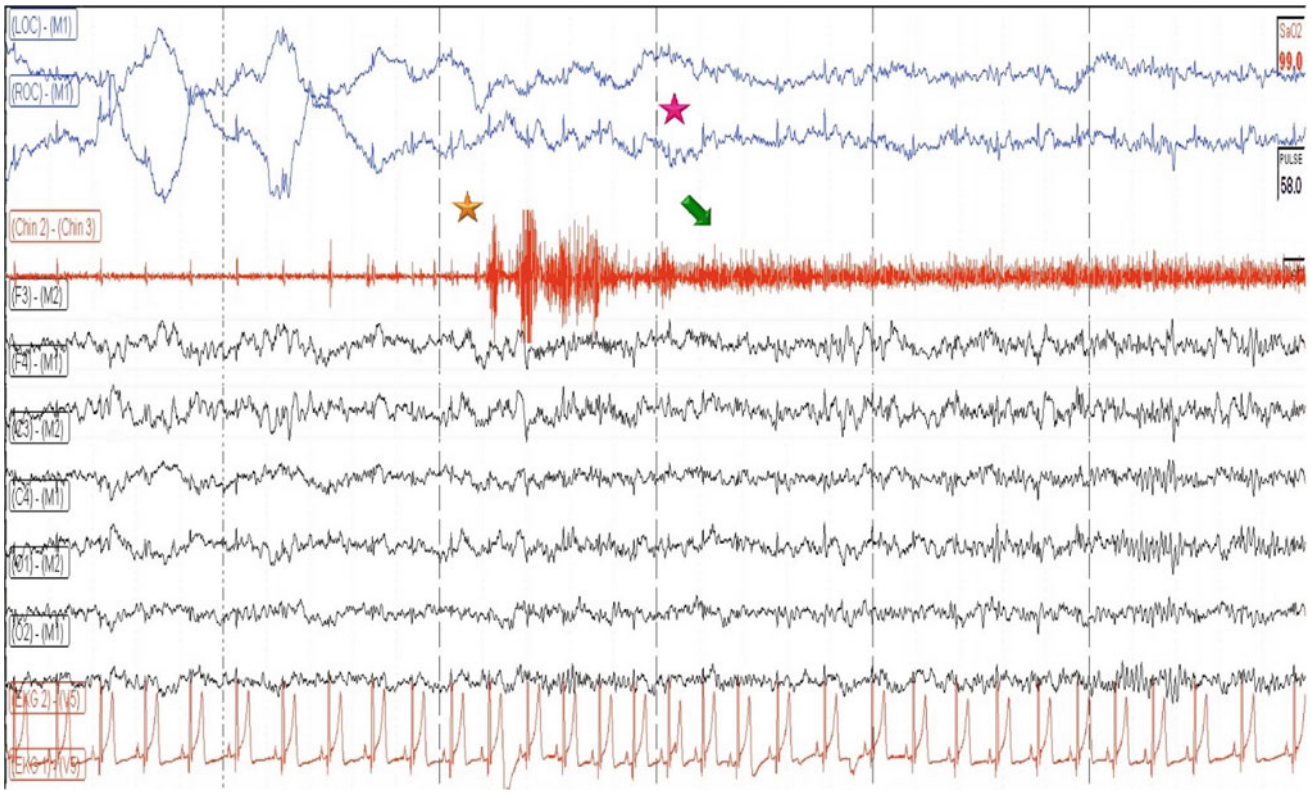


Fig. 24.26 This 30-s PSG epoch demonstrates the termination of stage R with an arousal (*gold star*), subsequent slow eye movement (*pink star*) and increased chin EMG (*green arrow*), with characteristics consistent with stage N1 sleep. This epoch should be scored stage N1 since the majority of the epoch demonstrates stage N1. Copyrighted to Raman K. Malhotra, MD

Arousals

Arousals can be scored during sleep stages if there is an abrupt change in the EEG frequency noted in the occipital or central derivations. This can be alpha, theta, or beta frequency (with the exclusion of spindle-frequency) that last at least 3 s with at least 10 s of stable sleep preceding the change (Fig. 24.30). During stage R, an arousal requires an increase in chin EMG lasting for at least 1 s. The use of other recording channels such as limb EMG, respiratory channels, and EKG may be used to help make the determination of an arousal, but EEG criteria must be met. Arousal can occur for a variety of reasons, some of which may be noted in the study (i.e., respiratory events and limb movements). Other times, the arousal may appear to be spontaneous or occurring due to an event not being monitored during the polysomnography (i.e., back pain and acid reflux).

Pediatric Scoring Rules

The AASM Manual for Scoring has separate scoring rules in children over 2 months of age post-term. Technical specifications for EEG, EOG, and EMG recordings are similar to adult rules with the exception of the distance between the chin EMG electrodes which often needs to be reduced from 2 cm to 1 cm and the distance from the eyes in EOG electrodes often need to be reduced from 1 cm to 0.5 cm in children and infants with small head size. Not all waveforms that are noted in adults are seen in infants even at two months old. Sleep spindles may be seen by age 4–6 weeks post-term and are present in all normal infants by age 2–3 months post-term [6]. At this age, the spindles are asynchronous between the hemispheres but become more synchronous over the first year of life. K complexes are usually present by age 4–6 months post-term. Delta slowing in order to score stage N3 sleep may first appear by 2 months of age

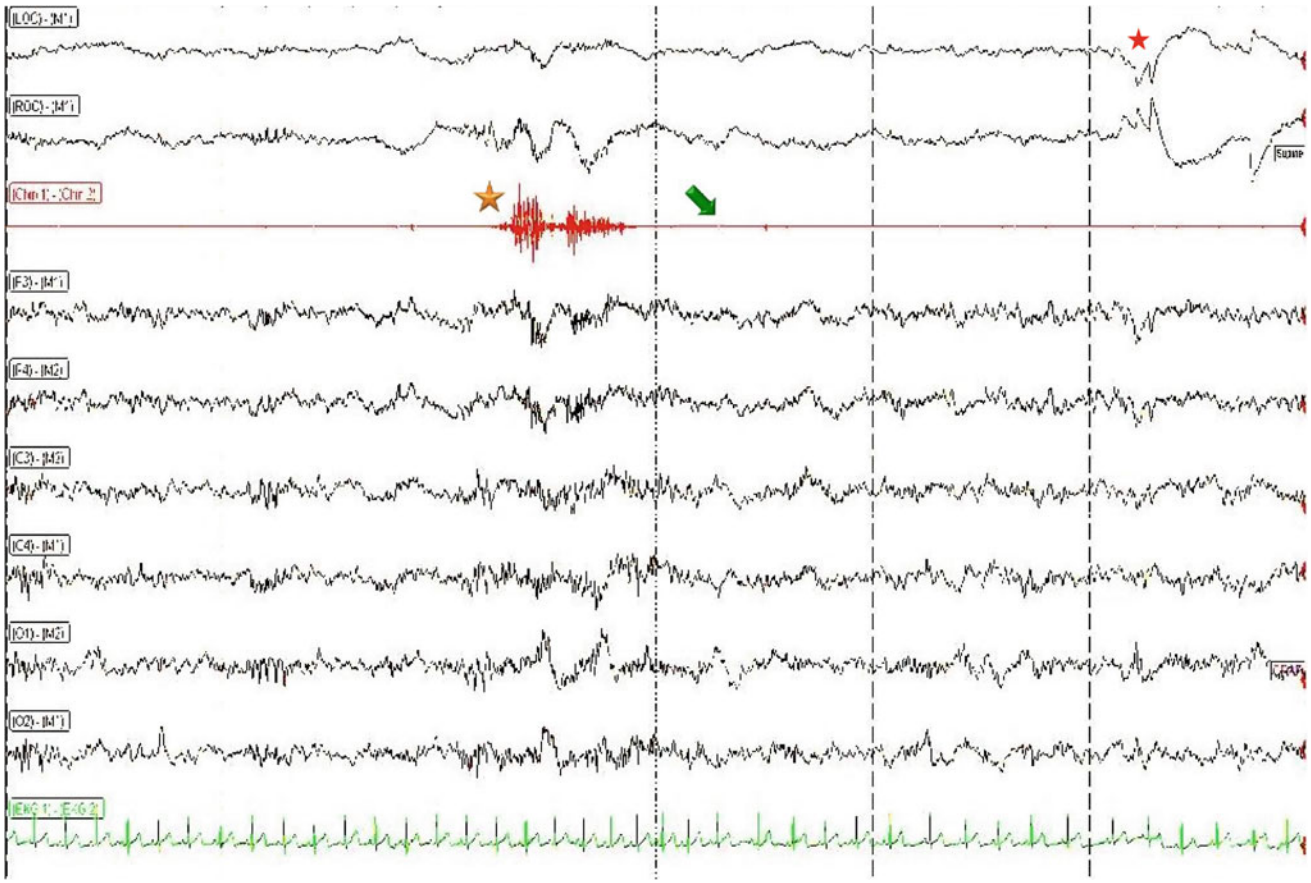


Fig. 24.27 This 30-s epoch is scored as stage R. There is arousal from stage R during the first half of the epoch (*gold star*), but the chin EMG tone returns to a low level (*green arrow*) and a rapid eye movement is noted (*red star*). Copyrighted to Raman K. Malhotra, MD

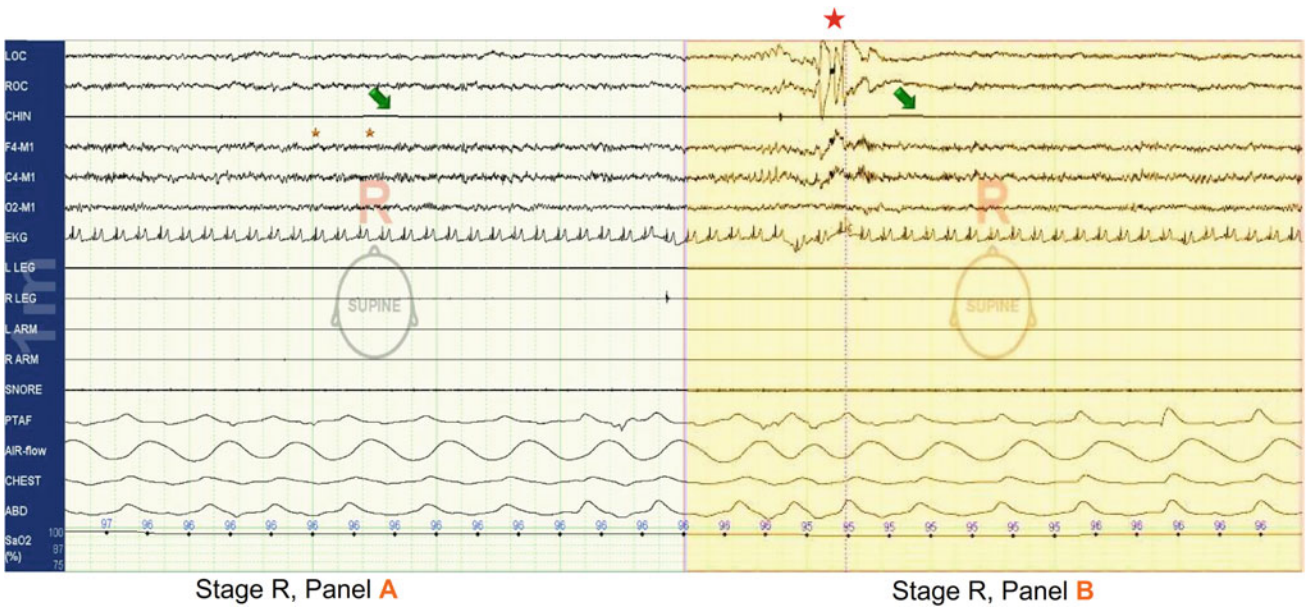


Fig. 24.28 These two consecutive 30-s epochs are both scored as stage R. Even though the rapid eye movements are only noted in the second epoch (*Panel B*), the first epoch (*Panel A*) can also be scored as Stage R because it has low-amplitude and mixed-frequency EEG (*gold stars*), no sleep spindles or K complexes, and low chin EMG tone (*green arrows*). Copyrighted to Alon Y. Avidan, MD, MPH

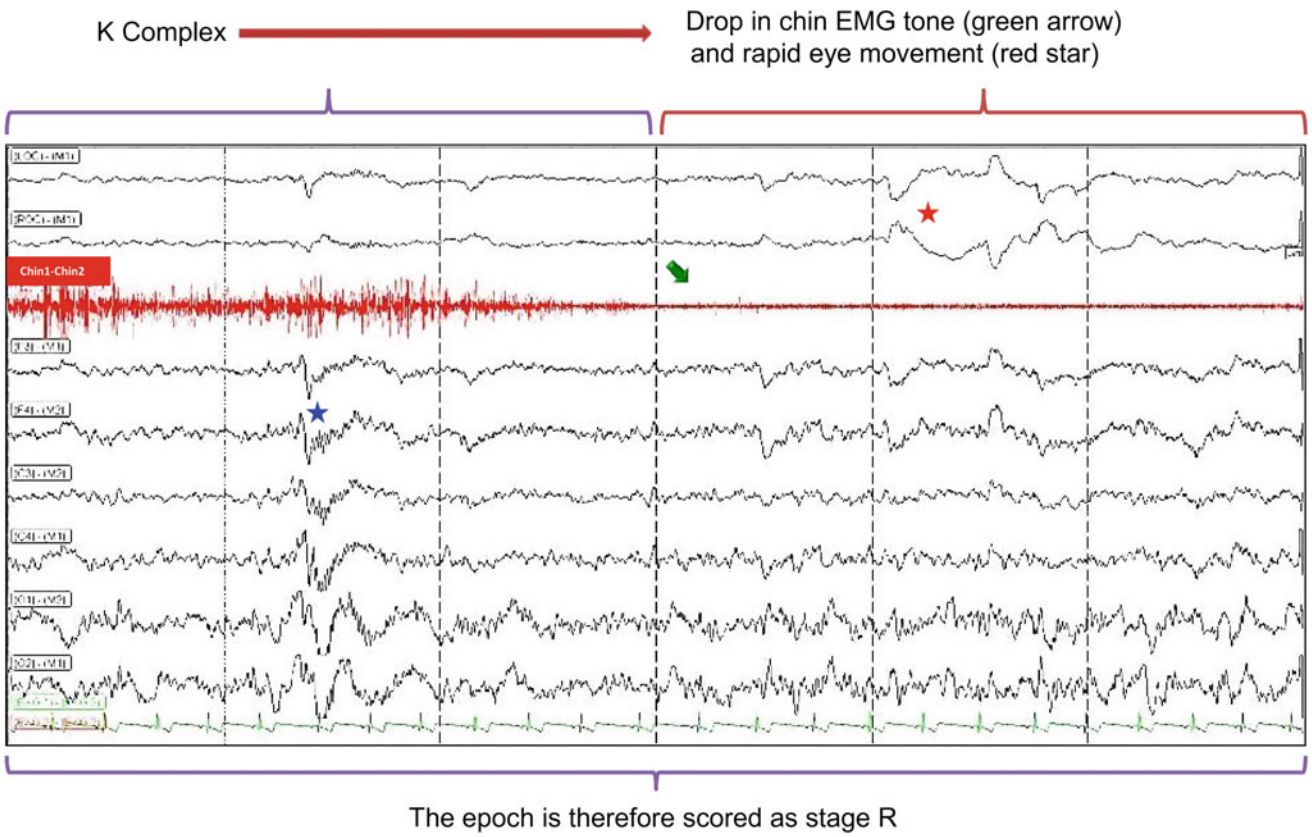


Fig. 24.29 This 30-s PSG epoch is scored stage R. Although there is a K complex (*blue star*) in the first half of the epoch, the entire epoch will be scored as stage R due to the drop in chin EMG tone (*green arrow*) and rapid eye movement noted in the second half of the epoch. Copyrighted to Raman K. Malhotra, MD

and is usually present by age 4–5 months post-term. When EEG markers are not present or clear to help score stages of sleep, it can be helpful to use other information, such as eye movements, chin EMG tone, and respirations to determine NREM versus REM sleep. If sleep spindles, K complexes, or delta slowing are not apparent in NREM sleep due to the age of the child being studied, sleep can be scored as stage N.

In children, the term "posterior dominant rhythm" is used instead of alpha rhythm. The posterior dominant rhythm (PDR) is the dominant reactive EEG rhythm over the occipital regions in relaxed wakefulness with eyes closed which is slower in infants and young children and attenuates with eye opening or attention. Frequency is 3.5–4.5 Hz when first seen in infants 3–4 months post-term, 5–6 Hz by 5–6 months, and 7.5–9.5 Hz by 3 years of age, and amplitude is usually >50 μV.

Stage W is scored in children if over half of the epoch is age appropriate PDR over the occipital region. If no PDR is discernible, score stage W if eye blinks at a frequency of 0.5–2 Hz, reading eye movements, or irregular, conjugate rapid eye movements associated with normal or high chin muscle tone are present. The PDR in infants and children can contain intermixed slower EEG rhythms such as posterior slow waves of youth (PSW). PSW are superimposed or fused with the PDR and bilateral but asymmetric at a frequency of 2.5–4.5 Hz. They block with eye opening and disappear with drowsiness and sleep. PSW are uncommon in children <2 years of age, have a maximal incidence between ages 8 and 14 years, and are uncommon after age 21 years.

Stage N1 is scored if the PDR is attenuated or replaced by low-amplitude, mixed-frequency activity for more than 50 % of the epoch. If children do not generate a posterior dominant rhythm, stage N1 can commence if EEG frequency slows by greater than or equal to 1–2 Hz from those of stage W (Fig. 24.31). It can also be scored if any of the following are present: slow eye movements, vertex sharp waves, rhythmic anterior theta activity, or hypnagogic hypersynchrony. Hypnagogic hypersynchrony (HH) can occur in stage N1 or N2 sleep. It consists of paroxysmal bursts or runs of diffuse, high-amplitude, sinusoidal, 75–350 μV, 3–4.5 Hz waves which begin abruptly, are usually widely distributed but often maximal over the central, frontal, or frontocentral scalp regions (Fig. 24.32). HH is seen in

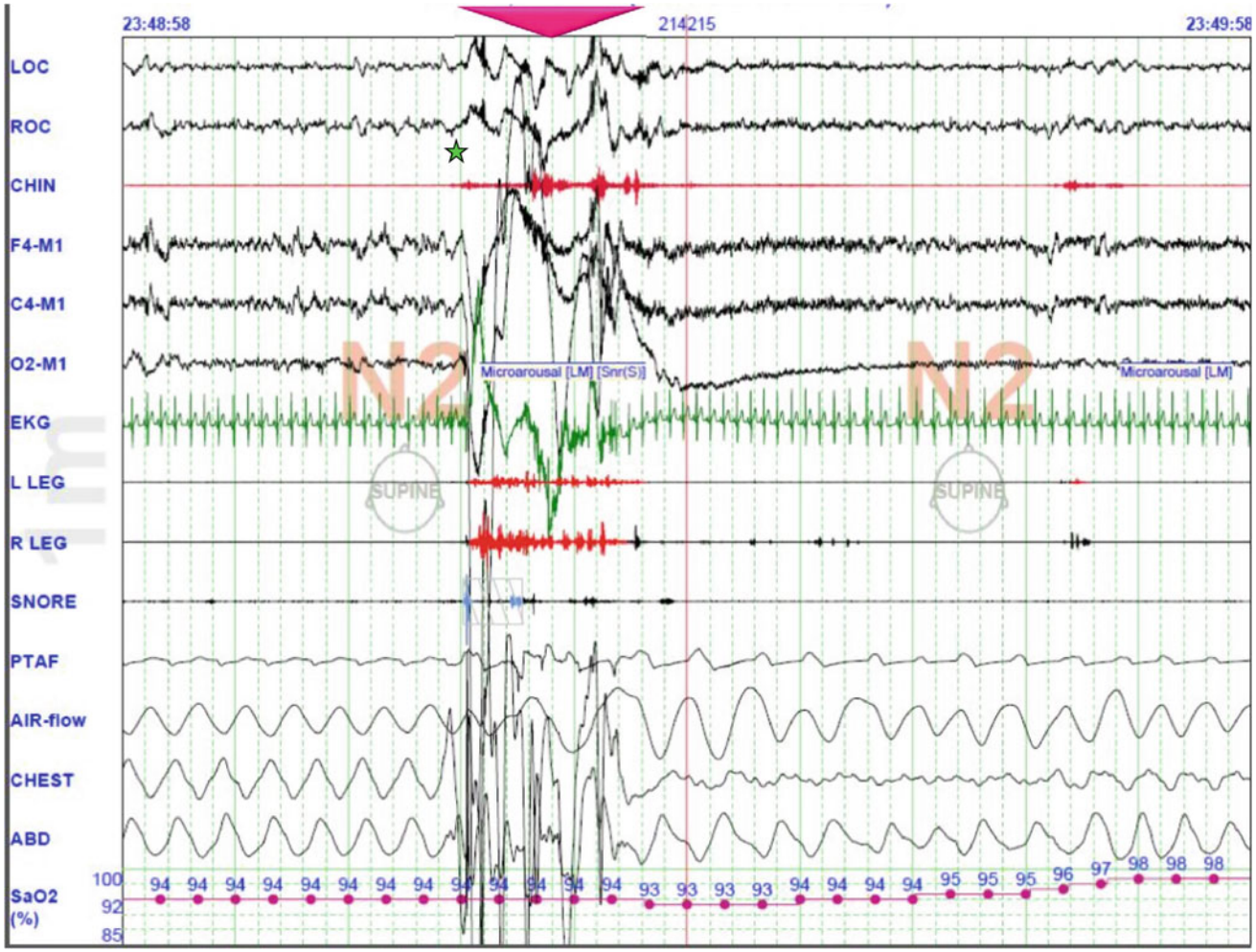


Fig. 24.30 This 60-s PSG epoch represents an arousal pattern. An arousal is scored during sleep stages N1, N2, N3, or R if there is an abrupt shift of EEG frequency including alpha, theta, and/or frequencies greater than 16 Hz (but not spindles) that lasts at least 3 s (*pink bar*), with at least 10 s of stable sleep preceding the change. Scoring of arousal during REM requires a concurrent increase in submental EMG tone. Copyrighted to Alon Y. Avidan, MD, MPH

approximately 30 % of infants at 3 months post-term, 95 % of all normal children ages 6–8 months, and is less prevalent after age 4–5 years; it is seen in only 10 % of healthy children by age 11 and is rarely seen after age 12 years.

Stages N2 and N3 in children are scored with the same rules that are used in adults. Stage R also uses the same rules as in adults. Of note, Stage R in infants and children resembles adults although the dominant frequencies increase with age: approximately 3 Hz activity at 7 weeks post-term, 4–5 Hz activity with bursts of sawtooth waves at 5 months, 4–6 Hz at 9 months, and prolonged runs or bursts of notched 5–7 Hz theta activity at 1–5 years of age. By 5–10 years of age, the low-amplitude, mixed-frequency activity in stage R is similar to that of adults.

Sleep Stage Changes Across the Night

Overall normal sleep stage pattern (sometimes called sleep macroarchitecture) across the night is fairly consistent. A healthy young adult will spend 7–8 h in bed and sleep 85–90 % of that time. It typically takes adult sleepers up to 20 min to fall asleep (possibly longer in a lab setting), and normal entry into sleep for an adult is through stage N1, which quickly evolves into N2. Stage N3 usually follows and persists for some time before giving way to an episode of stage R. Usually the duration of the first stage R episode is brief (5–15 min), and the sleeper then goes back into N2 and possibly N3 for the next hour and a half. Stage R re-occurs at this point and is usually longer in duration than the first

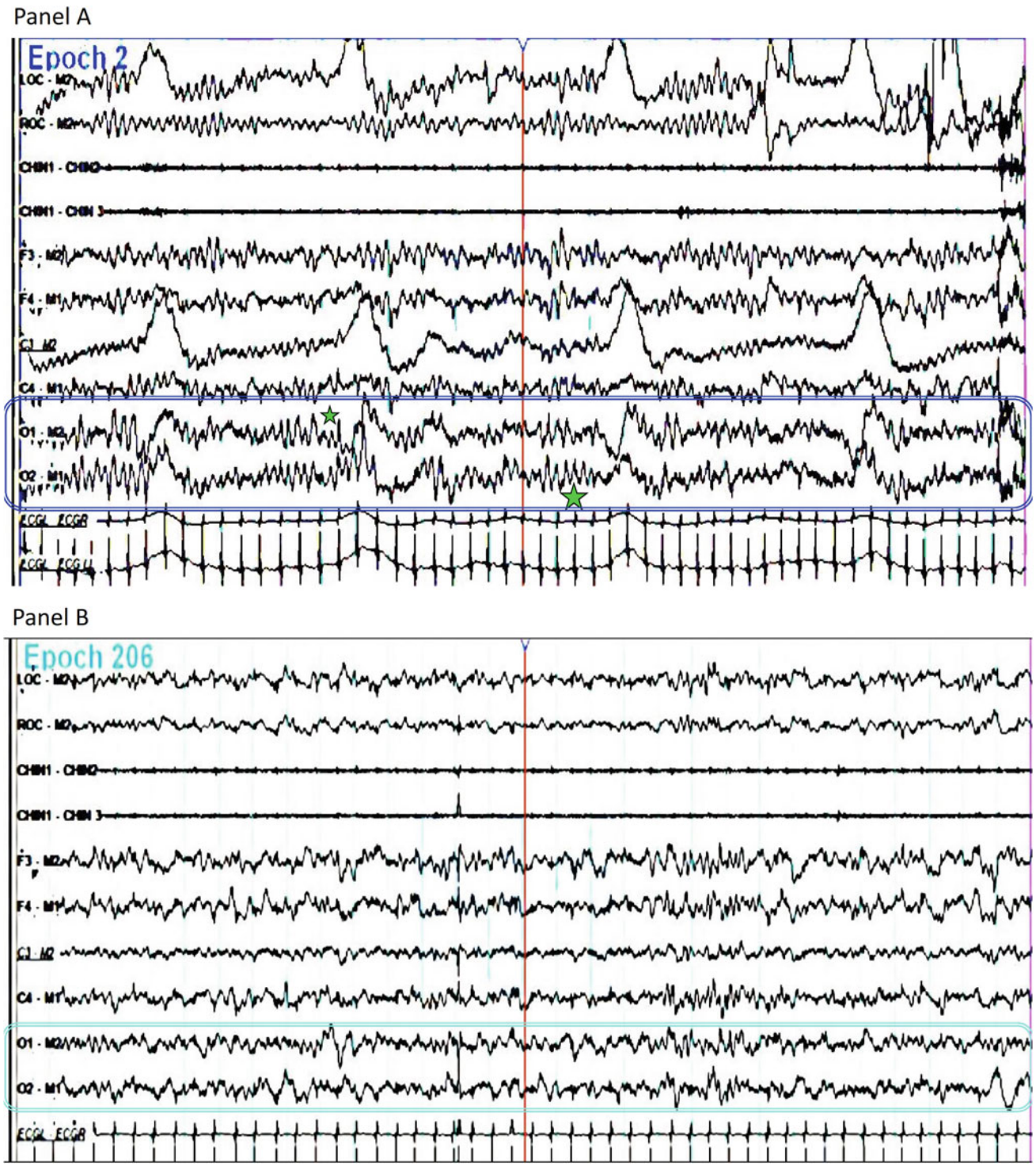


Fig. 24.31 *Panel A* 30-s PSG epoch in a 10 month old who has a posterior dominant rhythm (PDR) of 4–5 Hz as seen in the occipital leads (as noted by the *green stars*). *Panel B* 30 s PSG epoch in same 10 month old showing slowing of the PDR to 3–4 Hz and meeting criteria for scoring stage N1 sleep

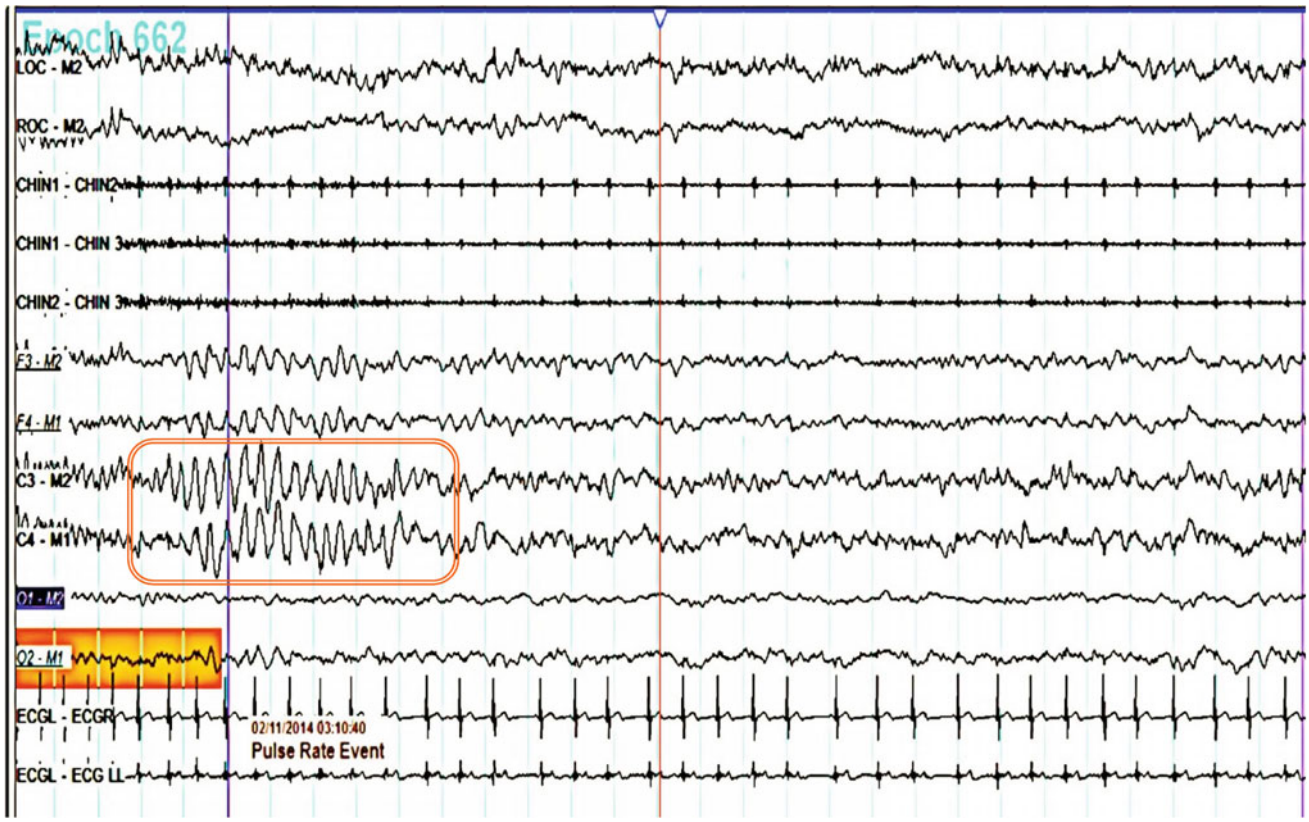


Fig. 24.32 This 30-s PSG epoch in a 2 year old demonstrates hypnagogic hypersynchrony (HH) within the *orange box*, seen most prominently in the central leads. HH is high-amplitude, sinusoidal, 75–350 μV, 3–4.5 Hz waves as noted by the *arrow*

episode [7]. Succeeding NREM-REM cycles usually have less stage N3, more N2, and longer stage R duration as the sleep period progresses. Thus, one could generalize a prototypical night's sleep as having most of the stage N3 in the first third of the night and most of the stage R in the second half of the night. The stage R comes in 4–6 discrete episodes occurring approximately 90–100 min apart. Overall, stage N2 will account for approximately half of the night's sleep and stage R will account for another fifth to quarter. Stage N1 should encompass less than 5 % of total sleep time, distributed mainly at sleep–wake transitions. The remainder of sleep time will consist of stage N3.

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Scoring of Sleep-Related Breathing Events

25

Robert Joseph Thomas

Introduction

Scoring respiratory events during sleep is a core requirement for sleep medicine and research. Criteria have evolved over the years, with changes in the primary signal (thermistor vs. nasal pressure), associations (various degrees of oxygen desaturation and arousal), and the montage used (full polysomnogram to cardiopulmonary monitoring). The scoring manual of the American Academy of Sleep Medicine (AASM) accessible through the Internet [1] is a living volume, which undergoes updates, and provides a commonly used standard. This chapter will not duplicate that effort, but will focus on issues critical to the appropriate interpretation of data and can usefully complement the AASM rules. A brief summary of the AASM scoring rules as of 2016 is as follows: (1) Obstructive and central sleep apneas (OSA and CSA), obstructive hypopneas, and Cheyne–Stokes respiration (CSR)/periodic breathing are scored as standards. (2) Obstructive hypopneas require a 30 % signal drop and an associated 3 % oxygen desaturation or an arousal. A 4 % desaturation alone is required for certain medical insurance coverage indications. (3) Central hypopneas and respiratory effort-related arousals are optional. (4) The same rules hold for diagnostic and therapeutic data. (5) Home sleep studies use 3 or 4 % oxygen desaturation to score hypopneas; non-hypoxic, non-apneic events (e.g., hypopneas without desaturation) are not scored. Thus, on ambulatory testing, the current guidelines require an associated oxygen desaturation regardless of the severity of respiratory abnormality unless apneas occur. (6) Central hypopneas require the absence of snoring, flow limitation, and thoracoabdominal paradox. (7) CSR cycle length requirement is ≥ 40 s.

Scoring of respiratory events occurs on the platform of scored sleep. Conventionally, sleep has been scored using 30-s epochs, into wake, rapid eye movement (REM), and non-rapid eye movement (NREM) stages. NREM stages are further characterized into grades, N1 through N3. Alternate methods of characterizing sleep include cyclic alternating pattern (CAP) of NREM sleep [2] and cardiopulmonary coupling (high-, low-, and very low-frequency coupling of autonomic and respiratory drives, modulated by cortical delta power) [3]. NREM stage N3 is usually associated with stable breathing, where discrete respiratory events or arousals are rare. However, such periods frequently occur outside N3, during a stable form of N2, when the EEG usually shows a non-CAP morphology.

Respiratory pathology during sleep overlays the natural physiology of sleep. Thus, wake hypoventilation generally worsens during sleep, especially during REM sleep, and may be exclusively seen during REM sleep. Vulnerable periods for NREM sleep are at sleep onset (at the start of the sleep period, after a REM period, or after major awakenings), during periods of spontaneous lightening, and before REM sleep. Periodic breathing is especially amplified during these transitional periods. Obstructive respiratory events may be seen during NREM or REM sleep, but dominance of obstructive events in NREM sleep raises the possibility of underlying periodic breathing. Body position, time of night, and circadian effects provide further modifiers, and each can increase severity. Scoring strategies that provide a single number for a night loses the dynamics of these complex interactions and is the dominant driver of night-to-night variability. That is, in a given stage or state of sleep, at approximately the same time of the night, and in the same body position, respiratory events are similar across multiple nights, but the proportion of these states will vary. Within a single night, the evolution of respiratory events is also impacted by changes in respiratory chemosensitivity and rostral fluid distribution.

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Scoring Centricity

When the usual polysomnogram signals are available (sleep, respiration, oximetry), scoring can be hypoxia centric (AHI 4 % and AHI 3 %), arousal centric (incorporating RERA's), or mixed (2016 AASM recommended criteria). Hypercapnia has never made it into the scoring rules, in part due to lack of measurement capability in the majority of adult-focused sleep centers. There is a biological basis to consider intermittent hypercapnia, if it is present, as a hypopnea qualifier, but the lack of widespread availability of technology makes clinical implications speculative.

Use of associated phenomena can provide important information to increase the confidence of individual events, but does not feature in the standard scoring rules. Examples include autonomic associations (heart rate increases, pulse plethysmographic amplitude reductions), limb movement, chin tone elevation and recovery, blood pressure surges, pulse transit time reductions, brief bursts of slow or rapid eye movements, reversal of paradox on effort channels, and a burst of bruxism activity. In an individual patient, a given signal can be especially informative regarding the quality of sleep state. For example, chin EMG tone elevations during NREM sleep are not part of the conventional arousal definition, but the duration and degree of elevation vary markedly between individuals and stay consistent within individuals. The same concept can be applied to the EEG (arousal duration or return to sleep) and heart rate responses to arousal—inter-individual variability is contrasted with intra-individual stability [4].

The spectrum of arousal phenomena on the EEG

Application of the AASM 3-second arousal rule imposes constraints that are not biologically based [5]. In the specific context of respiratory event termination, shorter degrees of alpha/beta intrusion (<3 s) or K complex and delta bursts are often associated with respiratory event termination and raise the consideration as arousal or event markers [5], even if they reflect protective responses. K complexes are isolated widely distributed cortical downstates [6], which can also be induced by disruptive stimuli. While it may have a sleep-protective function, the complex can draw attention to a potential arousing event. Thus, *arousal scoring* implies classic AASM arousals, while *arousal detection* could imply a broader spectrum of EEG transients to bias differentiation of significant versus non-significant respiratory events. These non-traditional approaches are especially useful when disease (dementia, epilepsy, stroke, trauma, and hydrocephalus) or medication distorts the EEG frequencies—such as benzodiazepines (fast frequencies) and atypical anti-psychotics (slow frequencies). A sleep fragmentation phenotype on PSG can be suggested by prolonged sleep–wake transitional instability (>10 min), low sleep efficiency (<70 %), persistently high N1 stage during positive airway pressure (PAP) titration (>15 %), and poor evolution of slow-wave sleep (<1 Hz) [7].

Sleep State Modulates Respiration

Airflow patterns and arousal thresholds are modulated by sleep macrostructure (REM and NREM sleep, stages of NREM sleep), sleep microstructure (CAP and non-CAP), sleep deprivation, medication, and age. There are data suggesting that NREM sleep is bimodal rather than graded, with stable and unstable regimes (Fig. 25.1), or alternatively conceptualized as effective and ineffective [3]. These periods of stability intrinsic to NREM sleep determine the instantaneous presence or absence of sleep apnea. Cardiopulmonary analysis shows stable breathing periods result in high-frequency coupling of respiration and heart rate variability, simultaneously associated with high EEG delta power. Such periods are not restricted to N3, but make up most of N2 in health. Intermittent periods of stable breathing are well recognized in patients with even severe obstructive sleep apnea, during both N3 and N2 [8]. Flow limitation can be prominent, and both hypoxia and hypoventilation may occur during these obstructed but stable periods. A prolongation of inspiratory time is typical during these periods of partial airway obstruction during stable sleep. These periods do have an impact on the EEG, but visual determination is not possible, and computational methods such as the respiratory cycle-related EEG change are required [9, 10]. The persistence of CAP-type features on the EEG may occur during slow-wave sleep associated with severe persistent flow limitation, suggesting the presence of concomitant disruptive influences.

Is an Arousal Necessary to Enable Airway Opening and Respiratory Recovery?

The standard teaching is that an arousal from sleep was necessary for airway opening. There is new information that only a proportion of respiratory recovery is arousal dependent and that blood gas changes can drive airway opening without an electrocortical arousal [11]. The degree of arousal does amplify associated autonomic features roughly proportional to the degree of alpha/beta intrusion [12]. However, stage and state modulation are almost certainly important. It is conceptually useful to consider NREM as manifesting bimodal stable versus unstable propensities and

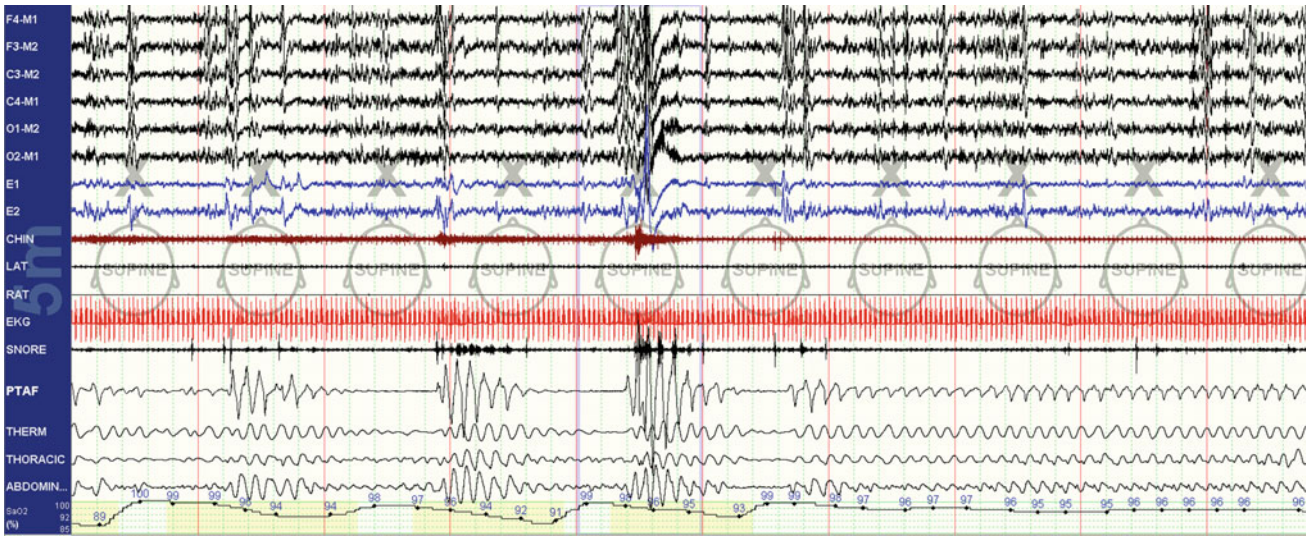

Fig. 25.1 Spontaneous switch from unstable to stable NREM sleep. 5-min polysomnogram snapshot of stage N2, showing the relatively abrupt switch from a state of respiratory event and arousals to a state with stable breathing and the absence of arousals

characteristics. For example, when sleep drive is high, and NREM state is stable, airway opening can likely occur without a classic electrocortical arousal, the high sleep drive masking EEG arousal recognition or simply preventing an arousal, allowing brain stem and chemoreceptor or mechanoreceptor-based respiratory reflexes to open the airway. When NREM sleep is in an unstable as reflected by CAP EEG or low frequency cardiopulmonary coupling, the networked driving of sleep state couples nearly all prevalent physiology and pathology. Thus, tidal volume fluctuations, EEG arousals, heart rate change and hemodynamic/autonomic oscillations, and even periodic motor activation are all coupled and occur nearly simultaneously. During such a condition, it is hard to be sure arousal is *necessary*, but arousals certainly *occur*, in close temporal relationship, to respiratory recovery. K complexes are frequent accompaniments of respiratory recovery and may reflect the interplay and interaction between sleep disruptive and restorative forces. Medications that increase slow wave, such as atypical anti-psychotics, can obscure the faster components of arousals, when clusters of slow waves may be the only visually evident marker of respiratory-related arousal. During REM sleep, respiratory fluctuations occur as part of the REM sleep state and independent of arousals (increase in EMG tone), and it is unknown whether these tidal volume and flow fluctuations when exaggerated but without EMG increases disrupt REM sleep. When REM-without atonia is also present, respiratory-related arousal and REM sleep scoring can be difficult and sometimes impossible.

Event Cycle Characteristics

Event Cycle Length

The cycle length (Figs. 25.2 and 25.3) of a respiratory event reflects the time to arousal, respiratory drivers, and effects of phasic suppression of muscle tone for REM sleep events and intrinsic network properties of the sleeping brain. The time to arousal is dependent on the input traffic to brain stem arousal centers, which may be from within (respiratory effort), somatic afferents from the upper airway, or visceral afferents (including respiratory chemoreflex sensing of O_2 in the carotid body, and CO_2 in the carotid body and retrotrapezoid nucleus neurons).

Respiratory driving may be reactive (response to upper airway obstruction) or active, when the respiratory chemoreflex arc is hyperactive as in congestive heart failure (CHF) [13], at high altitude [14], and after exposure to hypoxia (sensory long-term facilitation) [15]. Phasic effects of REM sleep can cause obstructive, central-looking, or pseudoperiodic patterns, the latter when eye movements occur with similar inter-phasic interval. This latter phenomenon can be incorrectly characterized as periodic breathing, especially if EEG is not available, as in home sleep testing.

The intrinsic network properties of the brain reflect the interactions between multiple components including the cortex, thalamus, various output systems such as respiratory, autonomic, and motor, and the afferent return from the latter systems through baroreflex and chemoreflex arcs. On the

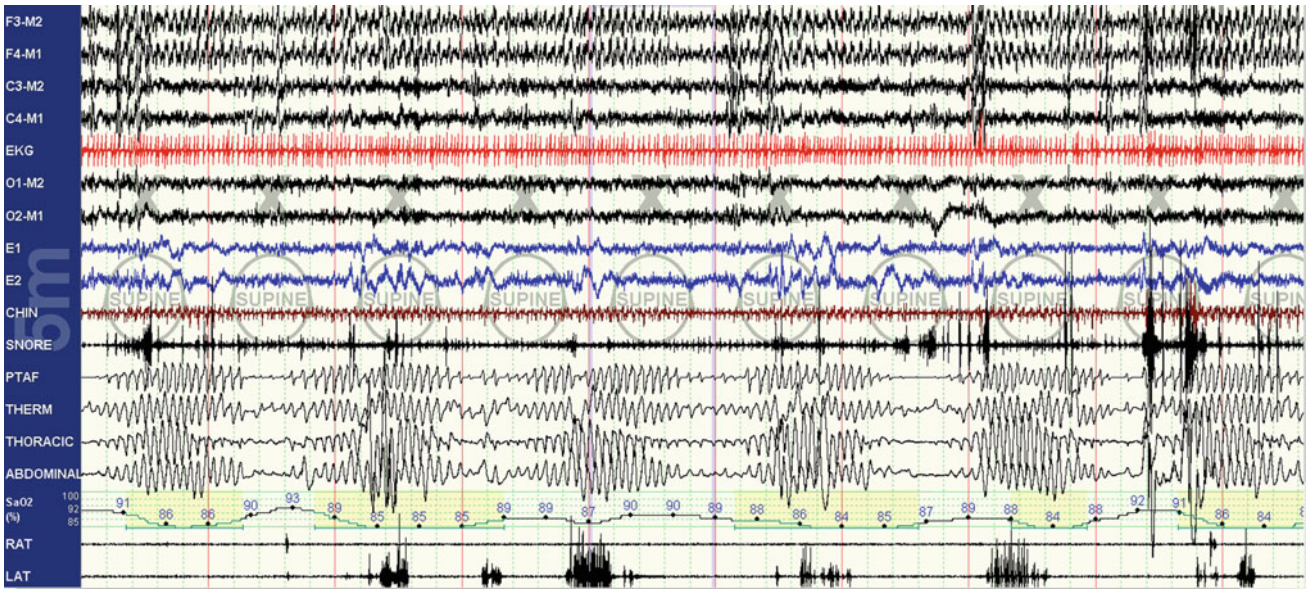

Fig. 25.2 Long-cycle periodic breathing. 5-min polysomnogram snapshot. Cycle times are close to 50 s, in this patient with congestive heart failure

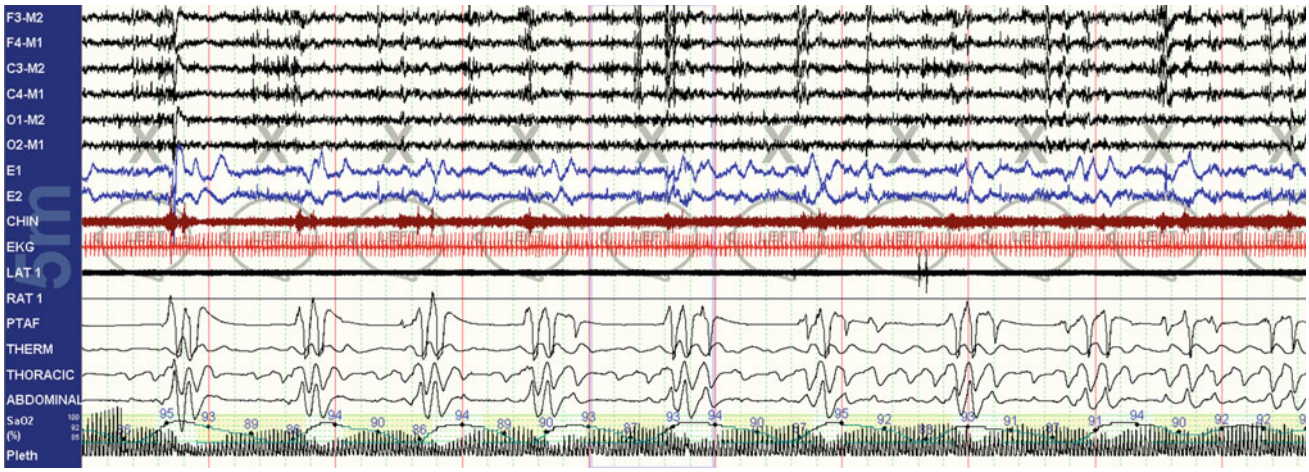

Fig. 25.3 Short-cycle periodic breathing. 5-min polysomnogram snapshot. Cycle times are about 30 s

surface EEG, this network property is represented by CAP. The CAP cycle length imposes an overall structure of the timing of pathological and physiological integrated multi-component repeats.

Event cycle length is entrainable. The best examples are high-altitude (short, less than 30 s, often 15–20 s) and CHF (long, most characteristically 60 s or longer) cycles. Adaptive ventilation can convert a short cycle to a long cycle; I have never seen this therapy convert a long to a short cycle. Respiratory cycle length, the time from one point of an event to a corresponding point, e.g., peak recovery to preak recovery, can also lengthen with supplemental oxygen or use of a non-vented mask to minimize hypocapnia [16], by prolonging the time to arousal. It is plausible that other rhythmic and repetitive arousing stimuli such as experimental auditory arousals can entrain "CAP," but there will be biological constraints on frequencies which can entrain sleep state. These biological constraints in the frequency of coupled multicomponent oscillations are determined by the network properties of the sleeping brain. Too frequent arousing stimuli will wake up the subject, but too infrequent stimuli will likely only transiently arouse the subject without entrainment to the cycle time of the arousing stimulus.

Event Cycle Timing

External driving of sleep respiration can occur with neurostimulators (e.g., vagal, nerve stimulator for epilepsy Fig. 25.4). These stimulation pulses will have a metronomic timing and can cause respiratory suppression with precise repeated timing. Outside experimental settings, metronomic auditory stimulation during sleep does not occur. Strong respiratory chemoreflex modulation, causing periodic breathing/CSR, is the most common cause of metronomic respiratory event timings usually accompanied by equally impressive (consistent timings) oximetry, heart rate, and blood pressure oscillations.

Ultra-Short Respiratory Events

The typical respiratory event evolves over 30–40 s. A commonality of repeat duration is also shared by periodic motor activation and A-phases of CAP. However, when respiratory chemoreflex driving is strong in the setting of normal cardiac function, cycle times shorten and can be as short as 20 s. This pattern strongly resembles that seen at high altitude. Travelers to high altitudes often experience restlessness, frequent brief arousals, and unrefreshing sleep [17], at least in part due to periodic breathing. In contrast to heart failure, the cycle times are 15–25 s, characterized by 2–5 large tidal volume breath clusters followed by apneas of 5–15 s in duration. There is a marked increase in arousals and reduction in slow-wave sleep likely related to hypoxia-induced carotid body sensitization narrowing the $PaCO_2$ reserve and increasing controller gain [18]. A male predominance has been reported [19]. In idiopathic CSA, similar to high altitude, cycles of central apneas are shorter (20–40 s) and not as gradual and smooth as in classical CSR [20, 21]. While 10 s is the standard minimum event length for scoring, shorter events with biological consequences should reasonably be tagged.

Ultra-Long Respiratory Events

Two types of long events are seen. In one pattern, there is prolonged and progressive flow limitation that is terminated by an arousal; this pattern is typical of the pattern called upper airway resistance syndrome. Though this entity has been folded into obstructive sleep apnea, the pattern is distinctive enough. The second pattern is seen in patients with CHF—long-cycle (>60 s) periodic breathing/CSR. One consideration when the event duration is long is that the apnea–hypopnea index/respiratory disturbance index (AHI/RDI) may underestimate severity as there are fewer but longer events.

Assessing Event Significance in Stable NREM Sleep—Periods of Stable Breathing

Respiration is stable during conventional slow-wave sleep. Though described from the early days of recognition of the clinical sleep apnea syndrome, the mechanisms have remained elusive. The state of the cortical sleep network seems important. Increased genioglossus tone and increases in CO_2 occur during the periods of stable breathing [8], with overt hypoventilation and hypoxia if flow limitation is severe. These respiratory features are more likely when obesity or reduced cardiopulmonary reserve is present. In the pediatric age group, obstructive hypoventilation is a common pattern during slow-wave sleep. Spontaneous periods of stable breathing periods do not occur during REM

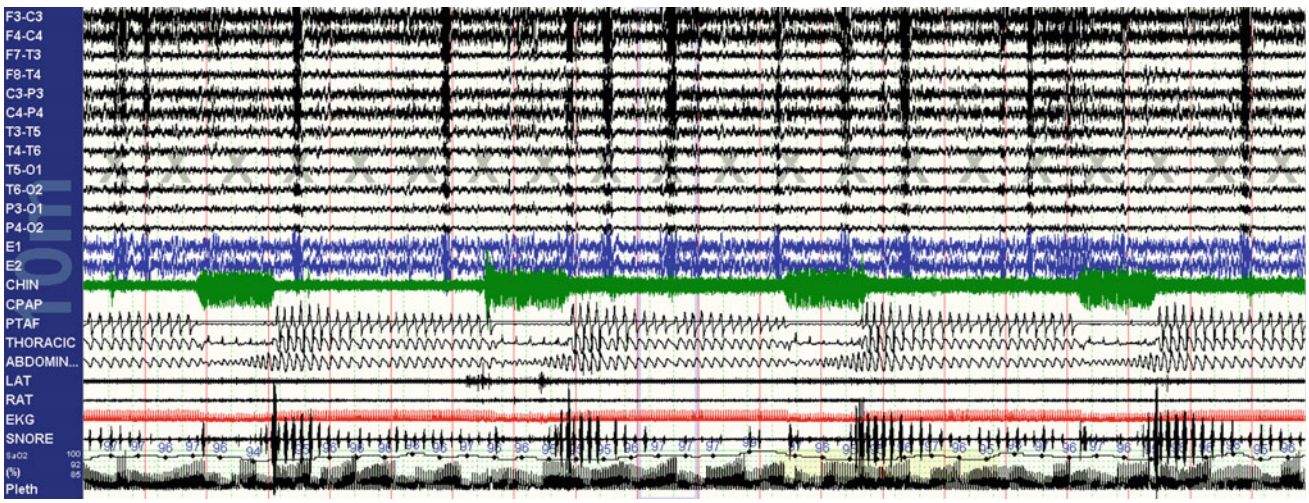

Fig. 25.4 Pseudoperiodic breathing from external driving. 10-min polysomnogram snapshot. Patient using a vagal nerve stimulator for refractory epilepsy. The block-like chin tone increase is a stimulation artifact. During the stimulation phase, there is respiratory suppression

sleep. However, a number of NREM-dominant apnea syndromes, including idiopathic central sleep apnea, periodic breathing, high-altitude sleep apnea, complex apnea/treatment-emergent central sleep apnea, and opiate-induced sleep apnea, show markedly improvements in stability during REM relative to NREM sleep. Metabolic control of respiration and CO_2 dependence on respiratory drive predominates during NREM sleep only.

The clinical problem with associating stable breathing phenomenon exclusively with slow-wave sleep by any definition is that such stable periods occur predominantly in N2, including those with no N3. Figure 25.5a–d demonstrates the impact of these periods in creating stable periods as a component across a dynamic range of pathology. Stable periods dominate the rebound effects of successful PAP titration, and the majority of time is usually N2. Some clues to the nature of this phenomenon can be gained from the concept of NREM sleep bimodality. The first clue came from the description of CAP and non-CAP from Italian researchers in the mid-1980s [22]. CAP and non-CAP periods occur across NREM sleep; non-CAP occurs in N2 or N3 [2]. Subsequently, the autonomic and respiratory associations of CAP/non-CAP were described [13]. Finally, the description of the cardiopulmonary coupling technique showed that NREM sleep has bimodal characteristics in health and disease. High-frequency coupling and low-frequency coupling periods show spontaneous switching and in relation to delta power. That is, high-frequency coupling is associated with high delta power, non-CAP EEG, stable breathing, strong sinus arrhythmia, and blood pressure dipping [3]. Low-frequency coupling is associated with unstable breathing (reaching scorable thresholds of sleep apnea in disease), cyclic variation in heart rate, CAP EEG, and blood pressure non-dipping. Thus, stable breathing periods reflect natural integrated network states of the brain and are amplified and readily recognizable in sleep apnea patients as the two states are markedly different on visual inspection. Benzodiazepines and related drugs increase non-CAP [23, 24] and may be expected to increase stable breathing periods. Zolpidem increases blood pressure dipping [25] and could do so through the induction of stable NREM periods.

The proportion of stable breathing periods will impact the computed apnea–hypopnea index, as these periods do not contribute to the metric. Varying proportions of stable breathing on a night-to-night basis can contribute to night-to-night variability of the apnea–hypopnea index. Successful positive pressure titration markedly increases stable breathing periods on the treatment night and can provide a false sense of success; using the apnea–hypopnea index on a given pressure can be incorrect due to this confound. No current metric captures this pathology, though quantifying the % of flow-limited breaths will provide one measure and is available in some device-related automated analyses. The duty cycle of respiration (% inspiration of the respiratory cycle) will increase during these periods from prolonged inspiration [26]. Audible snoring or recordable upper airway vibrations are frequently noted. The pattern of flow limitation (the shape of the flow-limited breath) may have individual characteristics (similar within the same individual). Analysis of respiratory cycle-related EEG changes during such periods show an impact on electrocortical activity [9].

Assessing Event Significance in REM Sleep

The natural tidal volume fluctuations that occur in REM sleep, especially during phasic REM sleep, can mimic "real" apneas and hypopneas. Of special concern during positive pressure titration, brief events that are not associated with arousals or oxygen desaturation should probably be ignored unless they are actual obstructive apneas.

NREM Versus REM Dominance

For practical purposes, periodic breathing and hypocapnic central apnea do not occur in REM sleep (exception, a patient with CHF who demonstrates periodic breathing during wake state). NREM dominance is well described in idiopathic central sleep apnea [27], periodic breathing associated with heart failure or stroke [28], opiate-induced sleep apnea [29], and high-altitude periodic breathing [30]. NREM dominance is also a feature of complex apnea/treatment-emergent central sleep apnea, regardless of the exact definition used [31].

The simplest method is the NREM versus REM AHI/RDI, but the following are confounds: (1) Body position: Only supine-to-supine comparisons are fair; (2) stage and state of sleep: Periods of stable breathing, which may be associated with N2 or N2 sleep, contribute little to the AHI/RDI, while REM sleep does not have a similar stable equivalent. Determining NREM dominance can be difficult in those with substantial obstruction, where two distinct patterns can coexist—periodic breathing during NREM sleep and obstructive events during REM sleep. The use of PAP usually clarifies the situation—REM disease is readily eliminated, while NREM disease is not.

Ataxic Respiration

When there is continuous variability of rate, volume, and rhythm of breathing during NREM sleep (nearly looking like respiration in REM sleep), often admixed with obstructive or

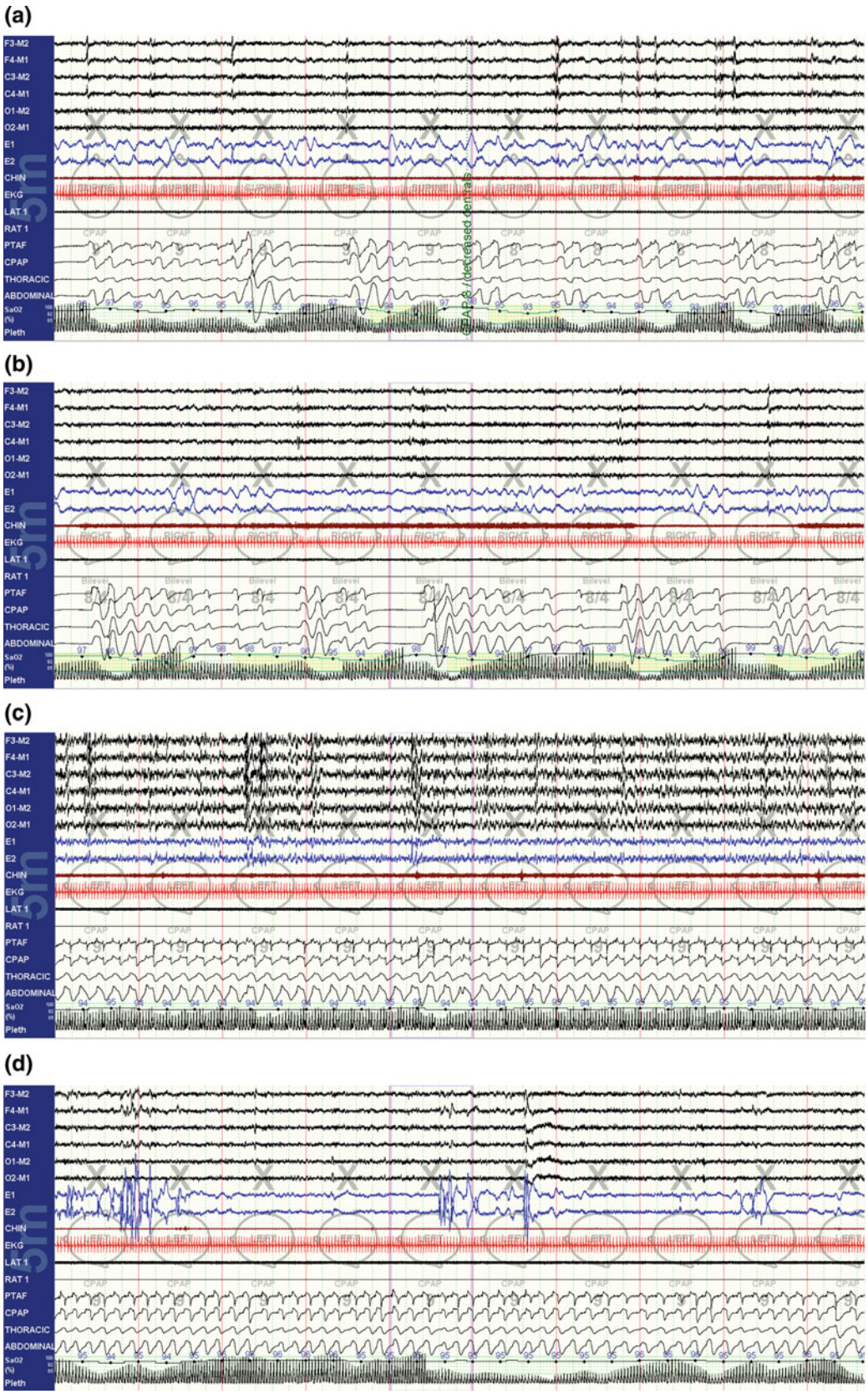

Fig. 25.5 **a** Effect of CPAP on high loop gain sleep apnea. Same subject as in Fig. 5.3. CPAP opens the airway, but the underlying rhythm continues. **b** Effect of non-adaptive bilevel PAP on high loop gain sleep apnea. Same subject as in Fig. 5.3. The cycle times prolong, likely due to worsening of hypocapnia. Events during titration often show minimal oxygen desaturation, or even signal reductions reaching thresholds for hypopnea, and may take atypical long, short, or ataxic patterns. **c** Stabilizing effect of "stable NREM" sleep on sleep apnea. Same subject as in Fig. 5.3. Conventional stage is N3. **d** Stabilizing effect of REM sleep on high loop gain sleep apnea. Same subject as in Fig. 5.3

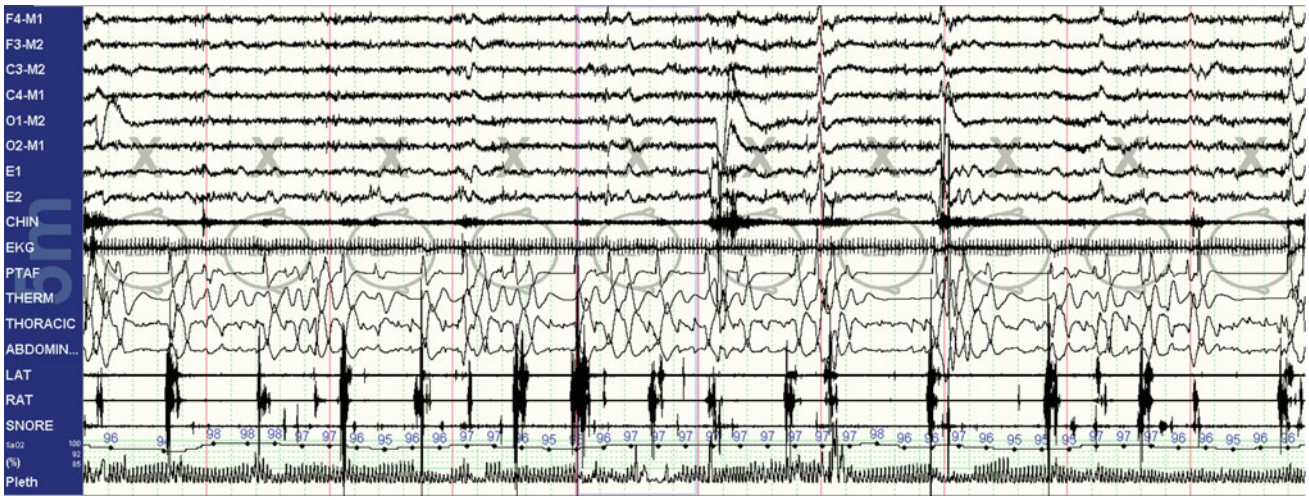

Fig. 25.6 Ataxic respiration from opiate use. 5-min polysomnogram snapshot. *Note* (1) relatively mild oxygen desaturation; (2) short but variable length central apneas; (3) arousals and periodic motor activation

central apneas of variable duration, the term may be used. The events may be so short, and the respiratory abnormality is devoid of predictable fluctuations that the standard rules may over score or underscore events. Opiate use is the most common cause [32, 33], but any brain stem neurological abnormality, such as multiple sclerosis, brain stem stroke, and craniovertebral junctional anomalies, may also exhibit these features. Opiate-associated ataxic breathing (Fig. 25.6) is usually accompanied by mild hypercapnia, and in general, ataxic breathing is sensitive to reductions in CO_2 by increasing ventilation such as by applying continuous PAP (CPAP).

Loop Gain—A Concept Relevant to Understanding Scoring Approaches and Limitations

Breathing during NREM sleep is under metabolic/automatic control and can be understood through interaction between its components: *controller*, *plant*, and *mixer*. The "controller" converts the signal from the chemoreceptors into a ventilatory drive for the plant (an anticipated ventilation for a given $PaCO_2$). The "plant" refers to the lungs, blood, and the tissues where CO_2 is stored. It is the effector of the controller that produces the change in $PaCO_2$ for a given change in ventilation stimulus. Its performance depends on mechanical and biochemical properties of its components (e.g., lung compliance, ventilation–perfusion matching, hemoglobin concentration). For most of the awake individuals, eupneic $PaCO_2$ ~40 mmHg and for sleeping individuals, it is ~45 mmHg. The "mixer" represents the time it takes for the capillary blood from the lungs to reach the chemoreceptors and is primarily a function of cardiac output.

Sensitivity (chemosensitivity) of each of the system's components to a change in input dictates how responsive the entire system is. This responsiveness has been termed "gain" or (▲ output/▲ input), an engineering term used to describe how stable or unstable a system is. The higher the gain, the less stable the system is. The controller gain is the (▲ Ve/▲ $PaCO_2$), and plant gain (▲ PaCO2/▲ Ve), and the mixing gain determines the speed with which changes in $PaCO_2$ and PaO_2 from plant are detected by the controller [34]. The overall gain of the system (loop gain, Ve disturbance/Ve production) determines the stability of the system and is the product of controller, plant, and mixing gains. Loop gain varies between individuals and with disease states [35]. High loop gain is found in systems with large swings in blood gases and ventilation, while low loop gain indicates a stable system but also one that may also not respond adequately to a change in ventilation.

The metabolic respiration control system is exquisitely sensitive and designed to maintain $PaCO_2$ homeostasis rather than oxygenation. Two levels of $PaCO_2$, the apneic and eupneic thresholds, are critical to its operation. As elegantly demonstrated by Bulow in the 1960s [36–38], *apneic threshold* represents a level of $PaCO_2$ below which breathing stops. *Eupneic threshold* is defined above. Below eupneic threshold, ventilatory drive is reduced, while above it is increased [39]. During sleep, the apneic threshold is usually 2–6 mm Hg below the eupneic sleeping $PaCO_2$ level, but only 1–2 mmHg below the wakefulness eupneic $PaCO_2$ level [40, 41]. This small difference between awake eupneic and sleep apneic $PaCO_2$ is one reason behind instability of the respiratory system during sleep. When loop gain is too high, periodic breathing, hypocapnic central apneas, and NREM dominance of sleep apnea emerge. When loop gain is too low, hypoventilation results. High loop gain protects

Table 25.1 Recognition of strong chemoreflex modulation of sleep breathing [7]

Polysomnographic feature	Relatively pure OSA	Chemoreflex-modulated SA
Periodic breathing, Cheyne–Stokes	Rare	Typical (often short cycle, <30 s in the absence of CHF)
Respiratory event timing	Variable (each event tends to have different durations)	Self-similar/metronomic
Severity during sleep state	Greater severity in REM	Minimal severity in REM
Effort signal morphology	Well maintained during obstructed breath	Complete or partial loss between recovery breaths
Flow–effort relationship	Discordant: Flow is reduced disproportionately to reduction in effort	Concordant: Flow and effort follow each other in amplitude
Arousal timing	Early part of event termination	Crests event, often in the center of the sequence of recovery breaths
Oxygen desaturation	Irregular, progressive drops, V-shaped contour	Smooth, symmetric, progressive drops rare
Response to continuous positive airway pressure	Normalization of flow, sleep, oxygenation, and ventilation	Persistence or "emergence" of central apneas or periodic breathing

respiration during REM sleep and may explain why NREM-mixed periodic breathing with obstruction improves or "disappears" during REM sleep.

Quantitative polysomnogram analysis has also been used to differentiate cardiac-related periodic breathing from non-cardiac causes and may help predict effectiveness of CPAP for CSA-CSB. In brief, loop gain can be determined from the ratio of ventilation length (VL) divided by the apnea length (AL) or (VL/AL). VL/AL > 1 [42] and cycle duration/length (CL = VL + AL) of > 45 s [43] are suggestive of CSA of cardiac cause. Loop gain (LG) can also be derived by the means of a duty ratio (DR = VL/CL) of periodic breathing, $LG = 2\pi/(2\pi DR - \sin 2\pi DR)$ [44]. In a pilot study of 14 CHF-CSB patients, LG was significantly higher among the non-responders and value of >1.2 predicted lack of response to CPAP in 7/7 patients [44]. Although simple to determine and encouraging from pilot data, such findings are limited to patients with already clear periodic breathing and should be validated in a larger, prospective manner. Table 25.1 summarizes some of the differentiating features of obstructive and chemoreflex driving of respiratory events.

Assessing Pathological Respiratory Chemoreflex Activation: Cheyne–Stokes Respiration and Central Hypopneas

The AASM scoring manual requires the following for scoring a CSR event: cycle length of 40 s or greater, a typical concordant waxing–waning of flow and effort, a minimum of 3 cycles with these characteristics for any single CSR event, and an overall CSR index of $\geq$5/h of sleep. The ICSD-3 specifies that these should make up $\geq$50 % of all scored events. Central hypopnea scoring is "optional" in the scoring standards, yet recognition of CSR is recommended.

The events that make up CSR are essentially strings of central apneas and hypopneas. However, events at both sea level (often) and high altitude (always), and in patients with positive pressure induced or amplified respiratory instability, have short cycles that are less than 30 s. If 40 s is a requirement, then these short-cycle events will be falsely characterized as obstructive.

Flow limitation excludes a "central hypopnea" in the scoring manual, yet this idea has been conclusively shown to be false from the following data: (a) At high altitude, a pure chemoreflex form of sleep apnea, flow limitation occurs frequently; (b) heart failure patients with otherwise classic CSR can demonstrate flow limitation; (c) the airway can close during polysomnographic central apnea [45, 46]; and (d) central hypopneas demonstrate flow limitation [47]. In clinical practice, snoring can be seen in association with CSR—but usually occurs associated with the arousal, while in more purely obstructive event, the snoring occurs during the event and transiently resolves during the arousal.

Recognition of CSA syndromes generally requires a full-night recording of standard polysomongraphy with special attention to inspiratory effort. Cardiopulmonary recordings may also be sufficient, with the limitation of inability to differentiate REM from NREM-dominant disease, which has diagnostic and therapeutic implications. The current gold standard to determine whether apnea is central (no inspiratory effort throughout the event) is the use of esophageal balloon catheter [48, 49]. Contrary to current

clinician perceptions and practice, a survey of 799 patients who underwent esophageal balloon placement during their sleep study revealed that 85 % felt minimal, if any, discomfort and only 3 % of patients refused the catheter on second occasion [50]. Attempts at using "less invasive" techniques such as respiratory inductive plethysmography or strain gauges, as well as pulse wave artifacts in the oronasal flow signal, produce unreliable results [51, 48]. Pulse transit time measurements can provide supportive information regarding central genesis. The lack of esophageal balloon data complicates the detection of *central hypopneas* even further. The exact threshold of when effort is adequate versus not is also somewhat arbitrary. Alternative strategies, using PSG-based algorithms, have been developed, but show only marginal accuracy (68 % in one study) [52].

A consistent feature of hypocapnic, heightened chemoreflex-mediated central apnea is predominance of events during NREM sleep, especially during non-slow-wave stages [7, 28, 53–55, 56, 57]. A metronomic self-similar appearance (identical event length and morphology in a consecutive series of events; consecutive hypopneas appear like clones of the preceding and following ones), even if individual events fulfill obstruction criteria, is typical, except in opiate-induced CSA, where variability of expiratory phase is characteristic. In contrast to hypocapnic CSA, in OSA and in many cases of hypercapnic CSA, the disease worsens markedly during REM sleep, especially if the motor neurons of the diaphragm are involved [34, 54]. Notable exceptions are congenital central hypoventilation syndrome (CCHS) and opioid-induced CSA, where the disease is worse in NREM sleep.

Treatment-Emergent Central Sleep Apnea (TE-CSA) and Complex Sleep Apnea

The $PaCO_2$ reserve is labile during NREM sleep [58] and arousals due to maladaption to PAP can occur and drive instability [31]. The compliance or pressure at which passive critical closing of the upper airway occurs (P_{crit}) shows overlap between patients with OSA and controls [59]. Variations in P_{crit} alone account for only a portion of variations in the AHI [60] or differences in phenotype [61].

In some patients with OSA, central apneas and periodic breathing emerge during the initiation of CPAP. This phenomenon is called treatment-emergent CSA in the ICSD 3rd edition and defined when there are 5 or greater central apneas and hypopneas per hour of sleep making up greater than 50 % of all respiratory events during titration of CPAP in those fulfilling obstructive apnea criteria during diagnostic polysomnography. The ICSD tries to clear some of the controversies over "complex sleep apnea" [62]. The existence of TE-CSA apnea as a unique entity has been controversial in the sleep world. The original description [58] noted a set of relatively unique features on *diagnostic* polysomnography and an incomplete treatment response that included induction of central apneas or persistent periodic breathing when CPAP was applied. The key feature is NREM-dominant central hypopneas or periodic breathing with obstruction, resolving spontaneously during REM sleep. That is, induction of central apneas was not required. A subsequent publication "defined" complex apnea proposing the currently deployed ICSD criteria [62], which also became the criteria used by medical insurance to qualify patients for the more expensive adaptive ventilators.

The ICSD allows the coexistence of periodic breathing and obstructive sleep apnea (a "splitting" approach). The term "complex apnea" (a "lumping approach") may have clinical utility in that a single term captures a number of ICSD categories with a common pathogenesis and identical responses to therapy. Central hypopneas are rarely scored in clinical practice, and thus, reports of complex/treatment-emergent sleep apnea, especially if using the ICSD treatment-emergent category and criteria, likely include only patients on one end of the spectrum of chemoreflex-driven instability than the middle of the obstruction-central continuum where a substantial minority of patients could belong. In these patients, short-cycle (≤ 30 s) periodic breathing, with features of admixed obstruction, highly reminiscent of high-altitude periodic breathing, can occur and was part of the original description [58]. It is possible that long cycles, ≥ 60 s, may be caused by subclinical cardiac diastolic dysfunction (proven by echocardiography), but data are lacking on cardiac function differences between patients demonstrating purely long- versus short-cycle events.

A consistent feature of patients with treatment-emergent/complex sleep apnea, documented in most publications, is disproportionate sleep fragmentation, which often persists despite reasonable respiration-targeted therapy. As arousals amplify hypocapnic instability, inadequate cohesion of the NREM sleep-related network activity seems to be the core pathology in some of these patients. This phenomenon is reminiscent of the reports of CHF patients, showing persistent sleep fragmentation beyond that attributable to respiratory events [63].

Titration Versus Diagnostic Data

The AASM recommends the same criteria for scoring respiratory events on both the diagnostic and therapeutic polysomnograms. However, eliminating apneas and significant hypoxia is more readily achieved, and much of positive pressure titration is focused on normalizing flow (eliminating RERA's). Thus, normalizing the RDI rather than the AHI is necessary. An even better target may be enabling stable

breathing. Scoring titration polysomnograms using the "recommended" criteria (3 % desaturation or arousal, 30 % signal change) will miss RERA's.

Oximetry Analysis

Three distinct oxygenation abnormalities have specific pathophysiological significance. Periodic breathing and central sleep apnea are associated with a "band-like" desaturation profile, as the individual dips are highly similar due to the self-similar event duration and severity typical of respiratory chemoreflex driving. A "V"-shaped desaturation is seen only during REM sleep and is a good reflection of the biological drive of REM sleep, as saturations begin to improve even before the termination of polysomnographic "surface" REM sleep. Finally, a "sagging" oxygen desaturation profile, where the return to baseline is progressively impaired, is often seen in hypoventilation. If CO_2 is monitored, an envelope of elevation that mirrors this sag may be seen. Figure 25.7 shows some of these patterns.

Capnometry Analysis and Hypoventilation

Measurement of CO_2 in the adult sleep laboratory has been neglected because of technical inadequacy (the development of cheap, rapidly responsive, and accurate monitor, similar to an oximeter) in clinical diagnostic application (not measured in the vast majority of sleep laboratories dealing with adults patients), tracking of home treatment responses in the ventilation community, and research exploring the basic science of hypercapnia at local and systemic levels [64]. Obesity hypoventilation syndrome requires daytime hypercapnia regardless of the severity of sleep hypercapnia—do we really need to wait until wake CO_2 regulation fails before recognizing an important sleep state dysfunction? The 10-min threshold for elevated CO_2 is fairly arbitrary—even if a reasonable minimum severity grading is necessary. Pediatric norms (>25 % of the total sleep time as measured by either the arterial PCO_2 or surrogate is spent with a PCO_2 >50 mmHg) are better defined from polysomnography, but the correlation of the degree of hypercapnia to cognitive and cardiovascular outcomes, if any, remains to be established.

What about high values of PCO_2 during brief periods of REM sleep in a patient with neuromuscular disease that cause arousals (and thus a transient reduction in CO_2) without quite hitting a duration (% total sleep time or a certain number of minutes above threshold) mark? There are instances when hypercapnia emerges once CPAP stabilizes respiration and sleep is no longer fragmented—prior to treatment, the repetitive arousals protected the patient from severe hypercapnia. Is hypercapnia on treatment as acceptable as hypercapnia before treatment? Do we call this treatment-emergent hypercapnia? The majority of sleep

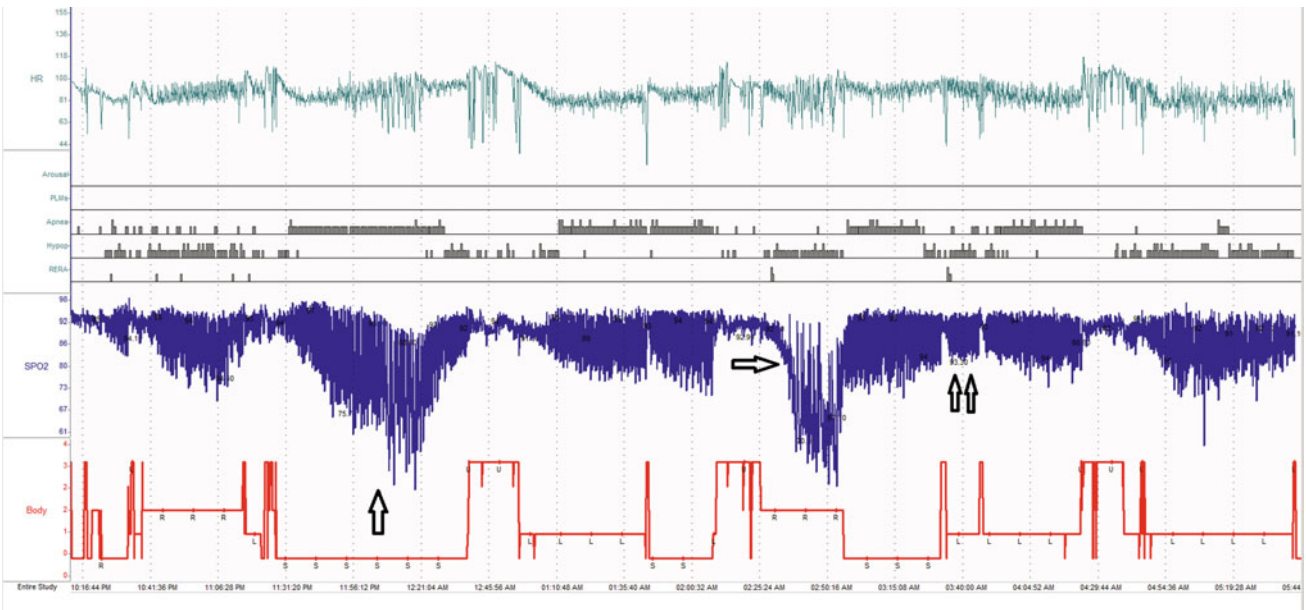

Fig. 25.7 Oximetry analysis. Home sleep study. Besides the obviously abnormal oxygenation, *note* **a** V-shaped desaturation virtually pathognomonic of REM sleep-related sleep apnea (*vertical single arrow*); **b** possible REM sleep hypoventilation (*right pointing arrow*): V-shaped desaturation and failure of return to baseline of oximetry; **c** band-like oxygen desaturation typical of periodic breathing. In this instance, the concomitant obstructive features resulted in greater desaturations that is typically seen with periodic breathing

laboratories do not have the technology (and thus not even the technical expertise) to manipulate CO_2.

There is unfortunately no polysomnographic feature equivalent to CSR to suggest hypoventilation, other than disproportionate oxygen desaturation, which can have other causes, such as ventilation–perfusion mismatch. Respiratory rate may be low (contributing to hypoventilation) or high (a response to hypercapnia) and thus not be diagnostically useful in adults, though in children tachypnea during sleep can suggest disease. Patients on opiates have a relatively unique phenotype of ataxic respiration, central apnea propensity, and mild hypercapnia. I have seen rare patients with classic CSR who are hypercapnic, especially when CHF develops in a previously obese hypercapnic patient, or when advanced chronic obstructive lung disease and heart failure coexist.

Adaptive Ventilation

Adaptive servo ventilation (and ventilators, ASVs) provides expiratory support, inspiratory pressure support (PS), and backup supportive responses guided by measures of ventilation or flow averaged over several minutes [65, 66]. Treatment with ASV is better tolerated than CPAP and is effective in suppressing central apneas and improving oxygenation. Positive effects on sleep architecture are less impressive. The ASVs distort the polysomnogram respiratory signals; scoring respiratory events and using scoring to guide titration and determine treatment efficacy require understanding this distortion and the algorithms of the individual devices.

The ResMed adaptive ventilator (VPAP^{TM} Adapt SV) [67–71] provides a baseline degree of ventilatory support and an auto-EPAP in the Auto mode. The subject's ventilation is servo controlled with a high-gain integral controller (0.3 cm H_2O per L/min per second, clipped to 4–10 cm H_2O) to equal a moving target ventilation of about 90 % of the long-term average ventilation (time constant 3 min). If the subject suddenly ceases all central respiratory effort, machine support (i.e., pressure swing amplitude) will increase from the minimum of 5 cm H_2O up to whatever is required to maintain ventilation at 90 % of the long-term average (up to a maximum of 10 cm H_2O, reached in approximately 12 s). Algorithm changes will likely continue, to improve patient–ventilator synchrony, such as dealing with slow breathing rates (current backup default is 15/min) and slow rates (maximum rate at which target ventilation can rise, currently 0.01389 L/min/sec) [66].

The Philips Respironics Bilevel positive airway pressure (BiPAP) autoSV Advanced (flow-targeted dynamic bilevel positive pressure ventilator) provides PAP support to sustain upper airway patency [72–74]. The expiratory pressure automatically adjusts within the available (or prescribed) range (4–25 cm H_2O). Expiratory pressures can also be set at fixed levels if desired. The algorithm's automatic backup rate is based on calculations performed on a moving window of the last 12 spontaneous breaths. The flow-targeted dynamic BPAP device modulates the maximum and minimum PS above the expiratory positive airway pressure (EPAP) as required to maintain a target peak inspiratory airflow: When the device detects normal breathing, flow-targeted dynamic BPAP operates like conventional CPAP by providing the minimal PS; when the patient does not maintain the target peak inspiratory airflow, the device increases the PS up to a maximum inspiratory positive airway pressure (IPAP), which can be set by the user. Peak flow is captured on a breath-by-breath basis and is monitored over a moving 4-min window; as one breath is added, the initial breath falls off. At every point within this 4-min period, an average peak flow is calculated, and the peak flow target is established around that average and is based on the patient's needs.

The Weinmann SOMNOvent CR is available in Europe and combines auto and adaptive pressure [75]. The pressure is measured using a pressure sensor, snoring is calculated based on the high-frequency variations of the pressure signal, and the flow is determined based on pressure and blower parameters. The minute ventilation is compared with the average minute ventilation in a moving window and is focused by 50 % on the last 2 min and by 50 % on the previous time. The treatment mode is called *anticyclic modulated ventilation*. The device applies three pressure levels: the IPAP, which represents the pressure level during inspiration; the EPAP, which represents the pressure level in the early expiration; and the end-expiratory positive airway pressure (EEPAP). The EEPAP regulation is based on the cumulative sum of obstructions within a 2-min epoch, not on single events. During periodic hypopneas, the algorithm increases the difference between IPAP and EPAP continuously to raise the tidal volume. During hyperventilation, the difference between IPAP and EPAP is reduced and can reach CPAP level (zero difference between IPAP and EPAP). During apneas, mandatory breaths are applied automatically.

Recognition and Scoring of Respiratory Abnormality During Adaptive Ventilation

Scoring respiratory events during adaptive ventilation needs to use both the conventional flow signal and the pressure output signal from the ventilator. The flow signal reflects the new output of patient + ventilator, and the pressure signal the output to achieve ventilation. This is roughly equal and opposite the patient's abnormality. The flow and effort signals combine patient and ventilator contributions and give a

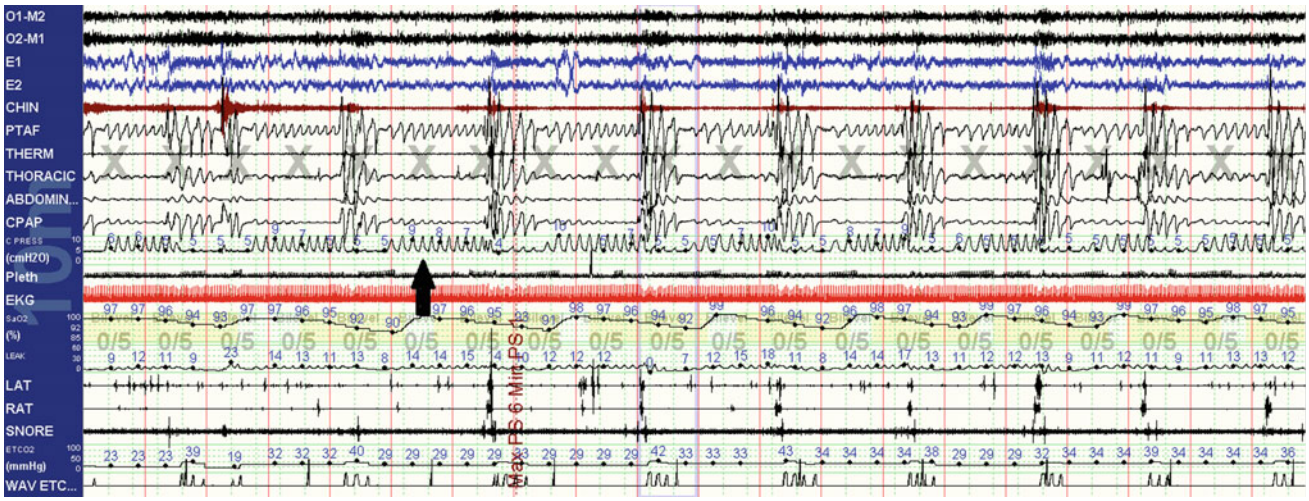

Fig. 25.8 Pressure cycling with adaptive ventilation. 5-min snapshot. The *arrow points* to typical pressure cycling of failing adaptive ventilation (CPRESS trace)

false sense of success. See Fig. 25.8 for excessive "pressure cycling," which is the response of an adaptive ventilator to ongoing periodic breathing. When pressure cycling persists, sleep fragmentation can be severe even if respiration is "improved." Speeding or slowing of the native respiration rate, hypocapnia, breath stacking (rapid ventilator delivered breath on top of the spontaneous breath), variability of expiratory duration mimicking an opiate effect are all patterns of patient–ventilator asynchrony. When the ventilator enables stable respiration, cycling between the minimum and maximum PS zone is minimal. These patterns can be see both on laboratory polysomnograms and from analysis of raw data from devices during use. Although adaptive ventilators can markedly reduce central apneas as conventionally scored, the recent results of the "Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure (Serve-HF)" study, where no clinical or biomarker improvements and increased mortality were noted in the ASV arm, suggest that this specific mode and machine have undesirable biological effects in chronic heart failure patients with reduced ejection fraction (≤ 45 %) and predominantly central sleep apnea [76].

Home Sleep Testing—Cardiopulmonary Recordings or Autonomic Activation-Based Approaches

The approach to score cardiopulmonary sleep measurements can be identical to conventional polysomnography, with the following differences: sleep or wake, REM, or NREM are not known, and EEG or EMG arousal phenomena are absent. Nevertheless, respiratory signal amplitude reduction, oxygen desaturation associations, event cycle time, periodic breathing, and stable breathing periods are readily identifiable, allowing generating metrics very close to conventional polysomnography. However, relatively mild respiratory disease can have substantial sleep quality impacts, and this is the obvious limitation of home sleep testing. Cardio-acceleration and finger plethysmographic amplitude reduction can be useful event tags (arousal equivalents) along with abrupt flow recovery of previously flow-limited breaths. The AASM guidelines restrict scoring to apneas and hypopneas with associated 3 or 4 % oxygen desaturation under the reasoning that arousals are not available to determine the presence or impact of arousals. However, there is ample useable surrogate information of high-probability respiratory events on home sleep testing—respiratory recovery with abrupt large amplitude breaths and associated cardioacceleration and plethysmographic amplitude reductions. There is further information in flow patterns such as plateau-like or downward sloping flow limitation and increases in duty cycles across a sequence of breaths associated with snoring and abrupt return to baseline of both features.

Autonomic tone-based devices incorporating pulse transit time into the analysis and the peripheral arterial tonometry (PAT)-based device [77–80] use the invariant sympathetic burst occurring with arousals—causing a blood pressure surge, cardio-acceleration, stiffening of the vascular tree, and reducing the amplitude of arterioles in the finger tip. The PAT device applies cuff pressure and complex algorithms that improve the precision of the pulse wave amplitude detection and integrates heart rate change, sympathovagal tone, and oximetry information to provide both

sleep quality and sleep apnea information. The analysis is automated and not readily accessible for direct visualization and manual correction if needed. Utility in phenotyping sleep apnea remains to be established (obstructive vs. central disease including periodic breathing detection). Phenotyping is more readily done currently during conventional scoring of flow and effort signals, and by spectral dispersion of low-frequency cardiopulmonary coupling [81].

Scoring Approaches to Positive Pressure Therapy Data

Flow-based and derivatives of flow data are readily available from positive pressure therapy devices [82].

Therapy Waveform Analysis—Continuous and Non-adaptive Positive Pressure Therapy

Direct visualization of data from CPAP machines (Fig. 25.9) can readily identify periods of stable and unstable breathing. It is more challenging to differentiate normal REM-related tidal volume fluctuations from obstructive hypopneas, but the absence of abrupt flow reversals and variability of rate and rhythm are suggestive of REM state effects. Periodic breathing is readily recognized, as are overt obstructive events. Differentiation of obstructive from central sleep apnea can be aided by device determination of open and closed airway apnea using forced oscillation. Individual manufacturers use different thresholds for the detection of individual events and periodic breathing, so discordance between automated detection and visual analysis is to be expected.

Waveform Analysis—Adaptive Bilevel Ventilation

The fundamental question is—what is the primary scoring channel? Adaptive ventilators by their very nature distort the respiratory signals. Thus, a maintained tidal volume can be any instantaneous proportion of patient and machine inputs, and a maintained tidal volume does not reflect biological stability of the respiratory system. However, by computing and displaying the pressure output from the adaptive ventilator, the "work" performed by the ventilator, which is targeted to be equal and opposite to the patients' respiratory output, provides the critical information required to assess efficacy. Pressure cycling reflects the need to respond to periodic breathing, and, if associated with arousals, oxygen desaturation or patient–ventilator desynchrony is marker of failure. Thus, the automatic tagging of current adaptive ventilators, which use percentage reductions in tidal volume, can overestimate success (low AHI flow in the presence of potentially disruptive pressure cycling). Scoring, manual or automated, should be based on both the tidal volume and the pressure output channels, and either one being abnormal can be used as event thresholds (similar to thermistor and nasal pressure for diagnostic polysomnography). Stable respiration in this context requires minimal pressure cycling and stable tidal volumes.

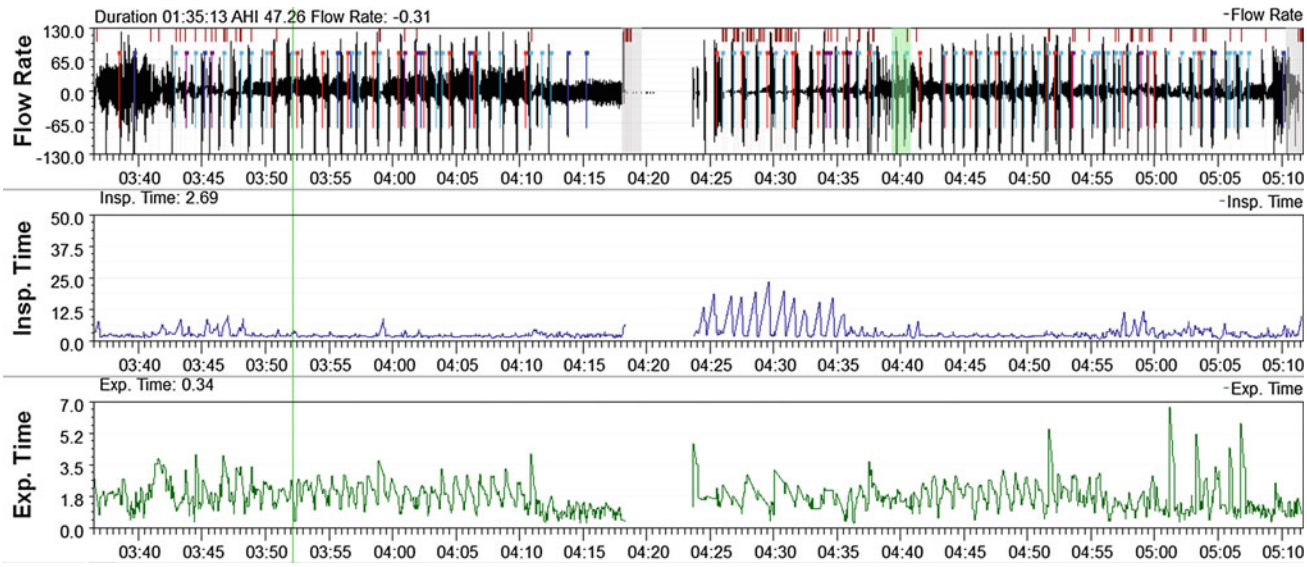

Fig. 25.9 Periodic breathing on CPAP, home therapy data. About 145 min of data. From *top* airflow, inspiratory time, and expiratory time. *Note* Repeated flow oscillations with a self-similar timing and marked variability of expiratory time across the entire period

Waveform Analysis—Ventilators

As sleep medicine specialists are increasingly drawn into the management of complex sleep ventilation problems, understanding the nature of pathology, ventilator–patient interactions, and the impact these have on device-generated and conventionally recorded signals will be needed. The SomnoNIV group has proposed criteria for the assessment of respiratory polygraphy in ventilator-dependent patients [83, 84]. Leak effects are critical in volume and adaptive ventilation more than standard continuous or bilevel ventilation. Abnormal triggering, patient–ventilator desynchrony, over-ventilation, induction of central sleep apnea, and atypical patterns of muscle activation (accessory muscle use) are only some of the challenges in this population.

Other Evidence of Suboptimal Therapy of Sleep Respiration

Several respiratory measures are likely stable in a given individual across nights. These include respiratory rate, inter-breath interval, inspiratory and expiratory time, duty cycle, and, in the case of modes with a backup rate, percentage machine- or patient-triggered breaths. Certainly, these measures "appear" stable across a night and multiple nights when viewing waveform/machine flow-based data. The commercial vendors do not provide the ability to compute such metrics, an area of development that may provide tools for improved therapeutic precision. Variability in the above-noted measures could be a sign of patient–ventilator asynchrony, instability of disease and ventilatory control, leak effects, and impact of sleep stage or state. Tracking such metrics over time may also provide early warning signals of deterioration.

Summary

Scoring of respiratory events using rigid criteria is often practical and pragmatic, but does not sufficiently capture the dynamic range of pathology in sleep-disordered breathing diagnosis and therapy. The AASM guidelines should be considered a minimum expectation, but is insufficient for research and identifying all valuable phenotypes. Scoring RERA's and periodic breathing should not be considered optional. Testing the usefulness of some of the ideas discussed in the chapter may move the field to more precise and biologically meaningful qualitative and qualitative metrics, including that driven by computational analysis. If treatment outcomes can be improved, new and old approaches can usefully coexist and inform each other in moving the art and science of sleep respiratory scoring forward.

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Part III
Clinical Topics

Approach to the Patient with Sleep Complaints

26

Sudhansu Chokroverty

Introduction

Several epidemiologic studies have clearly shown that sleep complaints are very common in the general population [1–26]. Two important multiple-center studies were conducted by Coleman and his colleagues [7, 8]. The first study [8], conducted over a 2-year period (1978–1980), included 4698 patients, each of whom underwent a polysomnographic (PSG) study. The proportions of diagnostic categories in those patients with sleep complaints, after excluding those evaluated for impotency, are 51 % with hypersomnia, 31 % with insomnia, 15 % with parasomnia, and 3 % with sleep–wake schedule disorders. A subsequent report by Coleman [8] on 3085 patients over a one-year period (1981–1982) showed remarkable consistency with the results of the first study. The most frequent disease categories included in these surveys were sleep apnea, narcolepsy, and insomnia related to psychiatric or psychophysiologic disorders.

The 1979 Institute of Medicine [6] study concluded that about one-third of all adults in the United States experienced some sleep disturbances. Surveys conducted more recently [11–14] confirmed these findings. Approximately 35 % of adults aged 18–79 years reported difficulty in the preceding year falling asleep, staying asleep, or both [11]. In the survey conducted between 1981 and 1985 by the U.S. National Institute of Mental Health Epidemiologic Catchment Area Study [10], 10 % reported difficulty in sleeping for 2 weeks or longer in the preceding 6 months, for which no medical or psychiatric cause could be found. In a 2005 telephone interview survey [1] of 25,500 individuals (aged 15–100 years) using the sleep-EVAL system covering 7 European countries (France, United Kingdom, Germany, Italy, Portugal, Spain, and Finland), nonrestorative sleep was prevalent in 10.8 % of this sample. The prevalence was higher in women than in men and was the highest in the United Kingdom and Germany, and lowest in Spain. The author concluded that nonrestorative sleep was associated with daytime impairment of function and the author identified several factors, such as young age, stress, anxiety, depression, or a physical disease as well as dissatisfaction with sleep. A high prevalence of insomnia was also noted by Morin et al. [2, 3].

Ohayon and Paiva [14] directed our attention to assessment of global sleep dissatisfaction as an indicator of insomnia severity in a general population survey in Portugal. Using the sleep-EVAL system, the authors interviewed by telephone 1858 participants aged 18 years or older who were representative of the general population of Portugal. The authors gave a figure of 28.1 % of the sample having insomnia symptoms for at least 3 nights a week, and global sleep dissatisfaction was noted in 10.1 % of the sample. The most frequent symptom was difficulty in maintaining sleep (21 %). Global sleep dissatisfaction was noted in 29.4 % of the subjects with insomnia symptoms. They noted daytime consequences more frequently among subjects with insomnia symptoms and global sleep dissatisfaction.

Some recent important international surveys were conducted by Soldatos et al. [4] and Leger et al. [15–17]. Leger et al. [15] reported the results of an international survey of sleep problems in the general population of the United States, France, Germany, Italy, Spain, and the United Kingdom. The sleeping problems imposed considerable burden, but were underreported and undertreated. In subsequent international questionnaire-based survey of sleep problems in primary care setting in 10 countries (5293 subjects), Ledger et al. [16] reported that a combination of all types of insomnia symptoms was the most frequent (38.6 %) complaint, and 20–33 % of those having combination of all types of symptoms had sever daytime impairment [17].

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The survey by Soldatos et al. [4] on International Sleep Well Day (March 21) in 2002 showed that 24 % of subjects did not sleep well and 31.6 % had insomnia. In a study of 10-year trend in insomnia problem among adult Norwegian population, sleep-onset insomnia was seen in 13.1–15.8 % and daytime impairment in 14.8–18.8 % [22]. The authors concluded that insomnia is on the rise in the general adult population in Norway. Results from two population-based prospective studies from Norway [23] (HUNT 2 in 1995–97 and HUNT 3 in 2006–08) comprising 24,715 people showed that chronic insomnia predicts cumulative incidence of several physical and mental conditions. In the Sao Paulo, Brazil epidemiologic sleep study [24], the prevalence of objective insomnia (using polysomnography in 1042 adults between 20 and 80 years) was 32 %. In a prospective cohort study of 23,447 US men, insomnia symptoms, particularly difficulty in initiating sleep and nonrestorative sleep, are associated with increased risk of mortality. A population-based longitudinal study from the Korean Genome and Epidemiology Study [26] (KoGES) covering 1247 individuals (40.1 % men; mean age = 54.3 years) over a four-year period reported highly prevalent and persistent insomnia symptoms in one-third of individuals and that sleep-interfering behaviors and poor sleep quality were the strongest risk factors for persistence of symptoms. In an earlier population-based longitudinal study (1395 adults followed up after 7.5 years), Vgontzas et al. [21] performed one-night polysomnographic study and observed that objective short sleep duration and mental health problems are the strongest predictors of persistent insomnia.

Self-reported sleep problems could be underestimated in the general population. In all of these studies, there is a prevalence of sleep complaints in about one-third of the adult population, and in about 10 % insomnia is a persistent complaint associated with impairment of daytime function. In a report by Ancoli-Israel and Roth [27], the percentage of individuals with insomnia symptoms is as follows: waking up feeling drowsy or tired, 72 %; waking up in the middle of the night, 67 %; difficulty going back to sleep after waking up, 57 %; difficulty falling asleep, 56 %; and waking up too early, 44 %. Martikainen et al. [28]. described the adverse impact of insomnia on somatic health problems in middle-aged individuals. In a population-based study, Young [29] reported excessive daytime sleepiness in one in five adults. Some important epidemiologic factors identified in various studies include old age, female gender, poor education and lower socioeconomic status, recent stress, depression, anxiety, alcohol, drug abuse, and a physical disease. It is important for physicians to be aware of this high prevalence of sleep disturbances, which cause considerable physical and psychological stress.

Categories of Sleep Disorders

An approach to a patient with sleep complaints must begin with a comprehensive knowledge of the disorders listed in the third edition of the International Classification of Sleep Disorders (ICSD-3) [30], so that the patient can be evaluated in a proper manner, paying particular attention to the history and physical findings before ordering laboratory tests. The ICSD-3 lists seven broad categories of disorders of sleep along with several subcategories under each category, as well as additional sleep-related disorders in Appendices A and B (see Chap. 27). The seven broad categories consist of (1) insomnia, (2) sleep-related breathing disorders, (3) central disorders of hypersomnolence, (4) circadian rhythm sleep disorders, (5) parasomnias, (6) sleep-related movement disorders, and (7) other sleep disorder.

The category of *insomnia* in ICSD-3 includes three types: chronic insomnia disorder, acute insomnia (short term), and other insomnia disorders (do not meet the criteria of other two types). In this edition, all the other pathophysiological subtypes listed in the ICSD-2 have been merged into a single category of chronic insomnia disorder. ICSD-2 subtypes considered the following: psychophysiologic insomnia; paradoxical insomnia (sleep state misperception); idiopathic insomnia; insomnia due to a mental disorder; inadequate sleep hygiene; behavioral insomnia of childhood; insomnia due to a drug or substance; insomnia due to a medical condition; insomnia not due to a substance, sleep-related breathing disorder, or other nonphysiologic condition, unspecified (nonorganic); and physiologic insomnia, unspecified (organic).

The category of *sleep-related breathing disorders* includes central sleep apnea syndromes, including primary central sleep apnea, central sleep apnea with Cheyne–Stokes breathing, central sleep apnea due to high-altitude periodic breathing, central sleep apnea due to a medical condition without Cheyne–Stokes breathing, central sleep apnea due to a drug or substance, primary central sleep apnea of infancy (formerly primary sleep apnea of newborns), primary central apnea of prematurity, and treatment-emergent central sleep apnea. Also included in this category are obstructive sleep apnea syndromes (OSASs), including adult obstructive and pediatric obstructive sleep apnea, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorder.

Central disorders of hypersomnolence which include narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia, Kleine–Levin syndrome, insufficient sleep syndrome, hypersomnia due to a medical condition, hypersomnia due to a drug or substance, and hypersomnia associated with a psychiatric disorder.

Circadian rhythm sleep disorders include delayed sleep-phase type, advanced sleep-phase disorder, irregular

sleep–wake rhythm disorder, non-24-h sleep–wake rhythm disorder, jet lag disorder, shift work disorder, circadian sleep–wake disorder not otherwise, specified (NOS).

Parasomnias are characterized by abnormal movements and behavior during sleep, but do not necessarily disrupt sleep architecture. Parasomnias include disorders of arousal (from nonrapid eye movement [NREM] sleep) (confusional arousals, sleepwalking, and sleep terrors, sleep-related eating disorders); rapid eye movement (REM)-related parasomnias (REM sleep behavior disorder; recurrent isolated sleep paralysis; and nightmare disorder); and other parasomnias (sleep enuresis, exploding head syndrome, sleep-related hallucinations, parasomnia unspecified, parasomnia due to a drug or substance, and parasomnia due to a medical condition).

Sleep-related movement disorders include restless legs syndrome (RLS), periodic limb movement disorder, sleep-related leg cramps, sleep-related bruxism, sleep-related rhythmic movement disorder, sleep-related movement disorder unspecified, sleep-related movement disorder due to a drug or substance, sleep-related movement disorder due to a medical condition, benign sleep myoclonus of infancy, and propriospinal myoclonus at sleep onset.

Isolated symptoms, apparently normal variants, and unresolved issues including long sleeper, short sleeper, snoring, sleep talking, sleep starts (hypnic jerks), hypnagogic foot tremor and alternating leg muscle activation during sleep, and excessive fragmentary myoclonus, which were listed in a separate category in ICSD-2, have been moved to relevant and most applicable sections in ICSD-3.

The *other sleep disorder* category containing sleep disorders that cannot be classified elsewhere in the ICSD-3 are listed here including environmental sleep disorder.

Appendix A includes sleep-related medical and neurologic disorders: fatal familial insomnia, sleep-related epilepsy, sleep-related headaches, sleep-related gastroesophageal reflux disease, sleep-related myocardial ischemia, and sleep-related laryngospasm.

Appendix B includes substance-induced sleep disorders (e.g., those induced by alcohol, opioid, cocaine, cannabis, sedative-hypnotic, anxiolytic, other stimulants, nicotine, hallucinogens, inhalants, and other psychoactive substances). Thus the ICSD-3 indicates major changes from the ICSD-2 in several areas. For example, the ICSD-3 has simplified classification of insomnias, expanded sleep-related breathing disorders, classified narcolepsy into type 1 and type 2 with slight changes in interpretations of sleep-onset REMs (SOREMs) in multiple sleep latency test (MSLT) and consolidated idiopathic hypersomnias and recurrent hypersomnias into single entities.

Clinical Characteristics of Common Sleep Complaints

More detailed discussion of common sleep complaints is provided in several chapters (Chaps. 27, 32, 33, 37–41, and 46–53) of this volume. The following sections summarize these complaints.

Some common sleep complaints are trouble falling asleep and staying asleep (insomnia); falling asleep during the day (daytime hypersomnolence); inability to sleep at the right time (circadian rhythm sleep disorders); and complaints of thrashing or moving about in bed with repeated leg jerking (parasomnias and other abnormal movements, including nocturnal seizures and RLS). Box 26.1 lists the common sleep complaints.

Box 26.1 Common Sleep Complaints

- Cannot sleep (trouble falling asleep and staying asleep, with nonrestorative sleep)
- Cannot stay awake (falling asleep during the day)
- Cannot sleep at the right time
- Thrashing and moving about in bed and experiencing repeated leg jerking.

Cardinal manifestations in a patient complaining of insomnia include all or some of the following:

- Difficulty falling sleep
- Frequent awakenings, including early morning awakening
- Insufficient or total lack of sleep
- Nonrestorative or unrefreshing sleep
- Daytime fatigue, tiredness, or sleepiness
- Lack of concentration or irritability
- Anxiety and sometimes depression
- Forgetfulness
- Preoccupation with psychosomatic symptoms such as aches and pains

Cardinal manifestations of hypersomnia include the following:

- Excessive daytime somnolence (EDS)
- Falling asleep in inappropriate places and other inappropriate circumstances
- Lack of relief of symptoms after additional sleep at night
- Daytime fatigue and inability to concentrate
- Impairment of motor skills and cognition.

Additional symptoms of hypersomnia depend on the nature of the underlying sleep disorder (e.g., snoring and apneas during sleep witnessed by a bed partner in patients

with OSAS; attacks of cataplexy, hypnagogic hallucinations, sleep paralysis, automatic behavior, and disturbed night sleep in patients with narcolepsy).

Etiologic Diagnosis

Insomnia and hypersomnia are symptoms and do not constitute a specific diagnosis. Every attempt should be made to find a cause for these complaints. The causes are described in several chapters in this book (Chaps. 32, 33, 37–41, 46–53) and are briefly enumerated here.

Insomnia is defined as an inability to obtain an adequate amount of sleep to feel restored and refreshed in the morning, and to function adequately in the daytime [30]. The insomnia complaint does not necessarily depend on the total hours of sleep. There is considerable individual variation in sleep requirement. The category of short-term insomnia (acute or adjustment insomnia) often results from an identifiable stressful situation. This lasts from a few days to a few weeks, 3 months at most. Once the stressful event is removed and the patient adjusts to the event, the sleep disturbance resolves. Causes of acute insomnia include a change of sleeping environment (the most common cause of transient insomnia, the so-called first-night effect; jet lag; unpleasant room temperature); stressful life events (e.g., loss of a loved one, divorce, loss of employment, preparing to take an examination); acute medical or surgical illnesses (including intensive care unit stays); and use of stimulant medications (e.g., theophylline, β-blockers, corticosteroids, digoxin, bronchodilators) or withdrawal of central nervous system (CNS) depressant medications. Causes of chronic insomnia are listed earlier in the section listing pathophysiologic subtypes of the ICSD-2 [31].

Etiologic differential diagnosis of EDS includes both physiologic and pathologic causes (see Chap. 3). Briefly, physiologic causes include sleep deprivation and sleepiness related to lifestyle and irregular sleep–wake causes. Pathologic causes of EDS include primary sleep disorders (obstructive sleep apnea and central sleep apnea syndromes, narcolepsy or idiopathic hypersomnia, circadian rhythm sleep disorders, periodic hypersomnia, occasional complaints in patients with RLS or periodic limb movements in sleep [PLMS], insufficient sleep syndrome, and inadequate sleep hygiene); general medical, psychiatric, and neurologic causes; and medication- and toxin/alcohol-related hypersomnia.

For patients complaining of abnormal movements and behavior during sleep, the differential diagnosis should include disorders of arousal from NREM sleep (confusional arousals, sleepwalking, and sleep terror); REM sleep parasomnias (REM sleep behavior disorder [RBD], recurrent isolated sleep paralysis, and nightmare disorder); and other parasomnias that were listed earlier. The differential diagnosis for patients complaining about abnormal movements and behaviors should also include the sleep-related movement disorders listed previously. In addition, sleep-related epilepsy, including nocturnal frontal lobe epilepsy, must be considered in the differential diagnosis of abnormal movements and behaviors during sleep.

Method of Clinical Evaluation

A physician equipped with this background knowledge should attempt to make a clinical diagnosis based on the history and physical examination of a patient who complains of sleep disturbance. Polysomnographic (PSG) study, the MSLT, and other laboratory tests must be confirmatory and secondary to the clinical diagnosis, which depends on a multifactorial analysis of many facets of a sleep complaint.

History

The first step in the diagnosis and assessment of a sleep/wakefulness disturbance is a careful evaluation of the sleep complaints. The history should seek information on sleep habits; drug and alcohol consumption; psychiatric, medical, and neurologic illnesses; history of previous illness; and family history [32–35] (Box 26.2).

Box 26.2 Clinical Evaluation by History of a Patient with Sleep Complaints

- Sleep history
- Sleep questionnaire
- Sleep log or diary
- Drug and alcohol history
- Psychiatric history
- General medical history
- Neurologic history
- History of previous illnesses
- Family history.

Sleep History

The sleep history [32–35] is fundamentally important and is the first step in identifying the nature of the sleep disorder. Symptoms during the entire 24 h should be evaluated, not just those that occur at sleep onset or during sleep at night. In addition to intrinsic and extrinsic dyssomnias, 24-h symptomatic evaluation helps diagnose and manage circadian rhythm sleep disorders. The clinician should pay attention to symptoms that occur in the early evening or at sleep onset (e.g., paresthesias and uncontrollable limb movements of RLS), during sleep at night (e.g., repeated awakenings,

snoring, and cessation of breathing in OSAS), on awakening in the morning (e.g., feeling exhausted and sleepy in OSAS), or in the late morning and afternoon (e.g., daytime fatigue and excessive somnolence in OSAS and irresistible desire to have brief sleep in narcolepsy). Early morning awakening may be noted in insomnia due to depression. Abnormal motor activities may be associated with RBD and other parasomnias and found in patients with seizures.

In evaluating sleep history, Kales and coworkers [32–34] enumerated six important principles: (1) define the specific sleep problem, (2) assess the clinical course, (3) differentiate between various sleep disorders, (4) evaluate sleep/wakefulness patterns, (5) question the bed partner, and (6) evaluate the impact of the disorder on the patient.

One should analyze the onset, frequency, duration, and severity of the sleep complaint; its progression, evolution, and fluctuation over time; and any events that could have initiated it [30]. An analysis of these factors may differentiate transient disorders from persistent ones. The physician should inquire about the patient's functional status and mood during the day, any medicines and their effects on the sleep complaint, and sleep hygiene [35].

Finally, psychological, social, medical, and biological factors and their interactions should be considered to understand the patient's problem [36]. An interview with the bed partner, caregiver, and, in the case of a child, a parent, is important for diagnosis of abnormal movements (PLMS or other body movements), abnormal behavior (parasomnias, nocturnal seizures), and breathing disorders during sleep. The bed partner may also be able to answer questions about the patient's sleeping habits, history of drug use, psychosocial problems (e.g., stress at home, work, or school), and changes in sleep habits.

Sleep Questionnaire

A sleep questionnaire containing a list of pertinent questions relating to sleep complaints; sleep hygiene; sleep patterns; medical, psychiatric, and neurologic disorders; and drug or alcohol use may be filled out by the patient to save time in obtaining the history.

Sleep Log or Sleep Diary

A sleep log kept over a 2-week period is a valuable indicator of sleep hygiene and can also be used to monitor progression following therapeutic intervention. Such a log should include notations of bedtime, arising time, daytime naps, amount of time needed to go to sleep, number of nighttime awakenings, total sleep time, and feelings on arousal (e.g., refreshed or drowsy).

Drug and Alcohol History

The physician should inquire about drugs that could cause insomnia (e.g., CNS stimulants, bronchodilators, β-blockers, corticosteroids, sedative-hypnotics) or hypersomnolence. In addition, the physician should have information about alcohol consumption and dependence as well as about insomnia related to drug withdrawal (e.g., intermediate- or short-acting benzodiazepines, nonbenzodiazepine hypnotics) [32–34]. Caffeine consumption and smoking should also be considered as contributing factors to insomnia.

Psychiatric History

Attention should be paid to signs of possible psychiatric or psychophysiologic disorders (e.g., depression, anxiety, psychosis, obsession, life stress, personality traits) [32–35]. If sleep disorders are secondary to a psychiatric illness, treating it alleviates the sleep disturbance in most cases. If the sleep complaint persists after such treatment, an additional cause or a primary sleep disorder should be suspected.

Medical and Neurologic History

The physician should question the patient about any reported symptom that has been associated with a variety of medical and neurologic illnesses (see Chaps. 41 and 47). These symptoms direct attention to secondary sleep disorders.

History of Past Illnesses

The patient history might contain information about past medical, psychiatric, or neurologic disorders that could be responsible for the present sleep disturbance. It is also important to learn about and evaluate the premorbid personality of the patient. Finally, a history of a drug or alcohol habit or use of street drugs may reveal the role of these agents in the sleep complaint.

Family History

In certain sleep disorders, family history is very important [32]. A family history is found in about one-third of patients with narcolepsy and RLS. OSAS, with or without obesity, has also been described in family members. There is a high prevalence of sleepwalking, sleep terrors, and primary enuresis in family members. Many neurologic disorders, including fatal familial insomnia, have a family history. Currently, an intensive search is ongoing for a gene specific for narcolepsy and RLS.

Physical Examination

It is essential to conduct a thorough physical examination of every patient with a sleep complaint. It may uncover clues to important medical disorders, such as those involving respiratory, cardiovascular, gastrointestinal, or endocrine systems, or to a neurologic disease, especially one affecting the neuromuscular system, cervical spinal cord, or brain stem region, which may cause sleep-related breathing disorders as well as insomnias. In OSAS, physical examination may

uncover upper airway anatomic abnormalities, which may need surgical correction if medical and continuous positive airway pressure (CPAP) treatments fail to relieve the symptoms. Examination may reveal systemic hypertension, which is a risk factor for sleep apnea. Box 26.3 lists physical findings which may be noted in patients with OSAS.

Box 26.3 Physical Findings in Patients with Obstructive Sleep Apnea Syndrome

- Obesity in the majority of patients (70 %)
- Increased body mass index (BMI) [body weight in kg/height in m^2]; overweight: 25 to 29 BMI;
- Obese: 30 or over BMI
- Increased neck circumference (>17 in. in men and >16 in. in women)
- In some patients, the following may be observed:
  - Large edematous uvula
  - Low-hanging soft palate
  - Large tonsils and adenoids (especially in children)
  - Retrognathia
  - Micrognathia
  - Polycythemia
  - Hypertension
  - Cardiac arrhythmias
  - Evidence of congestive heart failure.

Subjective Measures of Sleepiness

A variety of scales have been developed to assist the subjective degree of sleepiness. The Stanford Sleepiness Scale (Box 26.4) is a 7-point scale that measures subjective sleepiness but may not be reliable with persistent sleepiness. The Karolinska Sleepiness Scale [37] which is somewhat similar to the Stanford Sleepiness Scale is another subjective measure on a 9-point scare (1 = very alert; 9 = very sleepy).

Box 26.4 Stanford Sleepiness Scale
Modified from Hoddes et al. [38].

Score State Before Testing

1. Wide awake, active, and alert
2. Awake and able to concentrate but not functioning at peak
3. Relaxed, awake, and responsive but not fully alert
4. Feeling a little foggy
5. Difficulty staying awake
6. Sleepy, prefer to lie down
7. Cannot stay awake; sleep onset is imminent.

Another scale is the visual analog scale of alertness and well-being. In this scale, subjects are asked to indicate their feelings on an arbitrary line measuring from 0 mm on the left side to 100 mm on the right side. This scale has been used successfully in circadian rhythm disorders. The Epworth Sleepiness Scale evaluates general level of sleepiness [39, 40]. The patient is rated on eight situations each of which is scored as 0–3 (with 3 being the highest chance of dozing off). The maximum score is 24, and a score greater than 10 suggests the presence of excessive sleepiness (Box 26.5). This scale has been weakly correlated with MSLT scores.

Box 26.5 Epworth Sleepiness Scale*
Modified from Johns [39].

Eight Situations

1. Sitting and reading
2. Watching television
3. Sitting in a public place (e.g., a theater or a meeting)
4. Sitting in car as a passenger for an hour without a break
5. Lying down to rest in the afternoon
6. Sitting and talking to someone
7. Sitting quietly after a lunch without alcohol
8. In a car, while stopped for a few minutes in traffic.

*Scale to determine the individual scores: 0 = would never doze; 1 = slight chance of dozing; 2 = moderate chance of dozing; 3 = high chance of dozing. Total score is the sum of the individual scores.

Clinical Phenomenology

Clinical characteristics of some common sleep disorders are briefly described in the following sections. More detailed discussion can be found in several chapters of this volume (Chaps. 32, 33, 37–41, 44, 46–52).

Obstructive Sleep Apnea Syndrome

Based on the definition of 15 or more apneas or hypopneas per hour of sleep accompanied by EDS, the prevalence of moderate-to-severe OSAS in the latest Wisconsin sleep cohort study data [41] is 10 % in men and 3 % in women between 30 and 49 years, but 17 % in men and 9 % in women between 50 and 70 years. There is a strong association between OSAS and male gender, increasing age, and obesity. The condition is common in men older than age 40, and among women the incidence of OSAS is greater after menopause. Approximately 85 % of patients with OSAS are men, and obesity is present in about 70 % of OSAS patients. Several risk factors are associated with OSAS (Box 26.6).

Box 26.6 Risk Factors for Sleep Apnea

- Male sex
- Menopause
- Increasing age
- Obesity
- Increasing neck size (>17 in. in men and >16 in. in women)
- Alcohol consumption
- Smoking
- Racial factors (e.g., increasing prevalence in United States among African Americans, Mexican Americans, and Pacific Islanders)
- Familial aggregates
- Endocrine diseases (e.g., hypothyroidism, acromegaly)
- Craniofacial abnormalities (e.g., Marfan's, Pierre-Robin or Down syndrome)
- Increasing drug use
- Nasal allergies or congestion
- Autonomic failure
- Polycystic ovary syndrome.

The symptoms of OSAS can be divided into two groups (see Chap. 32): those occurring during sleep and those occurring during waking hours (Box 26.7). Nocturnal symptoms include habitual loud snoring, choking during sleep, and cessation of breathing and abnormal motor activities during sleep (e.g., shaking and jerking movements, confusional arousals, or sleepwalking), severe sleep disruption, heartburn as a result of gastroesophageal reflux, nocturnal enuresis (noted mostly in children), and profuse sweating at night. The daytime symptoms include EDS, which is characterized by sleep attacks lasting 0.5–2 h and occurring mostly when the patient is relaxing (e.g., sitting down or watching television). The prolonged duration and the nonrefreshing nature of the sleep attacks differentiate them from narcoleptic sleep attacks. Other diurnal events include personality changes such as impairment of memory, irritability, impairment of motor skills, morning headache, sometimes hypnagogic hallucinations, automatic behavior with retrograde amnesia, and hyperactivity (in children). In men, erectile dysfunction is often associated with severe and long-standing cases of OSAS [42]. Physical examination may reveal obesity in approximately 70 % of cases, in addition to anatomic abnormalities in the upper airway. In severe cases, polycythemia and evidence of cardiac failure, pulmonary hypertension, and cardiac arrhythmias may be noted (see Box 26.3).

Box 26.7 Signs and Symptoms in Obstructive Sleep Apnea Syndrome

Nocturnal Symptoms During Sleep

- Loud snoring (often with a long history)
- Choking during sleep
- Cessation of breathing (apneas witnessed by bed partner)
- Sitting up or fighting for breath
- Abnormal motor activities (e.g., thrashing about in bed)
- Severe sleep disruption
- Gastroesophageal reflux causing heartburn
- Nocturia and nocturnal enuresis (mostly in children)
- Insomnia (in some patients)
- Excessive nocturnal sweating (in some patients).

Daytime Symptoms

- Excessive daytime somnolence
- Forgetfulness
- Personality changes
- Decreased libido and erectile dysfunction in men
- Dryness of mouth on awakening
- Morning headache (in some patients)
- Automatic behavior with retrograde amnesia
- Hyperactivity in children
- Hearing impairment (in some patients).

OSAS is associated with increased morbidity and mortality as a result of both short-term consequences (impairment of quality of life and increasing traffic- and work-related accidents), and long-term consequences resulting from comorbid conditions such as hypertension, heart failure, myocardial infarction, cardiac arrhythmia, and stroke due to both supratentorial and infratentorial infarctions and transient ischemic attacks, as well as cognitive dysfunction, depression, and insomnia [43–46]. Several prospective longitudinal studies have shown a clear association between OSAS and systemic hypertension, which may be noted in approximately 50 % of patients with OSAS. In contrast, in about 30 % of cases of essential hypertension, OSAS is noted. Several studies have shown improvement of hypertension or reduction of need for antihypertensive medications after effective treatment of OSAS with CPAP titration (see Chap. 34). Pulmonary hypertension is noted in approximately 15–20 % of cases. Cardiac arrhythmias in the form of premature ventricular contractions, ventricular tachycardia, sinus pauses, and third-degree heart block as well as sudden cardiac death

have been attributed to OSAS. Heart failure, mostly systolic but also diastolic (in which the studies are limited), is associated with both obstructive and central sleep apneas but mostly central sleep apneas (including Cheyne–Stokes breathing) [44, 47, 48, 49, 50]. The presence of central apnea including Cheyne–Stokes breathing increases the mortality of patients with heart failure. Cognitive dysfunction is noted in moderately severe to severe OSAS patients, but this shows improvement after satisfactory treatment with CPAP titration (see Chap. 34). There is an increasing awareness about the presence of depression and insomnia in patients with OSAS but, in the absence of adequate studies, the exact prevalence and impact of these conditions on OSAS cannot be determined. There is also an increased association between OSAS and metabolic syndrome (a combination of hypertension, increased insulin resistance with type 2 diabetes mellitus, hypertriglyceridemia, and obesity) [45, 51, 52]. Recent studies have also shown an association between OSAS and an increased risk of cancer [53].

Narcolepsy-Cataplexy Syndrome

The onset of narcolepsy-cataplexy in most cases is in adolescents and young adults, with a peak incidence between the ages of 15 and 30. The ICSD-3 [30] divides narcolepsy into two types: narcolepsy type 1 and narcolepsy type 2. The ICSD-3 also lists a subtype as narcolepsy type 1 due to a medical condition, mostly CNS disorder (when CSF hypocretin levels are undetectable or very low) or narcolepsy type 2 (when CSF hypocretin level is similar to that noted in type 2). The major clinical manifestations of narcolepsy include narcoleptic sleep attacks (100 %), cataplexy (70 %), sleep paralysis (25–50 %), hypnagogic hallucinations (20–40 %), disturbed night sleep (70–80 %), and automatic behavior (20–40 %) (Box 26.8). In addition to the major manifestations, patients with narcolepsy may have several important comorbid conditions (Box 26.8): sleep apnea, PLMS, RBD, nocturnal eating disorder, anxiety and depression, obesity, and several fatigue unrelated to sleepiness. The classic sleep attack is an irresistible desire to fall asleep in inappropriate circumstances and at inappropriate places (e.g., while talking, driving, eating, playing, walking, running, working, sitting, listening to lectures, or watching television or movies; during sexual intercourse; or when involved in boring or monotonous circumstances). These spells last from a few minutes to as long as 20–30 min, and the patient generally feels refreshed upon waking. There are wide variations in frequency of attacks, anywhere from daily, weekly, or monthly to every few weeks to months. Attacks generally persist throughout the patient's lifetime, although fluctuations and rare temporary remissions may occur. Patients often show a decline in performance at school and work and encounter psychosocial and socioeconomic difficulties as a result of sleep attacks and EDS.

Box 26.8 Major Manifestations and Comorbid Conditions (Percentage Occurrence)

Major Manifestations

Narcoleptic sleep attacks (100 %)
Cataplexy (70 %)
Sleep paralysis (25–50 %)
Hypnagogic hallucinations (20–40 %)
Disturbed night sleep (70–80 %)
Automatic behavior (20–40 %).

Comorbid Conditions

Sleep apnea (Up to 30 %)
Periodic limb movements in sleep (10–60 %)
REM sleep behavior disorder (Up to 36 %)
Sleep-related eating disorder (prevalence not known)
Anxiety and depression (prevalence not known but may be up to 30 %)
Obesity (prevalence not known)
Severe fatigue unrelated to sleepiness (prevalence not known).

These sleep attacks are often accompanied by cataplexy, characterized by sudden loss of tone in all voluntary muscles except respiratory and ocular muscles. The attacks are triggered by emotional factors such as laughter, rage, or anger more than 95 % of the time. The attacks may become partial and are rarely unilateral. Most commonly, patients may momentarily have head nodding, sagging of the jaw, buckling of the knees, dropping of objects from hands, or dysarthria or loss of voice, but sometimes they may slump or fall forward to the ground for a few seconds. The duration is usually a few seconds to minutes, and consciousness is retained completely during the attack. Generally, cataplectic spells begin to occur months to years after the onset of sleep attacks, but occasionally cataplexy is the initial manifestation. Cataplexy is a lifelong condition, but it generally is less severe and may even disappear in old age. Rarely, status cataplecticus occurs particularly after withdrawal of anticataplectic medications. Sleep paralysis, hypnagogic hallucinations, disturbed night sleep, and automatic behavior are the other manifestations of narcolepsy-cataplexy syndrome. The clinical presentation of childhood narcolepsy-cataplexy may differ from adult presentation in having prolonged nocturnal sleep, daytime hyperactive behavior, and characteristic cataplectic facies (droopy facial appearance, tongue

protrusions, or perioral dystonic movements) not triggered by emotional excitement.

Symptomatic or secondary narcolepsy-cataplexy may result from diencephalic and midbrain tumors, multiple sclerosis, strokes, vascular malformations, encephalitis, cerebral trauma, and paraneoplastic syndrome, in which anti-Ma2 antibodies may present with narcoleptic-like sleep attacks and other manifestations. Symptomatic narcolepsy is associated with cataplexy and develops in children affected with type C Niemann–Pick disease.

Idiopathic Hypersomnia

Idiopathic hypersomnia closely resembles narcolepsy syndrome. This disorder is characterized by EDS that has a presumed but not proven CNS cause and is associated with a total 24-h sleep time of 660 min or longer documented by history, actigraphy, sleep logs, or PSG [30]. The onset of the disease is generally around the same age as narcolepsy (15–30 years). The sleep pattern, however, is different from that of narcolepsy. The patient generally sleeps for hours, but the sleep is not refreshing. Because of EDS, the condition may be mistaken for sleep apnea. However, the patient does not give a history of cataplexy, snoring, or repeated awakenings throughout the night. Some patients may have automatic behavior with amnesia for the events. Physical examination uncovers no abnormal neurologic findings. This disabling and lifelong condition should be differentiated from other causes of EDS (see Chap. 3). There is no clear association between idiopathic hypersomnia and human leukocyte antigens (HLAs). The MSLT shows evidence of pathologic sleepiness without sleep-onset REMs.

Insomnia

Insomnia is the most common sleep disorder affecting the population and is the most common disease encountered in the practice of sleep medicine. Insomniacs complain of difficulty in initiating and maintaining sleep, including early morning awakening and unrefreshing sleep occurring three times per week persisting for at least three months and associated with an impairment of daytime function. Short-term insomnia disorder (acute insomnia) may be associated with an identifiable stressful situation. Most cases of insomnia are chronic (chronic insomnia disorder) and comorbid with other conditions, which include psychiatric, medical, and neurologic disorders or drug and alcohol abuse. The ICSD-3 [30] lists a third category (other insomnia disorder) which does not meet the full criteria for the short-term or chronic insomnia disorder.

Restless Legs Syndrome

RLS (Willis–Ekbom Disease or WED) is the most common movement disorder but is uncommonly recognized and treated despite a lucid description of the entity in the middle of the last century. There is not a single diagnostic test for RLS/WED; hence, the diagnosis rests entirely on clinical features and is based on the International Restless Legs Syndrome Study Group (IRLSSG) criteria first established in 1995 [54], modified slightly in 2003 [55], and modified again in 2012 [56]. These criteria include essential criteria and supportive features as well as specifiers for clinical significance and course for RLS as listed in Box 26.9. These IRLSSG diagnostic criteria differ from the AASM (ICSD-3) [30] and the Diagnostic and Statistical Manual (DSM-5) diagnostic criteria. The ICSD-3 must include the specifiers for clinical significance in the diagnostic criteria whereas DSM-5 [57] diagnostic criteria require a frequency of at least three times a week and a duration of at least three months for RLS/WED symptoms. RLS/WED is a lifelong sensorimotor neurologic disorder that often begins at a very young age but is mostly diagnosed in the middle or later years. Prevalence increases with age and plateaus for some unknown reason around age 85–90. All five essential diagnostic criteria (see Box 26.9) are needed to establish the diagnosis of RLS. The overall prevalence has been estimated at about 7.2 % for adult populations, but the prevalence of most severe cases is approximately 2.7 %. In most surveys, the prevalence is greater in women than in men and the disease is chronic and progressive. Family studies of RLS suggest an increased incidence (around 40–50 %) in first-degree relatives of idiopathic cases. A high concordance (83 %) in monozygotic twins and complex segregation analysis suggests an autosomal dominant mode of inheritance. Linkage analysis documented significant linkage to at least five different chromosomes (12Q, 14Q, 9P, 2Q, and 22P). A recent genome-wide association study of RLS has identified common variants in certain genomic regions conferring more than 50 % increase in risks to RLS. These recent results linking certain genes to RLS suggest a biological basis for the condition.

Box 26.9 Five Essential Diagnostic Criteria For RLS/WED

Criterion 1. An urge to move the legs, usually but not always accompanied by uncomfortable sensations in the legs.

Criterion 2. The urge to move the legs with any accompanying unpleasant sensations begins or worsens during periods of inactivity or quiescence such as lying down or sitting.

Criterion 3. The urge to move the legs with any accompanying unpleasant sensations is partially or totally relieved by movement, such as walking or stretching, as long as the activity continues.
Criterion 4. The urge to move the legs with any accompanying unpleasant sensations during rest or inactivity only occurs or is worse in the evening or night than during the day.
Criterion 5. The above features are not accounted by another medical or behavioral condition (e.g., myalgia, arthritis, venous stasis, leg cramps, positional discomfort, or habitual foot tapping).

The sensory manifestations of RLS include intense disagreeable feelings that are described as creeping, crawling, tingling, burning, aching, cramping, knife-like, or itching sensations. These sensations occur mostly between the knees and ankles, causing an intense urge to move the limbs to relieve the feelings. Sometimes, similar symptoms occur in the arms or other parts of the body, particularly in advanced stages of the disease or when the patient develops augmentation (a hypermotor syndrome with symptoms occurring at least 2 h earlier than the initial period with intensification and spreading to other body parts) resulting from long-standing use of dopaminergic medications. Up to 30–50 % of RLS/WED patients complain of aching pain and not just uncomfortable sensation. Most of the movements, especially in the early stages, are noted in the evening when the patient is resting in bed. In severe cases, movements may be noted in the daytime when the patient is sitting or lying down. At least 80 % of RLS patients have PLMS and may also have periodic limb movement in wakefulness. The condition generally has a profound impact on sleep; often the patient seeks medical attention because of sleep disturbance, which is a problem of initiation, although difficulty in maintaining sleep also occurs because of associated PLMS. Neurologic examination is generally normal in the idiopathic form.

Parasomnias

Parasomnias can be defined as abnormal movements or behaviors, including those that occur into sleep or during arousals from sleep, intermittent or episodic, or without disturbing the sleep architecture [30]. The ICSD-3 lists 10 core categories of parasomnias. Several parasomnias may be mistaken for seizures, especially complex partial seizures and nocturnal frontal lobe epilepsy. Somnambulism, night terror, confusional arousals, sleep enuresis, RBD, and nightmares are some of the parasomnias that can be mistaken for seizures. Characteristic clinical features combined with electroencephalographic (EEG) and PSG recordings are essential to differentiate these conditions.

Sleepwalking (Somnambulism)

Sleepwalking is common in children between the ages of 5 and 12 (Box 26.10). Sometimes, it persists into adulthood or, rarely, begins in adults. Sleepwalking begins with an abrupt onset of motor activity arising out of slow-wave sleep during the first third of sleep. Episodes generally last less than 10 min. There is a high incidence of positive family history. Injuries and violent activities have been reported during sleepwalking episodes, but generally individuals can negotiate their way around the room. Rarely, the occurrence of homicide has been reported and sometimes abnormal sexual behavior occurs; sleep deprivation, fatigue, concurrent illness, and sedative-hypnotics are precipitating factors.

Box 26.10 Features of Sleepwalking (Somnambulism)

- Onset: common between ages 5 and 12 year
- High incidence of positive family history
- Abrupt onset of motor activity arising out of slow-wave sleep during the first third of the night
- Duration: <10 min
- Injuries and violent activity reported occasionally
- Precipitating factors: sleep deprivation, fatigue, concurrent illness, sedatives
- Treatment: precaution, benzodiazepines, imipramine.

Sleep Terror (Pavor Nocturnus)

Sleep terror also occurs during slow-wave sleep (Box 26.11). Peak onset is between the ages of 5 and 7 years. As with sleepwalking, there is a high incidence of family history of sleep terror. Episodes of sleep terror are characterized by intense autonomic and motor symptoms, including a loud, piercing scream. Patients appear highly confused and fearful. Many patients also have a history of sleepwalking episodes. Precipitating factors are similar to those described in sleepwalking.

Box 26.11 Features of Sleep Terrors

- Onset: peak is between ages 5 and 7 year
- High incidence of familial occurrences
- Abrupt arousal from slow-wave sleep during the first third of the night with a loud, piercing scream
- Intense autonomic and motor components
- Sleepwalking also seen in many patients
- Precipitating factors: stress, sleep deprivation, fever

- Treatment: psychotherapy, benzodiazepines, tricyclic antidepressants.

Confusional Arousals

These occur mostly before age of five years. As in sleepwalking and sleep terror, there is a high incidence of familial cases and the episodes arise out of slow-wave sleep but occasionally may occur out of stage N2 sleep. The patient may have some automatic and inappropriate behavior, including abnormal sexual behavior (sex-somnia or sleep sex) when the episodes occur in adults. The majority of spells are benign, but sometimes violent and homicidal episodes in adults have been described. Precipitating factors are the same as in sleepwalking or sleep terror.

REM Sleep Behavior Disorder

RBD is an important REM sleep parasomnia commonly seen in elderly individuals (Box 26.12). A characteristic feature of RBD is intermittent loss of REM sleep-related muscle hypotonia or atonia and the appearance of various abnormal motor activities during sleep. The patient experiences violent and dream-enacting behavior during REM sleep, often causing self-injury or injury to the bed partner. RBD may be idiopathic or secondary; most cases are now thought to be prodromal stage of neurodegenerative diseases. It is seen with increasing prevalence in patients with Parkinson's disease (PD), multiple system atrophy (MSA), and diffuse Lewy body disease with dementia (DLBD), and sometime seen in corticobasal degeneration, olivopontocerebellar atrophy, and progressive supranuclear palsy. Many patients with narcolepsy, a probable autoimmune disease causing depletion of hypocretin-containing neurons in the lateral hypothalamus, may also present with RBD. Some authors have proposed that RBD may be an α-synucleinopathy disorder because α-synuclein inclusions have been observed in many of the associated neurodegenerative diseases (e.g., PD, MSA, DLBD). RBD may precede many of these degenerative diseases by more than 10 years and up to 81 % of what was thought to be idiopathic RBD cases eventually develop neurodegenerative diseases. RBD may sometimes be drug induced (e.g., sedative-hypnotics, tricyclic antidepressants, anticholinergics, selective serotonin reuptake inhibitors) or associated with alcoholism and structural brain stem lesions. RBD has been linked to dopamine dysfunction based on positron emission tomography scan findings of reduced striatal presynaptic dopamine transporter and single-photon emission computed tomography scan findings of reduced postsynaptic dopamine D_2 receptors. A number of studies have demonstrated diverse potential markers of neurodegeneration in idiopathic RBD which include subtle cognitive dysfunction, awake EEG slowing, visuospatial impairment, impairment of olfaction and color vision, autonomic dysfunction (orthostatic hypotension in particular), midbrain hyperechogenicity, and subtle dopaminergic denervation (as noted in dopaminergic PET and SPECT imaging). REM sleep without muscle atonia is the most important PSG finding. Experimentally, similar behavior has been noted after bilateral peri-locus coeruleus lesions in cats.

Box 26.12 Features of REM Sleep Behavior Disorder

- Onset: middle-aged or elderly men
- Presents with violent dream-enacting behavior during sleep, causing injury to self or bed partner
- Often misdiagnosed as a psychiatric disorder or nocturnal seizure (partial complex seizure)
- Etiology:
  - Around 20% idiopathic
  - >80% causal association with neurodegenerative disorders, structural central nervous system lesion, or use of alcohol or drugs (sedative-hypnotics, tricyclic antidepressants, anticholinergics, selective serotonin reuptake inhibitors)
- Polysomnography: REM sleep without muscle atonia and excessive phasic muscle bursts
- Experimental model: Bilateral peri-locus coeruleus lesions
- Treatment: clonazepam or melatonin is beneficial in most of the cases.

Nightmares

Nightmares—intense, frightening dreams followed by awakening and vivid recall—occur during REM sleep. The most common time of occurrence, therefore, is from the middle to the late part of the night. Nightmares are typically normal phenomena. Approximately 50 % of children have nightmares beginning at 3–5 years of age. The incidence of nightmares continues to decrease as one grows older, and the elderly have very few or no nightmares. Nightmares are common after sudden withdrawal of REM-suppressant drugs and can also occur as side effects of certain medications, such as antiparkinsonian drugs, anticholinergics, and β-blockers.

Sleep-Related Eating Disorders

Sleep-related eating disorders are common in women between the ages of 20 and 30 and consist of recurrent episodes of involuntary eating and drinking during partial arousals from sleep. Sometimes, the patient displays strange eating behavior (e.g., consumption of inedible or toxic substances such as frozen pizza, raw bacon, and cat food). The episodes cause sleep disruption with weight gain; occasionally, injury has been reported. The condition can be either idiopathic or comorbid

with other sleep disorders (e.g., sleepwalking, RLS-PLMS, OSAS, narcolepsy, irregular sleep–wake circadian rhythm disorder) and with use of medications such as triazolam, zolpidem, quetiapine, and other psychotropic agents. The most common PSG findings are multiple confusional arousals with or without eating, arising predominantly from slow-wave sleep but also from other stages of NREM sleep and occasionally from REM sleep.

Catathrenia (Expiratory Groaning)

This entity, included in the sleep-related breathing disorder section as isolated symptom, is characterized by recurrent episodes of expiratory groaning (high-pitched, loud humming, or roaring sounds) that occur in clusters predominantly during REM sleep but may also occur during NREM sleep [58–60]. Polysomnographic findings resemble central apnea with protracted expiratory bradypnea without oxygen desaturation. Simultaneous audio recordings will bring out the characteristic groaning. The clinical relevance and pathophysiology of this condition remain unknown.

Sleep-Related Movement Disorders

The category of sleep-related movement disorders in the ICSD-3 [30] consists of relatively simple stereotyped movements disturbing sleep. RLS, PLMS, rhythmic movement disorder, bruxism, leg cramps, benign sleep myoclonus of infancy, and propriospinal myoclonus at sleep onset are included in this category.

Rhythmic Movement Disorder

Rhythmic movement disorder is noted mostly in those younger than age 18 months and is occasionally associated with mental retardation. It is a sleep–wake transition disorder with three characteristic movements: head banging, head rolling, and body rocking. Rhythmic movement disorder is a benign condition, and the patient outgrows the episodes.

Sleep-Related Leg Cramps

These are intensely painful conditions accompanied by muscle tightness that occurs during sleep. The spasms usually last for a few seconds but sometimes persist for several minutes. Cramps during sleep are generally associated with awakening. Many normal individuals have nocturnal leg cramps; the cause remains unknown. Local massage or movement of the limbs usually relieves the cramps.

Bruxism (Tooth Grinding)

Bruxism often presents between ages 10 and 20, but it may persist throughout life, often leading to secondary problems such as temporomandibular joint dysfunction. Both diurnal and nocturnal bruxism may be also associated with various movement and degenerative disorders such as oromandibular dystonia and Huntington's disease. It is also commonly noted in children with mental retardation or cerebral palsy. Nocturnal bruxism is noted most prominently during stages 1 and 2 NREM sleep and REM sleep. The episode is characterized by stereotypical tooth grinding and is precipitated by anxiety, stress, and dental disease. Occasionally, familial cases have been described. Local injections of botulinum toxin into the masseter muscle may be used to prevent dental and temporomandibular joint complications.

Laboratory Investigations

Laboratory investigations for sleep disorders should be considered an extension of the history and physical examination. First and foremost in the diagnosis of sleep disorders is a detailed history including sleep and other conditions as outlined earlier. This should be followed by careful physical examination to uncover any underlying medical, neurologic, or other causes of sleep dysfunction. Laboratory tests should include a diagnostic workup for the primary condition causing secondary or comorbid sleep disturbance and a workup for the sleep disturbance itself. The two most important laboratory tests for diagnosing sleep disturbance are PSG and the MSLT. Various other tests are also important for assessment of a patient with sleep dysfunction (Box 26.13).

Box 26.13 Laboratory Tests to Assess Sleep Disorder

- Diagnostic workup for the primary or comorbid condition causing sleep disturbance
- Laboratory tests for the diagnosis and monitoring of sleep disorders
  - Overnight polysomnography (PSG)
  - Multiple Sleep Latency Test (MSLT)
  - Maintenance of Wakefulness Test
  - Actigraphy
  - Video-PSG
  - Standard electroencephalography (EEG) and video-EEG monitoring for suspected seizure disorders
- Imaging studies
  - Upper airway imaging for obstructive sleep apnea syndrome
  - Neuroimaging studies (e.g., computed tomography, magnetic resonance imaging and cerebral angiography in cases of suspected neurologic illness causing sleep disorder);
  - Positron emission tomography and single-photon emission computed tomography in special situations

- Pulmonary function tests in cases of suspected bronchopulmonary and neuromuscular disorders causing sleep-disordered breathing
- Miscellaneous tests
  - Human leukocyte antigen for suspected narcolepsy
  - Cerebrospinal fluid hypocretin 1 level in suspected narcolepsy
  - Serum iron and ferritin levels for patients with restless legs syndrome
  - Electromyography and nerve conduction studies to exclude comorbid or secondary restless legs syndrome.

Polysomnographic Study

An overnight PSG study is the single most important laboratory test for the diagnosis and treatment of patients with sleep disorders, particularly those associated with EDS. An all-night PSG study is required rather than a single-day nap study. The single-day nap study generally misses REM sleep, and the most severe apneic episodes are noted during REM sleep. Maximum oxygen desaturation also occurs at this stage; therefore, a daytime study cannot assess severity of symptoms. For CPAP titration, an all-night sleep study is essential. To determine the optimum level of pressure during CPAP titration, both REM and NREM sleeps are required, including titration in supine position.

Indications for Polysomnography

Box 26.14 lists indications for overnight PSG in a sleep laboratory as proposed by the American Academy of Sleep Medicine (AASM). These include diagnosis of sleep-related breathing disorders, CPAP titration in patients with sleep-related breathing disorders, follow-up to assess effectiveness of treatment in OSAS patients, preoperative procedure in patients undergoing upper airway surgery for OSAS, evaluation of suspected narcolepsy, evaluation of atypical or violent parasomnias including RBD, and diagnosis of periodic limb movement disorder (PLMD) and nocturnal seizures [61, 62].

Box 26.14 Indications for Overnight Polysomnography

- A PSG study is routinely indicated:
  - For the diagnosis of sleep-related breathing disorders
  - For CPAP titration in patients with sleep-related breathing disorders
  - Before undergoing uvulopalatopharyngoplasty
  - For assessment of results after an oral appliance treatment for obstructive sleep apnea syndrome
  - For parasomnias if these are unusual or atypical or if the behaviors are violent or otherwise potentially injurious to the patient or others
  - For diagnosis of REM sleep behavior disorder
  - In patients suspected of having nocturnal seizures
  - A PSG study may be indicated for patients whose insomnia has not responded satisfactorily to a comprehensive behavioral or pharmacologic treatment program for the management of insomnia. If a sleep-related breathing disorder or associated periodic limb movements in sleep (PLMS) are strongly suspected in a patient with insomnia, a PSG study is indicated.
- A follow-up PSG is indicated:
  - When the clinical response is inadequate or when symptoms reappear despite a good initial treatment with CPAP.
  - After substantial weight loss or weight gain, which may have occurred in patients previously treated successfully with CPAP.
- An overnight PSG followed by a MSLT the next day is routinely indicated in patients with suspected narcolepsy.
- An overnight PSG is required in persons with suspected PLMS but is not routinely performed to diagnose restless legs syndrome.
- An overnight PSG, preferably video-PSG with multiple channels of EEG, is indicated in patients suspected of having nocturnal seizures.
- For parasomnias, the AASM [61] made the following recommendations: PSG is indicated for evaluating sleep-related behaviors that are violent or otherwise potentially injurious to the patient or others, as well as for patients who have unusual or atypical behaviors during sleep. PSG may also be indicated in situations with forensic considerations. However, PSG is not routinely indicated for typical and uncomplicated parasomnias.

PSG is not routinely indicated to diagnose or treat RLS/WED. PSG is indicated when a diagnosis of PLMD is considered as a result of a complaint by the patient or bed partner of repetitive limb movements during sleep, frequent awakenings, difficulty maintaining sleep, or EDS.

PSG is not routinely indicated for diagnosis of circadian rhythm sleep disorders or depression. Indications for PSG in patients with insomnia are somewhat controversial. The diagnosis of insomnia is basically clinical. The AASM guidelines [60] do not list PSG for routine evaluation of short-term or chronic insomnia disorder. PSG may be useful, however, when the cause of insomnia is uncertain or when behavioral or pharmacologic treatment is unsuccessful. If a patient with insomnia is suspected of having a sleep-related breathing disorder or PLMS, PSG is indicated as outlined earlier.

Indications for Ambulatory PSG

Box 26.15 lists indications and guidelines for unattended portable (ambulatory) PSG monitoring as proposed by the Task Force of the AASM [63].

Box 26.15 Guidelines for Unattended Portable (Ambulatory) PSG Monitoring (Home Sleep Apnea Testing [HSAT])

- Unattended portable PSG monitoring is indicated:
  - As an alternative to in-laboratory PSG in patients with a high pretest probability of moderate-to-severe obstructive sleep apnea (OSA)
  - For the diagnosis of OSA in patients for whom in-laboratory PSG is not possible because of immobility, safety concerns, or critical illness
  - To monitor the therapeutic response to treatment other than CPAP for sleep apnea
- Unattended portable PSG monitoring is not indicated for:
  - The diagnosis of OSA in those with significant comorbid medical disorders
  - The diagnostic evaluation of patients with suspected comorbid sleep disorders
  - General screening of asymptomatic individuals
- The recording must be supervised by a physician who is either board-certified in sleep medicine or eligible for such certification, who must review the raw data and edit if needed.
- An experienced technologist must apply the sensors.
- At a minimum, the recording must include airflow, respiratory effort, and blood oxygen saturation.
- A follow-up visit to review the results should be performed.
- A negative or technically inadequate recording in a patient with a high degree of clinical suspicion for OSA should require an in-laboratory PSG.

Polysomnographic Findings in Sleep Disorders [62]

Characteristic PSG findings in OSAS include recurrent episodes of apneas and hypopneas (Fig. 26.1) that are mostly obstructive or mixed and a few episodes of central apnea accompanied by oxygen desaturation and followed by arousals with resumption of breathing. An apnea–hypopnea index (AHI, the number of apneas/hypopneas per hour of sleep) of 5 or below is considered normal, and an AHI index of 5–15 may be considered evidence of mild OSA, 16–29 as evidence of moderate OSA, and 30 or more as evidence of severe OSA. Similarly, oxygen saturation of 85–89 % may be found in mild OSAS, whereas in moderate OSAS 80–84 % is typical and in severe OSA 79 % and below is the usual finding. An arousal index of up to 10 is considered normal, and 10–15 can be considered borderline; an arousal index above 15 is definitely abnormal. There are some sleep architectural changes in OSA (reduction of slow-wave and REM sleep); most of the sleep is spent in stage N2 sleep. Other findings include short latency, increased time spent awake after sleep onset, and excessive snoring. In patients with central sleep apnea syndrome, the apneas are all central for at least 50 % of apneas. PSG findings in patients with Cheyne–Stokes breathing consist of a characteristic crescendo–decrescendo pattern of breathing followed by apneas or hypopneas (Fig. 26.2) for at least 3 consecutive cycles and five or more central apneas or hypopneas per hour of sleep or at least 10 consecutive minutes of cycle duration.

Overnight PSG findings in patients with narcolepsy include short sleep latency, excessive disruption of sleep with frequent arousal, reduced total sleep time, excessive body movements, reduced slow-wave sleep, and sleep-onset REM (seen in 40–50 % of patients). Some narcoleptic patients may have associated sleep apnea, particularly central apnea. In approximately 9–59 % of patients, PLMS has been noted, and in up to 36 % of narcoleptic patients RBD has been described.

The characteristic PSG findings in RBD consist of absence of muscle atonia and presence of increased phasic electromyographic (EMG) activities in the upper and lower limbs during REM sleep. It is important to record EMGs from both upper and lower limbs because, in some patients with RBD, excessive EMG activities are present in the upper limbs but not in the lower limbs.

In RLS, PSG findings document sleep disturbance and PLMS (see Fig. 26.3), which is found in at least 80 % of patients. Diagnosis of periodic limb movement disorder is based on the PLMS index (number of periodic limb movements per hour of sleep) of 15 and over plus symptoms of sleep disturbance. A high PLMS index with arousal is more significant than an index without arousal.

Pitfalls of PSG

PSG is the single most important laboratory test for assessment of sleep disorders, particularly in patients presenting with EDS and those suspected of nocturnal seizures, parasomnias, or other abnormal motor activities. However, PSG has considerable limitations. There is no standardized uniform protocol used consistently in all sleep laboratories, making the comparison of the data from one laboratory to another somewhat misleading. The most severe limitations are that an overnight in-laboratory PSG is labor-intensive, time-consuming, and expensive. A single-night PSG may miss the diagnosis of mild OSAS, PLMS, parasomnias, and nocturnal seizures. PSG data and the patient's clinical

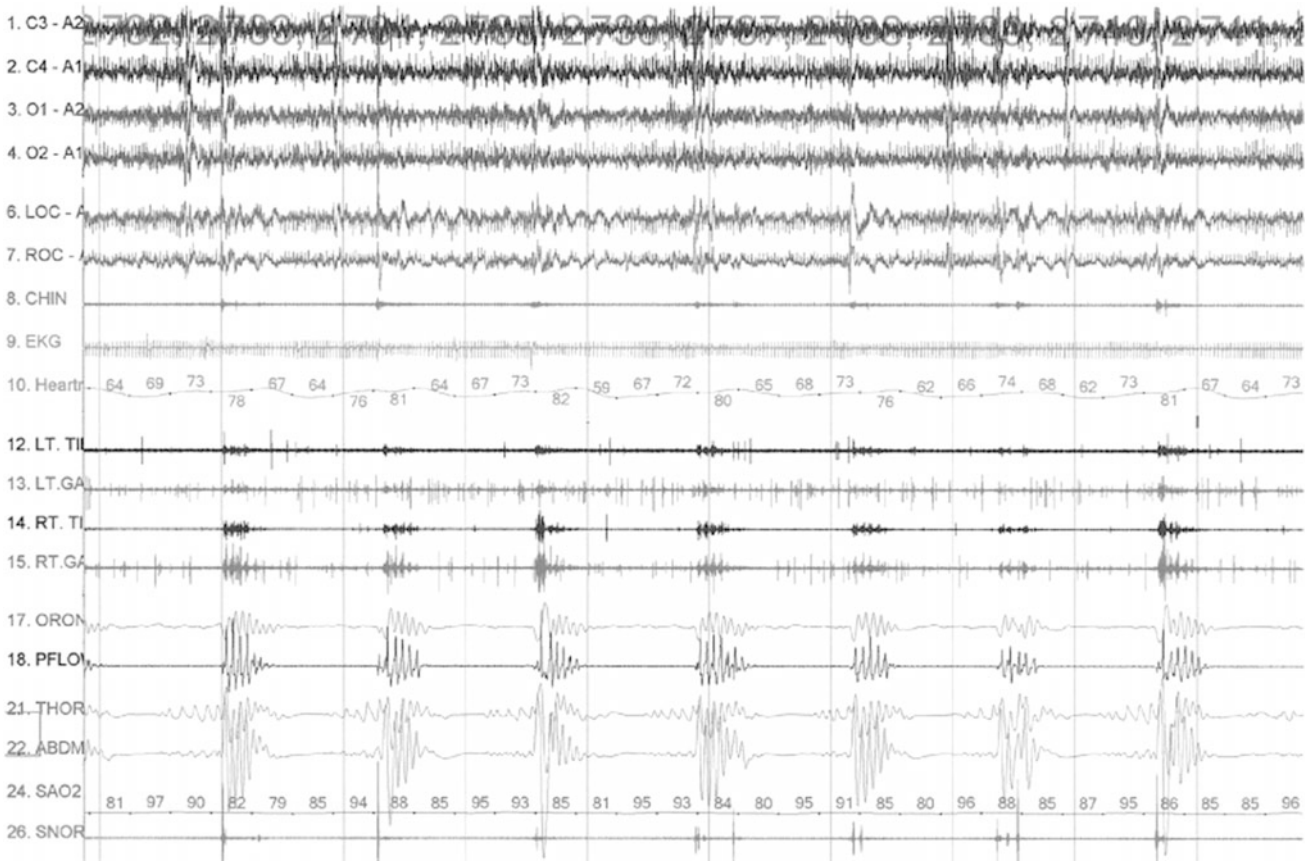

Fig. 26.1 Overnight polysomnographic (PSG) recording in a patient with upper airway obstructive sleep apnea syndrome (OSAS) showing recurrent episodes of mixed apneas (initial control followed by obstructive events) during stage 2 NREM (N2) sleep. Top 4 channels show electroencephalograms (international nomenclature). (A1, left ear; A2, right ear; Loc, left electro-oculogram; ROC, right electro-oculogram; CHIN, submental electromyogram (EMG); EKG, electrocardiogram; LT TA, left tibialis anterior EMG; LT GA left gastrocnemius EMG; RT TA, right tibialus anterior EMG; RT GA, right gastrocnemius EMG; ORON, oronasal airflow; PFLO, nasal pressure transducer recording airflow; THOR, chest respiratory effort; ABDM abdominal respiratory effort; SaO_2, Oxygen saturation (%) by finger oximetry; SNOR, snoring sound recording. l

findings may not be concordant. Standard PSG study cannot diagnose upper airway resistance syndrome definitively. PSG cannot determine the etiology of apnea–hypopnea syndrome. PSG is not helpful in the diagnosis of insomnia, the most common sleep disorder in the general population. PSG is not helpful in the diagnosis or treatment of circadian rhythm sleep disorders. PSG data may be confounded by first-night effects (e.g., increased wakefulness and stage 1 NREM sleep, and decreased slow-wave and REM sleep). Standard PSG does not measure arterial partial pressure of CO_2 and thus may miss hypoventilation, which is an early abnormality (particularly REM hypoventilation) in neuromuscular disorders. Standard PSG does not adequately measure cardiac function (one channel of electrocardiography [ECG] is inadequate), which may affect the prognosis of OSAS. Furthermore, cardiorespiratory sleep studies, which do not include EEG, may produce false-negative findings in mild-to-moderate OSAS patients. Standard PSG does not include autonomic monitoring, which may be important for assessment of autonomic activation as well as for assessing autonomic changes that are intense during sleep.

Video-Polysomnographic Study

A video-PSG study is important for documenting abnormal movements and behavior during sleep at night in patients with parasomnias, including RBD, nocturnal seizures, and other unusual movements occurring during sleep [62]. Parasomnias are generally diagnosed on the basis of a clinical history, but sometimes a video-PSG study is required to document the condition. For suspected nocturnal epilepsy, a video-PSG study using additional electrodes to include multiple-channel EEG and multiple montages covering both parasagittal and temporal regions bilaterally is required for optimal detection of epileptiform activities.

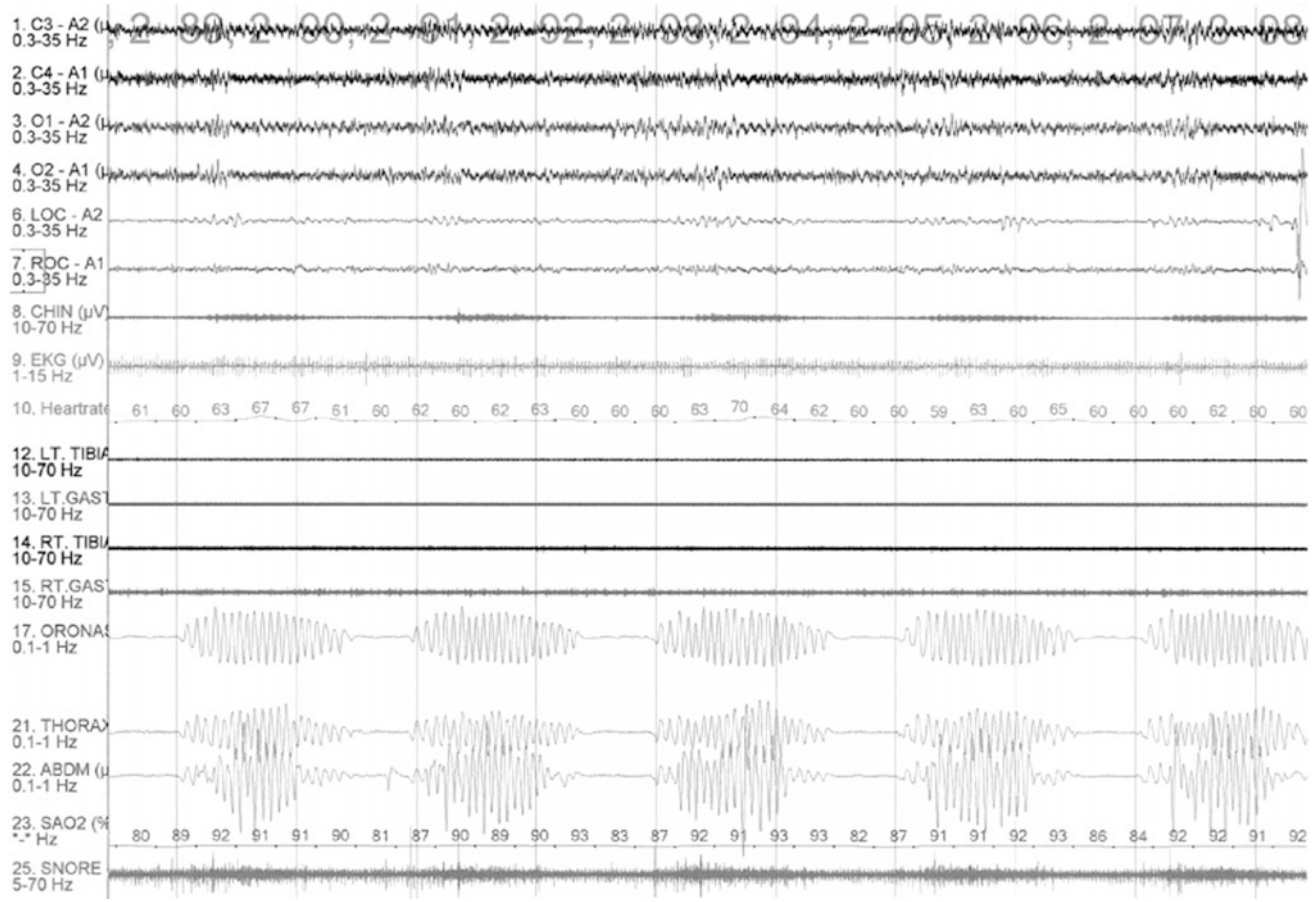

Fig. 26.2 PSG recording from a 70-year-old woman showing the classic crescendo–decrescendo pattern of Cheyne–Stokes breathing (CSB) during stage 2 NREM sleep. The presence of CSB throughout most of the NREM sleep (with marked decrement or absence during REM sleep) in this patient with a history of hypertension and excessive daytime sleepiness suggests occult left ventricular failure. The PSG montage is similar to that in Fig. 26.1

Ideally, if sleep epilepsy is suspected, video-PSG recordings should be interpreted using EEG analysis at the standard EEG speed of 30 mm/sec to identify epileptiform discharges. Multiple EMG channels to record from additional muscles (e.g., forearm flexor and extensor muscles, masseter and other muscles) for patients with suspected RBD and bruxism are recommended.

Video-PSG may help characterize the movements, differentiate one jerk from another, identify a specific entity, and most important, differentiate abnormal motor activities from nocturnal seizures. Video-PSG may aid in the diagnosis of other coexisting sleep disorders (e.g., OSAS, RBD, narcolepsy). Video-PSG does help us classify abnormal motor activities during sleep into several identifiable entities (e.g., motor parasomnias, nocturnal seizures, involuntary diurnal movements persisting during sleep, PLMS, excessive fragmentary myoclonus seen in a variety of sleep disorders, dissociative disorders, nocturnal jerks, and body movements seen in patients with OSAS). Many parasomnias may be mistaken for nocturnal seizures (e.g., confusional arousals, sleepwalking, sleep terror, sleep talking, bruxism, rhythmic movement disorder, RBD, nightmares, and dissociative disorders). RBD and nightmares occur during REM sleep. These conditions can be diagnosed and differentiated from one another based on characteristic clinical features combined with EEG and video-PSG findings. Box 26.16 lists indications for video-PSG.

Box 26.16 Indications for Video-PSG

- Unusual and complex arousal disorders
- Complex behaviors suspicious of RBD but not absolutely certain based on the history
- Behavior and motor events at night suggesting possible nocturnal seizure disorder
- EDS in patients with epilepsy, to determine whether excessive sleepiness is due to repeated nocturnal seizures, an undesirable side effect of antiepileptic medications, or an associative sleep disorder (e.g., sleep apnea)
- Suspected psychogenic dissociative disorder

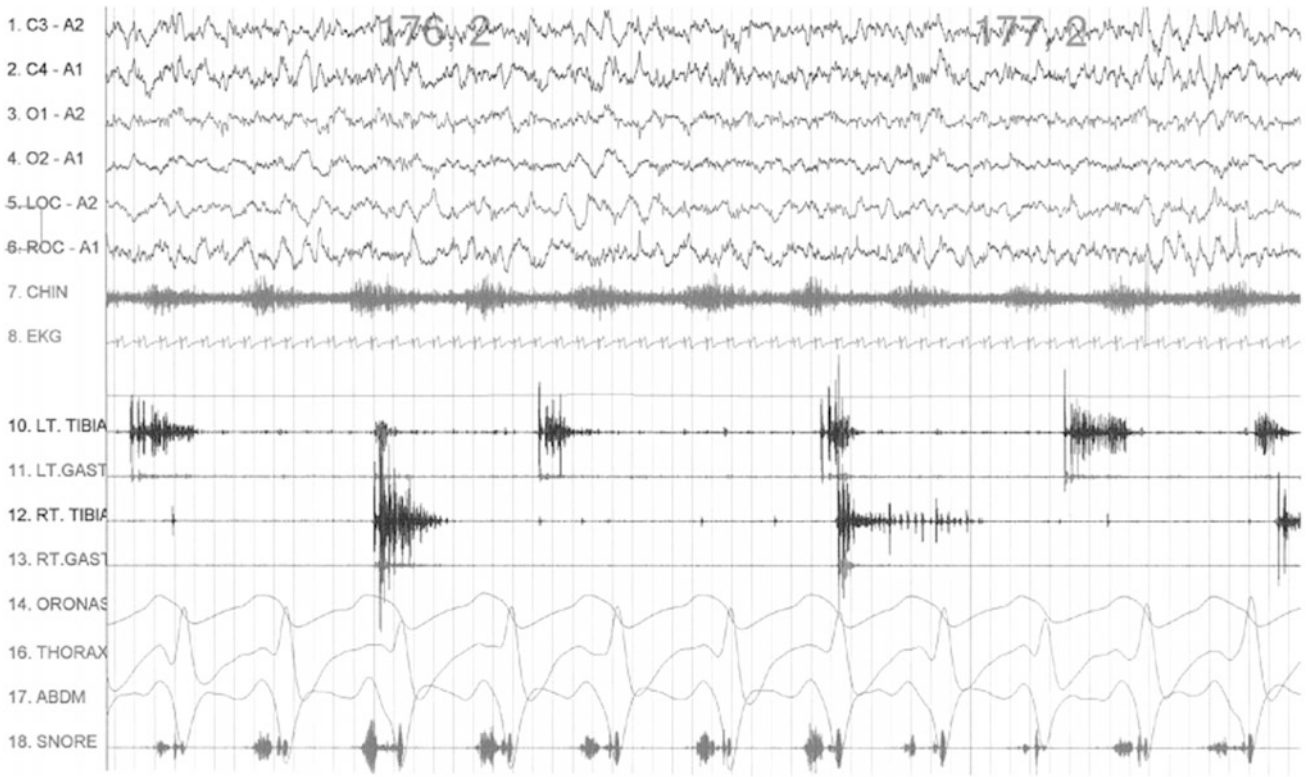

Fig. 26.3 Polysomnographic (*PSG*) recording showing periodic limb movements in sleep (*PLMS*) characterized by dystonic and dystonicmyoclonic electromyographic (*EMG*) bursts in left (*LT*) and right (*RT*) tibialis (*TIBIA*) and gastrocnemius (*GAST*) muscles during stage 2 (N2) non-rapid eye movement (*NREM*) sleep in an adult patient with restless legs syndrome (*RLS*). Top 4 channels show electroencephalograms (*EEG*) using international nomenclature. (A1, left ear; A2, right ear; LOC, left electroculogram; ROC right electro-oculogram; CHIN, submental EMG; EKG electrocardiogram; ORONAS, oronasal airflow; THORAX, chest respiratory effort; ABDM, abdominal respiratory effort (Reproduced with permission from Chokroverty [64])

- Sleep-related movement disorders (e.g., rhythmic movement disorders, bruxism), which may be mistaken for nocturnal seizures
- Involuntary diurnal movement disorder persisting during sleep
- Coexisting secondary sleep disorder (e.g., narcolepsy and RBD; OSAS and sleepwalking; narcolepsy and sleep apnea)
- For medicolegal purpose when the patient presents with violent behavior during sleep; video-PSG studies are mandatory to evaluate suspicions for correct diagnosis of parasomnias or seizure disorders.

Multiple Sleep Latency Test

The MSLT is an important test to effectively document EDS (see Chap. 22). Narcolepsy is the single most important indication for performing MSLT. The presence of two or more sleep-onset REM periods (SOREMP) from four or five nap studies (a SOREMP in the preceding overnight PSG study may substitute for one MSLT SOREMP) and sleep-onset latency of less than 8 min strongly suggest a diagnosis of narcolepsy [30] (Fig. 26.4). Abnormalities of REM sleep regulatory mechanisms (e.g., OSAS, insufficient sleep syndrome, use of REM-suppressant medications) or circadian rhythm sleep disturbance may also lead to REM sleep abnormalities during an MSLT.

Maintenance of Wakefulness Test

The maintenance of wakefulness test (MWT) is a variant of the MSLT (see Chap. 23), measuring a subject's ability to stay awake. It also consists of four to five trials of remaining awake occurring every 2 h. Each trial is terminated if no sleep occurs after 40 min or immediately after the first 3 consecutive epochs of stage 1 NREM sleep or the first epoch of any other stage of sleep [61, 62]. If the mean sleep latency is less than 8 min, it is then considered an abnormal test. The MWT is less sensitive than the MSLT as a diagnostic test for narcolepsy but is more sensitive in assessing the effect of treatment (e.g., CPAP titration in OSAS and stimulant therapy in narcolepsy).

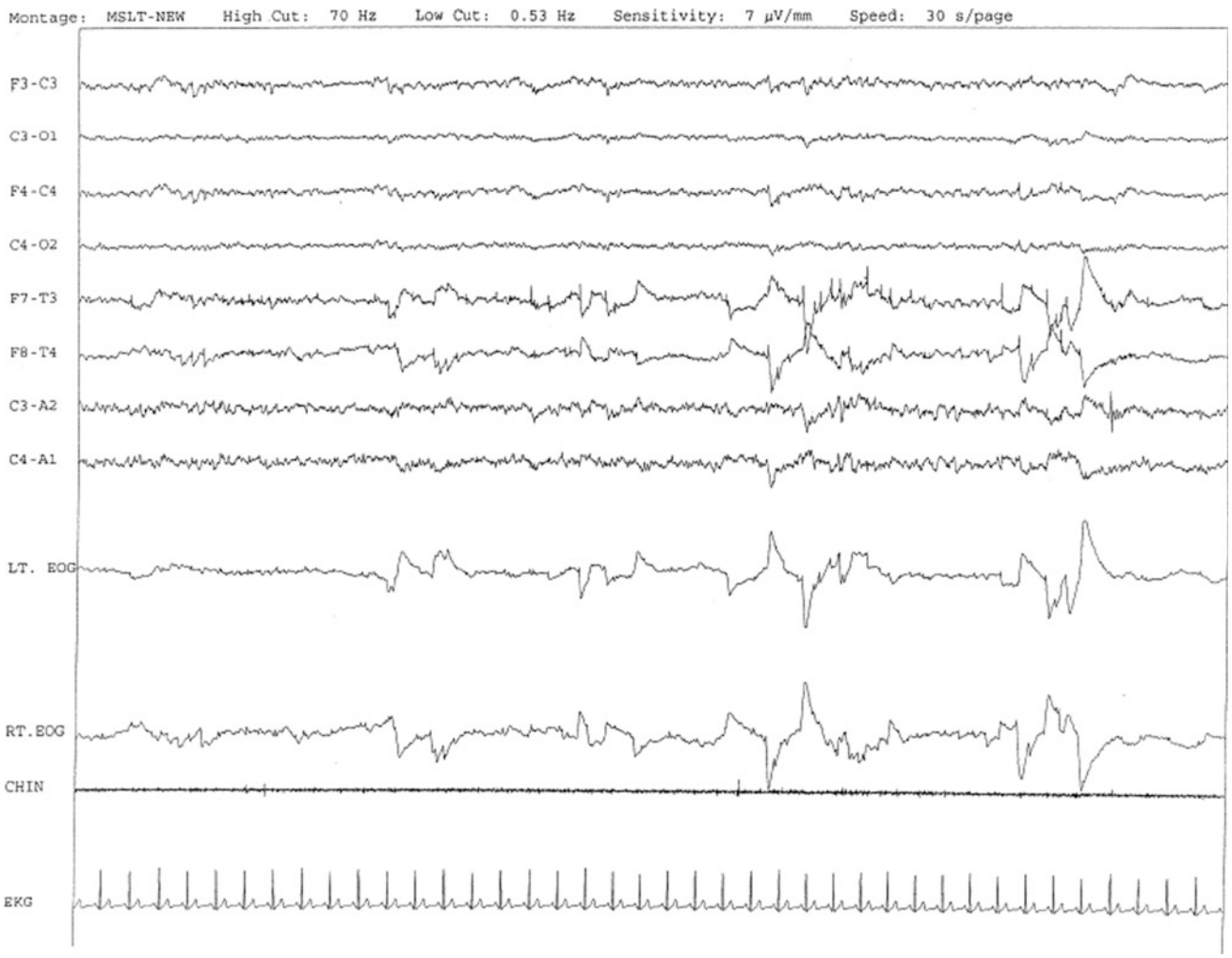

Fig. 26.4 A case of narcolepsy in a 60-year-old woman with new onset of intermittent episodes of sudden transient bilateral leg weakness, excessive daytime sleepiness, and intermittent periods of transient confusion. A daytime EEG was normal. Overnight PSG was significant for sleep architecture changes with an immediate sleep-onset latency, presence of only 1 REM cycle, with a decreased REM sleep percentage (7 %), an increased arousal index of 23 without associated apnea or periodic limb movements, and excessive fragmentary myoclonus in NREM and REM sleep. The MSLT showed a mean sleep latency of 1.6 min, consistent with pathologic sleepiness, and the presence of 2 (of 4) sleep-onset REM naps suggestive of REM sleep dysregulation as seen in narcolepsy. A 30-sec epoch from the MSLT showing the presence of sleep-onset REM occurring 7 min after sleep onset. Prominent REMs are seen in the EOG channels and anterior temporal EEG electrodes. Eye movements, characteristic of REM sleep, are noted as described. CHIN, electromyography of chin; EEG, top eight channels; EKG, electrocardiography; Lt. and Rt. EOG, left and right electro-oculograms. (Reproduced with permission from Chokroverty [64])

Standard Electroencephalographic Study

An EEG is necessary to investigate suspected epilepsy (see Chap. 44).

Ambulatory Electroencephalography or Polysomnography

Ambulatory EEG or PSG is sometimes useful for patients with suspected sleep epilepsy, for understanding circadian variation and for studying circadian rhythm sleep disorders. However, technical problems associated with unattended recording are serious limitations.

Actigraphy

This is another laboratory test for assessing sleep disorders that use an actigraph (also known as an actometer) worn on the wrist or ankle to record acceleration or deceleration of body movements (Fig. 26.5), which indirectly indicates the

state of sleep or wakefulness. The actigraph can be worn for days or weeks, and this test complements a sleep log or diary in diagnosing circadian rhythm sleep disorders (Fig. 26.6) and in assessing patients with insomnia (Fig. 26.7), including paradoxical insomnia or sleep state misperception; inadequate sleep hygiene; and prolonged daytime sleepiness. Actigraphy is useful to document rest–activity patterns over days and weeks when a sleep log is not able to provide such data. Advantages of actigraphy over PSG include the following: easy accessibility; inexpensive recording over extended periods of days, weeks, or months; recording of 24-h activities at all sites (home, work, laboratory); usefulness in uncooperative and demented patients when laboratory PSG study is not possible; ability to conduct longitudinal studies during therapeutic intervention (e.g., cognitive behavioral therapy or pharmacologic treatment) in patients with insomnia; usefulness in paradoxical insomnia; and ability to document delayed or advanced sleep-phase state or circadian rhythm sleep disorder, free-running type. Although not adequately standardized, actigraphy may have a role in patients with RLS and PLMS.

Neuroimaging Studies

Neuroimaging studies include anatomic and functional (physiologic) studies. These studies are essential when a neurologic illness is suspected of causing a sleep disturbance (see Chap. 41)

Pulmonary Function Tests

Pulmonary function tests are important for excluding intrinsic bronchopulmonary disease, which may affect sleep-related breathing disorders (see Chaps. 20 and 47).

Electrodiagnosis of the Respiratory Muscles

Electromyographic recordings of the upper airway and diaphragmatic and intercostal muscles may detect changes in these muscles in various neurologic diseases (see Chap. 41).

Other Laboratory Tests

Appropriate laboratory tests should always be performed to exclude any suspected medical disorder that may be the cause of a patient's insomnia or hypersomnia. These tests may include blood and urinalysis, ECG, Holter monitor ECG, echocardiogram chest radiography, and other investigations to rule out gastrointestinal, pulmonary, cardiovascular, endocrine, and renal disorders. In rare patients, when

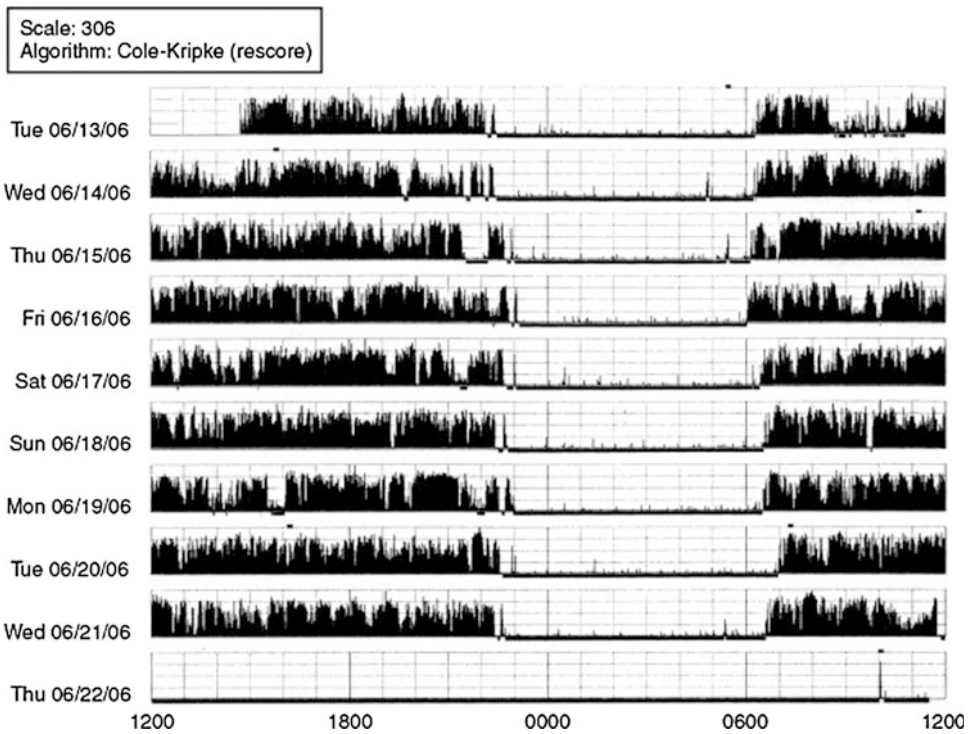

Fig. 26.5 Normal sleep–wake schedule. This wrist actigraphic recording from a 50-year-old healthy woman without sleep complaints shows a fairly regular sleep–wake schedule. She goes to bed between 10:30 and 11:00 P.M. and wakes up around 6:30 A.M. except on the fourth and eighth day. Physiologic body shifts and movements during sleep are indicated by a few *black bars* in the *white areas*. The waking period is indicated by *black bars*

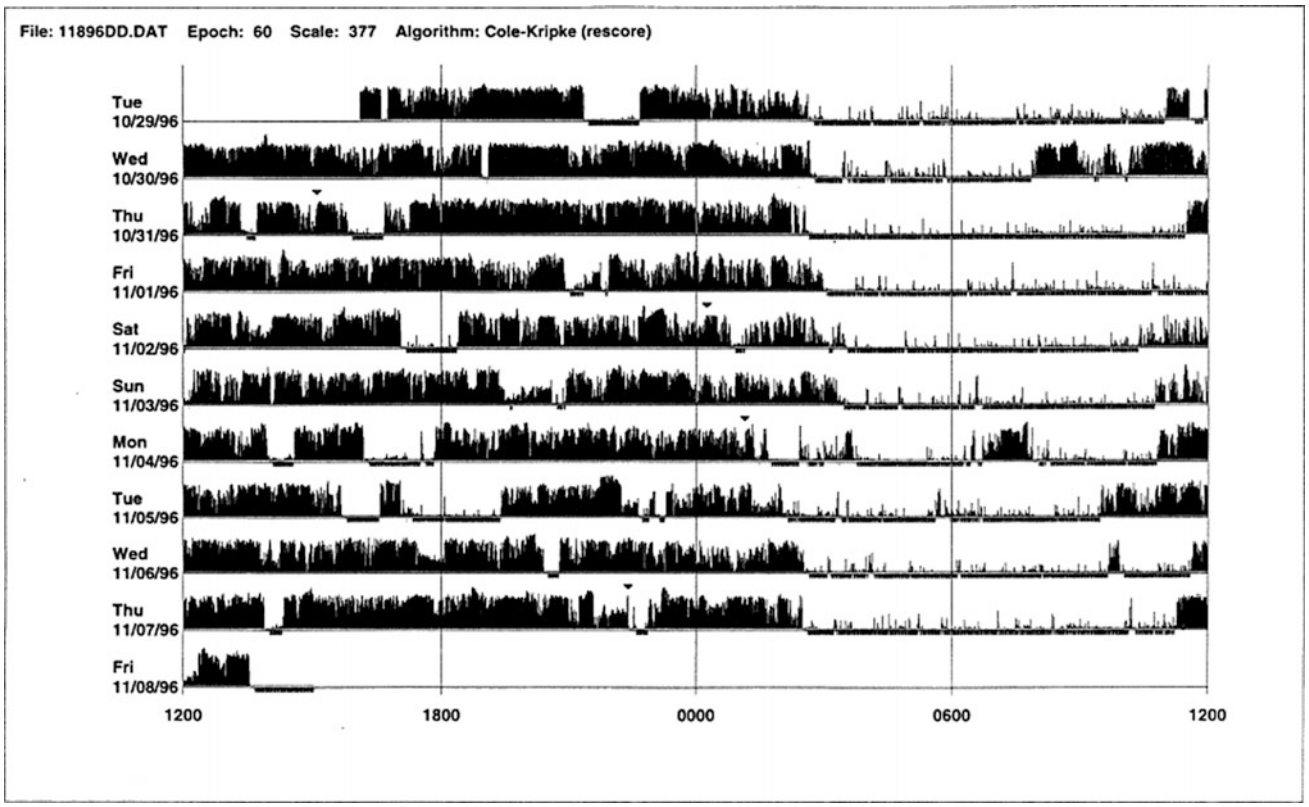

Fig. 26.6 Primary delayed sleep-phase syndrome. This wrist actigraphic recording is taken from a 29-year-old man with a lifelong history of delayed sleep onset and delayed wake-up time. The actigram shows his typical sleep period from 3:00 A.M. to 4:00 A.M. to 9:00 A.M. to noon (*white areas*). If he has to wake up early in the morning, he feels exhausted and sleepy all day. He feels fine if he is allowed to follow his own schedule. Melatonin at night did not help him. Morning bright light therapy was suggested but the patient declined. (Reproduced with permission from Chokroverty [64])

autonomic failure causes a sleep disturbance or sleep-related breathing disorder, autonomic function tests may be required for the diagnosis of the primary condition. In patients with narcolepsy, HLA typing may be performed because most patients with narcolepsy show positivity for HLA DR2 DQ1 and DQB1*0602 antigens. Another important test is measurement of cerebrospinal fluid hypocretin 1 levels, which are found to be low (<110 pg/ml) in patients with narcolepsy type 1 who are HLA DQB1*0602 positive. In patients with narcolepsy type 2 and in some other neurologic conditions, cerebrospinal fluid hypocretin may be low normal. In selected patients suspected of having a psychiatric cause of EDS, neuropsychiatric testing (e.g., the Minnesota Multiphasic Personality Inventory) may be helpful.

In patients with RLS, EMG and nerve conduction studies are important to exclude polyneuropathies or lumbosacral radiculopathies and other lower motor neuron disorders that may be associated with RLS or cause symptoms resembling idiopathic RLS. Other important laboratory tests in patients with RLS include those necessary to exclude diabetes mellitus, uremia, anemia, and other associated conditions. It is particularly important to obtain levels of serum iron (including serum ferritin and transferrin), serum folate, fasting blood glucose, blood urea nitrogen, and creatinine. In a subgroup of patients with RLS, serum iron and ferritin levels are found to be low; it is important to measure these because correction of these abnormalities may improve the condition. The role of nerve biopsy remains controversial. In the vast majority of patients, a nerve biopsy is not necessary, but it may be obtained for research purposes and when there is strong suspicion of polyneuropathy.

Principles of Management of Sleep Disorders

The first principle of treatment of sleep disorders is to find the cause of the sleep disturbance and vigorously treat the primary or comorbid condition causing the sleep

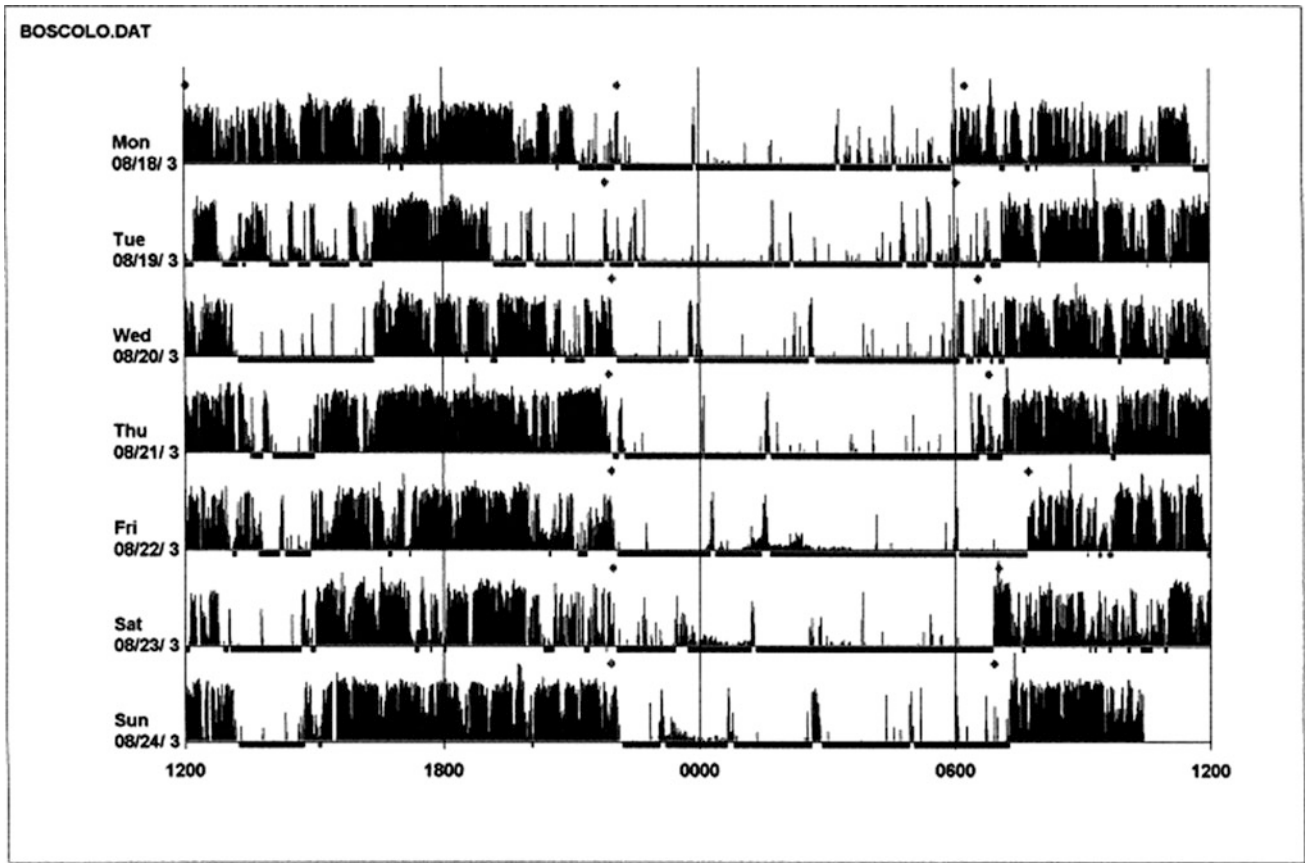

Fig. 26.7 Actigraphy in insomnia (sleep state misperception). A 59-year-old man complaining of insomnia since the age of 12 years was diagnosed to have an Axis 2 personality disorder (dependent personality) according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* as well as panic attacks, and is being treated with benzodiazepines (diazepam 3 mg, flurazepam 30 mg) and zolpidem 10 mg. He denies any symptoms of restless legs syndrome (RLS), excessive daytime sleepiness, or daytime sleep attacks. Subjective sleep duration is 3–4 h per night. In the past, he had used numerous drugs for sleep amelioration, but no clear and stable subjective improvement was noted. Actigraphic monitoring (during drug dosage reduction: diazepam 2 mg, flurazepam 15 mg, and no zolpidem) shows a clear misperception of sleep duration and quality. The recording shows normal nocturnal motor activity and sleep efficiency and duration; note sleep period during the afternoon. He complained of sleeping not more than 3 h each night. PSG on the third night revealed the following: TST, 387 min; SE, 73.5; WASO, 122 min; number of awakenings, 17; SWS %, 1.3; PLMS index, 1.9. (PLMS, periodic limb movements in sleep; PSG, polysomnography; SE, sleep efficiency; SWS, slow-wave sleep; TST, total sleep time; WASO, wake after sleep onset.) (Reproduced with permission from Chokroverty [64])

disturbance. If a satisfactory treatment is not available for the primary condition or does not resolve the problem, then treatment should be directed at a specific sleep disturbance. It is beyond the scope of this chapter to discuss the management of various neurologic and medical disorders causing sleep disturbances, and the reader is referred to several chapters (Chaps. 32–34, 36–38, 40, 41, 44, 46, 47, 48–51, 55) in this volume. Some general sleep hygiene measures (Box 26.17) should apply to all sleep disorder patients.

Box 26.17 Sleep Hygiene Measures

- Keep a regular sleep–wake schedule, including weekends.
- Avoid caffeinated beverages after lunch.
- Avoid smoking, especially in the evening.
- Avoid alcohol near bedtime.
- Restrict sleep to amount needed to feel rested.
- Do not go to bed hungry.
- Adjust bedroom environment.

- Do not engage in planning the next day's activities at bedtime.
- Exercise regularly for about 20–30 min, preferably 4–5 h before bedtime and not immediately before bedtime.

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International Classification of Sleep Disorders 27

Michael Thorpy

The *International Classification of Sleep Disorders* (ICSD-3) produced by the American Academy of Sleep Medicine was updated in 2014 [1] (Table 27.1). In 2013, the American Psychiatric Association (APA) published the revised version of the *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* (*DSM-V*) which includes a section entitled 'Sleep Wake Disorders,' an update of the DSM-IV section [2] (Table 27.2). The intention of the APA classification system was to produce a classification for mental health and general medical clinicians who are not experts in sleep medicine. However, the presence of two competing classifications produces some confusion, especially for health insurance companies and for epidemiological research. *The International Classification of Diseases* modified version, the ICD-10-CM [3], that will be adopted in the USA in 2015 contains a classification that more closely conforms to the ICSD-3 (Table 27.3).

DSM-V

The DSM-V contains 10 disorders or disorder groups: insomnia disorders, hypersomnolence disorder, narcolepsy, breathing-related sleep disorders, circadian rhythm sleep–wake disorders, non-rapid eye movement (NREM) sleep arousal disorders, nightmare disorder, rapid eye movement (REM) sleep behavior disorder, restless legs syndrome, and substance/medication-induced sleep disorder. These disorders have disrupted nocturnal sleep or daytime sleepiness as primary sleep complaints and are all associated with impaired daytime functioning.

The first entry in the DSM-V is insomnia disorder, and this diagnostic entry requires dissatisfaction with sleep quantity or quality and a complaint of difficulty initiating or maintaining sleep. There must be the presence of at least one sleep complaint, such as difficulty initiating sleep, which must be present at least 3 nights per week for at least 3 months. Non-restorative sleep is not a specific complaint in insomnia disorder but if present in isolation can be diagnosed as specified or unspecified insomnia disorder. The diagnosis of insomnia disorder can be coded along with other mental, medical, and sleep disorders. A little confusing is that the diagnosis can be specified as being episodic if it occurs for at least one month; however, acute and short-term insomnia which has symptoms of less than 3 months should be diagnosed as 'other specified insomnia disorder.'

Hypersomnolence disorder includes symptoms of excessive quantity of sleep, deteriorated quality of wakefulness, and sleep inertia. A diagnosis is made if there is a 3-month history of excessive sleepiness, despite a main sleep period of at least 7 h, in the presence of significant distress or other impairment and it is not due to another sleep disorder. Objective documentation is not required. This diagnosis can be coded along with other mental, medical, and sleep disorders. Narcolepsy is defined as recurrent episodes of sleep that occur for at least 3 months along with one of three additional features, such as cataplexy, hypocretin deficiency, or polysomnographic features, either a sleep-onset REM period (SOREMP) on a nighttime polysomnogram (PSG) or a multiple sleep latency test (MSLT) showing a mean sleep latency less than 8 min and 2 or more SOREMPs. So narcolepsy can be diagnosed in DSM-V if just sleepiness occurs for 3 months and there is a SOREMP on the nocturnal PSG. This has the potential of leading to errors in diagnosis as other disorders including obstructive sleep apnea syndrome (OSA) can produce similar features. Five subtypes are specified according to the presence or absence of hypocretin deficiency, autosomal dominant cerebellar ataxia, deafness and narcolepsy (ADCADN), autosomal dominant narcolepsy, obesity and type 2 diabetes (ADNOD), or secondary to another medical condition.

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Table 27.1 ICSD-3

	ICD-9-CM code	ICD-10-CM code
Insomnia disorders:		
Chronic insomnia disorder	342	F51.01
Short-term insomnia disorder	307.41	F51.02
Other insomnia disorder	307.49	F51.09
Isolated symptoms and normal variants:		
Excessive time in bed		
Short sleeper		
Sleep-related breathing disorders:		
Obstructive sleep apnea disorders:		
Obstructive sleep apnea, adult	327.23	G47.33
Obstructive sleep apnea, pediatric	327.23	G47.33
Central sleep apnea syndromes:		
Central sleep apnea with Cheyne–Stokes breathing	786.04	R06.3
Central apnea due to a medical disorder without Cheyne–Stokes breathing	327.27	G47.37
Central sleep apnea due to high-altitude periodic breathing	327.22	G47.32
Central sleep apnea due to a medication or substance	327.29	G47.39
Primary central sleep apnea	327.21	G47.31
Primary central sleep apnea of infancy	770.81	P28.3
Primary central sleep apnea of prematurity	770.82	P28.4
Treatment-emergent central sleep apnea	327.29	G47.39
Sleep-related hypoventilation disorders:		
Obesity hypoventilation syndrome	278.03	E66.2
Congenital central alveolar hypoventilation syndrome	327.25	G47.35
Late-onset central hypoventilation with hypothalamic dysfunction	327.26	G47.36
Idiopathic central alveolar hypoventilation	327.24	G47.34
Sleep-related hypoventilation due to a medication or substance	327.26	G47.36
Sleep-related hypoventilation due to a medical disorder	327.26	G47.36
Sleep-related hypoxemia disorder:		
Sleep-related hypoxemia	327.26	G47.36
Isolated symptoms and normal variants:		
Snoring		
Catathrenia		
Central disorders of hypersomnolence:		
Narcolepsy type 1	347.01	G47.411
Narcolepsy type 2	347.00	G47.419
Idiopathic hypersomnia	327.11	G47.11
Kleine–Levin syndrome	327.13	G47.13
Hypersomnia due to a medical disorder	327.14	G47.14
Hypersomnia due to a medication or substance	292.85 (drug-induced)	F11–F19
	291.82 (alcohol-induced)	
Hypersomnia associated with a psychiatric disorder	327.15	F51.13
Insufficient sleep syndrome	307.44	F51.12
Isolated symptoms and normal variants:		
Long sleeper		

(continued)

Table 27.1 (continued)

	ICD-9-CM code	ICD-10-CM code
Circadian rhythm sleep–wake disorders:		
Delayed sleep–wake phase disorder	327.31	G47.21
Advanced sleep–wake phase disorder	327.32	G47.22
Irregular sleep–wake rhythm disorder	327.33	G47.23
Non-24-h sleep–wake rhythm disorder	327.34	G47.24
Shift work disorder	327.36	G47.26
Jet lag disorder	327.35	G47.25
Circadian sleep–wake disorder not otherwise specified (NOS)	327.30	G47.20
Parasomnias:		
NREM-related parasomnias:		
Disorders of arousal (from NREM sleep):		
Confusional arousals	327.41	G47.51
Sleepwalking	307.46	F51.3
Sleep terrors	307.46	F51.4
Sleep-related eating disorder	327.40	G47.59
REM-related parasomnias:		
REM sleep behavior disorder	327.42	G47.52
Recurrent isolated sleep paralysis	327.43	G47.51
Nightmare disorder	307.47	F51.5
Other parasomnias:		
Exploding head syndrome	327.49	G47.59
Sleep-related hallucinations	368.16	H53.16
Sleep enuresis	788.36	N39.44
Parasomnia due to a medical disorder	327.44	G47.54
Parasomnia due to a medication or substance	292.85 (drug-induced) 291.82 (alcohol-induced)	F11–F19
Parasomnia, unspecified	327.40	G47.50
Isolated symptoms and normal:		
Sleep talking		
Sleep-related movement disorders:		
Restless legs syndrome	333.94	G25.81
Periodic limb movement disorder	327.51	G47.61
Sleep-related leg cramps	327.52	G47.62
Sleep-related bruxism	327.53	G47.63
Sleep-related rhythmic movement disorder	327.59	G47.69
Benign sleep myoclonus of infancy	327.59	G47.69
Propriospinal myoclonus at sleep onset	327.59	G47.69
Sleep-related movement disorder due to a medical disorder	327.59	G47.69
Sleep-related movement disorder due to a medication or substance	292.85 (drug-induced) 291.82 (alcohol-induced)	F11–F19
Sleep-related movement disorder, unspecified	327.59	G47.69
Isolated symptoms and normal variants:		
Excessive fragmentary myoclonus		
Hypnagogic foot tremor and alternating leg muscle activation		

(continued)

Table 27.1 (continued)

	ICD-9-CM code	ICD-10-CM code
Sleep starts (hypnic jerks)		
Other sleep disorder	327.8	G47.8
Appendix A:		
Fatal familial insomnia	046.8	A81.83
Sleep-related epilepsy	345	G40.5
Sleep-related headaches	784.0	R51
Sleep-related laryngospasm	787.2	J38.5
Sleep-related gastroesophageal reflux	530.1	K21.9
Sleep-related myocardial ischemia	411.8	I25.6
Appendix B:		
ICD-10-CM coding for substance-induced sleep disorders		F10–F19

Adapted from [1]

Table 27.2 DSM-V

Sleep–wake disorders
- Insomnia disorder
- Hypersomnolence disorder
- Narcolepsy
  - Subtypes:
    Presence or absence of hypocretin deficiency
    Autosomal dominant cerebellar ataxia
    Deafness and narcolepsy (ADCADN)
    Autosomal dominant narcolepsy
    Obesity and type 2 diabetes (ADNOD)
    Secondary to another medical condition
- Obstructive sleep apnea syndrome
- Central sleep apnea
- Sleep-related hypoventilation
  - Subtypes:
    Idiopathic hypoventilation
    Congenital central alveolar hypoventilation
    Comorbid sleep-related hypoventilation
- **Circadian rhythm sleep disorder**
  - Delayed sleep phase type
  - Advance sleep phase type
  - Irregular sleep–wake type
  - Non-24-h sleep–wake type
  - Shift work disorder
  - Unspecified type
- **Parasomnias**
  - Non-rapid eye movement sleep arousal disorder
    Subtypes:
    ◯ Sleepwalking type
    ◯ Sleep terror type
  - Nightmare disorder
  - Rapid eye movement sleep behavior disorder
- Restless legs syndrome
- Substance/medication-induced sleep disorder
- Other specified insomnia disorder
- Other specified hypersomnolence disorder
- Unspecified sleep–wake disorder
- Unspecified insomnia disorder
- Unspecified hypersomnolence disorder
- Unspecified sleep–wake disorder

Adapted from [2]

Obstructive sleep apnea syndrome (OSA) is defined as an apnea hypopnea index (AHI) of at least 5 per hour along with typical nocturnal respiratory symptoms, or daytime excessive sleepiness or fatigue. Alternatively the diagnosis requires an AHI of at least 15 regardless of accompanying symptoms. Mild is regarded as an AHI of 5 to less than 15, moderate 15–30, and severe greater than 30. Central sleep apnea requires the presence of 5 or more central apneas per hour of sleep. Subtypes include idiopathic central apnea, Cheyne–Stokes breathing, and central apnea comorbid with opioid use. Sleep-related hypoventilation has PSG evidence of decreased ventilation with either elevated CO_2 levels or persistent oxygen desaturation unassociated with apneic/hypopneic events. Idiopathic hypoventilation, congenital central alveolar hypoventilation, and comorbid sleep-related hypoventilation can be specified as subtypes.

Circadian rhythm sleep–wake disorders with five subtypes are defined as a persistent of recurrent pattern of sleep disruption due to an alteration or misalignment of the endogenous circadian rhythm and the individuals required sleep–wake schedule, along with symptoms of either insomnia or excessive sleepiness or both. The subtypes are the following: delayed sleep phase (DSP) type, advanced sleep phase (ASP) type, irregular sleep–wake (ISW) type, non-24-h (non-24) sleep–wake type, and shift work (SW) type none of which have specific diagnostic criteria. DSP and ASP can have familial subtypes. DSP can be subtyped as overlapping with non-24.

The parasomnias are subdivided into five disorders: non-rapid eye movement (NREM) sleep arousal disorder, nightmare disorder, rapid eye movement sleep behavior disorder, restless legs syndrome, and substance/medication-induced sleep disorder. Non-rapid eye movement sleep arousal disorder is divided into two types by the typical features of either sleepwalking or sleep terrors. The sleepwalking type is further subtyped if associated with sleep-related eating or sleep-related sexual behavior (sexsomnia). Confusional arousals as defined

Table 27.3 ICD-10-CM sleep disorders

F51 Sleep disorders not due to a substance or known physiological condition
- F51.01 Primary insomnia
- F51.02 Adjustment insomnia
- F51.03 Paradoxical insomnia
- F51.04 Psychophysiologic insomnia
- F51.05 Insomnia due to other mental disorder
- F51.09 Other insomnia not due to a substance or known physiological condition

F51.1 Hypersomnia not due to a substance or know physiological condition
- F51.11 Primary hypersomnia
- F51.12 Insufficient sleep syndrome
- F51.13 Hypersomnia due to other mental disorder
- F51.19 Other hypersomnia not due to a substance or known physiological condition

F51.3 Sleepwalking [somnambulism]
F51.4 Sleep terrors [night terrors]
F51.5 Nightmare disorder
F51.8 Other sleep disorders not due to a substance or known physiological condition
F51.9 Sleep disorder not due to a substance or known physiological condition, unspecified

G47 Organic sleep disorders
- G47.0 Insomnia, unspecified
  - G47.01 Insomnia due to medical condition
  - G47.09 Other insomnia
- G47.1 Hypersomnia, unspecified
  - G47.11 Idiopathic hypersomnia with long sleep time
  - G47.12 Idiopathic hypersomnia without long sleep time
  - G47.13 Recurrent hypersomnia
  - G47.14 Hypersomnia due to medical condition
  - G47.19 Other hypersomnia
- G47.20 Circadian rhythm sleep disorder, unspecified type
  - G47.21 Circadian rhythm sleep disorder, delayed sleep phase type
  - G47.22 Circadian rhythm sleep disorder, advanced sleep phase type
  - G47.23 Circadian rhythm sleep disorder, irregular sleep wake type
  - G47.24 Circadian rhythm sleep disorder, free running type
  - G47.25 Circadian rhythm sleep disorder, jet lag type
  - G47.26 Circadian rhythm sleep disorder, shift work type
  - G47.27 Circadian rhythm sleep disorder in conditions classified elsewhere
  - G47.29 Other circadian rhythm sleep disorder
- G47.30 Sleep apnea, unspecified
  - G47.31 Primary central sleep apnea
  - G47.32 High-altitude periodic breathing
  - G47.33 Obstructive sleep apnea (adult) (pediatric)
  - G47.34 Idiopathic sleep-related non-obstructive alveolar hypoventilation
  - G47.35 Congenital central alveolar hypoventilation syndrome
  - G47.36 Sleep-related hypoventilation in conditions classified elsewhere
  - G47.37 Central sleep apnea in conditions classified elsewhere
  - G47.39 Other sleep apnea
- G47.4 Narcolepsy and cataplexy
  - G47.41 Narcolepsy
  - G47.411 Narcolepsy with cataplexy
  - G47.419 Narcolepsy without cataplexy, NOS
  - G47.42 Narcolepsy in conditions classified elsewhere
  - G47.421 Narcolepsy in conditions classified elsewhere with cataplexy
  - G47.429 Narcolepsy in conditions classified elsewhere without cataplexy
- G47.50 Parasomnia, unspecified
  - G47.51 Confusional arousals
  - G47.52 REM sleep behavior disorder
  - G47.53 Recurrent isolated sleep paralysis
  - G47.54 Parasomnia in conditions classified elsewhere
  - G47.59 Other parasomnia
- G47.6 Sleep-related movement disorders
  - G47.61 Periodic limb movement disorder
  - G47.62 Sleep-related leg cramps
  - G47.63 Sleep-related bruxism
  - G47.69 Other sleep-related movement disorders
- G47.8 Other sleep disorders
- G47.9 Sleep disorder, unspecified

(continued)

Table 27.3 (continued)

Z72.820 Problems related to sleep
Z72.820 Sleep deprivation
Z72.821 Inadequate sleep hygiene
Z73.8 Other problems related to life management difficulty
Z73.810 Behavioral insomnia of childhood, sleep-onset association type
Z73.811 Behavioral insomnia of childhood, limit setting type
Z73.812 Behavioral insomnia of childhood, combined type
Z73.819 Behavioral insomnia of childhood, unspecified type

Adapted from [3]

in ICSD-3 are not included as a specific DSM-V disorder. Nightmare disorder is defined as repeated occurrences of extended, dysphoric, and well-remembered dreams that threaten the individual. Rapid orientation and alertness follow the episode and cause significant distress. It can be subtyped as that occurring during sleep onset, or associated with non-sleep disorder, other medical condition, or another sleep disorder. Rapid eye movement sleep behavior disorder (RBD) is characterized by repeated episodes of arousal with vocalization and/or complex movements from REM sleep documented by either PSG or a history suggesting a synucleinopathy. Sleep studies are not required as they are in the ICSD-3 diagnostic criteria for RBD. Restless legs syndrome (RLS) is an urge to move the legs accompanied by uncomfortable sensations in the legs with the typical features that occur at least 3 times per week for at least 3 months. It is unclear from where the definition of 3 times a week was derived. Sleep medication or substance-induced sleep disorder is a sleep disturbance either during or soon after substance intoxication or after withdrawal, or the substance is known to cause sleep disturbance. The substance should be specified.

Other specified insomnia disorder is specified when the insomnia does not meet the criteria for insomnia disorder, and other hypersomnolence disorder is diagnosed when the excessive sleepiness does not meet the criteria for hypersomnolence disorder. Similarly, unspecified sleep–wake disorder is diagnosed when the sleep–wake disorder does not meet the full criteria for the specified sleep–wake disorders. Unspecified forms of insomnia disorder, hypersomnolence disorder, and sleep–wake disorder exist.

International Classification of Sleep Disorders 3rd Revision

The *International Classification of Sleep Disorders* (ICSD-3) is a major revision of the ICSD-2 and was published in March of 2014. The main change was the simplification of the insomnia disorders and an expansion of the sleep-related breathing disorders.

The organization of the ICSD-3 produced a greater degree of standardization between disorder texts. It includes information in all the following categories where available: Alternate Names, Diagnostic Criteria, Essential Features, Associated Features, Clinical and Pathophysiological Subtypes; Demographics: Prevalence, Gender bias, Racial/ethnic bias, Cultural issues: Predisposing and Precipitating Factors: Risk factors, Familial Pattern (Genetics, Familial clusters); Onset, Course and Complications: Medical, Neurological, Psychiatric/social; Developmental Issues(Pediatric, Geriatric), Pathology and Pathophysiology, Objective Findings; Sleep logs, Actigraphy, Questionnaires, Polysomnography, Multiple sleep latency test, Neurological (Electroencephalogram, Cerebrospinal fluid, Neuroimaging, Electromyogram, Autonomic), Endocrine, Genetic testing; Respiratory (Arterial blood gas, Pulmonary function, Ventilatory response), Cardiac, (Electrocardiogram, Echocardiogram, Cardiac catheterization), and Serum chemistry. Several disorders are now classified as isolated symptoms and normal variants, which include excessive time in bed, short sleeper, snoring, catathrenia, long sleeper, sleep talking, excessive fragmentary myoclonus, hypnagogic foot tremor and alternating leg muscle activation, and sleep starts (hypnic jerks).

Insomnia Disorders

The insomnia disorders are characterized by one major disorder termed chronic insomnia disorder. This recognizes the fact that the clinical features of insomnia can be the result of a primary or secondary process but the consequences are similar no matter what is the etiology [4]. The previous terminology of primary insomnia is no longer used as the disorder is now recognized that whether it is comorbid with other medical or psychiatric disorders or exists in isolation is immaterial to the underlying insomnia process. The disorder still needs to be treated, and the treatment of the insomnia should occur irrespective of the treatment of any associated disorder. The diagnosis of chronic insomnia disorder rests upon a sleep symptom such as difficulty initiating sleep that occurs three times per week for at least 3 months and has daytime

consequences. The previous diagnostic types of insomnia in ICSD-2 such as psychophysiological insomnia and paradoxical insomnia are now no longer used although the initiating mechanisms and characteristics may still be important in understanding the insomnia and are therefore discussed in the text. The inclusion of short-term insomnia disorder with similar diagnostic criteria to chronic insomnia disorder applies to insomnia that is less than 3 months in duration. Excessive time in bed and short sleeper are included as isolated symptoms and normal variants, not as specific disorders.

Sleep-related Breathing Disorders

The sleep-related breathing disorders are organized into four main categories: obstructive sleep apnea (OSA) disorders, central sleep apnea (CSA) syndromes, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorder. The central sleep apnea syndromes are divided into eight types: two related to Cheyne–Stokes breathing (CSB), high altitude, substance, three primary CSA disorders of which one is infancy and the other prematurity, and a new entity entitled treatment-emergent central sleep apnea. The latter category applies to central apnea that follows CPAP administration.

Obstructive sleep apnea syndrome (OSA) is divided into adult and pediatric types. OSA adult maintains the criterion of 5 or more respiratory events per hour of sleep when studied in a sleep center or by out of center sleep studies (OCST), so long as typical symptoms are present, otherwise 15 or more predominantly obstructive respiratory events are sufficient to make the diagnosis. In the pediatric criteria, for those less than 18 years of age, only one obstructive event is required per hour of sleep so long as respiratory symptoms or sleepiness are present; alternatively, obstructive hypoventilation along with symptoms is required.

Central sleep apnea with Cheyne–Stokes breathing (CSA-CSB) is 5 or more central apnea or hypopneas per hour of sleep with a pattern that meets criteria for CSB. Central sleep apnea without CSB is diagnosed as central sleep apnea due to a medical disorder without Cheyne–Stokes breathing that occurs as a consequence of a medical or neurological disorder. Central sleep apnea due to high-altitude periodic breathing is central apnea attributable to high altitude of at least 1500 m but usually above 2500 m. Central sleep apnea due to a medicine or substance is most typically due to an opioid or respiratory depressant not associated with CSB. Primary central sleep apnea (CSA) is 5 or more central apneas or central hypopneas per hour of sleep in the absence of CSB and of unknown etiology. Primary central sleep apnea of infancy occurs in an infant with greater than 37 weeks conceptional age with recurrent, prolonged (>20 s duration) central apneas and periodic breathing for more than 5 % of total sleep time during sleep. Primary central sleep apnea of prematurity occurs in an infant of less than 37 weeks conceptional age with similar respiratory events.

Treatment-emergent central sleep apnea is diagnosed when five or more obstructive events during a PSG with CPAP showing resolution of obstructive events and presence of central apneas or hypopneas [5], without evidence of heart failure.

Central Disorders of Hypersomnolence

The central disorders of hypersomnolence comprise eight disorders. Narcolepsy has undergone a major revision with elimination of the terms, with or without cataplexy. Type 1 narcolepsy is that presumed to be due to hypocretin loss with either measured reduction in cerebrospinal fluid (csf) hypocretin or cataplexy with associated electrophysiological findings. Narcolepsy type 2 is that which is confirmed by electrophysiological studies in the absence of cataplexy or with a normal csf hypocretin level. A major change in the narcolepsy criteria is the addition of including a sleep-onset rapid eye movement period (SOREMP) on the nocturnal PSG as one of the two required to meet the MSLT criteria of two SOREMPs for diagnosis. This is based upon a study that indicates that the positive predictive value of a SOREMP on the nocturnal PSG for narcolepsy is 92 % [6]. Approximately 50 % of patients with narcolepsy will have a SOREMP less than 15 min on the nocturnal PSG. If the MSLT criteria are not met but narcolepsy type 1 is clinically suspected, then a possible strategy is to repeat the MSLT. The ICSD-3 also recognizes that narcolepsy can present differently in children and that the excessive sleepiness in children may manifest as a long nighttime sleep period or as resumption of discontinued napping. Cataplexy in children may include mouth opening with tongue protrusion, dystonic and dyskinetic facies, and unsteady gait which are not necessarily related to emotion.

Idiopathic hypersomnia is a single entity with elimination of the two ICSD-2 hypersomnia disorders that had specific sleep duration criteria. The new idiopathic hypersomnia disorder requires either an MSLT mean sleep latency of 8 min or less, showing fewer than two SOREMP, or a 24-h sleep duration of at least 660 min. The ICSD-2 category of recurrent hypersomnia has been reduced to a single entry, Kleine–Levin syndrome with a subtype of menstrual related Kleine–Levin syndrome [7]. The sleepiness must persist for 2 days to 5 weeks and at least once every 18 months. There must be at least one of the following symptoms during the episodes: cognitive dysfunction, altered perception, eating disorder, or disinhibited behavior.

Insufficient sleep syndrome is the new term for the previous more cumbersome term of behaviorally induced insufficient sleep syndrome. The reduced sleep must be present most days for at least 3 months. Extension of sleep time must result in resolution of symptoms. The other three items in the hypersomnia disorders section are hypersomnia related to a medical disorder, medication or substances, or psychiatric disorder.

Long sleeper is no longer regarded as a disorder but as a normal variant. There are no diagnostic criteria but a total sleep time of 10 or more hours is suggested as being usually accepted.

Circadian Rhythm Sleep–Wake Disorders

The circadian rhythm sleep–wake disorders comprise six specific disorders including delayed sleep–wake phase disorder (DSWPD), advanced sleep–wake phase disorder (ASWPD), irregular sleep–wake rhythm disorder (ISWRD), non-24 h sleep–wake rhythm disorder (N24SWD), shift work disorder (SWD), and jet lag disorder (JLD). These disorders arise when there is a substantial misalignment between the internal circadian rhythm and the desired sleep–wake schedule. Symptoms of insomnia and/or excessive sleepiness are the resulting symptoms. Specific general diagnostic criteria are given for circadian rhythm sleep–wake disorder (CRSWD). A three-month duration of symptoms is a requirement for diagnosing all these disorders except for jet lag disorder which has a requirement of jet travel across at least two time zones. DSWPD and ASWPD require that a sleep log, and if possible actigraphy, must demonstrate either a delay in the time of the habitual sleep period in the case of DSWPD, or an advance of the sleep period in the case of ASWPD, for at least seven days. IRSWRD requires documentation of the habitual sleep pattern that demonstrates no major sleep period and multiple irregular sleep bouts (at least three) during a 24-h period. N24SWD requires two weeks of documentation of a sleep–wake pattern that typically shows a delay each day with a circadian period longer than 24 h. This disorder is most typically seen in totally blind individuals. SWD requires a two documentation of the sleep–wake pattern by sleep log or actigraphy, preferably with light exposure measurement. JLD requires a complaint of insomnia or excessive sleepiness within one to two days of travel across at least two time zones. A circadian rhythm disorder not otherwise specified (NOS) is listed for patients who have a circadian rhythm sleep–wake disorder who meet all the criteria for CRSWD but not the specific types.

Parasomnias

The parasomnias are divided into three groups: the NREM-related parasomnias, REM-related parasomnias, and other parasomnias category. They are defined as undesirable physical events or experiences that occur during entry into sleep, within sleep, during arousal from sleep.

The NREM-related parasomnias comprise general diagnostic criteria for the group heading of disorders of arousal (from NREM sleep). Specific general diagnostic criteria are given for disorders of arousal (DA) and the detailed text applies to all of the DA's as no text is presented for each of the specific DA's except for diagnostic criteria. The main criterion is recurrent episodes of incomplete awakening from sleep that usually occurs in the first-third of the major sleep episode. Partial or complete amnesia for the episode is typical. Diagnostic criteria are given for three disorders: confusional arousals, sleepwalking, and sleep terrors. Confusional arousals are episodes of confusion or confused behavior that occurs while in bed. Sleepwalking is arousal associated with ambulation or other complex behaviors out of bed. Sleep terrors are episodes of abrupt terror, typically beginning with alarming vocalization such as a frightening scream. Sleep-related abnormal sexual behaviors are listed as a subtype to be classified under confusional arousals. Terminology for these behaviors includes atypical sexual behavior during sleep, sexsomnia, and sleep sex. The presence of an overlap disorder, in which RBD and partial arousal disorder (sleepwalking or sleep terrors) are comorbid in a person, may complicate the diagnosis of each disorder. The final NREM-related parasomnia is sleep-related eating disorder (SRED) that requires an arousal from the main sleep period to distinguish it from night eating syndrome (NES) which is excessive eating between dinner and bedtime, and SRED requires an adverse health consequence from the disorder [8]. SRED is one or more of the consumption of food or toxic substances, injurious behaviors in the pursuit of food, or adverse health consequences from recurrent nocturnal eating.

The REM-related parasomnias include REM sleep behavior disorder (RBD), recurrent isolated sleep paralysis (RISP), and nightmare disorder. RBD is repeated episodes of vocalizations and/or complex motor behaviors requiring the polysomnographic evidence of REM sleep without atonia (RWA) [9]. The episodes are usually correlated with simultaneously occurring dream mentation, leading to the frequent report of 'acting out one's dreams.' RISP is the recurrent inability to move the trunk and all of the limbs at sleep onset or upon awakening from sleep that lasts seconds

to a few minutes that causes distress or fear of sleep. Nightmare disorder is repeated occurrences of extended, extremely dysphoric, and well-remembered dreams that usually involve threats to survival, security, or physical integrity. The episodes are followed by rapid orientation to the environment and alertness. Significant distress and impairment in social, occupational, or other areas of functioning are reported. Up to 80 % of patients with posttraumatic stress disorder (PTSD) have nightmares although 50 % have resolution of the episodes within three months. Nightmares are common in acute stress disorder (ASD).

The other parasomnia section includes three specific disorders: exploding head syndrome (EHS), sleep-related hallucinations, and sleep enuresis. EHS is a complaint of a sudden noise or sense of explosion in the head either at the wake–sleep transition or upon awakening during the night associated with abrupt arousal. Idiopathic stabbing headache (ice-pick headache) and thunderclap headache usually do not occur at sleep onset or during sleep. Sleep-related hallucinations are predominantly visual hallucinations that are experienced just prior to sleep onset or upon awakening during the night or in the morning. Those occurring at sleep onset may be difficult to differentiate from sleep-onset dreaming. The form is usually of complex, vivid, relatively immobile images of people or animals sometimes distorted in shape or size. Sleep enuresis is involuntary voiding during sleep at least twice a week in people older than 5 years of age. Two forms are recognized, primary sleep enuresis in which the individual has never been consistently dry during sleep, and secondary sleep enuresis that occurs in a person who has been consistently dry during sleep for at least six months. Parasomnias associated with medical disorders, and medication or substance and unspecific parasomnia, comprise the other entries in this category. Sleep talking is a normal variant that can occur in both NREM or REM sleep and can be associated with parasomnias such as RBD or DAs.

The sleep-related movement disorders (SRMD) category comprises seven specific disorders: restless legs syndrome, periodic limb movement disorder (PLMD), sleep-related leg cramps, sleep bruxism, sleep-related rhythmic movement disorder (RMD), benign sleep myoclonus of infancy (BSMI), and propriospinal myoclonus at sleep onset (PSM). SRMDs are relatively simple, usually stereotyped movements that disturb sleep or its onset.

Restless legs syndrome (also known as Willis–Ekbom disease) is an urge to move the legs, usually accompanied by or thought to be caused by uncomfortable and unpleasant sensations in the legs. The symptoms consist of episodes beginning or worsening during periods of rest or immobility exclusively or that are partially or totally relieved by movement and that occur predominantly in the evening or night, and these features are not solely accounted for by another condition (RLS mimics). The ICSD-3 criteria also require the patients to have distress and impairment of functioning in several important areas (not part of the essential diagnostic criteria established by the International Restless Legs Syndrome Study Group or IRLSSG but widely accepted) but do not include any frequency or duration criteria as is contained in the DSM-V criteria.

PLMD is defined by the polysomnographic demonstration of periodic limb movements (PLMS) of >5/h in children and >15/h in adults that cause significant sleep disturbance or impairment of functioning. It is essential to establish a reasonable cause-and-effect relationship between the insomnia or hypersomnia and the PLMS. PLMD cannot be diagnosed in the presence of RLS, narcolepsy, OSA, or RBD, although PLMS commonly occur in these disorders. Sleep-related leg cramps are painful sensations that occur in the leg or foot with sudden, involuntary muscle hardness or tightness. They usually occur in the calf or small muscles of the foot and can be relieved by stretching the affected muscle. Sleep-related bruxism is tooth grinding during sleep that is associated with tooth wear or morning jaw muscle pain or fatigue. Ideally, polysomnographic monitoring with masseter muscle activity monitoring is helpful. RMD is repetitive, stereotyped, and rhythmic motor behaviors involving large muscle groups that are sleep related. The behaviors interfere with sleep or daytime functioning and can cause body injury. BSMI is repetitive myoclonic jerks that involve the limbs, trunk, or whole body that occurs from birth to 6 months of age during sleep. They occur exclusively during sleep which helps differentiate them from epileptic activity. As PSM mainly occurs during relaxed wakefulness and drowsiness as the patient attempts to sleep, the term ‘at sleep onset’ has been added to the propriospinal myoclonus name. The episodes are sudden jerks of the abdomen, trunk, or neck that disappear upon mental activation and with stable sleep. PSM can cause a complaint of insomnia. The three final categories are related to a medical disorder, medication or substance, and an unspecified parasomnia.

Isolated symptoms and normal variants include excessive fragmentary myoclonus (EFM), hypnagogic foot tremor and alternating muscle activation, and sleep starts (hypnic jerks). EFM is now regarded as a normal variant found on polysomnographic EMG recordings that are characterized by small movements of the corners of the mouth, fingers, or toes or without visible movement. Hypnagogic foot tremor (HFT) is rhythmic movement of the feet or toes that occurs in the transition between wake and sleep or in light NREM sleep, and alternating muscle activation (ALMA) is brief activation of the anterior tibialis in one leg with alternation in the other leg. Sleep starts (hypnic jerks) are brief,

simultaneous contractions of the body or one or more body segments occurring at sleep onset.

The final category in the ICSD-3 is a general other sleep disorder category for disorders that cannot be classified elsewhere.

Conclusion

The new ICSD-3 is a major advance over previous versions but it is unfortunate that some of the diagnostic criteria differ from that of DSM-V, for example, the criteria for narcolepsy. However, the DSM-V serves as an entry-level classification, mainly for psychiatrists, and it is to be hoped that in the future the two classifications will be merged into one that will cause less confusion not only for clinicians but also for agencies that reimburse for healthcare and provide for treatment options.

Appendix A lists several disorders that are coded in other sections of ICD 10 other than the sleep sections and include fatal familial insomnia, sleep-related epilepsy, sleep-related headaches, sleep-related laryngospasm, sleep-related gastroesophageal reflux, sleep-related myocardial ischemia. Appendix B lists the ICD sleep-related substance-induced sleep disorders.

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Epidemiology: Principles and Application in Sleep Medicine

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Markku Partinen and Erkki Kronholm

In sleep medicine, sleep has been traditionally conceptualized as a biomedical phenomenon with connections to social lifestyle factors. Epidemiologically, sleep may be reconceptualized also as a social behavior which is closely bound up with its social environment [1]. Epidemiology of sleep and its disorders is currently facing a challenge of possible consequences of rapidly changing societies on population's sleep, health, and functional well-being. An enormous variety of adverse health risks associated with sleep duration and quality as well as timing of sleep and wakefulness has been published. It is indeed amazing to ponder why seemingly so different health outcomes such as all-cause mortality, cardiovascular mortality and morbidity, metabolic diseases such as diabetes, metabolic syndrome, obesity, changes in immune function, changes in brain functions such as memory, learning, and affect as well as impairment in mental health, like depression, are all associated with self-reported sleep duration and/or insomnia. The evidence is strong and there is also biological plausibility behind these associations [2]. On the other hand, there is also evidence that, at least in some cases, there might be causal associations. What might then be the underlying function of sleep, impairment of which would be reflected in such a variety of detrimental health outcomes? And importantly, do these associations between sleep and health consequences have anything to do with changes in our societies and our lifestyle? In this chapter, some epidemiological principles are discussed in order to guide the reader into the epidemiological methods of sleep science followed by epidemiological figures of some common sleep disorders. Also, the current discussion in scientific community about sleep and society is partly reflected.

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Epidemiological Methods in Sleep Medicine

Epidemiological sleep medicine may be divided into clinical epidemiology and population-based epidemiological studies. Modern epidemiology includes study of chronic, evaluation of health status, and genetic and environmental factors associated with diseases or symptoms in defined populations [3–5]. A common misunderstanding is that epidemiological studies are limited to large population studies. Miettinen defines epidemiology as the discipline of how to study the occurrence of phenomena of interest in the health field [4]. Thus, it delineates major principles of study design and data analysis in research into frequency of occurrence of illness and related phenomena in human populations, whether in the community or in different clinical settings.

Analytical Studies

Research questions like whether an association exists between an exposure (e.g., short sleep duration) and a disease (e.g., cardiovascular disease) are examined in so-called analytical studies. There are two main types of analytical studies: experimental (also called interventional) studies and observational (also called descriptive) studies. For obvious reasons, observational studies in which observations are made without any intervention are usually applied into a large-scale epidemiological context. Observational epidemiological studies can be further divided into cross-sectional, cohort, and case–control studies [3–5].

Descriptive (observational) studies have many limitations. Classic examples are **cross-sectional studies** with data collected on a defined moment and **retrospective studies** that are based on existing medical histories or other previously collected data. In observational studies, distributions are given with, perhaps, some computations of statistical significance between different groups of subjects. Retrospective studies are highly dependent on the quality of collected data. Ideally, the data have been collected

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systematically by qualified researchers/clinicians/assistants and always in the same format on a database. Data should be collected using validated instruments. If the study population, or the sample, is representative of a target population (general population, hospital population), generalizations can be made to that base population, but not necessarily to other populations. In the latter case, the external validity of the study may be poor. In cross-sectional observational studies, the temporal relationship between outcome (disease) and exposure cannot be determined; therefore, they do not allow any causal or etiological inferences. Such inferences are more or less speculative. However, well-conducted cross-sectional observational studies can provide an accurate estimate of the prevalence of a given phenomenon/symptom/disease at one particular time point among the study population. Therefore, they are also called as **prevalence studies**.

Are retrospective studies useless? No, they may be very useful, for example, in explaining occurrence of different new findings/symptoms in well-defined setting, which allows generalizations to other populations. Hundreds of descriptive epidemiological studies on various sleep disorders have been published about sleeping habits and different sleep disorders from different countries.

Interventions (experimental studies) are commonly used in clinical epidemiological research, for example, to study the effect of a new hypnotic in insomnia, or to study the effect of weight loss in treatment of sleep apnea. Ideally, a **randomized controlled trial (RCT)** is designed.

Observational Population Surveys

Cohort and case–control studies are valuable in providing the time dimension in relationships between the exposure and outcome. In other words, they have prospective or retrospective study design. Therefore, they allow more inferences to be done when compared to cross-sectional studies. However, all observational studies are always vulnerable to influences by unpredictable confounding factors, which the researchers may be unaware or unable to control for.

Cohort studies. In epidemiology, the word "cohort" denotes to a population of subjects with defined characteristics in a defined setting and a defined time. Once a cohort has been defined, it exists forever. The established cohort remains even if all the persons in the initial cohort have died. A cohort may be static or dynamic. New persons, fulfilling the entry criteria, may enter a dynamic cohort after the initial cohort has been established. People in the cohort are followed up to determine incidence of defined outcomes such as occurrence of a disease, death, or some other outcomes. Longitudinal studies may be retrospective or prospective in time. Prospective **cohort studies** are also called follow-up studies or prolective cohort studies. Retrospective follow-up studies are also called "trohoc" studies, retrolective cohort studies, or retrospective cohort studies [3, 6]. A prospective **cohort** study may give huge amounts of valuable information. Examples of well-defined cohorts are the Framingham Cohort, Wisconsin Sleep Cohort, Sleep Heart Cohort, and the Finnish Twin Cohort.

The quality of a retrospective study depends on the quality of collected information in past time. We have only the information that has been saved. Missing data are a problem. If the subjects have always been examined and treated by the same personnel with use of the same standardized methods, we can usually trust the information.

Case–control studies. A well-designed and properly analyzed case–control study is an efficient way of answering many questions. Practical reasons of economy and feasibility often tell whether a case–control study is more appropriate than a cohort study. Usually, a case–control study is both faster and cheaper than a cohort study. The use and understanding of case–control studies is the development of modern epidemiology [4, 7]. The modern case–control study methodology was described in full for the first time in a classic study suggesting an association between smoking and lung cancer in the 1950s [8]. In a case–control study, cases and control subjects are collected and occurrence of defined risk factors preceding the onset of disease will then be analyzed. In this way, case–control studies are retrospective in nature. In a **nested case-control study,** the cases and their controls are selected from an existing cohort. To prove the results, a case–control study should usually be followed by a prospective study or by a RCT.

Data Collection

Most often questionnaires are used. Other possibilities include personal interviews, telephone surveys, and tabulation of information, e.g., from medical records.

Structured questionnaire is often a practical method. If possible, validated tools should be used. To allow comparability, the wording should mean same thing in different languages. In translating a questionnaire from one language to another, cross-translation, or back translation, should be used. Questionnaire studies are usually relatively cheap. If mailed, one needs funding for printing of the forms, envelopes (to send and prepaid return envelope), and mailing costs. In addition, one needs funding to enter data into a database.

Telephone surveys may be almost as good as personal interviews and considerably easier to do. Computer-assisted telephone interview (**CATI**) software can control the interview process and record the responses as the interview proceeds. It can be combined with random digit dialing [9] to identify subjects and to enhance the efficiency of telephone methods for

the data collection. In sleep research, they have been used quite often in Europe since the beginning of 1980s. Telephone surveys are often faster to do than mailed questionnaire studies. On the other hand, they are more expensive and they may exaggerate some figures. The National Institute of Mental Health Epidemiologic Catchment Area (ECA) study about psychiatric disorders including sleep disturbances was done in the early 80s [10]. The Diagnostic Interview Schedule (DIS) is a structured interview, administered by lay interviewers, that assigns a number of DSM-III using a computer algorithm. More recently, a similar method, called Sleep-EVAL, has been used mainly by one group of researchers [11, 12]. There are problems with such closed methods because the studies cannot be replicated by others. This means that it is difficult to judge the correctness of the results. In a properly conducted study, the wording of each question is given, or alternatively the wordings of all questions are given as an attachment, or in Internet.

We already know quite a lot about prevalence of different sleep disorders, but many more prospective longitudinal studies and genetic epidemiological studies are needed. Such studies are out of the scope of a cross-sectional telephone survey. Names, social security information, addresses, and other strictly personal information cannot be collected without written informed consent.

Personal face-to-face interviews using a structured questionnaire are a very good method supposing that the interviewers are properly trained and unbiased. Personal interviews are more expensive to carry out than mailed questionnaires or telephone surveys, but the response rate is, on the other hand, much better than in the other methods, especially if the interviewers travel to meet the persons.

In conclusion, at least in very large-scale studies, one should usually start with a well-designed questionnaire study. Telephone survey methods do not differ from other epidemiological survey methods. They can be used to estimate prevalence but they cannot be used to make final diagnoses. If needed, one can complete the questionnaire data by telephoning to those that did not answer to the questionnaire and ask them to send the questionnaire. In some cases, one can ask the questions by phone but caution is then needed before combining the data with the mail questionnaire data. Sometimes one can even visit persons who have not answered. Another approach is to pull a representative sample from the population to participate in thorough medical and laboratory examinations. This approach has been used, e.g., in the well-known Wisconsin Sleep Cohort study [13, 14], and the Finnish Health 2000 and 2011 cohort study [15].

Register-based studies. National registers may be used in epidemiological studies. In some countries (especially in the Nordic countries: Denmark, Finland, and Sweden), hospitalizations and other health-related data have been entered into National register for decades. With proper ethical permissions linking clinical and questionnaire data with register-based data allows researchers to gather information about medications, morbidity, occurrence of cancer, accidents, and other events on a longitudinal basis.

Size of population. Statistical estimation (calculating the values of parameters based on observed data) is more accurate in large samples than in small ones. This is caused by the decrease of random measurement error by increasing sample size. Consequently, the most efficient, but also expensive, method to reduce random measurement error is to increase the size of the study. Note, however, that a possible systematic measurement error does not depend on sample size. Sample size estimation and power calculations (statistical power analysis) may be used to estimate beforehand how large a sample is needed for sound statistical inferences in the study at hand (see below). The size of the population in an epidemiological study could easily be less than 30 (e.g., rare diseases) or more than 100,000. Large populations may give smaller confidence intervals meaning that even very small differences between compared groups will be statistically significant. But this does not necessarily mean that these differences are clinically (or even in any other way) meaningful. The researcher must make the final inferences, and they should not be based only on a ritualized null hypothesis significance testing as noted well by Cohen [16] several years ago. When interpreting the results, a useful way is to use the so-called effect size indices which are not statistical tests (and thus do not have any absolute cutoff points). They can be used in order to compare the size of the difference between groups or the size of the effect of the exposure with a known meaningful reference.

Power calculations. Power calculations should be done before a study is started [17, 18]. Before doing computations, one should determine the level of clinical meaningfulness of expected (hypothesized) results. This is done in order to determine what is the probability that the statistical test used in the study will be able to detect the effects of that expected size in the given study sample. From prior studies, we can estimate the expected standard deviation. Using statistical computer programs, it is easy to compute how many subjects are needed to find significant statistical differences, say, with a power of 80 or 90 %. Before starting a study, one should also compute costs of the study. For example, it would be illogical to spend excessive amounts of money to find a 5 min difference in total sleeping time, which is certainly not clinically significant.

In the case of small sample sizes, sufficient raw data should be reported so that readers can make their own inferences. Such studies may contain a lot of useful information. Researchers and editors seem to prefer "positive"

results leading to so-called publication bias. To avoid publication bias, also important negative results should be published if the hypothesis has been relevant, studies have been well conducted, and proper methods have been used. When raw data are given, meta-analytic methods can be used to combine results of several studies on the same topic in order to increase strength of the inferences.

The P Value

Among researchers, there is an increasing awareness about the dangers of the misuse of *P* values for null hypothesis significance testing (NHST). ***P value*** (N.B. that the *P* is originally a large "*P*") [3, 18], a pure statistical significance alone, that is, small *P* value, does **not** prove that the null hypothesis is not true given the observed data. The *P* value gives the probability of the observed data given that the null hypothesis is true [16]. It is notable that whether the null hypothesis is true or not is something we simply do not know. NHST is not designed to prove anything instead it is designed to reject the null hypothesis when it is not correct. NHST can do this only with more or less probability. This probability is called the statistical power or sensitivity of the study. If the information is too sparse (study sample includes too small number of subjects), the statistical power (sensitivity) of the study decreases, and the *P* value does not reject false null hypothesis. This is called Type II error or false negative statistical inference. In other words, one makes a false conclusion accepting the null hypothesis that there is no difference between, for example, two group means tested. If, on the contrary, very large populations are used and statistical power of the study increases so much that even very small differences will provide a very small P value. That is called Type I error or false positive statistical inference. In this case, one makes a false conclusion of rejecting a true null hypothesis and concluding that there is a "real" difference between, for example, two group means tested. Another problem in NHST is so-called alpha inflation meaning that *P* value becomes inaccurate when multiple NHSTs are conducted simultaneously [19]. Conducting multiple comparisons simultaneously increases the probability of Type I error. The problem is often counteracted by using corrections like Bonferroni correction. The take home message from the problems in NHST is that one should not make a research conclusion based merely on *P* value. What one should do is to analyze such data quantitatively. Cohen [16] recommends to report effect sizes in the form of confidence interval which instead of a single value is an interval estimate of a population parameter and contains all the information to be found in NHSTs. In addition, speaking about "significant" *P* values, one should always make clear that they are "statistically significant" and their significance or meaningfulness in other sense is a different issue.

Suppose that we are studying two different treatments Th1 and Th2. The mean total sleeping time (TST) during Th1 is 480 min, and the standard deviation is 20 min. Using Th2, the respective figures are 475 and 20 min. If we studied 15 subjects in both groups, the *P* value is 0.499 (statistically not significant), and the 95 % CI for the difference between means is −10 to 20 min. If we studied 125 subjects per group, the *P* value would have been less than 0.05 (probability that the difference is caused by chance is less than 5 %), and the CI would have been 0–10 min. In both groups, 1000 subjects would have given *P* value less than 0.0001 (statistically highly significant difference in total sleep time), and the CI would have been 3–7 min. The truth is of course that there was only a 5 min difference between the two treatments which is not clinically significant. In this example, the most useful information for a clinician is given by the smallest study, not by the largest study It should also be remembered that because NHST does not prove anything we must always rely, in the end, on replication. This is especially true as regards isolated findings.

Validity

The validity of a study may be divided into internal validity and external validity. ***Internal validity*** derives from the inferences that can be made based on the actual data. It is a measure of quality and of the study methods. Selection bias and information bias should be avoided and confounding factors should be identified and controlled. ***External validity*** is a measure of representativeness of the study population compared to a more general population. Good internal validity is needed to have good and adequate external validity. As Rothman writes: "The separation of relevant from irrelevant factors is the beginning of knowledge" [6].

For example, a study of a new drug among 18–70-year-old people with many exclusion criteria cannot be generalized to normal clinical patients of a treating physician, because many patients have some of the diseases that have been listed among the exclusions. The results can be generalized only to such patients that fulfill the same inclusion and exclusion criteria. This is often not taken into consideration when new treatments are entering the markets. For example, for most hypnotics, most studies are done with patients having chronic insomnia, lasting for more than one month. In spite of this, in many countries, the official label writes that this same hypnotic is indicated to treat insomnia on a short-term basis. We know that ideally hypnotics might be useful in initial short-term treatment of transient insomnia. We also know that there is no long term, say 3 years

clinical follow-up studies, of hypnotics treatment that have shown good efficacy without development of tolerance or adverse effects. Similar examples exist from almost all other types of drugs, not only hypnotics. A clinician must use her/his own clinical knowledge when making final inferences. In this respect, it is also interesting to note that pharmacologists, other theoreticians, and also investigators of RCTs may give instructions about how to treat a specified disease even if they have rarely or never taken the responsibility of treating such patients in real world.

Selection bias. An essential element of a study is a comparison of two or more groups for occurrence of a disease or exposure. One form of bias is a ***self-selection bias***. Another type of bias is ***diagnostic bias***. Many other types of selection bias exist. Some epidemiologic studies, e.g., on narcolepsy, are based on newspaper advertisements. People with given symptoms are asked to contact the researchers. Such studies may be used to have a rough estimate of prevalence of a very rare and serious disease such as central alveolar hypoventilation, but they cannot be used for insomnia, restless legs syndrome, or sleep apnea. Of course, one might use such selection methods when recruiting subjects into drug trials. One should keep in mind, however, that the subjects contacting a center do not necessarily represent a typical patient with the disease concerned. If study subjects are receiving honorary fees for participation, the bias may be even larger because the motivation to participate may be to earn money, and the subjects may report relief from the symptoms more easily. Same may be true when, e.g., opiates are studied. For this reason, drug screens should be used always when one is studying drugs with CNS effects.

Information bias. The information obtained and entered into a database should be based on comparable methods. To improve comparability, quantitative or semiquantitative scales should be used always when possible. Wordings such as "always," "often," "sometimes," and "rarely" may be interpreted differently by different persons. For one patient having a migraine attack once per month might mean "often." For another person it might mean "rarely." Having trouble sleeping "often" may mean "on 3–4 nights per month" or "on 3–4 nights per week." It is obvious that quantitative scales allow better comparisons between individuals. The basic Nordic sleep questionnaire (BNSQ) is an example of a questionnaire with quantitative wordings [20]. Similar wordings are used also in the Wisconsin Sleep Cohort studies and in many other studies. Qualitative research has its own benefits and usages that are not handled here.

Recall bias is an example of information bias. Diseased people often remember better some things that have occurred in the past. On the other hand, they may also misremember some things, for example, after reading about some possible adverse effects from an article. If one wants to have information about effects of an intervention/treatment, same measure should be used at baseline and later during time. Sometimes patients have been asked, e.g., "how do you find this treatment compared to another or compared to no treatment." If the treating physician is valued and respected by the patient, the placebo effect is great and the patient may evaluate the treatment effect as very good. The time lapsed between the exposure and the recall is an important indicator of the accuracy of recall. We have recently faced the problem of a potential recall bias, e.g., in studying the association between an adjuvanted pH1N1 vaccine (Pandemrix®) and narcolepsy. Having more information from prior medical reports and from other sources may help. The first contact with a health personnel (e.g., school nurse) may give a more reliable date of onset than trying to figure the date of onset if it occurred several years before.

Cultural changes in social psychology of the society may also lead to a specific information bias. People may change their answering behavior depending on how "important" or "acceptable" it is to speak about some issues in their cultural environment. Therefore, for example, today the current increasing public awareness of the importance of sleep and its disorders may modify people's answering behavior in a different way when compared to studies some decades ago.

Different types of risk factors. All causal factors are risk factors but many risk factors are not causal. As an example, eating ice cream is a "***statistical risk factor***" of drowning deaths, but of course eating ice cream is not "**a causal risk factor**" of deaths. There is only a temporal relationship. Most deaths by drowning occur at summer time when people eat more ice cream than during winter.

Five different types of risk factors may be defined as follows: proxy, overlapping, independent, mediating, and moderating risk factors [21]. *B* is a "***proxy risk factor***" for *A* for the outcome *O* if *A* and *B* are correlated, if there is no temporal precedence of either *A* or *B* or if *A* precedes *B*, and if, in either case, *A* dominates [21]. Let us take an example. Obesity (*A*) is one of the strongest risk factors of arterial hypertension (*O*). There is also evidence that obstructive sleep apnea (*B*) is a risk factor of *O*. In this case, obstructive sleep apnea may be considered as a proxy risk factor of obesity. Other proxy risk factors of obesity are excessive use of alcohol, chronic sleep deprivation, use of antipsychotics, lower socioeconomic status, etc. As an "***overlapping risk factor,***" neither *A* nor *B* has temporal precedence, *A* and *B* are correlated, and *A* and *B* are codominant. Smoking and use of alcohol are overlapping risk factors of many disorders. Kraemer et al. propose to call *A* and *B* "***independent risk factors***" if there is no temporal precedence of *A* or *B*, *A* and *B* are uncorrelated, and *A* and *B* are codominant. "**Mediating risk factors**": A mediator variable (*B*) explains how or why another variable (*A*) affects an outcome (*O*) [6, 21, 22]. This kind of relationship is common in medicine.

For example, in presence of genetic susceptibility for narcolepsy (e.g., HLA DQB1*0602), T-cell receptors may be mediated by different environmental factors causing loss of hypocretin neurons and narcolepsy type 1. According to Baron and Kenny [22], a "***moderator***" (*A*) specifies on whom or under what conditions another variable (*B*) will operate to produce the outcome (*O*). A moderator (*A*) is supposed to affect the relationship between the other variable (*B*) and the outcome (*O*), whereas a mediator (*B*) is supposed to be influenced by the other variable (*A*) directly. For example, certain CYP genotypes (*A*) moderate effects of, e.g., hypnotics (*B*) in treatment of insomnia to have longer total sleeping time (*O*).

Confounders. Understanding and controlling ***confounding*** has a central role in modern epidemiology. It must be separated from a risk factor. For example, age is not a causal risk factor but it is a potential confounding factor in many situations. For an extraneous factor to be a confounder, it must have an effect on the occurrence of disease, but it does not have to be a causal factor. In general terms, a confounding factor must be associated with both the exposure and the disease. One can consider the following flow/connections of development of a disease equation: exposure → altered physiology (altered body/mental functions) → disease. A variable measuring altered function is a risk factor for disease, and it is correlated with exposure, because it results from exposure. However, it is not a confounding factor because the effect of exposure is mediated through effect of altered physiology [4, 6].

Precision and Comparability of Information; Randomized Controlled Trials

Precision refers to reduction of random measurement error. Precision can be improved by increasing number of subjects or by increasing accuracy of obtained information by improving used measures. A statistical effort to correct for measurement error is to model it in the so-called measurement model. This approach is applied in modern statistical models belonging to the model family called structural equation models. However, most commonly errors occur during the process of selecting study subjects. The attendant random error is called **sampling error**.

The best method to gather new valid information about, e.g., a new treatment is a randomized controlled trial (**RCT**). In an experimental study, a population is selected for a planned treatment or intervention whose effects are measured by comparing the outcome in the experimental group with the outcome in a control group. For avoidance of bias, members of the intervention (treatment) group and the control group should be comparable except in the regimen that is offered them [23]. Allocation of individuals is ideally by randomization. Stratified sampling may be used.

In a valid experimental RCT study:

1. Populations are comparable (randomization in randomized controlled trials)
2. Information is comparable (use of blinding), and
3. Effects are comparable (use of placebo and/or active comparator treatment).

Standardization, Matching

After the data are collected, the effect of covariates may be controlled by use of various standardizations. Stratification and different standardization methods (direct or indirect standardization) are well described in most books of epidemiology. During the collection of the data, *matching* can be used. One must, however, avoid ***overmatching***. For example, if we want to study effects of obstructive sleep apnea syndrome on cerebral circulation, we could compare patients with OSAS to patients without OSAS. We select one control subject without OSAS for each patient with OSAS. If we match the subjects (matching of each pair) too strictly, say, for age, gender, body mass index, waist circumference, and blood pressure, we risk losing most differences. Instead of matching for all these variables, it is often better to analyze the results using potential modifiers and other common risk factors as covariates. One commonly used method is to apply logistic regression analysis. In all cases, it is important to work with an experienced epidemiologist/statistician already when designing a study.

Population-Based Rates

Prevalence. Prevalence is defined as the number of instances of a given disease or other condition in a given population at a designated time [23]. Most commonly, prevalence rates represent cross-sectional events, noted at a single point in time for the state of the group under study [3, 24]. This is called point prevalence. A period prevalence refers to the number of cases that occur during a specified period of time, e.g., one year. This is now rarely used. It usually takes some time to conduct a study and find all cases; and in such case, it is generally possible to estimate point prevalence (that can be called just "prevalence"). The prevalence rate is given as the number of cases for a specified number of persons in the population (number of cases at a specified time/number of persons in the population at that time). Prevalence focuses

on disease status, and it should not be confused with incidence.

Incidence. Incidence (I) has a focus on new events while prevalence focuses on disease status. Incidence rates represent longitudinal events, noted in the follow-up of a cohort. It is defined as the number of instances of illness commencing, or persons falling ill, during a given period of time in a specified (cohort) population (incidence = number of new cases during a specified period of time/number of persons exposed to risk of developing the disease during that period of time). Incidence thus refers to the number of new events or new cases in a defined period of time, whereas prevalence refers to the number of existing cases. It is essential to give the time unit that has been used when counting incidence rate. If one knows the incidence rate and the average duration of the disease concerned, one can assume that prevalence = incidence × duration (D) of the disease (using same unit of time, e.g., years). More generally [25], one can give that prevalence = $(I \times D)/(1 + (I \times D))$.

Bayes' theorem. In a clinical setting, a physician may estimate the probability that her/his patient has a defined disease by using the Bayes' theorem [26]. If one knows the prevalence of the disease in the population, the occurrence rate of a symptom or of a laboratory finding among the diseased and the sensitivity of a diagnostic test, one can estimate the occurrence of the disease (prevalence) in that population. According to the Bayes' theorem:

$$\text{Probability of the disease} = (\text{sensibility} \times \text{prevalence of the disease})/(\text{prevalence of the symptom}).$$

For example, what is the probability that our snoring patient has sleep apnea? We know from literature that about 90 % of patients with obstructive sleep apnea snore (sensibility). We also know that the prevalence of OSAS among men is about 4 % and that about 50 % of adult men, similar to our patient, snore at least sometimes. Hence, the probability of OSAS in our patient is $(0.9 \times 0.04)/0.5 = 0.072 = 7.2$ %.

Mortality rates. Mortality rate or death rate is the proportion of a population who die of a defined cause. The numerator is the number of persons dying, and the denominator is the total population in which the deaths occurred. The unit of time may be one calendar year or a longer period of time. In order to avoid bias arising from disproportions in age, gender, or race between the general (denominator; reference) population and the study population, the data are standardized. The indirect method is more popular than the direct method of standardization. As a result, *standardized mortality ratios* can be given. In long-term follow-up studies survival, mortality and also morbidity figures may be computed using different survival analyses.

Risk ratio and odds ratio. Risk is often used to describe rate of occurrence of a symptom or disease. Risk refers to probability that an event will occur within a defined period of time. A risk factor, or determinant of risk, is a factor or exposure that increases the probability of occurrence of a specified outcome. A risk factor may or may not be in causal relationship with the outcome.

Risk ratio (RR) or relative risk (also rate ratio) is the ratio of the probability (risk) of getting a disease (outcome) in a risk group (exposed subjects) divided by the probability (risk) of getting the same disease (outcome) in a reference group (non-exposed subjects). In the case of a rare disease, risk ratio approximates the odds ratio (OR). The OR is defined as the **odds** that an outcome will occur given a particular exposure, compared to the **odds** of the outcome occurring in the absence of that exposure. Instead of risk ratio, the odds ratio (cross-product ratio) and its 95 % confidence limits are widely used in epidemiological studies. Whenever possible (if meaningful prevalence or incidences are available), calculation of rate ratios (relative risks) is recommended because RRs are often easier to understand than ORs. OR always overestimates the RR. In addition, ORs are often misinterpreted as if they were equivalent to RRs [27]. If the lower limit of the 95 % confidence interval is greater than 1, the rate ratio is "statistically significant" with a P value less than 0.05, that is, the studied exposure is a "risk factor for the specified outcome." Similarly, if the upper 95 % confidence limit of a rate ratio is less than 1, the factor is "protective."

Normality and use of medians. What does "normal" mean in epidemiology? Sir Ronald Fisher regarded 95 % of the inner values of a distribution as common and the remaining 5 % as significantly uncommon. The outer 5 % of values is traditionally considered abnormal, but statistical or epidemiological theory does not support this view [3]. According to Feinstein, "Fisher's proposed boundary of uncommon occurrences was intended for inferential decisions about P values, not for descriptive decisions about normality. Nevertheless, after years of exposure to 0.05 as the magic level of stochastic significance, many clinicians have become thoroughly conditioned to accept the same boundary marker for abnormality" [3]. Many laboratories now use the term "customary range" instead of normal range. This term is more appropriate. It is also good for patients whose laboratory values are outside the customary range, because the values may be without any clinical significance even if they are out of the customary range.

Biological data do not always fit Gaussian normal curve. The distributions are often significantly skewed or bimodal. On such occasions, the usual mean ±2 standard deviations tactics is not appropriate. Unfortunately, one can still find that it is used in medical literature even if the data are not normally distributed. For example, one could read that the mean (± standard deviation) weight of children was

10 ± 12 kg. How does a child look if his/her weight is minus 2 kg (10 − 12 = −2)? One can have negative cholesterol or negative apnea index values, etc, if one gives means and standard deviations alone. Giving the confidence interval and range gives more information. In biological sciences and medicine, use of **medians** (the "middle value") and percentiles, even without means, is often better than means and standard deviations alone.

Median is easy to calculate and it describes the population better than the mean. It divides the population in two equal parts. To find the inner 95 % of the data, we need only to locate the 2.5 percentile point and the 97.5 percentile point. The procedure is simple, and by using it, we will never encounter impossible ranges.

Measures of effect size. Different measures may be used to have an idea about results of interventions and clinical trials. In particular, three measures are commonly used in evidence-based meta-analytical studies: **relative risk reduction (RRR)**, **absolute risk reduction (ARR)**, and the **number needed to treat (NNT)**.

Let us cite two examples. (1) Suppose that in a prospective follow-up study, 10 % of subjects treated with CPAP had a new cardiovascular event versus 20 % among the non-treated. These rates are also called risks of having a defined event; in other words, risk can be thought of as the rate of a defined outcome. (2) Suppose that in a randomized clinical trial on restless legs syndrome, 70 % of those with the active drug had significant amelioration of their symptoms versus 30 % in the placebo control group. In the same study, 1 % of those with active treatment and 0.3 % of those with placebo had hallucinations as an adverse effect.

Relative risk reduction. Relative risk measures how much the risk is reduced in the treatment group compared to the control group. In the first example above, 20 % of the control had a cardiovascular event compared to 10 % among those treated with CPAP. The CPAP treatment group had a 50 % (0.5) relative risk reduction. The formula is as follows: RRR = (CER − EER)/CER, where CER is the control group event rate and EER is the experimental group event rate. In the second example, the relative risk reduction of having hallucinations when using a placebo instead of the experimental treatment is 70 %, i.e., (1 − 0.3)/1. As we can see, the RRR is not a good indicator if the occurrence of an event is rare.

Absolute risk reduction. Absolute risk reduction is the absolute difference in outcome rates between the control and treatment groups, i.e., ARR = CER − EER. The absolute risk reduction does not confound the effect size with the baseline risk. In the first example above, ARR is 10 % (20 − 10% = 10 %). In the second example, ARR for hallucinations is 0.7 % (1 − 0.3) when using placebo. This figure is very small and easier to interpret than the large and not clinically significant relative risk reduction of 70 %. The ARR for having amelioration of symptoms is in this example, 70 – 30 % = 40 %.

Number needed to treat. Because the ARR is sometimes difficult to interpret, better indicators are needed. The **number of patients needed to treat (NNT)** in order to find a significant effect (e.g., cure and significant amelioration of symptoms) is a good indicator of a treatment effect [28]. The number needed to treat is simply another way to express absolute risk reduction. NNT = 1/ARR and it is the number of patients that would need to be treated to prevent one additional bad outcome. For the example of CPAP above, the NNT is 10 (1/0.1) and for the second RLS example, the NNT is 1/0.4 = 2.5. Thus, in the first example, 10 need to be treated and in the second example, only 3 patients. The number needed to have hallucinations, i.e., the **number needed to harm (NNH)** is in the second example 143 (1/0.007 = 142.8). If we compare 3 patients to 143 patients, we can clearly see that the benefits are much larger than harms in this respect. Of course, one must take all other adverse effects into account when the NNH is estimated. If the NNT is still larger than the NNH, then the treatment could be used. It is interesting to note already at this point that NNT of chronic insomniac patients with sedative hypnotics in a meta-analytic study of Glass et al. was 13 but the NNH was more than twice smaller than that number (NNH = 6). This means that the probability of doing harm to a patient was larger than that for doing good [29].

The NNT can be converted to an **NNT for a given patient** by estimating the **patient's susceptibility relative to an average control patient** in a trial report and dividing the reported NNT by this fraction F (i.e., susceptibility). For example, in the second scenario above, if a physician's 80-year-old patient is judged to be three times more susceptible as the average control patient to have hallucinations, then F = 3 and **NNT/F** = 143/3 = about 48. This means that one could still think about treating the patient with that drug, supposing that there is significant evidence about its effectiveness in old patients above 80 years of age. **The NNT can be computed also from the odds ratio and control group rate of events;** 95 % confidence limits for the NNT should also be given. Different tables and formulas exist in many statistical packages and also in the Internet, e.g., by searching "number needed to treat" using Google.

Effect size. Effect size (ES) is a commonly used index to measure the magnitude of a treatment effect. It is important to note that effect size indices are not statistical tests. Unlike significance tests, they are independent of sample size. ES measures are used especially in evidence-based meta-analytical studies that summarize the findings from a specific topic. Effect size (ampleur d'effet in French) is computed most commonly as the standardized difference between two group means. Originally, Cohen defined effect

size d as the difference between the means, $M_1 - M_2$, divided by standard deviation, s, of either group 1 or group 2, i.e., *effect size* $d = (M_1 - M_2)/s$.

This is an approximation of the theoretical formula for the standardized difference between two groups where the denominator should be the standard deviation of the population from which the groups are sampled. If it is unknown, it can be estimated in different ways. If the standard deviations of the groups are approximately the same, it can be assumed that they are estimating common population s. In this case, they can be pooled (s_{pooled}) to calculate Cohen's d index of effect size $d = (M_1 - M_2)/s_{pooled}$ [30, 31]. Usually, the subtraction of the means between the intervention (experimental) group and control group is done so that a positive difference means improvement and negative difference means deterioration. The pooled standard deviation is found as the root mean square of the two standard deviations. Modern statistical programs usually automatically compute also the pooled standard deviations, that is, the pooled standard deviation is the square root of the average of the squared standard deviations. When the two standard deviations are similar, the root mean square will not differ much from the simple average of the two variances.

Epidemiology of Sleep Disorders

The oldest epidemiological studies about sleep length are from the end of the eighteenth century. Among the most respected studies were those by Clement Dukes from England about the need of sleep of young children. Other well-known early studies are those by Hertel from Denmark, Bernhard from Germany, and Claparède from France [32, 33]. About 80–100 years ago, it was recommended that young children should sleep 10.5–13.5 h, 15-year-olds should sleep 9–10 h, and adults should sleep between 7 h 25 min and 8 h 23 min [34, 35], which does not differ significantly from present day self-reported figures of healthy adults having an average sleep length between 7 and 8 h. Women slept a little bit longer than men except in the case of mentally retarded subjects when the situation was reversed [36, 37].

Sleep disturbances increased with age as they do at present days. In the Laird's study [35] from 1931, at age 25, about 10 % of men were not satisfied with their sleep. At age 95, everybody reported some wakefulness each night. In the same study, more than 70 % of men reported some difficulty in going to sleep, and more than 40 % reported nightly awakenings. Different methods were used to help one to sleep. Reading was used by 25 %, and 18 % used relaxation techniques. Three percent of men used drugs to help them sleep. Two percent used alcohol to help them sleep [35]. The latter two figures differ significantly from those of present days.

Many epidemiological studies about sleeping habits have been done since 1960. In these studies, the average self-reported sleep duration varied between 7 and 8 h. In a questionnaire survey, 7.4 % of 1278 University of Florida students reported less than 6.5 h of night sleep, and 13.4 % reported more than 8.5 h [38]. In Scotland, 2446 subjects aged over 15 were inquired. Of the older subjects in the age group 65–74 years, 18 % complained of waking up before 5 a.m. The percentage decreased to 12 % after age of 75. Disturbed sleep was reported by less than 10 % of men aged 15–64. In the age group 65–74, disturbed sleep was a complaint in 25 % of men. In women, the respective percentage was 43 % [39]. In one classic study from 1979, Bixler et al. determined the prevalence of sleep disorders among 1006 households in the Los Angles metropolitan area [40]. The prevalence of past or current insomnia was 42.5 %. The prevalence of current insomnia was 32.2 %, and 7.1 % complained of excessive sleep.

Insomnia

The epidemiology of insomnia and insomnia-related symptoms is a bit blurred because of large variance in methods and case definitions used in different studies [41]. The view on insomnia is also changing in itself. Traditionally, insomnia was considered as "integrated into" psychiatric disorders. However, this view has changed. The current psychiatric DSM 5 as well as the 3rd International Classification of Sleep Disorders uses the term "insomnia disorder" as a distinction to "insomnia" as a symptom [42, 43].

Taking existing evidence together, about 2–18 % of adults usually complain of clinically significant persistent insomnia depending on the definition of insomnia and the population. Several studies suggest relatively consistently that about 10 % of middle-aged adults suffer from long-standing insomnia [40, 44–59]. Transient insomnia- and occasional insomnia-related symptoms are very common but prevalence figures vary greatly between studies from about 20–50 % [40, 55, 57, 60–64].

Chronic insomnia is often (in 35–69 % of cases) associated with psychiatric conditions. Most common comorbid condition in chronic insomnia is depressive disorder, which has been reported to be present in about 40–50 % of chronic insomniacs [49]. In one study, 93 % of depressed psychiatric inpatients had insomnia [65]. Among treatment seeking veterans of the 13 separate mental health diagnoses evaluated, all except dementia and schizophrenia were strongly associated with insomnia [41].

Insomnia and insomnia-related symptoms are associated with increasing age, at least up to the age of about 65 [53] and female gender particularly during the midlife years [66–68] being 1.4–2 times more common in women than in men.

About one-third of subjects older than 65 years have chronic insomnia. At very old age, the figures may be lower [46, 69]. In an Australian study, insomnia was persistent in 16.2 % of the community-dwelling population and in 12.2 % of institutional residents. Altogether 14.5 % of the elderly subjects living in the community used hypnotics regularly while the corresponding percentage was 39.7 among the institutionalized subjects [46]. However, while sleep problems may increase with age, active complaints to the physician may decrease with age [41]. Comorbidity and psychosocial influences are strong modifying factors underlying the association of insomnia and increasing age. Highest rates of self-reported insomnia symptoms have been reported for 18–24-year-old and 50–59-year-old men and women [70].

Aging process per se may not be the primary cause of insomnia among elderly people [71]. A 3-year longitudinal study [72] among 6899 men and women aged 65 and older suggested an annual incidence rate of insomnia approximately 5 %. Incident insomnia was associated with depressed mood, respiratory symptoms, fair to poor perceived health, and physical disability. Only 7 % of the incident cases of insomnia occurred in the absence of associated risk factors. Of the nearly 2000 survivors with chronic insomnia at baseline, almost 50 % did not report any symptoms after 3 years. The authors interpreted their results as not giving support to a model of incident insomnia caused by the aging process per se [72].

Among people complaining frequent or chronic insomnia and/or insomnia-related symptoms, the use of sleep medication is very common. It has been estimated that about 57–60 % of individuals complaining of frequent or chronic insomnia use sleep medication [73]. The association between medication use and insomnia is independent of other comorbidities [73]. The healthcare system is oriented to treat insomnia pharmacologically. Up to 60 % of adults seeking treatment for insomnia are prescribed sedative and/or hypnotic medications [73, 74]. This is reflected in recent prevalence figures of hypnotic medication use of 6–10 % among adult US population [75]. In US outpatient care, the number of office visits with insomnia increased by 13 % from 4.9 million visits in 1999 to 5.5 million visits in 2010. At the same time, however, the number of prescriptions for any sleep medication increased by 293 % from 5.3 in 1999 to 20.8 million in 2010 [76]. Somewhat older prevalence estimates among the general population have varied between 4 and 11 % [77–79]. Among 65–year-old or older, 9–15 % have been reported to use sleep medication nightly [80]. The use of hypnotic medication among insomniacs seems to be long standing [78]. The use of hypnotics in particular is associated with the use of psychotropic medication in general resulting in different multiuse combinations of hypnotics and sedatives with anxiolytics and psychotropic drugs [73].

Recently some studies have consistently reported that especially occasional self-reported insomnia symptoms, use of sleep medication, and perhaps also chronic insomnia in some countries show increasing long-term prevalence figures in the general adult population [55, 81–83]. An analogous trend was found also among adolescents in Finland [84]. In addition, the number and percentage of US outpatient office visits due to sleep-related problems and prescriptions for a sleep medication have also significantly increased [76]. The increasing trend of pharmacological treatment for insomnia has prompted warnings against possible overuse of medications among insomniacs [74]. In line with increasing prevalence figures, there is also an ongoing shift in prescribing sleep medication. There is some evidence that physicians have started to replace traditional hypnotics (benzodiazepines and their derivatives) by small doses of antidepressants and antipsychotics [85–87]. Theoretically, the latter medications may be more physiological as they may increase slow-wave sleep though their action on histamine-1 receptors [88]. Long-term epidemiological surveys of their benefits are, however, missing [89]. Self-reported insomnia-related symptoms have complicated underlying associations with individuals' socioeconomic status, general well-being, and quality of life as well as with different comorbidities [90, 91]. Different kind of information bias may complicate interpretation of various studies. However, it seems to be clear that something is happening in our time to which peoples' self-reported sleep quality is responding.

Efforts and official initiatives to reduce hypnotic use have been largely unsuccessful in healthcare system [92]. In particular in older individuals, adverse effects on cognitive and psychomotor functioning may result in increased risk of falls and traffic accidents [93]. Also, tolerance and dependence may develop. However, the interpretation of the established epidemiologic association between use of hypnotics and increased mortality has remained controversial. The association was reported first in the American Cancer Prevention Study [94]. Later, the follow-up data were reanalyzed and the "use of sleeping pills" and "tranquilizers" "often" associated with mortality with 1.5 hazard ratio when compared with non-users [66]. It is evident that "sleeping pills" at that time were different compounds and potentially more dangerous than those used today. However, the association has been later replicated approximately 20 times in different countries [75]. The association has been confirmed as regards total mortality [95, 96] and several specific causes of death such as cancer [75, 97, 98] and cardiovascular disease [99], among others. On the other hand, the strength of the association has usually not been especially strong. Median hazard associated with hypnotics among 24 studies was found to be <1.5 and only in four cases >2.0 after adjustments [100]. Negative findings have also been

reported [80, 101, 102]. Users and non-users differ from each other in several important ways as regards the comorbid conditions associated with insomnia itself, and it is practically impossible to control for all potential confounders. This makes the statistical analyses (or more accurately statistical inferences) of large observational studies complicated and difficult. The situation has created currently ongoing debate whether the association is causal or caused by confounding [103–106]. In any case, the clinicians should follow the principle of caution and the guidelines for temporary use of hypnotics.

Chronotype and insomnia. Interindividual variance in individuals' circadian preferences of the timing of their daily behaviors underly their phenotypical differences along a characteristic called chronotype. In parallel, different chronotypes differ in involuntary timing of physiological functions such as core body temperature, blood pressure, and hormonal secretion. Based on these behavioral and physiological differences, individuals can be classified into earlier timed morning types, the intermediate types, and the later timed evening types [107–110].

Epidemiology of chronotypes is new but currently rapidly evolving field of sleep epidemiology, although still in its beginning. Only few large epidemiological studies on chronotype have been so far published. Among the Finnish general adult population, the prevalence of clear morning types has been estimated to vary approximately from 29 to 47 %, and clear evening types from approximately 10–12 % [111–113]. A New Zealand study estimated approximately 10 % of 30–49-year-old population to be "definitely" morning types and approximately 40 % to be "moderately" morning types, 7 % "definitely" evening types and 5 % "moderately" evening types [114]. Evening type has been repeatedly shown to be associated with different health risks, for example, total mortality [113], cardiovascular disease and type 2 diabetes [115, 116], and depression [117, 118]. Of note, evening type is also associated with chronic insomnia complaints 2–3 times more often than morning type as well as use of sleep medication [112, 119].

Seasonal differences of insomnia. Occurrence of insomnia may vary depending on the season of the year. The results from the Nordic countries agree with each other [52, 120]. In Northern Norway, 41.7 % of women and 29.9 % of men had occasional insomnia. In general, complaints of insomnia are more common during winter than during other times of the year [121]. The reasons for this cannot be explained by the season (darker, colder climate, more rain, or snow) itself. Work and different lifestyle factors probably explain most of the variance, but we lack good evidence. In the Tromsø study, occurrence of insomnia during summer (summer insomnia) decreased with age, whereas the other seasonal types of insomnia increased with age [120]. Individuals also differ in their sensitivity or reactivity to seasons. Among high or moderate seasonality individuals, sleep problems suggesting insomnia as well as sleepiness have been shown to be more prevalent than among individuals of low seasonality group [122]. In clinical form, this is reflected in the association between depressive symptoms and seasons among patients suffering from seasonal affective disorder (SAD).

Insomnia in different occupations. Occurrence of sleeping problems varies by occupation and working times [123–126]. In a questionnaire survey of 6268 adults representing 40 different public sector occupations, 18.9 % of bus drivers complained of difficulty falling asleep. Among male directors and male physicians, the respective percentages were 3.7 and 4.9 %. Disturbed nocturnal sleep was complained most often by male laborers (28.1 % waking up at least three times a night) and female cleaners (26.6 %). Disturbed nocturnal sleep was rare among male physicians (1.6 %), male directors (7.4 %), female head nurses (8.9 %), and female social workers (9.4 %) [126]. The association of sleep and type of occupation are partly explained by working conditions, socioeconomic position, income, and probability of possible future unemployment [127, 128]. Accordingly, prevalence figures of insomnia-related symptoms are associated with great shifts in society's economic situation [129].

Psychiatric Disorders and Insomnia

Insomnia is associated with psychiatric disorders such as depression, anxiety disorders, alcohol dependence, and schizophrenia [130]. Traditionally, insomnia was considered a symptom of psychopathology. Until recently, insomnia was classified as a primary disorder if it was not related to mental disorders, and if it was, a diagnosis of secondary insomnia was given. These were the two most common DSM-IV insomnia diagnoses [131]. The differential diagnosis was, however, sometimes difficult. For example, in one study, 216 patients with insomnia were interviewed by one sleep specialist and one non-sleep specialist. By using DSM-IV criteria, 99 (46 %) were diagnosed as having insomnia related to mental disorders, and 48 (22 %) were diagnosed as having primary insomnia. A psychiatric disorder was rated as a contributing factor for 77 % of patients with a first diagnosis of primary insomnia [132]. It has been suggested that "comorbid" insomnia may be a more appropriate term than "secondary" insomnia [133]. Recently, DSM-V has divested the concept of primary/secondary insomnia and instead introduced "insomnia disorder" as the main diagnostic category for insomnia, leaving it possible to determine whether or not insomnia is comorbid with a psychiatric or somatic disorder [42]. In a large US community survey, the prevalence of insomnia without psychiatric comorbidity was 4.9 % [134]. Among those with comorbid insomnia in the past year, 25 % had major

depression, 19 % abused alcohol, 12 % had dysthymia, 9 % had panic disorder, 8 % abused drugs, 8 % had schizophrenia, and 2 % had somatization disorder [134]. In a World Health Organization (WHO) collaborative study, 25,916 primary healthcare patients were evaluated. Sleep problems were present in 27 % of the patients. Of the patients with insomnia, 51 % had a diagnosis of ICD-10 mental disorder, mainly depression or anxiety, abuse of alcohol, or a combination of different psychiatric disorders. 40 % of insomniacs reported using alcohol and over-the-counter medications to help them to sleep [135].

The relationship between psychiatric disorders and sleep is complex with bidirectional causation [136]. Insomnia is not only a symptom of psychiatric disorder but also a predictor of future incident depressive period, PTSD, and substance use. [10, 133, 137–140]. In a recent longitudinal study in 9683 young Australian women who were surveyed in 2000, 2003, 2006, and 2009, a new-onset depression and anxiety were predicted at each subsequent survey with two 2- to 4-fold OR estimates among those who reported sleeping difficulties "often" in 2000 [141]. In another study in 1584 adult patients seeking help from a private sleep medical center, suicidal ideation was consistently associated with different sleep complaints even when depressive symptoms were controlled for [142]. However, one placebo-controlled study in insomnia patients concluded that it may be the use of hypnotics, rather than insomnia itself, which is causal risk factor of future depression [143].

The overlapping of insomnia and psychiatric disorders results also in large mixed psychotropic drug use among insomniacs. In one telephone survey, it was estimated that among non-institutionalized French population 53 % of insomnia sufferers used at least one drug. Approximately, 20 % used hypnotics, 37 % anxiolytics, 7 % antidepressants, and 3 % other psychotropic drug [49]. Consequently, there is a potential risk of mixed drug overuse among insomniacs. Given that insomnia is associated with alcohol dependency one should remember that alcohol may have serious interactions with psychotropics, especially with hypnotics and sedatives. Among alcohol dependent patients, insomnia may also increase alcohol-related adverse psychosocial consequences [144].

Different stress factors belonging to more or less normal everyday life are also associated with insomnia and insomnia-related symptoms. Unemployment, being unmarried, separated, or widowed associate with higher prevalence of insomnia complaints in Japan as well as in other countries [145]. Different psychological complaints, psychological stress, symptoms of work-related stress, and mental exhaustion are associated with high prevalence of insomnia [47, 52, 77, 131, 146–149]. Simple methods, such as the five-item version of the Mental Health Index and some other questions, may be used to effectively screen workers with mental health and sleep problems [145, 150, 151].

Insomnia Among Patients with Neurological and Other Somatic Diseases

Parkinson's disease and dementia. Many neurological disorders are associated with disturbed sleep and insomnia. Parkinson's disease [152–161] and dementia [162–168] are typical examples. Sleep disorders occur in over 70 % of patients with idiopathic Parkinson's disease (PD), adversely affecting their quality of life. Among patients with Parkinson's disease, sleep disruption takes the form of sleep fragmentation with frequent and prolonged awakenings and daytime sleepiness. Nocturia, difficulty in turning over in bed, painful leg cramps, vivid dreams and/or nightmares, back pain, limb/facial dystonia, and leg jerks are the main causes of nocturnal awakenings in PD patients. Sleep disturbance gradually worsens with disease progression suggesting that it is related to the severity of the disease. Sleep disturbance may also be a complication of chronic levodopa therapy. In a survey of 100 PD patients, significant sleep complaints were found in 74 %. Sleep complaints were unrelated to patient age and the duration of disease but increased in prevalence with longer periods of levodopa therapy. Sleep abnormalities tended to increase in severity with continued treatment of PD. Dyskinetic side effects and on–off syndrome occur as well in patients with or without sleep complaints, but up to 98 % of patients experiencing psychiatric side effects also report sleep disruption [158]. A correlation with sleep disturbance and severity of PD exists [159–161, 169]. In an Indian case–control study, 149 PD patients and 115 age-matched healthy controls were asked about sleep disturbances using a questionnaire. Sleep problems were seen in 42 % of PD patients and 12 % of controls. Sleep disturbances included insomnia in 32 % versus 5 % of controls, nightmares 32 % versus 5 %, and excessive daytime sleepiness by 15 % versus 6 %. All sleep complaints were statistically more common in PD patients compared to controls and correlated with increased severity of the disease [154].

In a follow-up study, 142 of the initial 231 patients were re-evaluated after 4 years and 89 patients after 8 years [157]. Complaints of insomnia remained almost constant while problems related to turning in bed and vivid dreaming or nightmares increased during the follow-up. Insomnia was present in 54–60 % of the patients at each of the three study visits. Insomnia was related to disease duration, depression, and female sex [157].

Stroke and insomnia. Patients with stroke complain often of insomnia, and disturbed sleep may also be a risk factor of stroke or an indicator of other processes that are related to

stroke. Post-stroke depression is one such factor, but it does not explain everything. A sample of 277 stroke patients aged 55–85 had a psychiatric evaluation of 3–4 months after ischemic stroke. 56.7 % reported some type of insomnia complaint and 37.5 % fulfilled the DSM-IV criteria of insomnia. In 38.6 %, insomnia complaint had started before the stroke, and in 18.1 %, it started after occurrence of the stroke. Insomnia complaints correlated with increased disability, cognitive decline, anxiety, and increased use of psychotropic drugs [170]. In South Wales, 1986 men aged 55–69 completed a questionnaire on sleep patterns with help from their partners. They were asked about symptoms of disturbed sleep including insomnia, snoring, restless legs, obstructive sleep apnea, and daytime sleepiness (Table 28.1). During 10 years of follow-up, 107 men experienced an ischemic stroke and 213 had an ischemic heart disease event. About 1/3 of the men reported at least one symptom suggestive of sleep disturbance, and 1/3 reported daytime sleepiness. Compared with men who reported no such symptoms, the age-adjusted relative risk of an ischemic stroke was significantly increased in men with any sleep disturbance. The strongest association was with symptoms indicating sleep apnea (OR 1.97; 1.26–3.09) [171].

Other neurological and somatic disorders. Most subjects with mental retardation complain of some types of sleep disturbance [172, 173]. Insomnia is frequent among many other somatic disorders including different respiratory diseases [147, 174]. In a study by Dodge et al., the prevalence of insomnia was 31.8–52.4 % among adults with cough,

Table 28.1 Snoring as a risk factor of stroke

Study	Population	Methods; outcome	Stratification/adjustment	Type of snoring	OR (95 % CI)
Partinen and Palomäki [419]	50 male stroke patients and 100 hospital controls	Case–control, personal interview, neurological examination, CT/MRI; stroke versus others	Age, gender (men), BMI	Habitual snoring	10.3 (3.5–30.1)
				Often or always snoring	2.8 (1.3–5.8)
Koskenvuo et al. [406]	General population 4388 men, 40–69 years	Cohort study, 3 years follow-up, questionnaire, registry data; incidence of stroke or IHD	Age, gender (men), BMI, smoking, alcohol, HT	Often or almost	2.08 (1.5–3.77)
				Always snoring	(Stroke or IHD)
Palomäki [424]	177 Stroke patients and 177 hospital control patients	Case–control, questionnaire, neurological examination, CT/MRI; stroke versus others	Age, gender, alcohol, HT, IHD	Often or always snoring	2.13 (1.29–3.52)
Spriggs et al. [420, 423] others adj	326 IHD/stroke pat. and 345 community	Case–control, personal interview, neurological examination, CT/MRI; stroke versus others	Age, gender, BMI, smoking, alcohol, IHD, HT, AF, DM	Often or almost snoring	3.2 (2.3–4.4) adj for age and gender 1.7 (1.3–2.2) adj for all factors
Smirne et al. [420]	164 Stroke patients and 330 hospital control patients	Case–control, personal interview, neurological examination, CT/MRI; stroke versus others	Age, gender, BMI, smoking, alcohol, HT, DM, dyslipidemia	Often or always snoring	1.86 (1.20–2.87)
Jennum et al. [416]	804 70-year-old followed for 6 years	Cohort of 70-year-old men and women, snoring history and other information from medical records	Age, gender, BMI, smoking, alcohol, HT, social class, lipids, glucose, catechol	Often or always snoring	1.8 (1.1–3.6)
Neau et al. [417]	133 Stroke patients, and 133 non-hospital control patients	Case–control, personal interview, spouse present, neurological examination, CT/MRI, stroke versus others	Age, gender, BMI, DM, hypertension, cardiacarrhythmia	Habitual snoring	2.93 (1.28–6.75)
Hu et al. [283]	71,779 Female nurses, 40–65 years	Cohort study, 8 years follow-up, questionnaire, registry data; incident stroke versus no stroke	Age, smoking, BMI, hypertension, DM, hypercholesterolemia, familial IHD history and other covariates	Snoring regularly	1.88 (1.29–2.74) adjusted for age 1.35 (0.91–1.99) adjusted for all
				Occasional snoring	1.42 (1.07–1.89) adjusted for all

AF Atrial fibrillation, *DM* Diabetes mellitus, *HT* Hypertension, *IHD* Ischemic heart disease, *OR* Odds ratio

dyspnea, or wheezing. Among adults without respiratory symptoms, the prevalence was about 26 % [174]. In an older Swedish study, 18.8 % of men with obstructive pulmonary disease suffered from difficulties in maintaining sleep (DMS) and 12.4 % complained of excessive daytime sleepiness. Among diabetic men, DMS was complained by 21.9 % and difficulty initiating sleep was complained by 21.1 % [175]. In a large US telephone survey, nocturnal awakenings were complained by 41.5 % of patients with gastroesophageal reflux, 38.6 % of heart disease patients, and 27–38 % of patients with other somatic diseases [176].

Is Anticipation of Coming Health-Related Events Possible with Follow-up of Sleeping Pattern and Sleep/Wake Rhythm?

As mentioned above (see "psychiatric disorders and insomnia"), insomnia has been repeatedly shown to be a predictor of future incident depressive period, PTSD, and substance use. There is also increasing evidence that self-reported sleep duration is a statistically independent predictor of all-cause and cardiovascular mortality, and morbidity in large epidemiological follow-up studies in recent meta-analyses [177–179]. The association is U-shaped meaning that often both extreme ends of the self-reported sleep duration distribution are associated with increased risk. However, there is some variation among the results. For example, a U-shaped association was confirmed in some studies [180, 181], only among women but not in men [182], or only among men but not in women [183, 184]. In one study, only short sleep was associated with increased risk of stroke [185], and in some studies mainly long sleep was associated with risk of stroke [178]. A recent study suggested that use of sleep medication may be a strong modifier of the association between short sleep and health outcomes [186]. Also, negative findings have been reported as regards sleep duration and future health [187, 188]. One reason for the inconsistencies among findings may be that the interpretation of the association of self-reported sleep duration and adverse health outcomes is complicated [189, 190], and may be different in different populations or cultures.

Insomnia has been associated with future cardiovascular morbidity [191] and total mortality [192–194]. In one recent study, insomnia was associated with future diabetes but not with incident CVD [195].

Sleep Length; Natural Short and Long Sleepers

As described above, self-reported sleep duration is a statistical predictor of several detrimental future health outcomes. A U-shaped association of self-reported sleep duration and health outcomes suggests that among the general population there are two risk groups showing deviation from the population mean sleep duration. Within these groups, sleep-related health risks are supposed to be increased. The prevalence figure of these risk groups varies depending on the cutoff points used to determine short and long sleep duration. In Finland, it was estimated that among the general adult population there are 14.5 % (16.7 % of men and 12.5 % of women) short sleepers ($\leq$6 h) and 13.5 % (10.5 % of men and 16.1 % of women) long sleepers ($\geq$9 h) [196]. However, subpopulations of short and long sleepers are not homogenous. Cross-sectional studies have shown that in any time point in the general population, self-reported short and long sleep are associated with several health conditions (e.g., obesity, diabetes, hypertension, metabolic syndrome, and cardiovascular disease) and different lifestyle factors [181, 188, 192, 196–198]. In a cross-sectional study of 5419 adult men, a higher prevalence of diagnosed myocardial infarction was found among those who slept more than 9 h, while those sleeping less than 6 h per night had a higher occurrence of symptomatic coronary heart disease. This relationship remained after controlling for age, sleep quality, use of sleeping pills and tranquilizers, smoking, alcohol use, Type A score, neuroticism, use of cardiovascular drug, and arterial hypertension [199]. In a large population-based survey with 218,155 Australian adults aged 45 years and over 6 h versus 7 h sleep was associated with statistically significantly increased odds of heart disease (OR 1.11), diabetes (OR 1.159), stroke (OR 1.25), and high blood pressure (OR 1.08) (1.04–1.11). Long sleep ($\geq$9 h) was also significantly related to heart disease (OR 1.14), diabetes (OR 1.25), stroke (OR 1.50), and high blood pressure (OR 1.04) compared to 7 h of sleep [188]. In a meta-analysis of 12 prospective studies both long sleep (RR 1.45; 1.30–1.62) and in a lesser degree short sleep (RR 1.15; 1.07–1.24) were risk factors for stroke [178].

Consequently, probably relative large part of the sleep duration risk groups is at risk because of existing ill health (baseline comorbidities with deviation from the population mean 7–8 h of sleep duration). Therefore, it is important to adjust for comorbidities or individuals with a previous history of a given disease must be excluded from the analysis. Therefore, attention is paid to healthy short and long sleepers. Are they at risk?

In a given time point, healthy adults who sleep less than 6–7 h per night are called "natural short sleepers" and those sleeping more than 9.5 h of sleep "natural long sleepers" [189, 192, 200–203]. This concept makes an assumption that there is an underlying genetic factor which determines whether or not an individual is "a natural short or long sleeper" [189, 204, 205]. However, there are also individuals who have modified their sleep duration due to different external factors [204]. Consistent short sleepers may have a

smaller risk than average sleepers (7–8 h) who have become short sleepers or long sleepers later in their life [189]. Genetically, short or long sleepers are at higher risk than midrange sleepers [189, 192, 206].

The fact that an individual is capable, at least for some time, to modify his/her sleep duration and in this way possibly harm one's own future health has raised a question: Would it be possible that in our modern society sleep duration is gradually shortening among the general population either voluntarily or forced by external factors? It is clear that sleep is not just a biological phenomenon. Its behavioral execution differs in different cultures. For example, the practice of siesta (daytime napping) varies across different cultures [207]. A historian Roger Ekirch has published a fascinating study suggesting that in preindustrial era people in Western Europe experienced, on most evenings, two major intervals of sleep, bridged up to an hour or more of quiet wakefulness [208, 209]. During the past two centuries, the preindustrial segmented sleep pattern has been replaced by a consolidated nocturnal sleep in modern societies. Some studies have found a small long-term decrease in self-reported sleep duration among the general population, but the effect size is clinically meaningless [55, 210]. Recent reviews have concluded that there is no convincing evidence supporting the belief of a secular trend of sleep reduction in general population [211, 212].

Insufficient sleep is the most common cause of daytime fatigue and sleepiness. Insufficient sleep may be due to poor sleep with nocturnal awakenings, too short sleep, or due to some other cause. The lack of sleep may be due to "bad habits", or a discrepancy between biological and social circadian rhythms, or to some psychic or somatic pathology. In a Japanese study [202] among 3030 adult people, aged 20 or more, 29 % slept less than 6 h per night, and 23 % reported having insufficient sleep. Short sleep duration was the strongest predictor of excessive daytime sleepiness [202]. Similar figures have been published in Europe and USA [202, 213–215]. In Sweden, 12 % of adults had persistent chronic sleep loss, and 50 % of them also reported other concomitant sleeping difficulties. In subjects without sleeping difficulties, the most common cause of insufficient sleep was too little time for sleep [214]. In another study, the prevalence of insufficient sleep, defined as a difference of at least one hour between reported need of sleep and actual sleep length, was 20.4 % (16.2 % in men and 23.9 % in women). Almost half of those with insufficient sleep at baseline had it still 9 years later showing that the problem is often chronic. One-third of the liability to chronic insufficient sleep was attributed to genetic influences [215]. It should be, however, noted that "insufficient sleep" calculated as a difference between self-reported evaluations of one's need of sleep and self-reported usual sleep duration is not a direct measure of objectively determined sleep deprivation, and caution should be taken when interpreting the results of epidemiological studies on "insufficient sleep."

Daytime Sleepiness

Some prevalences of daytime sleepiness are shown in Table 28.2. Depending on the study and wording, the occurrence varies from very small 0.3 % to more than 30 % (see Table 28.2). As an average, the prevalence is between 5 and 15 %.

Sleepiness may be interpreted differently in different languages. The English word "sleepiness" is defined in the Random House Unabridged Dictionary and the Scribner-Bantam dictionary as "inclined to sleep, drowsy," and in Stedman's Medical Dictionary as "an inclination to sleep." Synonyms for "sleepy" include words such as tired and somnolent. Fatigue is a more general term describing, according to Stedman's, a state of lessened capacity for work and reduced efficiency of accomplishment, usually accompanied by a feeling of weariness, sleepiness, or irritability [216]. A more original description of fatigue is found in the highly appreciated French Dictionnaire des Termes Techniques de Médecine by Garnier and Delamare published in 1969, where fatigue is defined as "a state resulting from prolonged activity of an organ or system. It is translated as decrease of function and a particular sensation (feeling of fatigue) which is specific to each organ. The aim of training is to retard apparition of fatigue." Tiredness comes from the word tired, which is synonymous to weary, wearied, exhausted, fatigued, jaded, and bushed. In the Random House Unabridged Dictionary, "tired" suggests a condition in which a large part of one's energy and vitality has been consumed. One who is "tired" has used up a considerable part of his or her bodily or mental resources. One who is "fatigued" has consumed energy to a point where rest and sleep are demanded. Simple rest may decrease tiredness and feelings of fatigue but sleep is needed to relieve sleepiness. In sum, sleepiness is a preferred term to describe inclination to sleep or tendency to fall asleep.

Sleep-related breathing disorder is the second most common reason of excessive daytime sleepiness among adults after lack of sleep [201, 202]. Also, the use of hypnotic agents, other sleeping difficulties, and irregular sleep–wake schedule are related to daytime sleepiness. In most sleep laboratory populations, more than 75 % of patients with daytime sleepiness have sleep-related breathing disorders (most commonly obstructive sleep apnea syndrome), 20 % have narcolepsy, and 5 % have restless legs, periodic movements in sleep, or other sleep disorders. This does not reflect distribution in general population, where insufficient and/or poor quality of sleep explains most cases of sleepiness.

Table 28.2 Occurrence (%) of daytime sleepiness

Study	Size (*N*)	Population; age	Definition of sleepiness (wordings)	Methods	Percentage (%)
Sleeping too much					
Karacan et al. [520]	1645	General population; 18–70 years	Too much sleep	Questionnaire	0.3
Bixler et al. [40]	1006	General population; 18–80 years	Sleeping too much	Questionnaire	7.1 (current 4.2)
Ford and Kamerow [10]	7954	Population sample; 18–65+ years	Ever a period of two weeks or longer sleeping too much	Direct structured interview using Diagnostic Interview Schedule	2.8 (M), 3.5 (W)
Involuntary sleep attacks, sleeping episodes, irresistible sleep, chance of dozing					
Partinen [227]	2537M	Army draftees before military service; 17–29 years	Falls asleep at work	Questionnaire	6.4
Partinen and Rimpelä [521]	2016	Population sample; 15–64 years	Involuntary sleep attacks daily or almost daily	Phone interview	3.4 (M), 2.5 (W)
Billiard et al. [522]	58,162M	Army draftees; 17–22 years	Daily sleep episodes	Questionnaire	4.9
Klink and Quan [523]	2187	Population sample; 18–64 years	Falling asleep during the day	Questionnaire	12
Saarenpää-Heikkilä et al. [524]	574	Schoolchildren; 7–17 years	Sleeping during lessons often or always	Questionnaire (both subject and parents)	3 (B), 0 (G)
Hays et al. [525]	3962	Population sample; 65–85+ years	Most of the time sleepy, forcing to take a nap	Interview	25.2
Ganguli et al. [526]	1050	Population sample; 66–97 years	Ever becoming uncontrollably sleepy so that can't help falling asleep	Interview	18.9 (no gender difference)
Johns and Hocking [527]	331	Australian workers; 22–59 years	Chance of dozing; ESS > 10	Questionnaire including the validated ESS	10.9 (no gender difference)
Schmitt et al. [528]	668	Working population: post office clerks	ESS $\geq$ 10	Questionnaire	13
[a]Melame Melamed and Oksenberg [529]	532	Non-shift industrial workers Mean age 46.3 $\pm$ 7.6 years	ESS > 10	Questionnaire	22.6
Kaneita et al. [530]	28,714	General Japanese population; 20–70 + years	Do you fall asleep when you must not sleep (for example when you are driving a car)?	Questionnaire	2.8 (M), 2.2 (W)
Pallesen et al. [531]	2301	Population sample; 18–90 years	ESS > 10	Telephone interview	17.7
Excessive daytime sleepiness, sleepiness, feeling sleepy during daytime					
Partinen [227]	2537M	Army draftees; 17–29 years	Do you often feel sleepy during daytime? Are you more sleepy than your friends or workmates?	Questionnaire	35.8 9.5
Partinen and Rimpelä [521]	2016	Population sample; 15–64 years	Sleepier than fellow people	Phone interview	10 (M), 14 (W)
Lugaresi et al. [532]	5713	Population sample; 3–94 years	Sleepiness independent of meal times	Direct interview	8.7

(continued)

Table 28.2 (continued)

Study	Size (*N*)	Population; age	Definition of sleepiness (wordings)	Methods	Percentage (%)
Kelly et al. [533]	3543	Students; 13–18 years	Tiredness	Questionnaire	29.3
Martikainen et al. [224]	1190	Population sample; 36, 41, 46, 50 years categories	Tiredness/sleepiness (more tired than fellow people; or daily compulsory desire to sleep; or feeling tired every day)	Questionnaire	6.9 (M), 12.0 (W)
Saarenpää-Heikkilä et al. [524]	574	Schoolchildren; 7–17	Daytime sleepiness always or often	Questionnaire (both subjects and parents)	20 (B), 22 (G)
Janson et al. [147]	2394	Population sample; 20–44 years	Feeling drowsy in the daytime 3 per week	Questionnaire	16.0
Hublin et al. [201]	11,354	Population sample; 33–60 years	Daytime sleepiness daily or almost daily	Questionnaire	6.7 (M), 11.0 (W)
Ohayon et al. [534]	4952	Population sample; 15–100 years	Feeling sleepy during the day on a daily basis at least 1 month a lot or greatly (severe sleepiness) or moderately (moderate sleepiness)	Telephone interview using the Sleep-Eval system	Severe: 4.4 (M), 6.6 (W) Moderate 15.2
Ohida et al. [535]	106,297	Japanese adolescents; 12–19 years Junior and Senior High Schools	Do you feel excessively sleepy during the daytime?	Questionnaire	33.3 (B), 39.2 (G)

ESS Epworth sleepiness scale; *M* Man; *W* Woman; *B* Boy; *G* Girl

Narcolepsy

The prevalence of narcolepsy varies in population-based studies between 21 and 56 per 100,000 persons [217–235]. In some studies, sampling has been, for example, by newspaper advertisements and TV programs and these studies do not represent well-defined population samples. In addition, there are many unknown assumptions in some of the early studies and therefore these are not taken into consideration [226, 236–238]. The highest figures, around 160 or up to 590 per 100,000, are from Japan [219, 220, 230]. The lowest frequency, 0.23 per 100,000 population, is found in Israel [231, 239].

A simple screening method called the Ullanlinna Narcolepsy Scale (UNS) has been developed and validated [222]. The UNS consists of 11 items assessing cataplexy-like symptoms and tendency to fall asleep. The score varies from 0 to 44 and the cut point for diagnosing narcolepsy is 14. Using the UNS, the prevalence of narcolepsy with cataplexy was 26 per 100,000 population in adult Finns [223]. Very similar figures have been published from Hong Kong. Using the validated Chinese version of UNS, the prevalence rate of narcolepsy among southern Chinese was 34 per 100,000 (95 % CI 10–117). In Hong Kong, all narcoleptic subjects were HLA DRB1-1501 positive and 50 % were DQB1*06:02 positive [233]. Using the same methodology, the prevalence among Korean students is around 15 per 100,000 [240].

Cataplexy is one of the core symptoms of narcolepsy, but occasional cataplexy-like attacks may occur also in healthy subjects. Among young men, 16.5 % experience at least sometimes sudden weakness in some muscle groups that are associated with emotions. 3.7 % of young men had experienced such cataplexy-like symptoms often or almost during the past month [227]. In another study, 29.3 % of the people reported (at least once during his or her lifetime) feelings of limb weakness associated with emotions [223]. If this is considered as evidence of cataplexy and combined with the occurrence of daytime sleep episodes at least 3 days per week, 6.5 % of the population would have narcolepsy according to the minimal diagnostic criteria for narcolepsy of the ICSD. Clinical, polysomnographic, and CSF examinations of hypocretin allow more exact diagnosis and more precise occurrence rates [241–246].

In the current ICSD-3, narcolepsy is divided into narcolepsy type 1 (narcolepsy with certain cataplexy; narcolepsy with low CSF hypocretin; NT1) and narcolepsy type 2 (no cataplexy, CSF hypocretin normal; NT2). NT1 is

probably an autoimmune/autoinflammatory disease. NT2 is more heterogenous and iNT2, and idiopathic hypersomnia are very difficult to distinguish from each other. Using the new diagnostic classification, NT2, as well as idiopathic hypersomnia, seem to be much less common than NT1, but population-based epidemiological studies do not yet exist. Also, the existing prevalence studies, as shown in Table 28.3, must be interpreted with caution, as the criteria for diagnosis of narcolepsy have been variable. For example, in the Longstreth study only 50 % of the diagnosed narcolepsy with cataplexy were HLA DQB1*0602 positive [234], contrasting to almost 100 % positivity among NT1 patients in some recent studies [247–249]. Also, normal people may report of occasional cataplectic attacks and therefore it is uncertain if all subjects in that study, in fact, had true narcolepsy.

Incidence of narcolepsy. Studies on incidence of narcolepsy are scarce, but it seems that the incidence of narcolepsy is approximately 1 per 100,000 people per year [228, 248, 250, 251]. In Minnesota, the incidence of definite and probable narcolepsy with or without cataplexy was 1.37 per 100,000 persons per year (1.72 for men and 1.05 for women) [228]. In the same study, incidence of narcolepsy with cataplexy was 0.74 per 100,000 persons per year being highest in 10–19-year-olds (1.8/100,000/year) [228]. Computed from their data, the incidences of narcolepsy with

Table 28.3 Prevalence of narcolepsy. Studies on representative population samples

Study	Number (age range) country	Population, methods and comments	Prevalence per 100,000 (CI)
Solomon [229]	10,000 (16–34) USA	Black men. No precise information on cataplexy	20 (0–4.8)
Solomon [229]	189,196 USA	Male population sample. No precise diagnosis	3 (0.6–5.7)
Honda [219], Honda et al. [220]	12,469 (12–16) Japan	Population sample, Que, personal interview	160 (9–230)
Partinen [227]	2537 (18–29) Finland	Young male population, recruits, Que, PSG	79 (6–287)
Franceschi et al. [218]	2518 (6–92) Italy	Hospital patients, Que, PSG	40 (0–118)
Wilner et al. [231]	1800 (30–57) Israel (Jews)	Hospital patient sample, PSG, HLA typing	0.23 (N/A)
Martikainen et al. [224]	1190 (36–50) Finland	Population sample, Que	168 (18–604)
Tashiro et al. [230]	4559 (17–59) Japan	Population sample, Que	590 (369–816)
Al Rajeh et al. [217]	23,227 (all ages) Saudi Arabia	Population sample, personal interview, clinical examination	4 (0–13)
Wing et al. [232]	342 (N/A), Chinese, Hong Kong	Patient population, PSG, HLA typing	1–40 (N/A)
Hublin et al. [223]	11,354 (33–60) Finland	Population sample, Que, UNS, Phone interv., clin. exam., PSG, HLA typing	26 (0–56) with cataplexy
Ohayon et al. [225]	4972 (15–100) United Kingdom	Population sample, telephone survey	40 (0–96)
Ondzé et al. [235]	14,195 (15+) France	Patients consulting physicians, Que	21 (4–62)
Silber et al. [228]	Census data of Minnesota, USA	Record linkage of diagnosed patients; Incidence 1.4 (0.95–1.9)/100,000 persons/year	56 (42–73) 36 (25–50) with cataplexy
Wing et al. [233]	9851 Chinese Hong Kong	Population sample, phone interview, UNS, clin. exam., PSG, HLA typing	34 (10–117) with cataplexy
Ohayon et al. [226]	18,980, UK, Germany, Italy, Portugal, Spain	Population samples, telephone surveys	47 (N/A)
Shin et al. [240]	20,407 (14–19) Korea	Student population, UNS, interview, PSG, HLA typing	15 (0–31)
Longstreth et al. [234]	About 1.4 million (18+), USA, King County	Multiple overlapping methods, newspaper advertisements, newsletters, patients groups etc., interviews, HLA typing	30.6 (27.6–33.5) 21.8 (18.8–28.8) with cataplexy 15.3 (12.8–17.9) with DQB1*0602

CI Confidence interval; *N/A* Not applicable, not given or cannot be calculated; *PSG* Polysomnographic sleep studies; *Que* Questionnaire used as a screening method; *UNS* Ullanlinna narcolepsy score

cataplexy were 1.0 per 100,000 persons per year in people aged less than 40 years and 0.1/100,000/year in people aged 40 years or more.

After the adjuvanted H1N1-vaccinations, the incidence of narcolepsy increased significantly, especially in those European countries, where Pandemrix® vaccination was the only vaccination used [247, 250, 252–259]. In Finland, all patients with Pandemrix-associated narcolepsy were HLA DQB1*06:02 positive and all patients who have had a lumbar puncture have been type 1 with low CSF hypocretin levels [247, 248]. After Pandemrix vaccination in Finland, the average incidence of narcolepsy increased in people aged under 17 years from 0.3 to 5.3 per 100,000 people per year [247]. In a retrospective cohort study, the incidence of narcolepsy was 9.0 in the vaccinated as compared to 0.7/100,000 person-years in the unvaccinated individuals, the rate ratio being 12.7 (95 % confidence interval 6.1–30.8) [252]. Reports from other countries have also shown a statistically significantly increased risk of developing narcolepsy after Pandemrix® vaccination [250, 253–259]. The incidence rate in children before vaccination campaign was lower, e.g., in Finland than in Minnesota [228], and it is possible that some children had remained undiagnosed before the vaccination campaign. The incidence rates in children, adolescents, and also in adults rose anyway to a much higher level than ever before indicating a relationship with the vaccination. Recent immunological studies provide a link between Pandemrix and narcolepsy. The results have moved the focus from adjuvants onto the H1N1 viral proteins [248, 249, 260].

There are some interesting associations with time of birth and narcolepsy. In southern China, an excess of winter births has been found in subjects with narcolepsy-cataplexy [261]. In a large multicenter (Montpellier, Montreal, and Stanford) study, birth dates of 886 patients with a clear-cut diagnosis of narcolepsy with cataplexy were compared with birth dates of the comparative general populations. The birth rate of narcoleptic patients was highest in March (OR 1.45) and lowest in September (OR 0.63 compared to general population). No gender or country of origin differences were observed [262].

Snoring and Sleep Apnea

Habitual Snoring

Snoring is an inspiratory noise (occasionally also occurs during expiration) caused by vibration of the soft upper airways tissues, mainly soft palate and posterior faucial pillars. Snoring corresponds to partial obstruction of the upper airways, and complete obstruction is followed by an apnea. Almost everybody snores sometimes especially when sleeping in a supine position. It is well known that alcohol increases snoring. Habitual (almost every night or every night) snoring is practically always present in patients with obstructive sleep apnea syndrome (OSAS). Children and elderly people may not snore loudly. Instead, they are breathing with their mouth open. In the first large-scale epidemiological study on snoring, about 24 % of San Marino men and 14 % of San Marino women were reported to habitually snore [263]. In Finland, 9 % of adult men and 3.6 % of adult women reported snoring always or almost always when asleep [264]. A recent Finnish study found that when individuals with prior history of cardiovascular disease were excluded from the Health 2000 sample of adult ($\geq$30 years of age) population among the remaining 5177 individuals 17.8 % (11.9 % of women and 25.2 % of men) reported to snore habitually [265]. Among Hispanic–American adults, the age-adjusted prevalence rate of regular loud snoring was 27.8 % in men and 15.3 % in women [266]. Snoring increases with age up to 60–65 years and decreases in older age [264, 266–273]. In many studies, prevalence of snoring has been higher but in such cases history of snoring has often been asked with only two or three possible response alternatives. Because almost everybody snores sometimes snoring figures are high. Occasional snoring or snoring as a dichotomous variable is not related to significant pathology [265, 274, 275]. On the contrary, habitual almost every night snoring seems to be a risk factor for cardiovascular and cerebrovascular diseases [265, 274, 276]. For a clinician, this is important. Having a positive response to snoring is not sufficient. One needs to know how often someone is snoring. When asking for frequency, semi-quantitative scales with defined time frames should be used. For example, “often” can mean once a month for someone but almost every day for another. Snoring history is significant if someone snores on at least 5 nights per week; in other words, someone is a habitual snorer. One can ask further also about presence of sleep apnea (breathing cessations) and snoring stertorousness.

If someone snores almost every night very loudly and intermittently and someone (a cohabiting person) has noticed breathing pauses on about 3–5 nights per week, the probability of obstructive sleep apnea is high. If the subject has been snoring for more than 13 years, it is almost certain that he/she has sleep apnea [277]. The probability of sleep apnea increases further if the clinical examination is suggestive of sleep apnea. Some of the best-known strong indicators of possible sleep apnea include thick neck, large waist circumference (visceral fat), increased fat under the chin, pathological Mallampati score with large tongue and/or large tonsils, and narrow upper airways with high ogival hard palate. If the snoring and apnea history are positive and the clinical examination is suggestive of sleep apnea, the prior probability can be higher than 90 %. In other words, the

diagnostic certainty is better than that of a screening sleep recording. It is also important to recognize false positive responses from screening recordings. Unfortunately, a good clinical history and clinical examination are sometimes overlooked trusting too much on the results of sleep recordings.

The main underlying mechanism behind the associations of sleep-disordered breathing (habitual snoring) and cardiovascular outcomes is obstructive sleep apnea (OSA). However, heavy habitual (every night) snoring (i.e., partial upper airway obstruction) may influence pulmonary arterial pressure even without apneas, and expose the heart and circulation to a cascade of detrimental stimuli such as increased intrathoracic pressure, autonomic dysregulation, platelet activation, oxidative stress, and endothelial dysfunction resulting in the development of cardiovascular disorders [278], daytime sleepiness, insulin resistance, metabolic syndrome, and other health consequences [277–295].

Sleep Apnea

Sleep-related breathing disorders (SRBD) and sleep-disordered breathing (SDB) refer mostly to sleep apnea. In a large population-based study, more than 2000 adults, aged 40–85 years, had a polygraphic sleep recording [296]. The median apnea-hypopnea index (AHI) was 6.9/h in women and 14.9/h in men. The prevalence of moderate to severe sleep-disordered breathing (defined according to AASM as AHI $\geq$ 15) was 23.4 % (20.9–26.0) in women and 49.7 % (46.6–52.8) in men [296]. Can these results be interpreted as meaning that almost 50 % of over 40-year-old men have SRBD, which should be treated by nasal CPAP as current medical textbooks are suggesting? Many questions remain open. Sleep apnea is very common and it is associated with many health-related outcomes. More prospective studies as well as randomized studies are needed anyway. Using the current "pathological limit" of AHI (AHI $\geq$ 5), even more than 80 % of men and 60 % of women could be defined as "patients with sleep apnea," if we use the recent Swiss figures [296]. The current definitions of sleep apnea using AHI indices must be revised, as the "original" historical limits of AHI (mild $\geq$5, moderate 15–30, severe $\geq$30) have been "taken from the pocket" and they have not originated from physiological background.

Currently, the generally accepted prevalence of symptomatic and clinically significant OSAS (SRBD with excessive daytime sleepiness) among adult men is probably somewhere between 3 and 7 %, and in women the prevalence of OSAS varies from 2 to 5 %. There is an age relationship. The prevalence of OSAS among men aged 40–59 may be greater than 4 % or even much greater than 10 %. Although sleep apneas are frequently found among elderly subjects, the occurrence of clinically significant sleep apnea is less common in older age groups than among people aged 40–65. In young women, OSAS is rare, but after menopause, up to the age of 65, it is almost as common as among men. Sleep apnea is not rare among children. Apneas with AHI > 5 may be found in more than 14 % but symptomatic sleep apnea syndrome is rare [267, 269, 297–304]. In the first population-based studies, the prevalence of OSAS varied between 1 and 4 %, but recent estimation have been higher. Men have higher figures than premenopausal women. Among adults, children, and also among subjects with mental retardation, OSAS is highly associated with central obesity [13, 14, 269, 270, 272, 273, 279, 298, 299, 304–321].

Obstructive sleep apneas are part of the complex of "heavy snorer's disease" as defined by Lugaresi et al [322]. As stated above, heavy snoring is as such, without sleep apnea syndrome, a risk factor for many health outcomes.

Sleep apnea should be properly quantified, not only by an apnea index (AI) (or apnea-hypopnea index; AHI) but also by the number of oxygen desaturations, limitation of air flow, degree of daytime sleepiness, and by cardiovascular function. An AI of 5 or AHI of 10 is commonly used as a criterion of OSAS. The diagnostic criteria should be adjusted for age [315–317, 323–325]. It may be that while the occurrence of sleep apnea increases with age the clinical meaningfulness of apnea decreases among elderly people. Hence, occurrence of clinically significant sleep apnea syndrome is rare among elderly people, who often have many other diseases that may be indirectly associated with sleep apnea [326–330].

Risk Factors for Snoring and Sleep Apnea

Central Obesity, Thick Neck, and Obstructed Upper Airways

Central visceral obesity is the most important risk factor for snoring and sleep apnea. Obesity is commonly measured by body mass index (BMI), which is calculated as weight in kilograms divided by square of height in meters [331]. According to the WHO criteria, adults with a BMI of 25 kg/m^2 and over may be considered as overweight and those with BMI of 30 kg/m^2 and over are considered as obese. According to WHO, in 2006, more than 60 % of US and UK citizens were overweight and almost 30 % of US citizens were obese with BMI over 30 kgm^{-2}. In the Nauru Islands almost 80 % and in the French Polynesia 36 % were obese (see, e.g., WHO Web pages on statistics of BMI/obesity [332]).

The frequency of snoring and sleep apnea increases with obesity in all published epidemiological reports. The same is true for heavy snoring and sleep apnea. For example, in the Katz's study habitual snoring was found to occur in 7 % of

men and 2.8 % of women with a BMI of less than 27 kg/m^2 and in 13.9 % and 6.1 %, respectively, of those above this level [203].

Using multivariable analysis, the Oxford group of John Stradling first reported that neck size is more closely related to severity of sleep apnea than BMI [303, 333–335]. Neck size may be easily measured, and it is a useful indicator of upper body obesity. Several lines of evidence show that central obesity (large waist circumference) is related to increased risk of cardiovascular disease, diabetes, and metabolic syndrome [336–342]. Other clinical markers that are risk factors for sleep apnea include high Mallampati score and small cricomental space [335, 341, 343–348]. If the cricomental space is more than 1.5 cm, obstructive sleep apnea is unlikely; in the study of Tsai et al., its negative predictive value was 100 % (95 % CI 75–100 %) [348].

Anatomically narrow upper airways. Lean people may have abnormal upper airways. Anything that obstructs upper airways is a risk factor for heavy snoring and sleep apnea. Among known risk factors are large adenoids or tonsils, and rhinitis [349–353]. Other abnormalities in upper airways are, e.g., those found in different dysmorphic syndromes, in mentally disabled people, in acromegaly, and familial amyloidosis [354–362].

In sum, obesity is linked with probability of snoring and sleep apnea, but BMI is not the best indicator of obesity. Therefore, at least, waist circumference, neck circumference, and cricomental space should be measured in all future clinical and epidemiological studies on snoring and sleep apnea. Waist- and neck circumference as well as the cricomental space may be estimated relatively well also in surveys that are based on questionnaires using different pictures of the head and neck. Responders can then choose the picture that resembles most their own faces. The collar size of a shirt correlates well with actual neck circumference.

Other Risk Factors for Snoring and Sleep Apnea

Among 2187 subjects representative of a general adult population in Tucson, major independent risk factors for snoring were male gender, age between 40 and 64 years, obesity, and cigarette smoking [363]. Snoring was more common in subjects who regularly used alcohol or hypnotics. The effect of smoking may be related to upper airway inflammation and edema caused by cigarette smoke.

Alcohol increases upper airway resistance and tends to induce obstructive sleep apnea in healthy people and especially among chronic snorers [349–353, 364–368]. This is probably due to the acute centrally depressing effects of alcohol. Among other risk factors, hostility is associated with habitual snoring [369].

Ethnic Differences in Occurrence of Snoring and Sleep Apnea

Prevalence and incidence of sleep apnea vary according to ethnicity (Table 28.4). In a study in Singapore comparing prevalence of snoring among Chinese, Malay, and Indian, the average prevalence of snoring was 6.8 % (53–83 %). The ethnic differences were significant. Among Chinese, 6.2 % (4.4–8.1), among Malay 8.1 % (6.1–10.2 %), and among Indians 10.9 % (85–13.4 %) snored. The minimum whole population prevalence by the most restricted symptom criteria for defining sleep breathing-related disorder was 0.43 % (0.05–0.8 %) [308]. In Singapore, some estimations have given a prevalence of 15 % for sleep apnea [370]. This figure is based, however, only on a small sample of people and it may not be representative of the whole Singapore population. Therefore, the figure is probably too high. The reasons may be related to differences in craniofacial anatomy and also to environmental effects. Examples of the latter include obesity which seems to be significantly more common, e.g., among African Americans and also among Saudi Arabian women than in people of Caucasian origin [308, 316, 371–374]. Reasons for higher occurrence of obesity are multiple, and socioeconomical factors should not be forgotten. Unemployment, alcoholism, and lack of financial security are known to be associated with higher figures of obesity. It must be emphasized that there is still a considerable lack of epidemiological data regarding the prevalence of OSA in Asian communities and consequently all inferences about the differences across Asian and European ethnicity should be made with caution [375].

Snoring and Sleep Apnea in Children

Snoring or obstructive sleep apnea is common in children of all ages. It must be noted that among children snoring may not be loud. A manifestation of obstructed upper airways may be that the child always sleeps with open mouth. Among 1615 Italian children, aged 6–13, 118 children (7.3 %) were habitual snorers. Children with rhinitis were more than twice as likely to be habitual snorers than others. There was a positive correlation between parental smoking and the presence of snoring in children [349]. In Iceland, 3.2 % of 555 children aged 6 months to 6 years snored often or always [270]. The estimated minimal prevalence of obstructive sleep apnea in that age group was 3.2 %. In one study among 4–5–year-old children, significant sleep and breathing disorders occurred in 0.7 % [376]. In a Spanish study, the prevalence of sleep-disordered breathing among

Table 28.4 Occurrence of obstructive sleep apnea and sleep apnea syndrome

References, country	Population subjects	Age (years)	Criteria; comments	Prevalence (%)
Lavie [302], Israel	1262 men	18–67	AI > 10, symptomatic	1.0–5.9
Telakivi et al. [304], Finland	1939 men	30–69	Habitual snoring, EDS, RDI > 10	0.4–1.4
Gislason et al. [269], Sweden	3201 men	30–69	Habitual snoring, EDS, AHI > 10	0.7–1.9
Cirignotta et al. [267], Italy	1170 men	30–39 40–59 60–69	AI > 10, symptomatic AI > 10, symptomatic AI > 10, symptomatic	0.2–1.0 3.4–5.0 0.5–1.1
Stradling and Crosby [303], Great Britain	893 men	35–65	ODI_4 > 20, symptomatic ODI_4 > 10 ODI_4 > 5	0.3 1.0 4.6
Haraldsson et al. [301], Sweden	846 men	30–69	Positive history of OSA, EDS, and PSG	2.8–5.5
Young et al. [13], USA	352 men 250 women	30–60 30–60	Hypersomnia and RDI $\geq$ 5	4.0 (M) 2.0 (W)
Gislason et al. [306], Iceland	2016 women	40–59	Habitual snoring, EDS, PSG	>2.5
Olson et al. [273], Australia	1233 men 969 women	35–69	AHI $\geq$ 15 AHI $\geq$ 10 AHI $\geq$ 5	4–18 7–35 14–69
Bearpark et al. [300], Australia	294 men	40–65	RDI $\geq$ 10 EDS and RDI $\geq$ 5	10.0 $\geq$3.0
Gislason et al. [306], Iceland	555 children	0.5–6	Habitual snoring or apneas, ODI_4 > 3	>2.9
Ohayon et al. [318], Great Britain	2078 men 2894 women	15–100 15–100	N/A, telephone survey; no PSG N/A, telephone survey; no PSG	2.4–4.6 0.8–2.2
Kripke et al. [297], USA	165 men 190 women	40–64 40–64	ODI_4 > 20 ODI_4 > 20	5.4–13.2 2.1–8.3
Marin et al. [298], Spain	1360, men and women; quota	>18	Habitual snoring, apneas, EDS, clinical examination, oximetry	Men: $\geq$2.2 Women: $\geq$0.8
Bixler et al. [315], USA	4364 men 741 in lab	20–100	AHI $\geq$ 10 and daytime symptoms with EDS	3.3 45–64 years: 4.7
Ng et al. [308], Singapore	2298	20–74	Questionnaire with strict criteria; no PSG	0.43 (0.05–0.8)
Puvanendran and Goh [370], Singapore	220 interviews, 106 in lab	30–60	Habitual loud snoring, EDS, AI > 5	15
Zamarron et al. [299], Spain	76; random sample	50–70	Medical history, examination, AHI $\geq$ 5	AHI $\geq$ 5: 28.9 % OSAS: 6.8 %
Bixler et al. [317], USA	12,219 women 1000 in lab	20–100	AHI $\geq$ 10 and daytime symptoms with EDS	1.2 Pre: 0.6 Post + HRT: 0.5 Post: 2.7
Özdemir et al. [312], Turkey	2638 men 2701 women	20–107	Questionnaire. History of stopping to breath when sleeping; no PSG	6.4
Heinzer et al. [296], Switzerland	1024 men 1097 women	40–85	Polysomnographic recordings	Men: AHI $\geq$ 5: 83.8 % AHI $\geq$ 15: 49.7 % Women: AHI $\geq$ 5: 60.8 % AHI $\geq$ 15: 23.4 %

In order to diagnose obstructive sleep apnea syndrome, a subject must have verified sleep apnea and he/she must be symptomatic with EDS or other symptoms of OSAS. The highest figures above are in studies where the subjects may not have been symptomatic. In those cases, the prevalence figures represent only occurrence of apneas and not prevalence of OSAS

EDS Presence of excessive daytime sleepiness; *PSG* Polysomnographies were done; *Pre* Premenopause; *Post* Postmenopause; *HRT* Hormone replacement therapy

adolescents aged 12–16 was 1.9 % [377]. Adenotonsillar hypertrophy is the most common cause of upper airway obstruction in infants and children [352, 378, 379].

Sleep Apnea Among Elderly People

Habitual snoring seems to decrease after age of 65 or 70 years [380]. In a random sample of 5201 Medicare enrollees, 65-year-old or older, 33 % of the men and 19 % of the women reported loud snoring. Snoring was less frequent in people that were aged over 75. Observed apneas were reported by 13 % of men and 4 % of women [381]. In California, 19–24 % of people older than 65 years have an AI > 5, and 62 % of elderly people have a respiratory disturbance index (RDI) $\geq$ 10 [324, 325, 380]. The clinical significance of the high frequency of sleep apnea among elderly people remains to be seen. Presence of sleep apnea in an elderly subject does not mean that he/she has OSAS, and it does not mean that all elderly subjects with AHI or RDI over 10 should receive CPAP. In a cohort of 426 elderly people those with a RDI $\geq$ 30 had significantly shorter survival but the RDI was not an independent predictor of death among the elderly subjects during five years of follow-up when age, cardiovascular disease, and pulmonary disease were used as covariates [326]. The frequent occurrence of sleep apnea means, on the contrary, that we should perhaps use higher cut-point values of AI and AHI for elderly people [315].

Arterial Hypertension

Several cross-sectional and also prospective studies have shown that among middle-aged adults there is an association of habitual snoring, sleep apnea, and arterial hypertension. The causality is still not clear, but habitual snoring usually precedes development of hypertension. In other words, snoring and especially habitual snoring is a risk factor for developing hypertension [283–285, 288, 289, 326, 382–385]. The association seems to be independent of the effects of BMI, age, gender, smoking, use of alcohol, and physical activity. In case–control studies, the prevalence of sleep apnea among patients with essential hypertension is 25 % or higher [296, 386–393].

In practice, this means that if there is a history of habitual snoring and/or sleep apnea, and if the upper airways anatomy is suggestive of sleep apnea, a polysomnographic study must be done to verify or rule out clinically significant sleep apnea. According to many studies, the odds of having sleep apnea is significantly increased in presence of arterial hypertension [296]. In middle-aged adults with drug-resistant hypertension, the prevalence of OSA may be over 80 % [394].

In the study of Enright et al. among elderly people, loud snoring, observed apneas, and daytime sleepiness were not statistically significantly associated with hypertension or prevalent cardiovascular disease [381].

Heart Disease

There is an association between habitual snoring and/or obstructive sleep, and cardiac arrhythmias [395–402].

Coronary heart disease and myocardial infarction are more common among habitual snorers and untreated patients with sleep apnea than among non-snorers or people with sleep apnea. The average odds ratio for coronary heart disease of habitual snorers versus never or occasional snorers has been in most published studies about 1.9 or higher [266, 283, 285, 403–405]. The association remains after adjustment for arterial hypertension and BMI. In one of our studies, results were adjusted for BMI, history of arterial hypertension, smoking and alcohol, and the odds ratio decreased only slightly to 1.71 (95 % CI 0.96–3.05) [406]. However, in our recent study, the adjusted OR for stroke events was 1.65 (95 % CI 1.06–2.57) but for coronary events nonsignificant 1.13 [265]. In Australia, 101 male patients with myocardial infarction and 53 male control subjects were investigated [407] and a significant association of sleep apnea with myocardial infarction was found. The association was independent of age, BMI, arterial hypertension, smoking, and cholesterol level. Adjusted risk of myocardial infarction increased with increasing level of sleep apnea. Men with an AI > 5.3 had 23.3-fold (95 % CI 3.9–139.9) higher risk of myocardial infarction than did men with an AI < 0.4. The mean AI was 6.9 in patients with myocardial infarction versus 1.4 in the control subjects [407].

Also cardiac insufficiency/congestive heart disease seems to be more common among patients with sleep apnea and/or Cheyne–Stokes breathing than among subjects without sleep apnea [408–413].

Again, consistent with results that have been discussed above, these associations are found mainly among middle-aged subject and they are weaker among elderly people [414, 415].

Snoring and Stroke

Habitual snoring (snoring almost always or always when sleeping) is a significant and independent risk factor for cerebrovascular disease, but snoring per se, i.e., snoring rarely or sometimes, is not. In other words, there is an association between often or always snoring and ischemic cerebrovascular disease [265, 283, 406, 416–423].

The most important factors associated with brain infarction are age, male gender, arterial hypertension, various abnormal cardiac conditions, diabetes mellitus, and cigarette smoking. In addition to these established risk factors, however, there is evidence that suggests a link between habitual (almost every night or every night) snoring, OSAS, and stroke. In the first case–control study, 50 male patients with brain infarction were compared with 100 male hospital control subjects without any vascular diseases [419]. The risk ratio of brain infarction between often or always snorers and occasional or never snorers was 2.8 (95 % CI 1.3–5.8). The risk ratio was 10.3 (3.5–30.1) when habitual (every night or almost every night) snorers were compared with occasional or never snorers [419]. The independent contribution of habitual snoring as a risk factor for brain infarction was confirmed in another case–control study [424] of 177 male patients and control subjects matched for age and sex. After adjustments for several confounding variables, the independent odds ratio relating to often or always snoring and stroke remained at 2.13 (1.3–3.5) [424]. Spriggs and others [423] used community controls which may have altered the relationship. During the interview, another person from the household was present to increase validity of the history. In the Spriggs et al. study, 36 % of hospital controls snored often or always. Among community controls, 33 % of men and 28 % of women snored often or always. When admission to hospital because of stroke was compared, the odds ratio for often or always (regular) snorers versus non-regular snorers was 3.2 (2.3–4.4). After adjustment for BMI, smoking, alcohol drinking, previous history of cerebrovascular disease, ischemic heart disease, hypertension, atrial fibrillation, and diabetes, the adjusted OR for stroke in regular snorers was 1.7 (1.3–2.2), which was still statistically significant [423]. One important finding in the Spriggs study is that the prognosis after stroke was worse for regular snorers than for non-snorers. In the study by Smirne et al., the adjusted (age, gender, obesity, diabetes, dyslipidemia, smoking, use of alcohol, and hypertension) odds ratio for "often or always snoring" in relation to ischemic brain infarction was 1.86 (1.2–2.87) [420]. Neau et al. studied 133 patients, aged 45–75, and 133 control subjects matched for age and gender. During the interview, the spouse was present so that reliable history about snoring was obtained. Neau et al. used the same categorization for snoring as Partinen and Palomäki, according to which habitual snorers are those who reportedly snore always (every night). They defined as "snorers" those who snore often or always. "Non-snores" included never snorers and also occasional snorers, which is probably the correct way of categorization [417]. In that French study, the prevalence of habitual snoring was 23.3 % among patients with stroke and 8.3 % among their controls. The odds ratio for habitual snoring was 3.4 (95 % confidence interval, 1.5–7.6). The odds ratio for "often or always snoring" was 1.7 (95 % confidence interval 1.03–2.93). Even after adjustment for age, sex, arterial hypertension, cardiac arrhythmia, and obesity, the odds ratio of habitual snoring for stroke remained statistically significant (2.93; 95 % confidence interval 1.28–6.75). The risk of ischemic stroke was especially high among habitually snoring older men with arterial hypertension while the odds ratio did not reach statistical significance (OR 1.42; 95 % CI 0.51–3.99) [417] As a conclusion there seems to be a real association between habitual (defined as almost always or always snoring, i.e., snoring on at least 5 nights per week) snoring and brain infarction. Long-term cohort studies and more case–control studies are needed to confirm this.

The problem with cohort studies is that stroke is not as common as ischemic heart disease and large number of incident cases is needed. Therefore, until now there are few [275, 283, 406, 425] published prospective cohort studies looking for habitual snoring as a risk factor of stroke. We asked about snoring history in the Finnish Twin Cohort for the first time in 1981 and all subjects have been followed since then. This would allow us more than 30 years follow-up time and we aim to evaluate the situation during the coming years. In our first follow-up that was published in 1987, we did not have enough incident stroke cases so we had to pool the cardiovascular morbidity with cerebrovascular morbidity. At that time, the odds ratio for ischemic heart disease and brain infarction combined was 2.08 (1.5–3.77) [406].

The Nurses' Health Study includes 71,779 female nurses aged 40–65 at baseline in 1986, and it is the largest cohort study including questions about snoring and other sleep-related items [283]. Women with cardiovascular end points at baseline were properly excluded. The 398 incident strokes (60 never snorers, 288 occasional snorers, and 50 regular snorers) in that cohort during 8 years of follow-up allowed already some analyses. Snoring was asked as "Do you snore?" with three categories: "regularly," "occasionally," or "never." Although this classification differs from the preferred classification, the group "regularly" is probably quite close to the category of "often or always snoring" or the more strict "habitual snoring" that has been used in Finland and in France. Hu et al. [279] adjusted the results for age, BMI, smoking, menopausal status, history of myocardial infarction, consumption of alcohol, physical activity, sleeping time, diabetes, and hypercholesterolemia. The age-adjusted relative risk of stroke for regular snorers compared with never snorers was 1.88 (1.29–2.74). In a multivariate adjusted model, the relative risk remained significant for occasional snorers ($N = 288$) versus never snorers (1.42; 1.07–1.89). Because there were only 50 regular snorers, the adjusted relative risk was a little bit lower (1.35; 0.91–1.99). The relative risk of combined cardiovascular and cerebrovascular events for regular snoring was

1.33 (1.06–1.67) [283]. Recently, from the same Nurses' Health Study cohort, 935 women aged 43–69 years have been studied in more detail for the association between snoring history and cardiovascular disease [392]. In a multivariate analysis, more frequent snoring was directly associated with triglycerides ($P = 0.02$) and inversely with HDL cholesterol levels ($P = 0.03$) and adiponectin ($P = 0.03$). In the same study, longer sleep was associated with increased levels of C-reactive protein after adjusting for age, BMI, different lifestyle factors, family history of diabetes, glycemic control, and use of medications. The usually snoring women were as follows: older ($P = 0.03$), more obese ($P < 0.0001$), centrally obese with larger waist–hip ratio ($P = 0.005$), physically less fit ($P = 0.03$), using more alcohol ($P = 0.04$), more often hypertensives ($P = 0.0001$), more often users of insulin ($P = 0.006$), and premenopausal ($P = 0.02$) than never or occasional snorers [392]. These results suggest that snoring history and other sleeping history should be combined with other biomarkers of cardiovascular disease (CVD) risk.

In the MESA cohort, 5338 people of various ethnicities have been followed for an average of 7.5 years. In that study, habitual snorers had similar incident CVD and mortality rates compared with normal participants [425]. Habitual snoring was defined in that study as snoring at least on 3–5 days per week, which may be too low cutpoint, as habitual snoring should be defined as snoring on 6–7 days per week or as snoring every night or almost every night. Also, only 76 cases of stroke had occurred, and the authors discussed that their analyses may have been underpowered to detect a unique association between snoring and cerebrovascular events [425]. In Busselton, Australia, a community sample of 380 subjects was followed for 17 years. Snoring was not significantly related to all-cause mortality, incident cardiovascular disease, or stroke [275]. Both studies [421, 422] indicate anyway that snoring without presence of sleep apnea may be harmless. Therefore, one should ask separately also for the presence of sleep apnea as well as presence of sleep apnea that has been diagnosed.

Sleep Apnea and Stroke

Poza et al. [426] studied 79 consecutive patients of both sexes with cerebral infarction and 248 age and sex matched controls. They obtained data reflecting arterial hypertension, diabetes mellitus, hypercholesterolemia, smoking and drinking habits, coronary heart disease, cardiovascular disease, snoring, respiratory pauses during sleep and daytime sleepiness, by using a standard questionnaire to interview every subject and spouse. 34 % of the stroke patients and 27 % of controls were snorers and complained of apnea during sleep ($P = 0.19$). 19 % of patients and 11 % of controls presented snoring, respiratory pauses during sleep and daytime sleepiness simultaneously, suggesting obstructive sleep apnea syndrome ($P = 0.06$). The difference was statistically significant among subjects younger than 65 years. OSAS was found in 29 % of the patients and in 7 % of controls ($P = 0.006$). A multiple logistic regression analysis confirmed the independent effect of moderate to severe OSAS as a risk factor for ischemic stroke (adjusted OR 4.54). In people younger than 65 years, OSAS, regardless of its severity, was also an independent risk factor for ischemic stroke, with an adjusted OR of 5.78 [426]. Since then prospective studies have also shown an association between diagnosed sleep apnea and stroke. In the MESA cohort, 7.5 years follow-up study physician-diagnosed sleep apnea was associated with higher incidence of composite CVD including various cardiovascular events and stroke (hazard ratio 1.89 (1.22–2.93)) [425]. In a historical Canadian cohort study, sleep apnea was associated with CVD and mortality, and OSA-related factors other than AHI were shown as important predictors of composite cardiovascular outcome [427] pointing out that the severity of sleep apnea should not be judged only by respiratory indices.

Circadian Variation of Strokes and Snoring

Ischemic strokes occur most commonly in the morning before noon [428, 429]. In a study by Tsementzis et al., cerebral infarction was most common between 10 a.m. and noon, when the highest blood pressures are usually recorded [430]. In another study, most (57 %) of the 151 strokes occurred between 6 a.m. and noon [431]. In a meta-analysis of 31 publications, Elliott reported the circadian timing of 11,816 strokes [432]. There was a 49 % increase (95 % CI 44–55 %) in strokes between 6 a.m. and noon as compared with expectations that there is no circadian variation. All three studied subtypes of stroke had a significantly higher risk between 6 a.m. and noon (55 % for 8250 ischemic strokes, 34 % for 1801 hemorrhagic strokes, and 50 % for 405 transient ischemic attacks) [432]. Detailed information about circadian variation of different types of stroke is, however, still limited. Chaturvedi et al. [433] analyzed stroke onset using detailed classification of stroke subtypes. They analyzed data of 1272 patients who had a documented time of stroke symptom onset, and all stroke subtype determinations were made by a single specialist. Most atherothrombotic strokes (25.7 %), cardioembolic strokes (30.5 %), and strokes of other/unknown mechanism (27.1 %) occurred between 6:01 a.m. and 12:00 noon. The greatest portion of lacunar strokes (31.6 %) were present on awakening. More than one half of the infarcts in this series were either present on awakening or occurred in the mid- to late-morning hours [433].

Nocturnal and early morning strokes are related to habitual snoring and obesity. In one study, relation of the time of onset of stroke and snoring history was analyzed in 167 consecutive male patients. In 70 cases (41.9 %), cerebral infarction initiated during sleep or immediately after awakening [434]. Of the 70 infarctions with an onset at night or immediately after awakening, 48 patients had a history of snoring often or always (68.6 %). The respective percentage among the other 97 patients was 41.2 %. The difference was statistically significant, OR for often or always snoring was 3.1 (1.7–5.9; $P < 0.001$). The odds risk remained significant when age, arterial hypertension, BMI, smoking, consumption of alcohol, and diabetes mellitus were taken into account [434]. Changes in blood pressure after awakening in the morning may cause a breakthrough of the autoregulation of the cerebral blood flow. In normal conditions, nothing happens, but under unfavorable conditions, an infarction may follow.

Jimenez-Conde et al. [435] studied 813 patients with ischemic stroke. 127 them had a stroke during sleep (15.6 %). Obesity was a factor associated with sleep strokes. Adjustment for age and gender revealed that atrial fibrillation (AF) was less frequent in the group of sleep-related strokes. Sleep-related strokes were more severe and functional outcome at 3 months was worse than for strokes occurring at other times of day. The authors conclude that "while sleep could be associated with a lesser stroke occurrence, it could also be associated with a higher severity" [435]. The authors did not have specific data on snoring or sleep apnea, but the finding that obesity was more prevalent among subjects with sleep strokes is suggestive that habitual snoring and sleep apnea might explain at least part of that association.

Snoring, Sleep Apnea, and Dementia

In a study by Reynolds et al., AI > 5 was found in 42.9 % of demented patients, 17.6 % of depressives, and 4.3 % of controls. A significant association between sleep apnea and dementia of the Alzheimer type was found in women but not in men. Moreover, severity of dementia was significantly correlated with apnea index [436]. Vitiello and Prinz had the same finding that the association exists among women when 24 female patients with Alzheimer's disease were compared with 26 control subjects. The mean AHI among the female patients with Alzheimer's disease versus control subjects were 9 ± 3 and 2 ± 0.4, respectively [437]. In a case–control study of 46 patients with Alzheimer's disease, 37 patients with multi-infarct dementia, and a random sample of 124 elderly community residents, the demented patients snored twice more frequently than the controls. No difference in the occurrence of snoring was found between the two types of dementia [438].

Snoring, Sleep Apnea, and Sudden Death

In the first study analyzing relationships between history of habitual snoring and sudden death, an autopsy was performed in 460 consecutive cases of sudden death among 35- to 76-year-old men. The closest cohabiting person to each deceased was interviewed. The mean age of the deceased was 55.4 years, and the mean BMI was 26.3 kg/m^2. Among the obese snorers ($N = 82$), apneas had been observed "occasionally," "often," or "habitually" in 49 cases [439]. Death was classified as cardiovascular in 186 cases (40.4 %). Cardiovascular cause of death was more common among the habitual and often snorers than among occasional or never snorers. Habitual snorers died more often while sleeping. Habitually snoring was found to be a risk (odds ratio, 4.07; 95 % confidence interval, 1.45–11.45) for cardiovascular early morning death between 4 and 8 a.m. [439].

Subjects with obstructive sleep apnea (OSA) die often at night. Polysomnograms and death certificates of 112 Minnesota residents were reviewed [440]. Sudden death from cardiac causes occurred in 46 % of people with OSA, as compared with 21 % of people without OSA ($P = 0.01$). For people with OSA, RR of sudden death from cardiac causes from midnight to 6 a.m. was 2.57 (1.87–3.52). This is contrary to people without OSA, who had the highest RR (2.10) between 6 a.m. and noon. The higher the apnea-hypopnea index, the higher was the RR of sudden death between midnight and 6 a.m. [440].

Evolution of Obstructive Sleep Apnea Syndrome

Several studies have shown an increased risk of cardiovascular complications and death in patients with at least moderate (AI > 20) or severe (AI > 40) OSAS [441–444]. The increased risk is found especially among middle-aged people with sleep-disordered breathing, but not in elderly people when several other comorbidities and risk factors are present [288, 327, 445–447]. CPAP treatment reduces mortality [448, 449]. Two recent long-term follow-up studies have been published. In Australia, after a mean follow-up time of 13.4 years, subjects with moderate to severe sleep apnea had greater risk of all-cause mortality (fully adjusted hazard ratio [HR] = 6.24, 95 % CL 2.01–19.39) than subjects without sleep apnea. Mild sleep apnea with RDI 5–14.9 was not an independent risk factor for higher mortality

[450]. In an 18-year follow-up of the Wisconsin Sleep Cohort all-cause mortality risk, adjusted for age, sex, BMI, and other factors was significantly increased with severity of sleep apnea. The adjusted HR for all-cause mortality with severe versus no sleep apnea was 3.0 (1.4–6.3). After excluding persons who had used CPAP treatment, the adjusted HR for all-cause mortality with severe versus no SDB was 3.8 (1.6–9.0). The adjusted HR for cardiovascular mortality was 5.2 (1.4–19.2) [451].

CPAP ameliorates quality of life of the patients with OSAS [452–457]. In a 3-month randomized study of 71 patients using the Euroqol quality of life measurement, CPAP added 8 and a lifestyle treatment added 4.7 quality adjusted life years (QALYs) as compared to no treatment [457].

CPAP is effective in treatment of moderate and severe sleep apnea, but the effect is very small if there are no symptoms of daytime sleepiness [456, 458–462].

OSAS has also economic consequences. Untreated patients use significantly more healthcare resources than treated patients [452, 463–470].

Parasomnias

The parasomnias represent a group of undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousals from sleep. Parasomnias in children are quite common. Up to more than 60 % of people have experienced some parasomnias at least now and then in their childhood. One to ten percent of children have got often some parasomnias. In adults, parasomnias are rather uncommon. The prevalence of often occurring parasomnias is between 0.1 and 1 %. In this way, it is more likely that parasomnias are seen at sleep clinics than, e.g., narcoleptics. It is important to differentiate parasomnias from nocturnal epileptic phenomena.

Recently, a series of studies on nightmares in Finland had taken place. Across the cross-sectional time, series of eight National FINRISK study samples (1972; 1977; 1982; 1987; 1997; 2002 and 2007) frequent nightmares were reported in 4.6 % of women and 2.8 % of men. Of note, among war generation, the prevalence figures were 7.0 % in women and 7.2 % in men [471]. Symptoms of depression and insomnia were the strongest predictors of frequent nightmares in this data set. Also, several factors related to psychological and physical well-being were associated with nightmare frequency [472].

An interested reader should also consult other chapters in this book as well as other epidemiological studies and reviews on parasomnias [473–481]. Epidemiological studies of parasomnias are difficult because most often one must depend only on history. Thus, the ranges of occurrence are very variable, and the figures must be interpreted with caution. Parasomnias occur in close association with other sleep disorders. For example, patients with sleep apnea talk often in their sleep, and patients with restless legs syndrome may also have nightmares or other parasomnias. Genetic factors play an important role in different parasomnias [474].

REM Sleep Behavioral Disorder

The prevalence of REM sleep behavioral disorder (RBD) in general population is not known, but it may be close to prevalence of violent behavior during sleep which is about 1.6 % [482]. There is more and more evidence that REM sleep behavioral disorder (RBD) may be a preexisting symptom of a future synucleinopathy [483–485], and there is some evidence that in dementia disappearance or reversal of the day/night rhythm is associated with severity of dementia. For many reasons, there is a need to develop unobtrusive methods for long-term monitoring of sleep/wake and circadian activity patterns among neurological patients and among elderly people both in nursing homes and at home. Our group has monitored, using a small wrist-worn intelligent watch, demented and non-demented subjects living in a nursing home, and analyzed how changes in measured sleep correlated with the subjective assessment of sleep quality, daytime alertness, use of medications, and health. The activity signal data together with subjective assessments of sleep quality and daytime vigilance were collected from 42 volunteers (aged 56–97 years; 23 demented and 19 non-demented) for at least 10 days. The demented subjects had lower daytime activity and higher nocturnal activity than the non-demented subjects. Correlations between the activity parameters and self-assessments were weak but statistically significant. We also found correlation between functional ability and diurnal activity [164]. New methods of 24 h beat-to-beat monitoring of blood pressure should also be developed as, e.g., systolic blood pressure drop may be an early biological marker of future Parkinson's disease [485].

Restless Legs Syndrome

Restless legs syndrome (RLS) has been named Willis-Ekbom disease after Thomas Willis and Karl-Axel Ekbom. It is a common neurological disorder characterized by an urge to move associated with unpleasant sensory feelings mainly in the lower limbs. Rest—lying or sitting still—provokes the symptoms. In particular in premenopausal women, the syndrome is often associated with

abnormalities of iron transport and storage [486–488]. Many subjects with RLS have low levels of serum ferritin (<50 μg/l). Due to lack of tissue iron (ferritin), dopaminergic dysfunction may occur at cerebral or spinal cord level [488, 489]. Epidemiologic studies have shown that the condition is common in populations derived from northern latitude (e.g., from Northern Europe).

Restless legs syndrome is common (Table 28.5). Among adults, the prevalence of RLS symptoms is between 5 and 15 %. According to the REST study [490], the prevalence of clinically significant RLS is around 2.7 % varying between 1.3 and 4.2 %, the highest figure being from France. In a large (N = 10,263) French study [491], the average prevalence of RLS was 8.5 % (N = 870 fulfilled the IRLSSG criteria); 56.1 % of the 731 persons with complete information had at least moderate RLS having the International RLS Study Group severity score of at least 11 [491]. Using the Bayes' theorem, we can estimate that about 4.8 %

Table 28.5 Prevalence of RLS

Study, country	Population (N)	Methods, criteria	Prevalence (%)
Europe			
Ekbom [536], Sweden	Physician's practice, N = 500	Presence of restless legs (original criteria), interview and neurological examination	5
O'Keeffe et al. [537], Ireland	Acute care geriatric service patients, N = 317	Presence of restless legs, interview	5 (31 % of patients had ferritin <18 ng/ml vs. 6 % in controls)
Rothdach et al. [378, 538], Germany	Elderly population sample, age 65–83 years, N = 369,196 men, 173 women	IRLSSSG criteria, interview and neurological examination	Overall: 9.8 M: 6.1, F: 13.9 65–69 years: 9.8 70–74 years: 12.75 75+ years: 7.4
Schmitt et al. [528], Switzerland	Postal office clerks N = 668	IRLSSSG criteria, questionnaire	4
Ulfberg et al. [494], Sweden	Male population sample, age 18–64 years, N = 4000	IRLSSG criteria, questionnaire	5.8
Ulfberg et al. [495], Sweden	Female population sample, age 18–64 years, N = 200	IRLSSG criteria, questionnaire	11.4
Ohayon and Roth [539], UK, Germany, Italy, Portugal, Spain	Random population samples, age 15–100 years, N = 18,980	Telephone survey, Sleep-EVAL with the ICSD-criteria	RLS: 5.5 PLMD: 3.9
Ulfberg et al. [493], Sweden	Blood donors in a blood donation unit, N = 946,618 men, 328 women	IRLSSG criteria, questionnaire, blood examination	M: 14.7, W: 24.7 Women with iron deficiency: 37.5
Rijsman et al. [540], Netherlands	Patients in general practice >50 years, N = 1437	IRLSSG criteria, questionnaire	7.1
Van de Vijver et al. [519], UK	Primary care patients N = 1,561,692	RLS diagnosis had been done and recorded in a GP Database	0.25
Berger et al. [499], Germany	General population age 20–79 years, N = 4310	IRLSSG criteria, interviews and physical examination	10.6
Tison et al. [491], France	General population, age 18+ years N = 10,263; 4762 men, 5501 women	IRLSSG criteria, interview	8.5 M: 5.8, W: 10.8 IRLS > 10: 56.1
Allen et al. [490], USA, France, Germany, Spain, UK	General population (18+ years) N = 15,391; 1884 in France, 1929 in Germany, 1768 in Italy, 1896 in Spain, 1950 in UK and 5964 in USA	IRLSSG criteria, interview "the REST study"	Any frequency: 7.2 At least once weekly 5.0 At least twice/w 4.1 (**2.7**)[a] France: 5.5 (**4.2**)[a] Germany: 2.0 (**1.3**)[a] Italy: 3.1 (**2.4**)[a] Spain: 3.1 (**2.0**)[a] UK: 4.9 (**2.3**)[a]

(continued)

Table 28.5 (continued)

Study, country	Population (*N*)	Methods, criteria	Prevalence (%)
Högl et al. [541], Austria	General population, 50–89 years *N* = 701	IRLSSG criteria, interview, medical examination, laboratory examinations	10.6 M: 6.6, W: 14.2 IRLS > 10: 44.6
Björvatn etl al. [492], Denmark, Norway	General population, age 18+ years, *N* = 2005	IRLSSG criteria, telephone interview	11.5; 18–29 years: 6.3 M: 9.4, W: 13.4
North America; USA and Canada			
Lavigne and Montplaisir [542], Canada	Population sample, age 18+ years, *N* = 2019	Leg restlessness at bedtime, face-to-face interviews	10–15
Phillips et al. [329], USA	Population sample age 18+ years, *N* = 1803	Telephone interview, presence of restless legs 5 or more times/month At least once per month	18–29 years: 3 30–79 years: 10 80+ years: 19 All ages: 19.4
Allen et al. [490], USA	General population, age 18+ years, *N* = 5964	IRLSSG criteria, interview "the REST study"	4.8 ≥2/w: 3.1
Near East			
Sevim et al. [543], Turkey	General population, adults *N* = 3234, 1591 men, 1643 women	IRLSSG criteria, interview by neurologists	3.19 M: 2.5, W: 3.9
Asia			
Tan et al. [544], Singapore	Population sample, *N* = 157 aged 55+ years, and 1000 patients aged 21+ years	IRLSSG criteria	0.6 in the population 0.1 among the patients
Bhowmik et al. [545], India	Case-control study. *N* = 121 hemodialysis patients and 99 control patients	Questionnaire with RLS criteria; ENMG	Hemodialysis: 6.6 Control patients: 0.0
Suzuki et al. [497], Japan	Japanese pregnant women, *N* = 16,528	Questionnaire survey in 500 maternity services	19.9
Kim et al. [546], South Korea	General population *N* = 9939	IRLSSG criteria, interview	12.1 M: 8.5, W: 15.4

[a]In the rest study, the prevalences per country refer to symptoms occurring at least on two days per week and the figures in parenthesis refer to percentage of subjects who report having RLS symptoms at least twice weekly with moderate or severe impact on quality of life. The figures in parentheses reflect clinically significant RLS
M Men; *W* Women

of adults in France have at least moderate RLS. This figure is quite close to the 4.2 % figure from the REST study for French adults. 21.2 % of the French had at least severe RLS (IRLS score > 20) giving an estimated prevalence of 1.8 % for at least severe RLS. Similar or higher figures have been published from the Nordic countries [492–495].

The prevalence of RLS is significantly higher among women than men, and it increases by age. About 20 % or more of pregnant women suffer from RLS [496–498] especially during the third trimester with different degrees of severity. RLS during pregnancy is related to low ferritin and folate levels. Not only RLS often occurs during pregnancy, but also the risk of having RLS later in life increases by number of pregnancies. In a German study [499], the overall prevalence of RLS was 10.6 %. The prevalence among women was about two times higher than among men. The prevalence among nulliparous women did not differ significantly from that among men up to age 64, but the risk of RLS increased gradually with each pregnancy. Having one child increased the odds ratio (OR) to 1.98 (95 % confidence interval 1.25–3.13), 2 children increased the OR to 3.04 (2.11–4.40), and 3 or more children increased the OR to 3.57 (2.30–5.55) [499].

Restless legs syndrome symptoms are frequent in many diseases. Among European/Caucasian patients with end-stage renal disease [500–502], the prevalence may be much higher than 20 %. In one US study among 308 patients on hemodialysis, RLS symptoms were present during the past 6 months in 68 % of patients with Caucasian origin and in 48 % of patients with African–American origin [503]. This figure is very different from Indian figures. Only one patient from 65 patients (1.5 %) with chronic renal failure and none of the 99 control subjects complained of having RLS [504]. RLS is also frequent among patients with either juvenile or adult type 2 diabetes. The association is not found among young adolescent patients with diabetes [505], but it is found in older patients. The association may be explained by the increased frequency of small fiber sensory

neuropathy, which is known to be often present in patients with RLS. In a case–control study of 124 patients with type 2 diabetes and 87 controls, RLS was diagnosed in 17.7 % of the diabetics and in 5.5 % of controls. In a multivariate logistic regression, presence of polyneuropathy was the only statistically significant risk factor with an OR 7.88 (1.34–46.28) [506]. RLS has been associated also with attention deficit hyperactivity disorder (ADHD), fibromyalgia, rheumatoid arthritis, familial amyloidosis, those receiving an organ transplantation, other sensory polyneuropathies, multiple sclerosis, spinal stenosis, or other spinal pathology [488, 489, 507–517]. In a recent study, patients with RLS had higher lifetime prevalence of migraine than non-RLS controls (53.2 % vs. 25.5 %, $P = 0.005$; matched-OR 1.3 [$P = 0.019$]; and adjusted odds ratio (OR) 3.8 [$P = 0.03$]). No significant associations were found between RLS and active migraine with aura or inactive migraine [518]. The associations may be explained by either central or spinal dopaminergic pathophysiology that are probably related to iron metabolism or by peripheral neuropathic effects.

Although RLS is common, it is still poorly recognized. In UK General Practice Database, Van de Vijver et al found that only 3877 diagnoses of RLS had been done between 1994 and 1998 among almost 1.6 million persons, giving a prevalence of 0.25 %. Also, the incidence was small; 41 diagnoses of RLS per 100,000 person-years had been done [519]. In the REST study, 337 (81.0 %) of the 416 patients with clinically significant RLS (the RLS sufferers) reported discussing their symptoms with a primary care physician, and only 21 (6.2 %) were given a diagnosis of RLS.

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Genetics of Sleep and Sleep Disorders

29

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Introduction

After more than a century of modern scientific study of sleep, its biological function remains an enigma. In all mammals and birds and in some invertebrates such as drosophila, a substantial portion of life is spent in this behavioral state, and we know that lack of sleep or disturbed sleep has strong negative consequences on health and performance. Because of the conservation of this behavior during evolution (since its appearance), it is believed that sleep must fulfill a fundamental and vital biological need. As a complex behavior, sleep is influenced by both genetic and environmental factors as was demonstrated early on in familial and twin studies that assessed the role of genes in sleep and sleep disorders. The current progress in sequencing the genomes of species as different as human, mouse, zebrafish, and drosophila brought great expectation that genes related to sleep and sleep disorders could be identified. The discovery of a point mutation in the prion protein gene as the cause of fatal familial insomnia (FFI), followed by the discovery of the role of hypocretins in human narcolepsy, proved that through genetic approaches unexpected molecular pathways or new sleep-related genes could be discovered.

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Genetics of Normal Sleep and the Electroencephalogram

Sleep and wakefulness are complex behaviors and thus are influenced by many genetic and environmental factors. Twin studies are of interest to determine the respective contribution of genetic and environmental factors to a given phenotype. The first study of genetics of sleep can be dated to a publication by Geyer in 1937 [1]. He reported a higher concordance of sleep habits of monozygotic (MZ) than dizygotic (DZ) twins. In 1951, Gedda [2] reported rare cases of concordant long sleepers (up to 15 h) in MZ twins. Gedda and Brenci [3] first estimated that the heritability of sleep duration is over 30 %. These authors later confirmed that sleep duration is highly similar even in twins living apart, discounting the influence of environmental effects [4]. Results from twin studies also showed that the waking electroencephalographic (EEG) patterns of MZ twins have a much higher resemblance than those of DZ twins or unrelated subjects, again confirming that this highly complex phenotype might be tightly controlled by genes and little affected by environment. In 1966, Zung and Wilson [5] performed the first polysomnographic sleep recordings in twins and found the temporal sequence of sleep stages to be almost completely concordant between MZ twins. More recent observations indicate that even the pattern of rapid eye movements (REMs) presents higher concordance between MZ than DZ twins [6] and that between 40 and 50 % of the variance in sleep duration and the presence of a sleep disorder can be accounted for by genetic effects [7, 8]. These and other studies have shown that a number of sleep aspects are strongly determined by genes.

Animal studies (mainly in mice and rats) show the presence of considerable interindividual variations in the different aspects of sleep even when animals are kept under identical environmental conditions from birth. Nevertheless, when several inbred strains of mice or rats are recorded, a far greater interstrain than intrastrain variability is reported for non-REM (NREM) and REM sleep, again indicating that environmental factors play a secondary role [9–17]. As

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every aspect of sleep needs to be considered as a separate complex trait, a systematic approach is necessary to identify the genetic factors underlying each of these traits. In the early 1970s, Valatx [9] pioneered the experimental genetics of sleep by studying inbred, recombinant inbred, and hybrid mice. He reported that several aspects of sleep, including the amount of paradoxical sleep, are controlled by genetic factors [10, 11]. These studies, complemented with a diallelic study by Friedmann [12], clearly suggested that, although some aspects of sleep can follow a simple segregation, most other sleep traits cannot be predicted by classic genetic laws. Among many animal models [18], the fruit fly *Drosophila melanogaster* is a highly valuable one for dissecting the molecular mechanisms underlying sleep. This invertebrate shows all the features of sleep: It has a consolidated, circadian period of inactivity, which is characterized by increased arousal thresholds as well as a specific posture and resting place, and its rest is homeostatically regulated [19, 20]. Thus, rest in *Drosophila* is a sleeplike state. Moreover, this model organism is small, economical, and rapidly reproducing and has fewer genes, constituting an excellent tool for genetic analyses [21]. So far, nearly 20 genes have been identified in fruit flies that regulate sleep and some of these genes were also characterized in the mouse model [22].

One of the major advantages of animal models is the possibility of genetic manipulation by loss or gain of function of key genes. Based on the available knowledge in physiology and pharmacology, candidate genes can be identified and experimentally manipulated to assess their role in sleep. The first transgenic investigations in the field of sleep research included the cytokine pathway [23], with *Il1a*, *Il10, Tnf,* and *Tnf* receptors 1 and 2; the neurotransmitter pathway [24], with dopamine, histamine, and serotonin; and the clock genes [22, 25]. So far, hundreds of reports in transgenic animals suggest that in almost all cases, some significant sleep effects are observed confirming the involvement of the underlying genes. Therefore, the candidate gene approach is only valuable in verifying whether a gene of interest has any detectable effect and cannot help in identifying new genes.

Since sleep and wakefulness are very different in terms of brain activity, physiology, and behavior, it is reasonable to expect that there are differences also at the level of gene expression. Moreover, the temporal dynamics of sleep homeostasis, indexed as EEG delta power in NREM sleep, are compatible with the dynamics of gene expression, and sleep deprivation could thus lead to changes in gene expression. This should help to find genes functionally relevant to the homeostatic regulation of sleep, although it cannot be ruled out that the changes in expression of some of these genes are merely driven by the sleep–wake distribution instead of being functionally relevant.

In 1990, by using the substractive hybridization techniques in rats sleep deprived for 24 h, Rhyner and colleagues [26] were the first to isolate several messenger RNA (mRNA) clones with relative increased or decreased expression in the brain. Analysis of the structure of two of these clones identified neurogranin and dendrin [27]. Neuner-Jehle et al. [28] demonstrated that mRNA and protein for neurogranin and dendrin were differentially modulated in different regions of the rat brain by prolonged wakefulness. The laboratory of Cirelli and Tononi has continued this work to include changes in gene expression after spontaneous periods of sleep and wakefulness and long-term sleep deprivation in rats [29]. They have used several techniques such as mRNA differential display and complementary DNA microarrays to systematically screen brain gene expression. These authors have screened 10,000 of the 30,000 genes estimated to be expressed in the rat cerebral cortex, and their results indicate that approximately 5 % seem to be modulated by sleep and wakefulness [30]. The majority of genes are upregulated during sleep deprivation/spontaneous wakefulness relative to sleep. The same genes changed their expression during spontaneous wakefulness and sleep deprivation, but in the latter condition, the changes were more pronounced. A few genes are upregulated during sleep, but so far, their function remains mostly unknown (e.g., membrane protein E25). Similar results were reported by other groups in mice [31–33].

Modulated genes include a few functional categories [31–34] such as immediate early genes, transcription factors, growth factors, adhesion molecules, heat shock proteins, neurotransmitters, hormone receptors, metabolism and energy proteins, transporters, and enzymes.

Two major classes of genes are rapidly induced after only 3–6 h of wakefulness or sleep deprivation: the immediate early genes/transcriptional factors (*Homer1a*, *Arc*, *Fos,* and *NGF1-A*) and the mitochondrial genes. The immediate early genes are a specific class of genes that are rapidly induced by a variety of extracellular stimuli. The expression of *Fos* (a protein released during cellular or activation) is increased in the ventrolateral preoptic area during sleep, suggesting a sustained cellular activity in this area during sleep [35, 36]. After 6–8 h of wakefulness, there is an upregulation of genes related to energy metabolism such as those for glucose transporter (*Glut1*), glycogen synthase, and glycogen phosphorylase. The genes for several heat-shock proteins and chaperones, such as *HSP60, HSP70,* and *BiP,* are also upregulated [31, 37, 38]. These findings illustrate that the molecular genetics approach, complemented with other genetic techniques, is powerful in identifying new genes that are implicated in sleep homeostasis and that the mouse, rat, and drosophila models are appropriate models, especially when used in parallel.

Although these data demonstrate that the molecular approach is a valuable tool to find sleep genes, a gene that does not show transcriptional modification may nonetheless play an important role. New techniques are emerging to profile gene expression at the cellular level, such as laser capture microdissection [39], polyA-binding protein tagging [31], or

ribosome tagging [40] combined with high-throughput linear amplification of RNA and RNAsequencing [41, 42]. Nevertheless, these techniques are not suitable for the identification of constitutively expressed sleep genes, which can only be discovered by forward genetics.

Conceptually, the forward genetic approach is the most powerful strategy for the isolation of genes involved in any biological process, since it is the only approach that does not make any biased assumptions. In the genomewide search for genes affecting a particular phenotype, no a priori assumptions on the gene systems involved are made. Although this approach may lead to already known physiologic mechanisms, its strength is that systems previously unknown to be involved in sleep may be uncovered. Therefore, a genomewide search is the method of choice if we are to discover new "sleep" genes.

Mutagenesis

Whereas the quantitative trait loci (QTL) analysis (see later) aims at identifying "naturally" occurring allelic variants or gene mutations that modify sleep, mutagenesis is based on a randomly induced mutation approach. A strong mutagen such as ethylnitrosourea (ENU) is used to mutate spermatogonia. Assuming a mutation frequency of 0.0015 per locus per gamete [43], there is approximately a 50 % probability of finding a dominant mutation by screening a first generation of 650 offspring. With high-throughput screening for either dominant or recessive mutations, a major effect on a given trait can be identified. The individual mouse or fruit fly for which an aberrant phenotype has been identified has then to be crossed to establish the mode of inheritance of that trait. The isolation of *Clock* is an excellent example of the feasibility of this technique [44, 45]. After the treatment of mice with ENU, Vitaterna et al. [44] observed a mouse exhibiting a longer circadian period of approximately 25 h when kept in constant darkness. This mouse was crossed with a wild-type mouse to establish the mode of inheritance of the trait. The mutated animal carried a semidominant mutation in a locus required for the maintenance of normal circadian rhythmicity. Linkage analysis mapped this trait onto chromosome 5; a positional cloning was undertaken, and the mutated gene *Clock* (Circadian Locomotor Output Cycle Kaput) was identified [45]. Later, this technique allowed the discovery of *Rab3a,* with a mutation that altered both circadian period and homeostatic response to sleep loss, in the mouse [46].

The choice and success of each of the approaches are determined by the gene effect. Although some mutations can induce remarkable phenotypic changes, others produce only subtle effects that, in addition, can be confounded by gene–gene interactions (epistasis) and genetic background (modifier gene) [47]. Mutagenesis is therefore more successful for fully penetrant dominant or recessive mutations, whereas QTL analysis is more powerful in detecting natural allelic variations controlling complex traits [48].

QTL Analysis

QTL has been proposed as a powerful approach in the genetics of complex traits. A quantitative trait is a phenotype showing continuous variations in a population. Generally, complex phenotypes such as sleep are regulated by multiple genes, each of them having a small effect. The QTL technique is based on DNA natural polymorphisms, which are nonlethal mutations preserved in a population because of their neutral, subtle, or advantageous effect. As discussed in this section, QTL analysis can be successfully applied to the genetic dissection of both the sleep amount and the sleep EEG.

QTLs for Sleep Amount

The 24-h amount of sleep also shows highly significant differences between inbred mouse strains [9, 11, 15]. The two extremes regarding the amount of sleep over a 24-h period are AKR/J (AK) and DBA/2J (D2) strains. AK mice sleep 3 h more than D2 mice. Multiple genes may be found to be responsible for this difference, and therefore, a QTL analysis is appropriate. A first QTL analysis was performed in 7 CXB (BALB/cByJ × C57BL/6ByJ) recombinant inbred lines for the amount of REM sleep, and four QTLs were identified on chromosomes 5, 7, 12, and 17 [49]. Toth and Williams [50] studied sleep in a larger CXB recombinant inbred panel and found QTLs on chromosomes 4, 16, and 17. Both QTL studies reported different loci for the duration of diurnal and nocturnal and for total REM sleep time during 24 h, suggesting that different genes are involved in the expression and regulation of REM sleep. In both studies, none of the QTLs could satisfy a stringent statistical significance level certainly due to the small number of recombinant inbred strains (7–13).

A significant QTL was identified in 25 BXD recombinant inbred lines (C57BL/6 and DBA/2) on chromosome 1 for the amount of REM sleep in the 12-h light period [51]. Overall, between 40 and 60 % of the variance in sleep amounts and distribution can be explained by the additive effects of 6–15 genes in BXD recombinant inbreds, indicating, as for other complex traits, a polygenic basis for sleep. So far, no significant QTL has been found for the amount of NREM sleep [49, 51].

QTLs for Sleep EEG

In 1996, van Beijsterveldt et al. [52] recorded the waking EEGs of 91 MZ and 122 DZ twins during quiet resting with eyes closed. Spectral powers were calculated for the frequency bands alpha, beta, delta, and theta. The average heritabilities for all these frequencies bands were 76 % for delta, 89 % for theta and alpha, and 86 % for beta. In other

words, the rhythmic brain electrical activity is one of the most heritable traits in humans [52–54]. This important finding in humans was extended to the EEG activity during sleep in mice by using quantitative genetic analysis and in MZ twins in humans [14, 55, 56].

Quantitative analysis of the spectral EEG activity during sleep demonstrates an important variation between different inbred strains for both REM and NREM sleep [14]. The theta peak frequency (TPF) was found to vary greatly with genotype [14, 57]. The TPF was significantly different between C57BL/6J (B) and BALB/cByJ (C) mice during REM sleep, the first being slow (5.75–6.25) and the second fast (6.75–7.75). Over 80 % of the interstrain variability could be explained by genetic effects. In BXC F1 mice, the TPF was similar to that of B and significantly faster than C mice, suggesting that the C allele was recessive. By using 89 polymorphic markers, QTL analysis in 47 F2 mice identified a single highly significant locus on mouse chromosome 5, suggesting the presence of an autosomal recessive phenotype under the control of a single gene. This single locus could explain more than 65 % of the variance. After genotyping a backcross population, a strong linkage was found with the polymorphic marker D5Mit240. By genotyping 200 additional backcross mice and recording sleep in 31 selective recombinant mice, the region of interest was narrowed down to 2.4 cM. Different candidate genes were analyzed, and the short-chain acyl-coenzyme A dehydrogenase gene (*Acads*) within the region showed a spontaneous mutation in C mice. This finding suggests a major role for mitochondrial β-oxidation during sleep, which is fatty acid chain-length specific because long-chain acyl-coenzyme A dehydrogenase (*Acadl*) deficiency does not affect theta frequency. This finding constitutes the first identification of a sleep QTL [57].

It was also noticed that, during NREM sleep, DBA/2J (D2) mice show a reduced delta activity and have their EEG dominated by theta activity compared to most other inbred strains. The theta–delta ratio (TDR) on relative power spectra was determined for B6 and D2 mice and differed by more than 5 standard deviations [58]. The TDR of the F1 mice was similar to that of B6 mice and significantly different from D2 mice, suggesting that the D2 allele is recessive. A panel of 25 BXD recombinant inbred lines was recorded and QTL analysis was performed with more than 800 polymorphic markers on the whole genome. A single significant QTL was identified in the centromeric region of chromosome 14 that was responsible for more than 55 % of the total variance, clearly indicating the presence of an autosomal recessive gene. Fine mapping revealed a single-nucleotide polymorphism in the second untranslated exon of the retinoic acid receptor beta gene (*Rarb*). The different transcripts of this gene were amplified by reverse transcriptase polymerase chain reaction and sequenced. Seven polymorphisms including the biallelic marker were found between B6 and D2, one silent in the coding region and five in the untranslated 5′ regions. To test this candidate gene, we recorded different transcript knockout mice and their D2 hemizygotes. While the *Rarb* knockout had increased delta activity, a complete recovery of delta power was observed in *Rarb1,3*/D2, confirming the implication of this gene. *Rarb* transcripts were expressed at significantly higher levels in the brains of D2 compared to B6 mice, indicating that the polymorphisms in the gene had an effect on the transcription in vivo. By testing six other inbred strains, we noticed that only *Rarb1* varied with delta power. Retinoic acid, the active derivative of vitamin A, plays a major role during ontogenesis and particularly during the development of the brain through dopaminergic pathways. Sleep and the sleep EEG are also developmentally regulated. Whether it is through brain development and plasticity or through dopaminergic pathways that *Rarb* regulates the contribution of delta activity during slow-wave sleep (SWS) remains to be documented [58, 59].

QTLs for Sleep Homeostasis

Two main processes regulate sleep: a circadian and a homeostatic process. 122 Delta power, a measure of EEG activity in the 1 to 4 Hz range, in SWS is in a quantitative and predictive relationship with prior wakefulness. Delta power is negatively correlated with the response to arousing stimuli [60] and SWS fragmentation [61] and therefore can be seen as a measure of SWS intensity. Sleep loss evokes an increase in delta power during subsequent SWS that is proportional to the loss [62–64], whereas excess sleep results in an attenuation of delta power. [65] The time constant for the accumulation of a need for NREM sleep (increase in delta power), but not for its decline, varies greatly between inbred mouse strains [64]. QTL analysis was performed in 25 BXD recombinant inbred strains for the segregation of the rebound of delta power after 6 h of sleep deprivation. Results showed that additive genetic factors accounted for more than 67 % of the total variance [64]. By analyzing 788 polymorphic markers for a genomewide scan, a significant QTL was identified on chromosome 13 and a suggestive one on chromosome 2. The QTL on chromosome 13 explained 49 % of the total variance in delta power rebound, suggesting the presence of a major gene. Confirmation of the chromosome 13 QTL was obtained in baseline recordings of the same animals. This result suggests that sleep need is under strong genetic control and genes can be identified underlying NREM sleep homeostasis.

By using gene profiling in three inbred mouse strains differing in their sleep need, we have identified *Homer1a* as the best transcriptional marker of sleep need [31]. Interestingly, *Homer1a* maps exactly to the same chromosome 13 QTL that we had already identified for sleep need. We have also generated transgenic mice to investigate the transcriptional changes occurring in *Homer1a*-expressing neurons in the brain after sleep deprivation. Again, *Homer1a* was identified together with four other activity-induced genes, all

upregulated by glutamate. Homer1 proteins are postsynaptic density proteins linking metabotropic glutamate receptors to other intracellular effectors mediating the effects of *N*-methyl-D-aspartate and aminohydroxymethyl isoxazole propionate receptors as well as the intracellular calcium stores. Activation of Homer1a disrupts this signaling pathway and buffers the intracellular calcium. Our findings suggest a role for sleep in intracellular calcium homeostasis for protecting and recovering from the neuronal activation imposed by wakefulness. Since *Homer1a* is also induced by electroconvulsive therapy and antidepressants, we propose that its induction by sleep deprivation might correlate with the well-documented antidepressant effects of sleep deprivation.

Genetics of Sleep Disorders

Normal sleep is a highly complex behavior in its regulation and physiology, and a single defect at the molecular level of one of its component can cause a dysregulation and lead to a very disabling sleep disorder. As the molecular mechanisms of normal sleep are just beginning to be elucidated, the study of sleep disorders might be an alternative approach to understand the sleep function and to find new drug targets. With the recent discovery of the hypocretin deficiency in canine and human narcolepsy, the genetics of sleep and sleep disorders appears as a very promising avenue in our understanding of sleep disorders. Familial and twins studies indicate an important influence of genetic factors on sleep disorders, and the recent linkage analysis and candidate gene analysis on multiplex families resulted in the discovery of gene mutations, susceptibility factors, or linkage evidence in several sleep disorders. Three diseases are reported to result from a single-gene mutation: FFI, familial advanced sleep-phase syndrome (FASPS), and primary insomnia. A unique narcolepsy case has also been observed to be caused by a single-gene mutation. Most other sleep disorders have complex genetics with susceptibility genetic factors and environmental effects.

Disorders Caused by a Single Gene

Fatal Familial Insomnia

In 1986, Lugaresi et al. [66] described a 53-year-old man who suffered from progressive insomnia, dysautonomia (pyrexia, diaphoresis, myosis, and sphincter disturbances), dysarthria, tremor, and later myoclonus and coma, identifying the first sleep disorder for which a gene mutation has been identified: FFI. Two sisters of the patient and several relatives had the same symptoms leading to coma and death after 9 months. The major features of FFI include a progressive reduction of sleep duration, an early disappearance of sleep spindles, a loss of SWS, and the disintegration of the NREM-REM sleep cycle [67]. This autosomal dominant disease affects both sexes equally, with high penetrance, and leads uniformly to death. Parchi et al. [68] observed on postmortem tissues a massive neuronal loss and astrogliosis in the mediodorsal thalamic nuclei in association with relatively modest amounts of abnormal prion protein. Selective atrophy, loss of neurons, and astrogliosis of the anteroventral thalamic nucleus cause behavioral changes, whereas impairment of the mediodorsal thalamic nucleus disrupts sleep and wakefulness and is associated with the loss of EEG spindle activity [69]. The damage of serotonergic and γ-aminobutyric acid (GABA)ergic neurons leads to sleep–wake disturbance [66, 67]. The degenerations of the thalamic nuclei are caused by a point mutation at codon 178 of the prion protein gene (*PrP*) on chromosome 20 [70].

Familial Creutzfeldt–Jacob disease (CJD) is also associated with codon 178 mutation (substitution of asparagine for aspartate) and spongiform degeneration leading to dementia, but the two conditions differ at codon 129, with all FFI patients having a methionine and CJD patients having a valine at this position. Furthermore, homozygosity at codon 129 seems to have a clinical course of less than 1 year, severe insomnia, continuous motor overactivity, and severe dysautonomia [71]. The prion protein becomes protease resistant in the brain and is implicated in a group of disorders of the central nervous system termed *spongiform encephalopathies,* but the mechanism by which the mutant prion protein exerts its toxic effects remains unknown.

In 1999, Mastraianni et al. [72] described a patient with symptoms and lesions very similar to those of FFI but lacking the mutation at codon 178, suggesting a sporadic form of fatal insomnia. Parchi et al. [73] reached the same conclusion by studying five new patients. Mastraianni inoculated mice with brain homogenates from subjects having FFI or sporadic fatal insomnia and observed the same type and distribution of cerebral lesions [72]. Therefore, fatal insomnia can occur in the absence of the D178 N mutation.

Familial Advanced Sleep-phase Syndrome

FASPS is an abnormality of human circadian behavior that segregates in a highly penetrant autosomal dominant manner. Polysomnographic measurements of sleep and plasma melatonin and body temperature rhythms indicate that all measures are phase advanced by 4 h [74]. Genetic studies in drosophila, fungi, plants, and animals led to the identification and characterization of clock genes responsible for circadian behavior [75]. In mammals, several genes are determinant for circadian oscillation: *clock, bmal1, per,* and *cry.* Toh et al. [76]. found a four-generation family linkage between FASPS and the marker D2S395 on chromosome 2qter where the *PER2* gene maps. An *hPer2,* a human homolog of the *Drosophila period* gene, was found to be

mutated in affected members of one family with FASPS [76]. A mutation at position 2106 (A to G) of the hPer2 complementary DNA leading to a substitution of a serine at amino acid 662 for a glycine (S662G) is therefore responsible for FASPS in this family. The mutation affects the casein kinase I epsilon (CKIε)-binding domain of hPER2 protein and causes hypophosphorylation of CKIε in vitro. In a mammalian clock model, mPer2 is a positive regulator of the Bmal1 feedback loop, raising the possibility that phase advance of hPer2 could phase advance the feedback loop [77]. However, not all the families tested, and not all members of the same family, are linked with the hPer2 locus, suggesting a genetic heterogeneity in FASPS.

Another study identified a missense mutation (T44A) in the human CKIδ gene in a three-generation family affected by FASPS [78]. An A-to-G mutation was identified to be responsible for a threonine-to-alanine alteration at amino acid 44 in the CKIδ protein. This mutant kinase also decreases the enzymatic activity in vitro. When this mutated gene was introduced into *Drosophila,* it was found to lengthen the circadian period. Transgenic mice were also created with a human BAC clone containing the entire wild-type CKIδ gene with the T44A variant, and an opposite effect was observed: free-running periods were significantly shorter in these mutant mice. This suggests that the interactions of the clock components as part of the circadian network may be different or species dependent [78].

Short Sleep

Sleep length varies considerably and is normally distributed in most species. Nevertheless, short and long sleep durations run in families and might be genetically controlled. Short sleepers have been of interest to understand how sleep is regulated and seem to be under a higher sleep pressure [79]. Whether a single gene may regulate sleep duration was questioned but in some families, the trait seems to segregate in an autosomal dominant manner. He et al. [80] sequenced several genes involved in circadian rhythms in 60 short sleeper families and identified a point mutation in the transcription factor *hDEC2*. The exact function of DEC2 is not clearly understood but may act as a negative regulator of the circadian clock [81]. The identified mutation in hDEC2 (proline-to-arginine 385) was introduced into mice and caused a 1.2-h longer circadian period and shorter sleep. Similar experience with drosophila also resulted in shorter sleep, confirming that the mutation affects causally the sleep length [80]. Nevertheless, hDEC mutations seem to be extremely rare and so far only a single family with a mutation has been identified.

Primary Insomnia

Molecular studies of primary insomnias are very rare, but a study reported a missense mutation in a single patient with chronic insomnia. This mutation is a substitution of the amino acid arginine for histidine at position 192 (R192H) in exon 6 of the gene coding the $GABA_A\beta3$ subunit, altering $GABA_A$ receptor function in vitro [82]. The β3 subunit is suggested to be implicated in sleep processes by the observation that β3 knockout mice are not responsive to the hypnotic action of oleamide [83].

Narcolepsy

In 2000, Peyron and colleagues reported the first case of human narcolepsy caused by a point mutation, impairing hypocretin trafficking and processing [84]. A patient with severe symptoms and a very early age at onset (6 months) had a T-to-G transversion in the pre-prohypocretin gene, resulting in a leucine-to-arginine substitution in the signal peptide. Whether this mutation was a de novo or inherited could not be determined.

Familial forms of narcolepsy are very rare and probably represent less than 2 % of all narcolepsy cases. Available families suggest that narcolepsy might be caused by a single-gene mutation and two previous studies have localized two different loci on chromosome 4 and 21 but the underlying mutations were not identified [85, 86]. More recently, a large family with 12 affected members was identified in Spain. Linkage analysis in this family localized a single locus on chromosome 6. Exome sequencing in 3 affected members revealed a single mutation within the linkage region on chromosome 6 [87]. The missense mutation (a c.398C>G) was found in the second exon of myelin oligodendrocyte glycoprotein (MOG), only in affected family members. Transient expression of the mutant MOG in mouse oligodendrocytes showed aggregated subcellular localization, strongly suggesting an abnormal function [87].

Mutations in DNA methyltransferase 1 (DNMT1) were recently reported in several families with a rare condition known as cerebellar ataxia, deafness, and narcolepsy [88, 89].

Disorders with Human Leukocyte Antigen Association

REM Sleep Behavior Disorder

REM sleep behavior disorder (RBD) is a parasomnia that mainly affects middle-aged or older men. It occurs only during REM sleep and is characterized by the loss of skeletal muscle atonia related to REM, resulting in complex and vigorous dream-enacting behaviors [90]. An association with drug use, toxic exposure, and neurologic disorders is reported [91]. Gagnon et al. [92] reported that RBD was detected using polysomnographic recordings in about 33 % of patients with Parkinson's disease. RBD-type behaviors may be seen in up to 25 % of Parkinson's disease patients

[93] and may appear before the onset of motor symptoms of this disorder in approximately 40 % of older-onset RBD patients [94]. RBD is also associated with dementia with Lewy bodies [95]. These two associations reflect an underlying synucleinopathy. Genetically, RBD seems associated with the human leukocyte antigen (HLA) DQw1 allele, more precisely with DQB1*05 and DQB1*06 [96]. Replication studies are needed and should be facilitated by the increasing number of patients diagnosed with this disorder.

Sleepwalking

Sleepwalking is a frequent childhood parasomnia, affecting up to 20 % of children [97], but generally disappears at adulthood [98]. Sleepwalking is a disorder of arousal occurring during SWS [99], generally shortly after sleep onset, and resulting in complex movements including walking during sleep with a partial or complete amnesia the next day. Epidemiologic surveys, including familial and twins studies, suggest a strong genetic predisposition in sleepwalking [100–102], with over 50 % of concordance for MZ compared to 10–15 % for DZ twins [100, 101, 103]. The prevalence of sleepwalking in first-degree relatives of an affected subject is at least 10 times greater than in the normal population [100]. Two modes of inheritance have been proposed, multifactorial [103] and autosomal recessive with incomplete penetrance [104]. In a study in 60 caucasian subjects and their families, we have reported a positive association between the HLA DQB1*05 subtype [105]. The frequency of DQB1*05 was increased in sleepwalking patients, while DQB1*0602 (associated with narcolepsy) was slightly decreased. Detailed analysis in families indicated that the polymorphic amino acid Ser74, shared by all DQB1*04 and *05 alleles, is the HLA DQB1 polymorphism most tightly associated with this parasomnia. DQB1*05 has also been implicated in RBD [96]. A common genetic predisposition to sleepwalking and RBD may explain the coexistence of both disorders in some patients. Further replication and family studies are needed to confirm this association.

Kleine–Levin Syndrome

Kleine–Levin syndrome is a rare and mainly sporadic disorder characterized by periodic hypersomnia and different behavioral abnormalities such as cognitive and mood disturbances, compulsive hyperphagia, hypersexuality, and dysautonomics [106–109]. The etiology of Kleine–Levin syndrome is unknown, although an intermittent dysfunction at the diencephalic–hypothalamic interface was suggested [110, 111]. Another hypothesis is an imbalance in serotonergic or dopaminergic systems or an abnormality in the metabolism of these neurotransmitters [112, 113]. Familial forms are extremely rare but Katz and Ropper reported a familial case with two affected siblings [114]. The sister and brother shared the HLA DR2 and DQ1 antigens. In a study in 30 unrelated patients and their families, we have observed an increased frequency of the HLA DQB1*0201 allele (28.3 vs. 12.5 % in controls) [115]. Three of the patients but none of the controls were homozygous for this allele. In 17 heterozygous parents, 11 (64.7 %) had transmitted this allele, suggesting a preferential transmission. The recurrence of the episodes, the frequent infectious precipitating factors at onset, young age at onset, and the association with HLA DQB*0201 are in favor of an autoimmune etiology for this disorder [115].

Delayed Sleep-phase Syndrome

Despite normal sleep architecture, delayed sleep-phase syndrome (DSPS) is characterized by a persistently delayed sleep onset and offset. Shibui et al. [116] found that the melatonin rhythms of these patients were delayed compared to controls. However, the mechanism underlying this disease is still unknown, although different hypothesizes have been proposed: a prolonged intrinsic period beyond the range of entrainment to the 24-h day, a reduced sensitivity of the oscillator to photic entrainment, or an abnormal coupling of the sleep–wake cycle to the circadian rhythm [117–119]. Although DSPS seems to have a heterogeneous etiology, associations with HLA DR1 [120] and PER3 gene polymorphisms [121, 122] have been reported. The exact role of PER3 is not clearly established, but this protein heterodimerizes with PER1 and PER2 and CRY1 and CRY2 before entering the nucleus to inhibit the transcriptional CLOCK/BMAL1 complex [123, 124]. An alteration of PER3 phosphorylation could change its function and alter the cellular circadian machinery.

Narcolepsy

Narcolepsy is a rare and disabling disorder characterized by a tetrad of symptoms: cataplexy, excessive daytime sleepiness, sleep paralysis, and hypnagogic hallucinations [125, 126]. In Western countries, the prevalence is 0.03–0.1 % of the general population [127]; in Japan, the prevalence is the highest [128], and in Israel, the lowest [129]. The onset of the disease occurs between 15 and 30 years of age with a potential effect of the month of birth [130–132], generally with both sexes equally affected. The major abnormality in narcolepsy is an intrusion of REM sleep-like features during wakefulness, such as hypnagogic hallucinations, sleep paralysis, and cataplexy and an inability to stay asleep during the nighttime and awake during the daytime [133–135]. Less than 2 % of narcolepsies are familial but the risk for first-degree relatives is 20–40 times higher than for the general population [136]. This indicates a strong genetic influence on the development of the disease. However, twin studies reported only 25–31 % concordance, clearly indicating a major importance of environmental factors [137].

Numerous studies have demonstrated that narcolepsy has one of the tightest associations with a specific HLA allele. First an association with HLA class I Bw35 was reported in Japanese patients, whereas in caucasians, HLA Bw7 was associated [138, 139]. In the early 1980s, a 100 % association with HLA DR2/DQw1 was shown in Japanese patients [138] and up to 98 % in Caucasians [140]. Four alleles corresponding to DRB1*15:01, DRB5*01:01, DQA1*01:02, and DQB1*06:02 are associated with the disease. About 88–98 % of patients affected by narcolepsy with clear cataplexy are HLA DQB1*0602 positive, versus 40–60 % of narcolepsy patients with mild or atypical or no cataplexy [141]. The contribution of HLA is complex and recent results indicate that other DQB1 alleles increase or protect against narcolepsy [140, 142].

Although HLA DQB1*0602 remains the best genetic marker for narcolepsy, other genetic factors contribute to its susceptibility. Several studies have sought associations with non-HLA gene polymorphisms. A significant association between narcolepsy and the monoaminergic pathway involving monoamine oxidase A (MAO-A) and the catechol-*O*-methyltransferase (COMT) gene was reported [143–145]. A sexual dimorphism in the activity of the COMT gene as well as an effect on the severity of daytime sleepiness suggests a more critical alteration of the dopaminergic/noradrenergic than the serotonergic pathways in the pathophysiology of narcolepsy [144]. *COMT* genotype seems to influence sleep-onset REM periods together with sleep paralysis. Another study reported an involvement of tumor necrosis factor (TNF)-α promoter polymorphism in narcolepsy [146]. *TNFA* may be another susceptibility gene, particularly in association with HLA DRB1*15:01 [147]. Another association with TNF receptor 2 has been reported in Japanese patients, indicating the possibility of an additive effect [148]. Nevertheless, these candidate gene studies are commonly difficult to replicate and more recently are abandoned and replaced by genomewide association studies (GWAS) where hundreds of thousands of single-nucleotide polymorphisms (SNPs) are genotyped at once all over the genome. Thus, a first GWAS in Japanese patients found an association with variants in CPT1B and CHKB on chromosome 22 [149]. The first GWAS in Caucasians did not confirm the association found in Japanese but noted a new association with several variants within the T-cell receptor alpha locus (*TCRA*) [150]. This association was confirmed by us in European narcolepsy patients, and an additional but protective HLA variant (DQB1*06:03) was also discovered [142]. Another GWAs found evidence for association between narcolepsy and common variants in P2RY11 [151]. Given the implication of the immune system in the pathophysiology of narcolepsy, a large international study including 1886 narcolepsy patients and over 10,000 controls were carried out with a custom genotyping array that contained all variants within the genomic regions involved in all immune-related disorders (so-called immunochip study) [152]. This study discovered 2 new immune-related genes associated with narcolepsy: *TNFSF4* and *CTSH*, strengthening the immune origin of the disease [152]. However, in a recent study by us in 1261 European narcolepsy patients, only variants within the HLA and TCRA, could be replicated [140].

Narcolepsy is also found in dogs and is clinically and electrophysiologically similar to the human disease. Through linkage analysis and positional cloning, mutations in the hypocretin-2 receptor were identified as the cause of canine narcolepsy [153]. Simultaneously, a similar phenotype in mice was observed after a targeted deletion of the pre-prohypocretin gene [154]. The human 131 amino acid pre-prohypocretin is encoded by a gene on chromosome 17q21 and is synthesized by neurons located exclusively in the lateral, posterior, and perifornical hypothalamus [155]. A mutation in the pre-prohypocretin gene was identified in an atypical case of narcolepsy, but so far, no mutation has been found in hypocretin receptors genes. In a few post-mortem narcoleptic brains, an 85–95 % reduction in the number of hypocretin neurons has been reported, strongly suggesting that a selective destruction of hypocretin neurons in the hypothalamus is the most probable etiology for narcolepsy [84, 156]. Since 90 % of human cases of narcolepsy are sporadic and monozygotic twins show only partial concordance (25–31 %), the development of the disease should involve environmental factors directly interacting with genetic susceptibility factors. Therefore, because of the tight association with HLA, an autoimmune process could be the cause of an acute or progressive and selective degeneration of hypocretin-containing neurons in the hypothalamus. Environmental factors might trigger narcolepsy by inducing an autoimmune reaction that targets hypocretin-containing neurons.

Disorders with Other Gene Associations

Obstructive Sleep Apnea Syndrome

Obstructive sleep apnea syndrome (OSAS) is a common, chronic, and complex disorder characterized by repetitive episodes of upper airway obstruction that occur during sleep, usually associated with a reduction in blood oxygen saturation. OSAS typically leads to excessive daytime sleepiness, an increased risk of high blood pressure, and cardiovascular complications. Snoring is one of the main symptoms of OSAS, but while 30–50 % of the general population snores, only 4–5 % are affected by OSAS [157]. The concordance rates for snoring and OSAS are higher in MZ than DZ twins, with heritabilities of about 50 % [157, 158]. Numerous families of patients have been reported to be

at significantly higher risk. The segregation is explained by the fact that most of the risk factors involved in the pathophysiology of this condition are largely genetically determined. Body fat distribution and metabolism (especially upper body obesity), craniofacial dysmorphism, central regulation of breathing, and neural ventilatory control abnormalities predispose to the obstruction of the upper airways. Palmer et al. [159] performed a 9-cM genome scan on 66 white pedigrees and found linkage between the apnea–hypopnea index and chromosome 1p (lod score = 1.39), 2p (1.64), 12p (1.43), and 19p (1.4). Body mass index was linked to significant markers on 2p (lod score = 3.08), 7p (2.53), and 12p (3.41). After adjustment for body mass index, suggestive lod scores for OSAS persisted only on chromosome 2p (1.33) and 19p (1.45) [159].

Three other studies reported a possible link between apolipoprotein E ε4 and OSAS [160, 161, 162]. Apolipoprotein E is a polymorphic protein encode by three alleles at a single-gene locus on chromosome 19q13. The same allele has been associated with Alzheimer's disease and cardiovascular disease in the general population. The probability of moderate to severe sleep-disordered breathing is significantly higher in patients with apolipoprotein E ε4, independently of age, sex, body mass index, and ethnicity. This potential association is not, however, confirmed in older patients (>79 years old). A polymorphism in angiotensin-converting enzyme was also reported in moderate OSAS and was found to be tightly associated in hypertensive patients [163]. Finally, another study indicated an association between haptoglobin polymorphism and OSAS complicated with cardiovascular disease, suggesting that haptoglobin phenotype is an important susceptibility factor [164]. Several international GWASs are underway to find new association with different features of OSAS.

Restless Legs Syndrome

Restless legs syndrome (RLS) is one of the most common sleep and movement disorders, affecting 2–5 % of the general population [165]. According to the diagnostic criteria, RLS is characterized by an irresistible desire to move the limbs, usually associated with paresthesias and/or dysesthesias and motor restlessness, and results in nocturnal insomnia and chronic sleep deprivation [165]. RLS affects both sexes equally and the age at onset is variable, although early onset and anticipation phenomena have been reported in familial cases [166, 167]. Several studies reported that more than 50 % of patients with RLS had a positive family history and that an affected person is three to six times more likely to have a family history than an unaffected person [165]. The symptoms start or worsen at rest and improve with activity. In over 87 % of cases, RLS is associated with periodic limb movements in sleep (PLMS) [168]. The pathophysiology of RLS is still unknown, although dopaminergic dysfunction and brain iron metabolism abnormalities have been implicated [169].

Pedigree analysis in families of 12 pairs of monozygotic twins suggested an autosomal dominant mode of inheritance and 83 % concordance in monozygotic twins [170]. A genetic basis of this syndrome is supported by studies reporting a positive family history in 63–92 % of patients, strongly suggesting that a significant portion of the familial aggregation is due to genetic factors, proposed to be transmitted with an autosomal dominant mode of inheritance with incomplete penetrance and probable anticipation effect [171, 172]. An RLS susceptibility locus has been mapped on the short arm of chromosome 12 in a large French Canadian family (lod score = 3.59) [173]. Two main candidates in the region are the neurotensin gene (12q21), an important modulator of dopaminergic transmission, and the homolog of the *Drosophila* clock gene *timeless* (12q12-q13). However, another study could not confirm the susceptibility locus in either of the families studied [174]. Other mapping studies in different ethnic groups are needed because the RLS locus on chromosome 12 has been mapped based on a recessive mode of inheritance, while in most familial cases, a dominant mode of inheritance and variable expressivity is evident. This could suggest a genetic heterogeneity for the disease. Accordingly, in a large Italian family with RLS and PLMS, evidence for linkage was obtained on chromosome 14q based on an autosomal dominant mode of inheritance [166]. Another study identified 9p24-22a as a new susceptibility region in two American families, again with the assumption of an autosomal dominant mode of inheritance [175]. Finally, another linkage analysis in a large Italian family reported a suggestive locus on chromosome 19p13 [176]. A putative association between a polymorphism of MAO-A and RLS was reported [177], while another study indicated that a polymorphism of neuronal nitric oxide synthase, which maps to the RLS locus on chromosome 12q, is associated with RLS in whites [178]. As for narcolepsy, several large GWASs were also performed in RLS and/or RLS with PLMS. Five variants within MEIS1, BTBD9, PTPRD, MAP2K5 (SCOR1), and TOX3 were discovered [179–182]. Genetic variations of several of these genes were shown to be also associated with iron homeostasis [181, 183].

Primary Nocturnal Enuresis

Primary nocturnal enuresis is another common type of parasomnia in children, affecting 10 % of 7-year-old children and even 1–2 % of adolescents. Nocturnal enuresis is bed-wetting beyond the age of 5 years, when nocturnal bladder control would normally be expected. Enuresis is referred to as primary if the patient has not had at least 6 months of nocturnal continence. Familial and twins studies have suggested a genetic background for enuresis, although

psychosocial environmental factors have a major modulatory effect [184]. Backwin [185] showed that the incidence of the illness is highest in families in which both parents have been enuretic (77 %). In most cases, enuresis has an autosomal dominant mode of transmission with high penetrance (90 %) [186]. Four gene loci on chromosomes 8q, 13q, 12q, and 22q11 have been identified to be involved in primary nocturnal enuresis, suggesting its heterogeneity and the involvement of different pathways, including the bladder, the kidney, or the central control [184, 186, 187]. A Finnish study in twins reported a concordance rate of 0.43 for MZ versus 0.19 for DZ twins in childhood, whereas it was 0.25 versus 0, respectively, in adulthood [188]. A linkage analysis study reported a 2-point lod score of 4.2 in six families with dominant primary nocturnal enuresis around the aquaporin-2 (*AQP2*) water channel locus (12q) [189]. However, no mutation in the coding sequence was detected, excluding this gene in families in which the disease co-segregates with chromosome 12q.

Conclusions

The number of sleep disorders for which a genetic contribution can be established is expanding rapidly, and both genetic linkage and GWAS of large number of families and cases affected by a well-defined sleep disorder should be systematically undertaken to lead to the discovery of the genetic basis of the disorders and finally to their eventual evidence-based treatment. An interesting and striking feature of an important number of sleep disorders is that they are strongly associated with HLA, suggesting a hypothetical interrelationship between sleep and the immune system that still needs to be discovered. We know that microbial products and cytokines strongly influence sleep–wake behavior and the architecture of sleep, and we know that in humans the primary response to antigens following viral infections is associated with acute enhanced sleep amount, and also that growth hormone-releasing hormone and interleukin-1 have a sleep-promoting effect. However, no direct molecular mechanism has been identified that could link these observations. The relationship between the immune system and sleep–wake behavior may arise at different levels: immune-related molecules could play a role in the development of certain disorders, as hypothesized in narcolepsy, or sleep and brain immunity could be related through stress factors or may even have a regulatory effect on each other.

Finally, two new fields will need special attention in the near future: pharmacogenomics and pharmacogenetics. Pharmacogenomics involves genomewide analysis of the genetic determinants of drug efficacy and toxicity, while pharmacogenetics is the study of genetic causes of individual variations in drug response. Because evidence-based treatments for sleep disorders are rare, investigating the molecular bases of drug response might reveal new pathways where future drugs can be targeted.

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Nutrition and Sleep

30

Markku Partinen

Introduction

The worldwide epidemic of obesity is currently one of the greatest public health problems. Obesity with high body-mass index has increased globally, and it is the leading risk for the global burden of disease in many parts of the world [1]. Despite declines, tobacco smoking including second-hand smoke remained the leading risk in North America and western Europe. Dietary risk factors and physical inactivity collectively accounted for 10 % of global disability-adjusted life years in 2010, with the most prominent dietary risks being diets low in fruits and high in sodium [1]. Several lines of evidence have shown that disturbed sleep has harmful effects on health, and it may be hypothesized that insufficient sleep and other sleep disorders might be among the important risks in increasing the global burden of disease [2].

Obesity is a strong risk factor for cardiovascular diseases, and it is also an important risk factor for obstructive sleep apnea. New information about effects of nutrition in psychiatric and neurologic diseases has been published during the past 10–20 years. In clinical practice, many narcoleptics of excessive afternoon sleepiness after heavy lunches and especially after eating meals with high contents of carbohydrates. Effects of different types of meals on sleep have been investigated, particularly in the 1960s and 1970s, but amazingly little is still known about effects of food on sleep and alertness. Dietary factors most likely play a much more important role in the regulation of daytime vigilance than what is recognized. As early as the 1960s, Roberts and his collaborators [3] found that, especially in African-Americans, there was an association between diabetes and narcolepsy. They also found that eating carbohydrates during the daytime worsened sleepiness of narcoleptic subjects [3]. More recently, restless legs syndrome (RLS) has been associated with low ferritin levels, suggesting a possible dysfunction in iron metabolism [4–6]. Starting from revolutionary theories by Magistretti and Pellerin [7], there is increasing evidence that glial cells (mainly astrocytes) have a crucial role in brain metabolism [8, 9]. Much new information has also been published about the important role of the enteric nervous system (ENS) and the brain–gut relationship [10–12]. It is possible that nutrition is much more important in sleep–wake regulation, sleep disorders, and the global well-being of our brains than what is currently known.

The most important factors regulating sleep duration and vigilance levels are length and quality of sleep, duration of waking time, and different social and biological *Zeitgebers* (external cues). Also, various medications and nutritional factors have effects on sleep–wake regulation. The direct effect of foods on the central nervous system (CNS) may occur by different routes: direct nervous connections through the vagus nerve and nucleus tractus solitarius (NTS), cognitive processes, and humoral effects.

Enteric Nervous System and Sleep

Signals from different receptors in the gut are transmitted to the CNS by neural connections and humoral effects. The afferent fibers of the gut–brain neural connection run through afferent vagal and sympathetic nerves. The different sensors respond to mechanical stimuli (distention of the stomach, contractions of the intestine) and to chemical stimuli from nutrients in the lumen of the gut and from gut hormones, neurotransmitters, neuromodulators, cytokines, and inflammatory mediators produced by the bacterial flora in the gut (Table 30.1). Almost all if not all neuromediators of the ENS are involved also in sleep/wake regulation or regulation of circadian rhythms. The most studied transmitters are printed in **boldface** and some new transmitters with increased recent interest in sleep research are printed in *italics*. The neural stimuli travel from sensory neurons to interneurons. Different motor, secretory, and vascular reflex activities exist in the body. Information from different parts of the gut also passes to the brain stem for vasovagal reflexes and to the spinal cord

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for different spinal reflexes. In the brain stem, most afferent vagal fibers terminate on the NTS. There is a viscerotropic representation of different parts of the enteric system in the NTS. From the NTS, information goes up to the hypothalamus and the amygdala; this information probably plays a role in satiety and emotional aspects of eating and may be

Table 30.1 Neuromediators in the enteric nervous system

• Acetylcholine
• **Adenosine**
• Agouti-related peptide
• Angiotensin II
• Calbindin
• Calcitonin gene-related peptide
• **Cholecystokinin**
• *Cocaine- and amphetamine-regulating transcript peptide*
• **Corticotropin-releasing hormone**
• Cortisol
• **Delta sleep-inducing peptide**
• **Dopamine**
• **GABA (gamma-aminobutyric acid)**
• *Galanin*
• Gastrin-releasing peptide
• **Glutamate**
• **Ghrelin**
• **Growth hormone-releasing hormone**
• Incretins gastric inhibitory polypeptide
• Glucagon-like peptide-1
• *Histamine*
• **Insulin**
• **Leptin**
• *MCH (melanin-concentrating hormone)*
• *α-Melanocyte-stimulating hormone*
• Neuromedin B
• *Neuromedin U and neuromedin S (in the SCN)*
• Neuropeptide Y
• Neurotensin
• *NO (Nitric oxide)*
• **Noradrenaline (norepinephrine)**
• Opioid peptides dynorphin
• Endorphins
• Enkephalins
• **Orexins** (hypocretin), especially orexin A
• Peptide YY (peptide tyrosine tyrosine)
• Pituitary adenyl cyclase activating peptide
• *Prostaglandins (in the gut, especially E and F)*
• Serotonin (5-HT), especially 5-HT_3, 5-HT_4, and 5-HT_{1p} receptors
• **Somatostatin**
• **Substance P**
• Thyrotropin-releasing hormone
• **Vasoactive intestinal peptide**

important in the regulation of alertness, sleepiness, and sleep–wake regulation.

Cholecystokinin and many other humoral factors have a role in the CNS-ENS network. The regulation of the sleep–wake cycle is complex, and there are different theories. The important brain transmitters in sleep–wake regulation include norepinephrine, acetylcholine, 5-hydroxytryptamine (5-HT), dopamine, glutamate, histamine, adenosine, γ-aminobutyric acid (GABA), and hypocretin. Also, prostaglandins and different peptides have an effect on regulation of alertness/sleepiness. In the past, the focus was on norepinephrine, acetylcholine, and 5-HT. They all play important roles, but do not explain "why we sleep." The role of adenosine and regulation of brain energetics is probably central. During wakefulness, extracellular adenosine increases; this increase in adenosine decreases wakefulness and causes sleepiness. Caffeine, the most common stimulant, is an adenosine receptor antagonist.

Role of Neuromediators

Peptides and Hormones

Cholecystokinin is a mixture of peptides, of which octapeptide is the most effective. It is secreted by duodenal and jejunal cells after eating food. Cholecystokinin acts on the gall bladder and the pancreas, stimulating bile production and the release of pancreatic digestive enzymes. It also acts on vagal neurons projecting to the brain stem, giving a signal of satiety that inhibits further need for eating.

Ghrelin is a peptide containing 28 amino acids. It is secreted mainly in the stomach, but its receptors (growth hormone secretagogue receptors) are present widely in the gastrointestinal (GI) tract, the ENS, and also in the CNS neurons around the arcuate nucleus. In the GI tract, ghrelin has prokinetic effects, and centrally it increases appetite. It acts on the hypothalamus to stimulate feeding, counteracting the inhibitory effects of leptin and peptide YY_{3-36} (PYY_{3-36}; see later). Through its actions on the GABA system, ghrelin inhibits pro-opiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART) neurons and decreases production of α-melanocyte-stimulating hormone (*α-MSH;* see later) in the arcuate nucleus area, inhibiting the anorexigenic effects of *α-MSH* (i.e., increasing food intake).

Leptin is a protein of 167 amino acids and is manufactured mainly in fat cells in adipose tissue. The amount of circulating leptin correlates positively with the amount of fat in the body. Leptin has many CNS effects. It counteracts the effects of neuropeptide Y (NPY), agouti-related protein (*AgRP*), and GABA containing neurons and activates production of α-MSH in the arcuate nucleus. As a consequence, leptin is catabolic. It decreases appetite and inhibits food intake, contrary to ghrelin. A decrease in leptin is associated with an increase in hunger and appetite.

The inhibitory effects of leptin last long time, in contrast to the rapid inhibition of eating behavior produced by cholecystokinin and the slow suppression of hunger between meals mediated by PPY_{3-36}. Both leptin and ghrelin have been investigated in several studies attempting to find a relationship between obesity, sleep apnea, and weight loss, but leptin does not seem to have significant effect in weight loss therapy [13–15]. Leptin is low among subjects with anorexia nervosa [16] Low levels of leptin are also associated with hyperactivity, and it has been hypothesized that leptin could have a role in the treatment of severely hyperactive patients [16].

Neuropeptide Y is a potent feeding stimulant secreted by cells in both the gut and the hypothalamic neurons. It causes increased storage of ingested food as fat. NPY inhibits transmission of pain signals to the brain.

Peptide YY_{3-36} is close in structure to NPY but, contrary to NPY, is a potent inhibitor of feeding. PYY_{3-36} is released by cells in the intestine after meals. The secretion increases with the amount of calories eaten, especially when these derive from proteins rather than from carbohydrates or fats. This may explain partly why people who eat a lot of carbohydrates are often hungry, developing obesity.

α-Melanocyte-stimulating hormone (*α-MSH*) is an anorexigenic melanocortin. Melanocortins are products of POMC gene in the arcuate nucleus in the mediobasal hypothalamus. Other melanocortins include ACTH, β-MSH and γ-MSH, β-endorphin and met-enkephalin. Alpha-MSH is responsible for production of melanin (tannin) by melanocytes in skin and hair in humans. The POMC cells are glucose-sensing cells [17]. They act to suppress appetite and food intake. In addition to central effects, melanocortins act on adipocytes by stimulating lipolysis and inhibiting leptin secretion. The melanocortins, α-MSH probably as the most important, are dominant anorexigenic peptides and important regulators of food intake.

AgRP blocks the action of α-MSH in the arcuate nucleus and is also involved in the regulation of food intake. The hypothalamic POMC and AgRP neurons are major targets of leptin and insulin action in the brain. As noted above, leptin stimulates POMC/CART and inhibits AgRP secretion [18].

Hypocretins (*orexins*) [19, 20] are produced by about 70,000 cells in the lateral hypothalamus. They were originally considered to be important particularly in central control of food intake. Hypocretin is an "orexigenic" neuropeptide, increasing food intake (N.B. interestingly in narcolepsy, with loss of orexin, weight gain is often observed), contrary to "anorexigenic" neuropeptides that decrease food intake. It is now evident that hypocretins have a much larger spectrum of action, including energy homeostasis, sleep–wake behavior, nociception, reward-seeking behavior, and drug addiction [10, 21, 22]. Hypocretin-producing cells can be directly modified by peripheral signals. They are sensing peripheral glucose, and they have receptors for leptin and

ghrelin [23]. Hypocretins are also widely present in the GI tract [10]. In the ENS, they have a role in regulation of GI motility, and also in gastric, intestinal, and pancreatic secretions. The relationships among enteric regulation, eating behavior, regulation of arousal, narcolepsy [24–26], and the orexin-hypocretin system remain to be further clarified. It is most probable that there are important interactions that explain many of the symptoms, including the effects of fasting and carbohydrate intake on the vigilance of narcoleptic subjects versus normal people.

Melanin-concentrating hormone (*MCH*) An important interaction exists between hypocretin cells and intermingling MCH cells in the lateral hypothalamus. Both hypocretin-producing cells and MCH cells are *glucose-sensing cells*—sensing blood glucose concentrations. Decrease in glucose stimulates hypocretin cells and inhibits MCH cells (increasing alertness and food intake) [23, 27–29]. Increase in blood glucose inhibits hypocretin cells and stimulates MCH cells (decreasing alertness and decreasing food intake). Both hypocretin and MCH projections are widely distributed. They are located close to each other, having synaptic interconnections, and modulating each other's cellular activity. According to these theories, the MCH–hypocretin interactions are crucially important in the regulation of food intake and energy balance. MCH cells are involved also in regulation of REM sleep and in narcolepsy and disturbed MCH and propiomelanocortin system may be related to development of obesity in narcolepsy [30, 31].

Anandamine is an endocannabinoide that is produced in the small intestine. It is "orexigenic," i.e., it increases appetite. Anandamine has a role especially in the hedonic regulation of eating. It is involved in removing unnecessary short-term memories. It is also responsible for slowing down movements, making people feel relaxed and calm [32].

Insulin is produced in pancreas by β cells in islets of Langerhans. The effects of insulin on glucose- and lipid metabolism are known better than those of the other mediators. Insulin increases satiety and decreases appetite. Insulin stimulates POMC/CART neurons in the arcuate nucleus, generating an anorexigenic signal [18].

Serotonin

Serotonin (5-HT) is an important neurotransmitter in the CNS with important effects on sleep–wake regulation. It also has an important role in regulation of GI function through an interaction with the ENS. The ENS can be considered the body's second brain, with more than 100 million neurons of different types. Up to 60–90 % of the total body amount of 5-HT is in the GI tract, and 2–20 % of all enteric neurons express 5-HT. The control of 5-HT's release from enterochromaffin cells is complex. Stimulatory receptors include β-adrenergic receptors, muscarinic and nicotinic acetylcholine receptors, and 5-HT_3 receptors. Inhibitory receptors include α_2-adrenergic, histamine H_3, $GABA_B$, adenosine A2, and 5-HT_4 receptors. In the GI tract, 5-HT is eliminated mainly by monoamine oxidase metabolism [11, 33].

An interesting element from the point of view of sleep and movement disorders is the 5-HT_{1p} receptor. This receptor is probably involved in the secretory and peristaltic reflexes of the GI tract. The molecular identification of this receptor is not yet clear. Lui and Gershon [34] suggested that this receptor is a heterodimer of the 5-$HT_{1B/1D}$ receptor and the dopamine D_2 receptor. Other studies have also shown that dopamine is involved in GI tract regulation. Gershon's group has also shown in knockout mice that intestinal motility is abnormal when D_2 is absent [35]. A dysfunction of the intestinal dopamine system probably explains many of the GI symptoms, especially problems of constipation that are usually present very early among patients with Parkinson's disease (PD). It remains to be seen whether there are some associations with symptoms of RLS, lack of iron, and dysfunction of the 5-HT–dopamine system of the GI tract.

Irritable Bowel Syndrome and Role of the Intestinal Microbiota

Irritable bowel syndrome (IBS) is one of the most common GI disorders. It is twice as frequent among women as among men. IBS is related to dysfunction of the enteral serotonin system. There are no published systematic epidemiologic studies about the occurrence of IBS among patients with RLS. In our own clinical database, GI symptoms had been tabulated from 141 RLS patients (unpublished observations). Of these patients, 17 (12 %) had GI symptoms that could be diagnosed as IBS type. Because we had not tabulated this history systematically, the true prevalence might be higher. On the other hand, about 29 % of patients with IBS have RLS [36].

Intestinal microbiota has a role as a regulator of autoimmune diabetes in animals, and probably also in humans [37]. The role of gut microbiota in other human HLA-associated autoimmune diseases, including narcolepsy, remains to be studied. Small intestine bacterial overgrowth (SIBO) is common in RLS. In a recent series, SIBO was found in almost 70 % of patients with RLS [38]. In a randomized study, all 20 patients with RLS had marked improvement in their RLS symptoms after treatment of SIBO [39]. The therapy of SIBO was based on rifaximin, which is a rifamycin-based nonsystemic antibiotic, meaning that the drug will not pass the GI wall into the circulation [39–41]. Although treatment with antibiotics may be

beneficial, the spectrum of gut microbes is changed, which may be followed by various adverse effects and symptoms that may last years. Changes in the gut microbiota may be involved in many neurological and psychological symptoms [42]. The intestinal microbes are also known to be able to produce many neurotransmitters such as GABA, serotonin, melatonin, catecholamines, histamine, and acetylcholine [42–44]. Different diets have been advised for patients with IBS. Some beneficial results have been obtained by use of probiotics and by FODMAP diet. That diet is low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) that are poorly absorbed by the small intestine and fermented by bacteria in the large intestine [45].

Case Example

A 53-year-old male biochemist developed severe insomnia 3 weeks after returning from a congress in South America. He had difficulty falling asleep and he woke up repeatedly, sleeping only 2–3 h. After 3 weeks of insomnia, he became exhausted and consulted our sleep clinic. He was lean. One week before consultation, he had started zopiclone and fluoxetine because he was diagnosed to have depression, which he denied. There was no previous history of insomnia. The polysomnography at the laboratory was consistent with his history. Total sleep time was only 2.3 h, and there was no slow-wave sleep. No apnea or periodic limb movements were found.

In the clinical interview at the sleep clinic, it was found that he had diarrhea with a fever during his travel. He took ciprofloxacin for 5 days but, because he continued to have diarrhea, he consulted an internist. A variety of laboratory tests were done to exclude all potential bacterial, viral, and tropical diseases. Nothing specific was found, but he was given two more antibiotics, including metronidazole. The diarrhea became much better, and his body temperature was between 37.0° and 37.3 °C. Insomnia developed one week after the last antibiotics had been taken. The problem was discussed with the patient. The internists concluded that he had had either bacterial or viral enteritis but no serious disease had been found. He speculated that the strong antibiotics had destroyed the entire bacterial flora, including healthy saprophyte bacteria.

Because his general condition was quite good, we decided to stop further laboratory examinations and start down-titrating zopiclone and fluoxetine. He also started to take omega-3 fatty acids, and *Lactobacillus casei/Enterococcus faecium* to normalize his intestinal flora. We encouraged him to restart exercise. After three weeks, he began to sleep normally as he had done before. His insomnia was of a psychophysiologic type, and anxiety (fear of some severe disease) probably also played a role. It is possible that his insomnia could have been caused by a change in the intestinal flora, and hence changes in the ENS-CNS regulation. The amelioration of his insomnia by reintroducing bacteria in the diet, without any other treatment, is in favor of this theory.

Role of Neurosteroids

Neurosteroids are synthesized in astrocytes, oligodendrocytes, Schwann cells, Purkinje cells, hippocampal neurons, and retinal amacrine and ganglion cells [46, 47]. Cholesterol is transported to glial mitochondria, where it is converted to pregnenolone. In the cytosol, pregnenolone is then converted to different neurosteroids such as allopregnanolone and dehydroepiandrosterone (DHEA). DHEA is a precursor of testosterone, which is converted to estradiol by an aromatase [46, 47]. Vitamin D is also an important neurosteroid [48]. Synthesis of neurosteroids is regulated by interactions between neurons and glial cells.

Neurosteroids have many important actions. Allopregnanolone activates neuronal $GABA_A$ receptors having anxiolytic, sedative, sleep-inducing, and anticonvulsant effects. Benzodiazepines, alcohol, and γ-hydroxybutyrate increase brain levels of allopregnanolone. Thus, these drugs may potentiate GABAergic transmission directly and also by increasing allopregnanolone. Pregnenolone sulfate, DHEA, and DHEA sulfate (DHEA-S) are inhibitory, noncompetitive modulators of $GABA_A$ and positive modulators of *N*-methyl-D-aspartate (NMDA) receptors by facilitating calcium influx. Estradiol inhibits NMDA receptors. Neurosteroids acting on NMDA are implicated in cognition, neuroprotection, and neurotoxicity. While pregnenolone sulfate is excitotoxic to cortical and retinal cells, DHEA and DHEA-S have neuroprotective effects against glutamate toxicity. However, the exact mechanisms of such neuroprotective effects are not clear.

Neurosteroids have been implicated in many neurologic and psychiatric disorders, including epilepsy, neurodegenerative diseases, schizophrenia, and depression. For example, depression is associated with reduced levels of allopregnanolone in cerebrospinal fluid. Antidepressant treatment with fluoxetine increases allopregnanolone levels [49]. There is also some evidence that DHEA helps in the treatment of depression. The beneficial effect of DHEA correlates with a decrease in glucocorticoids, which are increased in depression.

There is increasing evidence about many important roles of neurosteroids in regulation of vigilance as well. It remains to be studied whether nutritional factors could also play some role in this. DHEA is marketed in pharmacies and health shops. Little is known about possible positive (and, perhaps, also negative) long-term neuropsychiatric effects of nutritional factors that may cause changes in brain neurosteroids.

Role of Neurohormetic Phytochemicals

Several lines of evidence have shown that diets rich in fibers, vegetables, and fruits are associated with reduced risk of cardiovascular disease and many neurologic diseases [50]. There is also evidence that a vegetarian diet helps in weight control, and in this way prevents obesity and occurrence of obstructive sleep apnea. As stated previously, rapidly absorbed low-fiber carbohydrates induce sleepiness. Therefore, a vegetarian diet with a lot of fiber and slowly absorbing "good" carbohydrates is better for staying alert during waking time. Some of the positive effects are explained by antioxidant effects of different phytochemicals, but there is also evidence that some effects may be due to subtoxic effects of some neurotoxic molecules in the gut.

Hormesis refers to a paradoxical process in which low doses of a given toxic substance, or radiation, induce beneficial effects while larger doses of the same substance are toxic to cells and organisms [51–53]. Examples of endogenous molecules with neurohormetic actions are nitric oxide, carbon monoxide, glutamate, and calcium. Neuroprotective natural substances include α-tocopherol, lycopene, resveratrol (red grapes, red wine, peanuts, and soy), sulforaphanes (broccoli), catechins (green tea), allicin and allium (garlic), curcumin (turmeric), hypericin (in St. John's wort), and many others. In randomized clinical trials, hypericin (*Hypericum* extracts) has shown clinical efficacy comparable with the efficacy of some commonly used antidepressants, including citalopram, paroxetine, and fluoxetine [53–60]. This is of interest to sleep specialists because antidepressants are also used in treating insomnia, especially if it is thought to be associated with underlying depression. Much more research is needed to find out if natural substances affect sleep–wake behavior.

Hot spices may disturb sleep, perhaps by a neurohormetic action. In one study on six young men, tabasco and mustard in the evening reduced slow-wave and stage 2 sleep, reduced total time awake, and prolonged sleep onset. The spicy food in the evening elevated body temperature during the first sleep cycle. It is possible that capsaicin affects sleep by its effects on body temperature [61].

Caffeine, Adenosine, and Sleep

Caffeine, used mainly in the form of coffee, is the world's most common psychoactive drug. Caffeine is present in coffee, tea, cola, energy drinks, and chocolate, and it induces wakefulness. Its stimulant properties depend on its ability to reduce adenosine transmission in the brain. Caffeine acts as an antagonist to adenosine A1 and especially to adenosine A2 receptors [62]. Huang and collaborators found in knockout mice that caffeine increased wakefulness in both wild-type mice and A1 receptor knockout mice, but not in A2a receptor knockout mice. Thus, caffeine-induced wakefulness may be due mainly to its effects on adenosine A2a receptors [63]. Porkka-Heiskanen and her collaborators [64–66] have also recorded human sleep electroencephalograms (EEGs). The longer the previous wakefulness period is, the longer and deeper is the following sleep. The inhibitory neuromodulator adenosine is one promising candidate for a sleep-inducing factor. Its concentration is higher during wakefulness than during sleep, it accumulates in the brain during prolonged wakefulness, and local perfusions as well as systemic administration of adenosine and its agonists induce sleep and decrease wakefulness. The hypothesis is that adenosine accumulates in the extracellular space of the basal forebrain during wakefulness, increasing the sleep propensity. The increase in extracellular adenosine concentration decreases the activity of the wakefulness-promoting cell groups, especially the cholinergic cells in the basal forebrain. When the activity of the wakefulness-active cells decreases sufficiently, sleep is initiated. During sleep, the extracellular adenosine concentrations decrease, and thus, the inhibition of the wakefulness-active cells decreases, allowing awakening and a new wakefulness period [65].

In addition to coffee, caffeine is found in tea, cola drinks, energy drinks, and chocolate. Theobromine is also present in large quantities in chocolate. Dark chocolate is stimulating; 100 g of 70 % chocolate corresponds to 1–2 cups of coffee depending on strength of the coffee and size of the cup. Caffeine is a CNS stimulant. Its actions are variable among different people. Caffeine is absorbed rapidly, and peak activity is achieved in 30–60 min. The duration of action is usually 4–6 h, but in elderly subjects with slower metabolism, the duration may be up to 16–20 h. Insomniacs are usually advised to avoid coffee after 6:00 PM, but in some sensitive persons with insomnia, coffee at noon may disturb falling asleep in the evening.

One cup of coffee contains 75–125 mg of caffeine. A large amount of caffeine, usually over 300–500 mg (depending on individual sensitivity), causes restlessness, anxiety, trembling, tinnitus, and feelings of euphoria/delirium. Everyday use of more than 500 mg of caffeine leads to caffeinism with insomnia, fatigue, and different psychosomatic symptoms. It has been estimated that perhaps 10–20 % of coffee drinkers have caffeinism. Chronic coffee drinkers have often developed tolerance to caffeine, and some people may drink more than 10 cups of coffee daily. They have withdrawal symptoms if they do not have their coffee. Coffee is a well-known factor disturbing sleep [67–69]. Two or three cups of coffee (or in sensitive persons just one cup) before bedtime is followed by difficulty falling asleep and restless sleep.

Landolt et al. [70] administered 200 mg of caffeine in the morning and analyzed the sleep stages and EEG power spectra during the subsequent night in nine healthy men.

They also measured caffeine levels in saliva, which decreased from a maximum of 17 μmol/L 1 h after intake to 3 μmol/L at 23:00 in the evening. Compared to placebo, sleep efficiency and total sleep time were significantly reduced after the morning intake of caffeine [70]. Slow-wave sleep decreases and amount of stage 1 sleep usually increases after drinking coffee. Insomnia and RLS are more frequent among habitual coffee drinkers than among others. Paradoxically, in some persons, one or two cups of coffee may ameliorate quality of sleep. The reason can be behavioral conditioning, but it is also known that caffeine has a stimulating effect on both breathing and cardiac function. In patients with RLS, symptoms worsen by drinking a lot of coffee. Missak postulated that the human body—in cases of iron deficiency and chronic renal failure—may produce a substance similar to caffeine [71].

Epidemiologic studies have provided evidence that caffeine, an adenosine receptor antagonist, reduces the risk for PD [72–75]. There are indications of specific interactions between striatal adenosine A2a and dopamine D_2 receptors. In one study, the dopaminergic effects of caffeine were examined with [^{11}C]raclopride positron emission tomography in eight healthy habitual coffee drinkers after 24 h of caffeine abstinence. Compared to oral placebo, 200 mg of oral caffeine induced a 12 % decrease in midline thalamic binding potential ($p < 0.001$). These findings indicate that caffeine has effects on dopaminergic neurotransmission in the human brain, which may be different in the striatum and the thalamus [73]. Caffeine and other A(2A) receptor antagonists are also potentially neuroprotective, which may explain some of their favorable effects [74–76].

Glucose, Lactate, and Glial Cells

The main sources of energy for the brain are glucose and lactate. According to Magistretti's theory, lactate may be the most important source of neuronal energy [7, 9, 77]. Most of the glucose from brain capillaries enters glial cells through the blood–brain barrier. In astrocytes, glucose is metabolized into lactate by glycolysis. The rate of lactate metabolism depends on brain activity and use of oxygen. Mitochondrial function should be intact for proper functioning.

Besides the heart, the CNS is the only part of the body that may have both functional and structural changes after hypoglycemia. However, the brain resists fasting better than other organs. The brain uses glucose at a rate of about 70 mg/min and contains about 1–2 g of glucose, which is sufficient for about 90 min if no more glucose is obtained from circulation. There are no strong associations between behavioral symptoms and plasma glucose levels, but fatigue and other symptoms usually occur when glucose levels are below 1.5–2 mmol/L. Common reasons for hypoglycemia are overdose of diabetic medications, high insulin levels, and severe malnutrition.

Glutamate, adenosine, and GABA have crucial roles in controlling brain energetics and lactate formation in the astrocytes. Monocarboxylate transporters (MCT1 and MCT4 in astrocytes and MCT2 in neuronal cells) are needed in the transfer of lactate from astrocytes to neurons [9, 78]. It is important to note that alpha- and beta-adrenoceptors exist in the surface of astrocytes [79]. Norepinephrine activates these adrenoceptors and stimulates glycogenolysis in astrocytes, which then produce lactate from glucose and release it to provide necessary energy for neurons [9, 80].

These theories also fit findings of Haydon and collaborators about the importance of glial cells in control of synaptic transmission, neuronal activity, and sleep [81–83]. Also Newman, Montana et al., and Zhang et al. have pointed out the role of astrocytes in regulation of synaptic activity [84–86], and, as Hertz and Zielke have written, astrocytes may be the "stars of the show" [87]. All functions of glutamate are regulated by astrocytes. Glutamate is the most important excitatory brain transmitter, and all is dependent on the ability of astrocytes to produce glutamate and glutamine [87]. The studies by Aubert and his collaborators of CNS lactate kinetics support these findings, indicating that neurons are lactate-consuming cells, whereas astrocytes are lactate producers [88]. Lactate production by the astrocytes increases with enhanced glutamatergic activation, and consumption of lactate by neurons also increases as a result of glutamatergic activity [8, 88]. It may well be that many neurologic and psychiatric diseases will turn out to be mainly glial diseases. This may also be true for fatigue and sleepiness. One of the main roles of sleep is to ensure sufficient energy for waking brain activity. To understand this better, the glial–neuronal network should be investigated, rather than concentrating our research efforts on neuronal synaptic relationships. If neurons do not have enough food (energy) of proper quality, they may starve and will not function normally [9].

In sum, the astrocyte-neuron lactate shuttle (ANLS) model, as Pellerin and Magistretti call it, can now be recognized as a major theory of brain energetics. The ANLS model helps to understand also neuronal plasticity, neurodegeneration, memory consolidation, and functional brain imaging [9]. The relations of sleep disturbances (sleep deprivation, fragmented sleep) and in the regulation of the ANLS need to be studied in more detail.

Meals, Dietary Nutrients, and Sleep

Effect of different nutrients on sleep has been studied in a large survey of 4500 people. Use of the following nutrients was associated with shorter sleep latency: alpha carotene,

selenium, dodecanoic acid, and calcium. For example, the following nutrients were associated with better sleep and less awakenings during sleep: avoiding excessive salt, eating carbohydrates, use of vitamin D, dodecanoic acid, and lycopene [89]. Nonrestorative sleep was associated with butaneoic acid, lack of calcium, lack of vitamin C, lack of water, excess moisture, and excess cholesterol. Daytime sleepiness was associated with increased moisture, more caffeine/theobromine, less potassium, and less water [89]. These different elements will be handled in more detail below.

Rapidly Absorbing Carbohydrates, Large Meals, and Tryptophan

The hedonic regulation of food intake is powerful and it may be a key element in development of obesity. In normal weight subjects, the hedonic eating behavior is in balance with the homeostatic control of energy intake [90]. In obesity, the hedonic drive for eating may outweigh the homeostatic control of eating, leading to excess of energy intake. In a French study, rats were allowed to choose between water sweetened with saccharin and intravenous cocaine. Almost all (94 %) rats preferred saccharin water instead of cocaine. Rats preferred also natural sugar (sucrose) over cocaine. In order to abolish this finding, high doses of cocaine, causing intoxication, were needed [91]. Sugar and sweet food can induce reward and craving in humans that are at least comparable in magnitude to those induced by addictive drugs [92].

Clinicians treating narcoleptics know that rapidly absorbing carbohydrates induce sleepiness in the afternoon among their patients. What about the effect of carbohydrates in normal subjects? Most studies in which different foods have been compared with each other show that carbohydrates at lunch induce afternoon sleepiness more than proteins. In a study by Spring et al. [93], normal adults consumed either a high-protein or high-carbohydrate meal. Two hours later, their mood and performance were tested. Women, but not men, reported greater sleepiness after a carbohydrate as opposed to a protein meal. Men, but not women, reported greater calmness after a carbohydrate as opposed to a protein meal. Age of subjects had an effect on the response to meals. When meals were eaten for breakfast, persons older than 40 years felt more tense and less calm after a protein-rich than after a carbohydrate-rich meal. Older subjects did not like a morning protein meal as much as a carbohydrate meal, but objective performance was impaired more after a carbohydrate-rich lunch than after a protein-rich lunch. Sustained selective attention, as measured by dichotic shadowing, was impaired in the afternoon after consuming a high-carbohydrate lunch. In sum, these findings suggest negative effects on concentration after a high-carbohydrate, low-protein lunch [93].

In another study, fatiguing effects of lunch after carbohydrate-rich meals were compared to other types of meals [94]. Observed behavioral changes were correlated with changes in plasma glucose, insulin, and amino acids. Only the carbohydrate meal significantly increased fatigue, which could not be attributed to hypoglycemia because plasma glucose remained elevated. The afternoon fatigue began when the carbohydrate meal elevated plasma tryptophan but ended even though the ratio remained elevated. According to Christensen, fatigue after a high-carbohydrate lunch cannot be explained only by reactive hypoglycemia or sweet taste and could partially be explained by the hypothesis that fatigue parallels an elevation of tryptophan and effects endogenous opioids [95]. Associations among a carbohydrate-rich meal, an increase of tryptophan, and feelings of fatigue have also been confirmed in other studies [96].

Rapid increase in insulin and its effect on tryptophan are related to symptoms of fatigue. In particular, after rapidly absorbing carbohydrates as well as after a glucose intolerance test, insulin is rapidly increased. This rapid increase in insulin is associated with an increase in the ratio of tryptophan to large neutral amino acids (LNAAs) causing abnormal neuroglycopenic symptoms. In practice, this may be seen as “sugar drunkenness” [96]. These findings have been confirmed by Cunliffe et al., who found that subjects consuming a pure carbohydrate meal were more tired with feelings of fatigue and had had slower reaction times. A general feeling of mental or central fatigue was noticed after a pure isocaloric fat meal. The ratio of tryptophan to LNAAs was decreased after a pure fat or mixed meal and rose after a pure carbohydrate meal. The authors concluded that central and subjective fatigue after carbohydrate intake may be related to an increase in tryptophan relative to other competitive amino acids. Pure fat intake may also have a negative influence on CNS arousal [97].

Wheat, Starch, Amylopectins, and Postprandial Sleepiness

Celiac disease is well-defined autoimmune disorder. It occurs in genetically predisposed people. In celiac disease, ingestion of gluten leads to damage of the small intestine. Gluten is a protein that is found in rye, barley, wheat, and foods made with these grains. Patients with celiac disease suffer from abdominal bloating, pain, gas, diarrhea, pale stools, and weight loss. They may have skin rash due to dermatitis herpetiformis, iron deficiency anemia, and tingling sensations in the legs. They may mimic symptoms of restless legs. The prevalence of celiac disease is about one

percent. Celiac disease may be a cause of a sleep disorder, but gluten may not be the most important factor in grains, that may cause sleepiness.

Wheat, other grains, potatoes, and other sources of starch may cause sleepiness also directly by increasing blood glucose and insulin levels. It is to be noted that wheat bread may cause a faster and higher increase in blood sugar than ingestion of sugar. The amylose-amylopectin ratio is one of the factors explaining glucose- and insulin-response differences. Foods with higher amylose content are accompanied by a lowered metabolic response and lower increase in glucose and insulin than foods with higher amylopectin content. Of the starchy foods, legumes with high fiber content elicit a much lower postprandial response of glucose and insulin, and hence less postprandial sleepiness than food rich in starch [98, 99]. Legumes are also good sources of high-quality proteins. The amount of amylose and amylopectins depends on many factors. For example, macaroni has a lower amylose-amylopectin ratio than spaghetti, and it increases blood glucose more than spaghetti.

The amount of food eaten is also related to feelings of sleepiness. Solid foods cause more sleepiness than liquid foods. Valuable studies have also shown that the larger the meal, the sleepier the person is afterward [100]. It may be that filling the stomach with plenty of food might have a stronger effect than different constituents of food per se [101].

Eating in the Evening and Night Sleep

Sleepiness and fatigue after lunch are usually unwanted. For this reason, people wanting to avoid postlunch sleepiness should avoid rapidly absorbing carbohydrates and large meals. Needless to say, alcohol during lunch increases sleepiness. On the contrary, in the evening, the sleep-facilitating effects of carbohydrates may be beneficial. Recently, Afaghi et al. [102] explored the effect of the glycemic index (GI) on sleep in 12 healthy men. Their subjects were administered standard, isocaloric (3212 kJ; 8 % of energy as protein, 1.6 % of energy as fat, and 90.4 % of energy as carbohydrate) meals of either Mahatma (GI = 50 [low]) or Jasmine (GI = 109 [high]) rice 4 h before their usual bedtime. On another occasion, the same high-GI meal was given 1 h before bedtime. Sleep onset latency shortened significantly after a high-GI meal compared with a low-GI meal. The high-GI meal given 4 h before bedtime had better action on sleep latency than the same meal given just 1 h before bedtime (9.0 ± 6.2 vs. 14.6 ± 9.9 min; $p = 0.01$) [102]. This finding confirms earlier studies showing that a (light) carbohydrate-rich diet during dinner may be beneficial for sleep.

Adding tryptophan may enhance the action of carbohydrates. A controlled double-blind study lasting five weeks evaluated whether eating of cereals enriched with nutrients facilitating sleep could help to improve infants with sleep disorders. A "sleep facilitating cereal" product containing 225 mg tryptophan, 5.3 mg adenosine-5′-P, and 6.3 mg uridine-5′-P per 100 g of product. As compared to similarly tasting cereals without added nutrients, the administration of enriched cereals led to an improvement in sleep [103]. In another study, the same group found that cereals enriched with tryptophan (60 mg tryptophan in 30 g cereals per dose) eaten at both breakfast and dinner increased actigraphically measured sleep efficiency, actual sleep time, immobile time, and decreased total nocturnal activity, sleep fragmentation index, and sleep latency [104].

According to common knowledge, heavy meals late in the evening disturb night sleep. Driver and collaborators studied effects of different types of evening meals and of a 10-h fast (no evening meal) on body temperature and night sleep. Seven healthy people participated. Meals of varying energy content and episodes of sleep influence body temperature. Lower rectal temperatures were measured during the fast than following the meals. Higher energy content of the evening meal associated with higher body temperatures at night. No differences were observed in the subjective or polysomnographic sleep measures [105]. A transient heavy evening meal, 2–3 h before going to bed, or a 10-h fast may not alter significantly sleep of previous good sleepers. However, the higher body temperature after heavy meal reflects higher autonomic activity, and there is evidence for example in insomniacs and in patients with narcolepsy that higher core body temperatures (and lower peripheral temperatures) are associated with less sleepiness and lower quality of night sleep [106, 107].

Contents of meals may also be related to the circadian type. In a Japanese study, evening-type persons, as compared to morning-type persons, had significantly lower energy-adjusted intake of protein, calcium, magnesium, zinc, vitamins (D, riboflavin, B6), and vegetables and with a higher intake of noodles [108]. In other words, evening chronotype may be associated with inadequate dietary habits such as low vitamin and mineral intake.

Postlunch Fatigue

A siesta after lunch is still common in some parts of the world, although it has disappeared from most developed countries. Also in developed countries, a feeling of tiredness in the afternoon is common. According to Bell [109], 71 % of narcoleptics and 9 % of healthy adults suffer often or always from postprandial sleepiness. The vigilance level has a bimodal pattern: Alertness is at its lowest level after midnight, and there is another dip in alertness occurring during the afternoon independent of whether one has been

eating or not. The effects of different types of meals have been studied. There is evidence that heavy meals cause more fatigue than light meals. There is also agreement that alcohol during lunch causes sleepiness in the afternoon. In clinical settings, there is some evidence that rapidly absorbing carbohydrates in particular cause more sleepiness and fatigue after lunch than slowly absorbing carbohydrates and proteins. Eating carbohydrates at breakfast, on the contrary, may not increase daytime sleepiness. In another study, subjects also tended to feel more sleepy and fatigued 2–3 h after a high-fat, low-carbohydrate breakfast than after low-fat, high-carbohydrate breakfast [110].

Obesity and Sleep

Obesity is an epidemic, especially in Western countries. It is believed that the epidemic is a consequence of eating too much food with energetic value combined with a decrease in physical activity. This is probably true, but it does not explain everything. In the medical world, research on cardiovascular diseases has been one of the primary foci. High-cholesterol levels are associated with an increase in cardiovascular morbidity. Therefore, the food industry has been developing foods with no cholesterol, and people are advised to avoid butter and fats. However, the food industry has also been developing more and more foods and soft drinks with high sugar content (e.g., Coca-Cola, Pepsi-Cola). Despite eating less, fat people become more and more obese, suggesting that other factors must be involved.

From a physiologic standpoint, body fat is deposited in excess amounts when caloric intake exceeds caloric expenditure [111]. Most of our calories are expended in a resting state. We know that obese patients with sleep apnea have difficulty losing weight. It has been questioned whether obese people have a lower resting metabolism than lean people. Are obese people like diesel motors? Using whole-body direct calorimetry and other methods that enable measurement of basic metabolism, researchers have shown that obese subjects often have lower resting metabolic rates that persist after weight reduction, that people with a high genetic propensity for obesity often show this decreased resting metabolism before they become obese, and that these people are more likely to regain their weight after weight reduction. The mechanism of the low resting metabolic rate in many obese people is not known [111]. Eating less food with high energy content is needed to lose weight. Also, avoiding rapidly absorbing carbohydrates should be an element in weight reduction. Avoiding fats and increasing exercise do not help if an obese subject continues to drink sweet soft drinks and eat a lot of potatoes, white bread, or sweets. It is important to note that, with excess caloric intake, carbohydrates convert to fat. Citrate from the citric acid cycle diverts from mitochondria into cytosol for fatty acid synthesis. After a meal rich in carbohydrates, insulin release from the pancreas causes a 30-fold increase in glucose transport into adipocytes.

Several prospective epidemiological studies have shown that there is a relationship between sleep length, sleep quality, and obesity. Both short sleep (too short sleep relative to individual need of sleep) and poor sleep quality increase the risk of developing obesity, and consecutively type 2 diabetes and metabolic syndrome [112–117]. In experimental studies, sustained sleep fragmentation in mice affects brain temperature, food intake, and glucose tolerance [118]. Different neuronal networks and transmitters are involved as discussed earlier in this chapter.

Dietary Patterns and Sleep

Effect of Fasting on Sleep

Effects of fasting on sleep length differ depending on the study. Fasting was associated with shorter sleep in some human studies and with increased sleep in others. Results of studies on the effect of fasting on sleep architecture are somewhat divergent. Fasting, resulting in decreased energy intake, seems to be associated with an increase in slow-wave sleep, and a decrease in rapid eye movement (REM) sleep and sleep stages 1 and 2. In the earlier studies, this was explained by the restorative function of slow-wave sleep [119, 120]. In the 1980s, it was thought that sleep was mainly for the brain and had little restorative value [121]. It is now known that sleep not only is important for the brain, but also has a restorative function [13, 122]. The relationship is complex. In experimental studies, caloric restriction protects the brain against aging and disease, while restriction of sleep has an opposite effect. Markers of oxidative stress were lower in cultured neuronal cells treated with caloric restriction serum compared with those treated with ad libitum serum [123].

Muslims fast during the ninth month (Ramadan) of the Islamic Hijra calendar. Hijra is a lunar calendar, and Ramadan occurs at different times in the seasonal year over a 33-year cycle. Fasting during Ramadan occurs daily from sunrise to sunset. The effects of the intermittent type of fasting during Ramadan differ from those of continuous fasting. In one study, the main finding was that during Ramadan, evening sleep latency was increased and nocturnal sleep architecture was modified. Slow-wave sleep and REM sleep decreased during Ramadan. The effects of Ramadan fasting on nocturnal sleep have been explained by changes in drinking and meal schedule, rather than an altered energy intake, which may be preserved [124]. In another study, Ramadan diurnal fasting induced an increase in subjective

and objective daytime sleepiness, measured by MSLT, associated with changes in diurnal rectal temperature [125]. Later bedtime during Ramadan shortens consistently night sleep by about an hour or more, which explains probably a part of the increased daytime sleepiness [126, 127].

Ketogenic Diet and Sleep

The ketogenic diet has been used for a long time in the treatment of severe epilepsy. It is efficient but it is usually only a temporary solution. Some efforts have been made to develop other diets that are based mainly on lowering amounts of carbohydrates in order to lower blood sugar levels without inducing marked metabolic ketosis. Early results have been promising. Again, these diets are based on Magistretti's theories and on theories about the role of astrocytes [7, 9, 85, 128]. Hypocretin and MCH cells are sensing glucose levels. Lower blood glucose is associated also with higher hypocretin and lower MCH levels increasing alertness [23]. It is possible that in fact brain cells, especially glial cells, perform better when glucose levels are lower. This is followed also by better synaptic function and less paroxysmal activity.

According to theories on brain energetics, the ketogenic diet could help people to sleep better and have better alertness during the daytime. Hallbook et al. [129] have published first results supporting this idea. They examined 18 children with treatment-resistant epilepsy. All children had polysomnography studies before starting a ketogenic diet and after three months on the diet. Eleven children were evaluated after staying on the diet for one year. Seizures were controlled with the diet, and it was associated with decreased total sleep and total night sleep. There was no change in amount of slow-wave sleep, and REM sleep was increased. Stage 2 sleep was decreased ($P = 0.004$), and sleep stage 1 was unchanged. There was a significant correlation between increased REM sleep and improvement in quality of life.

Brown has formed an interesting hypothesis to explain the positive mental effects of a low-carbohydrate diet [130]. Better vigilance, feelings of well-being, and feelings of mild euphoria have been attributed to increased production of ketone bodies, which can replace glucose as an energy source for the brain, as Magistretti has postulated [7, 9]. Brown noted that one of these ketone bodies, β-hydroxybutyrate (BHB), is an isomer of γ-hydroxybutyrate, which is used as treatment for alcohol and opiate dependence and also for narcolepsy with cataplexy. Brown hypothesized that the positive mental effects with fasting and a low-carbohydrate diet may be due to shared actions of BHB and GHB on the brain. BHB, like GHB, is a weak partial agonist for $GABA_B$ receptors [130].

Ketogenic diet has many adverse effects, and it may not even be necessary to achieve clinical results. In a study by Johnson et al., ketogenic and nonketogenic low-carbohydrate diets were equally effective in reducing body weight and insulin resistance, but the ketogenic diet was associated with significantly more adverse effects [131].

Power Naps

Short naps preceded by intake of caffeine or "power naps" have shown to be an efficient way of increasing alertness in the workplace or when driving a car. First, 100–150 mg of caffeine is taken in the form of coffee or an energy drink. This is followed by a 15- to 30-min-long nap. During short naps, caffeine is absorbed and postnap drowsiness (sleep drunkenness) may be avoided. Alertness is increased for 3–6 h [132–134]. Some physicians advise elderly people to avoid daytime naps. There is, however, no good evidence showing that a nap in the afternoon would be harmful for night sleep, providing that the nap has been short enough (<1 h) [135]. According to some recent information, frequent long daily naps may be related to underlying medical pathology [136], but according to Naska et al. [137] naps of any duration may be healthy. Clearly, more studies are needed on the health effects of daily naps.

Alcohol and Sleep

Excessive use of alcohol is associated with complaints of insomnia. Alcohol shortens sleep latency, but it may also disturb sleep later at night. Two or more drinks of whiskey or other liquors increase snoring and are a strong risk factor for obstructive sleep apnea [138–141]. There is also evidence that heavy drinking of alcohol is associated with smoking, obesity, poor physical condition, ill health behavior, and insomnia. One or two glasses of alcohol may help a person to fall asleep, but more than two glasses worsen the quality and architecture of night sleep [142–144], in addition to causing snoring and sleep apnea. Larger amounts of alcohol (0.5–1 g/kg body weight) diminish REM sleep during the first third of the night, but there is often a rebound of REM sleep later at night. This correlates with awakenings early in the morning. If alcohol is used in larger quantities, REM sleep is diminished during the whole night. The blood alcohol level at the time of going to sleep correlates with a decrease in REM sleep [145]. According to many studies, alcohol decreases slow-wave sleep, but according to other studies, slow-wave sleep, especially during the first third of the night, may increase. In any case, the normal sleep architecture is easily disturbed with larger

doses of alcohol. Alcoholics sleep poorly. Even worse, the sleep of alcoholics may be disturbed for many years after drinking has stopped [146]. This must be taken into account when treating insomniacs with a history of alcoholism since they may need psychological support for many years.

Could alcohol be used as an alternative to hypnotics? There is evidence that one glass of wine or spirits in the evening may help in falling asleep both among working adults and elderly people. There have been some studies in residential facilities for the elderly, where use of hypnotics has been compared with use of wine or sherry. In a randomized study, one glass of alcohol was better than one tablet of a hypnotic [147]. Use of hypnotics is a problem in geriatric institutions, because use of hypnotics among elderly people is associated with increased mortality. There is very little evidence of benefits for long-term every-night use of hypnotics, but many studies have shown risks of routine hypnotic use [148–153]. Alternatives to hypnotics are needed, especially for elderly people. One of them is a social hour. In some residential facilities for the elderly, one glass of wine or sherry, served in a day room/living room, is offered during a social hour in the evening. It is possible that most of the beneficial effects are explained by behavioral factors [147, 154]. The elderly people who are given a glass of sherry do not usually drink it immediately, but stay in the day room/living room for some time. This results in a delay in going to bed, which is associated with fewer awakenings during early morning hours after midnight.

Essential Fatty Acids and Sleep

The polyunsaturated fatty acids (PUFAs) such as linoleic acid, α-linolenic acid (α-LA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are essential fatty acids in many mammals, including humans (see *Nutrition and Development of the Central Nervous System* later). α-LA is a precursor of DHA, and EPA is converted to DHA in the body. A sufficient amount of PUFAs from food is necessary for health and well-being. Both DHA and EPA are omega-3 acids, and both may be obtained by eating fish oils. The American Heart Association has recommended that the amount of long-chain omega-3 fatty acids should exceed 650 mg/day. In Britain, more than 1000 mg/day has been recommended by the British Heart Association [155]. Fatty fish is the best source of omega-3 fatty acids. One hundred grams of salmon contains about 1000 mg of omega-3 fatty acids and 100 g of herring contains about 2000 mg. White fish meat contains much less of these essential fatty acids than fish with fatty meat. There is increasing evidence that a reduced amount of ingested omega-3 fatty acids is associated with fatigue, depression, and problems of attention. Omega-3 fatty acids have been tested in the treatment of subjects with attention deficit disorder and in subjects with depression, female subjects with borderline personality disorder, fatigue in multiple sclerosis, memory disturbances, dementia, and some other neuropsychiatric diseases. Some randomized controlled studies have shown that omega-3 acids help, but there are also conflicting results and more well-conducted randomized studies are needed [155–169].

There is some evidence showing that essential fatty acids may modulate sleep. Fagioli from Italy studied eight children who were fed by total parenteral nutrition without essential lipids and seven other children who received a daily supplement of essential lipids in their parenteral nutrition. Slow-wave sleep was significantly decreased in the group of children who did not receive fatty acids as compared to those who did [170]. Omega-3 fatty acids are also necessary for early brain development and infant sleep. Cheruku et al. [171] measured plasma DHA from 17 women at parturition. They found a significant positive correlation with concentration of DHA and quality of the newborn infants' sleeping patterns as measured by a sleep mattress method. This is thought to relate to more mature brains of the newborn infants. Lack of omega-3 fatty acids may be related to sleep disturbance in depressives [172]. Palmitoleic and oleic acid are precursors of a sleep-inducing oleamide [173, 174]. Linoleic and eicosadienoic acid could be helpful for maintaining sleep also because they are precursors of the sleep mediator prostaglandin D2 [175].

Narcolepsy and Meals

In the 1960s, Roberts and his collaborators studied 326 narcoleptic patients. They reported that, of 40 African-Americans in their narcolepsy population, 70 % had recurrent hypoglycemia without diabetes mellitus [176]. In routine clinical practice, many patients with narcolepsy often complain of excessive sleepiness in the afternoon, particularly if they have eaten a lunch rich in carbohydrates and especially if they have eaten a sweet dessert. Avoiding a heavy, carbohydrate-rich lunch and desserts helps them to be more alert in the daytime. Based on this experience, patients with narcolepsy should be routinely advised to avoid rapidly absorbing carbohydrates, especially at lunchtime. On the contrary, as noted already above, a light evening meal with carbohydrates may ameliorate night sleep.

In spite of clinical experience, there is very little scientific knowledge about the effects of different types of meals on symptoms of narcolepsy. Bruck et al. [177] studied 12 narcoleptics and 12 matched controls in a double-blind crossover study. They measured behavior after a light lunch supplemented with a drink of either 50 g of glucose or placebo (in the form of an artificially sweetened drink). In the narcoleptic subjects, glucose was associated with

decreased wake duration, reduced latency to sleep onset, and more spontaneous and induced sleep stage changes during a Wilkinson auditory vigilance task. The subjects also had a sleep EEG during a 45-minute nap. In a polygraphic score of sleepiness (PSS) [178], more slow-wave sleep stages were observed after glucose than after placebo. Eleven of the 12 narcoleptics had significantly more REM sleep after glucose as compared to the placebo drink [177]. The authors discussed their results in relation to serotonin synthesis and an increase in insulin after glucose.

Sodium oxybate, a pharmacologic compound related to GHB, is considered today as one of the best treatments for narcolepsy with cataplexy. Sodium oxybate also ameliorates nocturnal sleep. The mechanisms of action are not fully understood. Its effect on the GABA system is considered to be important, but it is tempting to think that some of the effects may be similar to the effects of a ketogenic diet. Brown noted that BHB, a ketone, is an isomer of GHB; both are also partial agonists of $GABA_B$ receptors [130].

In a study by Husain et al. [179], the effects of a low-carbohydrate, ketogenic diet on sleepiness and other narcolepsy symptoms were studied among nine patients with narcolepsy. The patients with narcolepsy were asked to adhere to the Atkins diet plan, and their symptoms were assessed using the Narcolepsy Symptom Status Questionnaire (NSSQ). The NSSQ-Total score decreased by 18 % from 161.9 to 133.5 ($P = 0.0019$) over 8 weeks. Subjectively, patients with narcolepsy experienced modest improvements in daytime sleepiness when they were on a low-carbohydrate, ketogenic diet [179].

Obesity among narcoleptics is common [180–183]. One could assume that lack of hypocretin in narcoleptics could be associated with increased feeding behavior, overeating, and obesity. Arnulf and her collaborators studied 13 narcoleptics and 9 healthy age/sex/ethnicity-matched controls [184]. Their patients with narcolepsy (both typical narcolepsy-cataplexy syndrome and narcolepsy without cataplexy) tended to be overweight. There was no significant difference in the basic metabolic balance. Overweight narcoleptics had lower resting energy expenditure and food intake than patients with normal weight and controls, indicating calorie restriction. Plasma glucose, cortisol, thyroxine, thyroid-stimulating hormone, prolactin, and sex hormone levels did not differ between groups. Narcoleptic patients had more problems in eating behavior, and they also had more signs of bulimia compared to controls. In sum, in this study, low hypocretin values were not associated with obesity per se, but the narcoleptic subjects tended to eat more than needed, causing them to be overweight. The overweight narcoleptics tended to have lower energy consumption at rest, as do many other overweight people compared to people of normal weight [26, 111]. This makes weight loss more difficult.

Narcolepsy without cataplexy, idiopathic hypersomnia, and attention deficit hyperactivity disorder (ADHD) has some similarities in their symptomatology. According to a theory by Russell and Killian, ADHD may be caused by disordered brain energetics with insufficient astroglial production of lactate [185, 186]. Modafinil and methylphenidate are used in treatment of narcolepsy and CNS hypersomnias. Their action in ADHD may be explained also by stimulation of the glial cell surface adrenoceptors, and hence by stimulated production of lactate in astrocytes, leading to better energy balance in the brain [186].

Dietary Minerals and Sleep

Iron

Iron has an important role in many enzymatic processes. Sufficient iron in the CNS is necessary for normal functioning of dopamine receptors. Tyrosine hydroxylase regulates dopamine synthesis. Iron and tetrahydrobiopterin are cofactors of tyrosine hydroxylase. Iron is also linked to functions of GABA, serotonin, and opioid peptides. In experimental cell cultures, dopaminergic cells of the substantia nigra can be destroyed by chelation of iron by desferoxamine. Adding opioids in these cell cultures is protective. Iron also has a catalytic effect in oxidative mechanisms of the CNS. Measuring serum ferritin and soluble transferring receptor from a venous blood sample allows estimation of tissue iron levels. In RLS, S-ferritin is often low, in which case giving iron per os, or intravenously in more severe cases, should be part of the treatment.

In patients with disturbing symptoms of RLS (Willis–Ekbom disease), 50–70 μg/L is commonly used as the lower limit at which one should consider giving iron supplementation, even if hemoglobin is normal. Usually the soluble transferrin receptor values are also low. Iron should be given as Fe^{2+} (bivalent iron) together with vitamin C to increase absorption of iron from the gut. If ferritin levels do not rise and the symptoms are bothersome, intravenous iron might be considered. Nondextran formulations such as Ferinject® or Venofer® are shown to be safer than older dextrans. Several studies have already shown the benefits of intravenous iron [187, 188], beginning with the early experiences from Sweden in the 1950s [189].

Yehuda and Yehuda [190] noted that in young children, sleep disturbances, fatigue, and possible learning disturbances may be related to iron deficiency early in life. A relationship between sleep disturbance, restless legs, and iron deficiency in children with autism spectrum disorder has been reported [191].

Kuhn and Brodan studied the effects of 5 days of sleep deprivation on the circadian rhythm of serum iron in a group

of six healthy male volunteers. Sleep deprivation markedly reduced the mean level of iron, diminished the absolute and relative amplitude of oscillations, disturbed the shape of the daily course of serum iron, and gradually decreased the computative acrophase (i.e., shortened the period of rhythm). Forty-eight hours of recovery resulted in only a partial normalization of all the observed changes [192].

Symptoms of ADHD are often reported by patients with narcolepsy, and some of the symptoms of narcolepsy resemble those of ADHD. RLS is significantly associated with ADHD and both conditions have been associated also with low levels of ferritin [191, 193, 194]. RLS is frequent also in narcolepsy. About 15 % or more of patients with narcolepsy seem to have RLS [195, 196]. Accumulation of iron in the brain, mostly in the form of ferritin, is associated with an elevated risk of developing neurodegenerative diseases such as PD [197]. High ferritin levels have been associated also with some autoimmune diseases, such as multiple sclerosis [197, 198]. In patients with RLS, serum ferritin levels are often low, but in patients with narcolepsy and concomitant RLS, serum ferritin levels were higher than in narcolepsy patients without RLS [195].

Copper, Zinc, and Other Minerals

Copper acts as a cofactor in many enzymatic processes, including those mediated by ceruloplasmin, monoamine oxidases, cytochrome oxidase, and superoxide dismutase. The largest part of dietary copper (96 %) is bonded into ceruloplasmin and ferroxidase, which are needed in many phases of iron metabolism. Lack of copper can manifest as neutropenia, microcytic anemia, growth disturbances, or slowing of erythropoiesis. Copper deficiency also may present as myeloneuropathy resembling vitamin B_{12} deficiency. Menkes' syndrome is an example of a genetic disturbance of copper metabolism causing deficiency of copper. Wilson's disease is an autosomal recessive disease that causes accumulation of copper in the liver and brain. It is practically impossible to take in too much copper from a normal diet. Intake of large amounts of vitamin C, zinc, iron, and cysteine worsen the absorption of copper from the gut. Lack of copper may also occur after poor diet, excessive consumption of zinc tablets, and bariatric surgery [199].

Zinc is also required in many enzymatic processes (carbonic anhydrase, alkaline phosphatases, many different dehydrogenases, etc.). In the CNS, zinc is abundant in the so-called zinc-containing synapses of glutamatergic neurons. Such neurons are located mainly in the prefrontal lobe; frontal dysfunction may result from lack of zinc. Conversely, bivalent zinc may cause excitotoxic damage. Other minerals (e.g., magnesium, manganese) are also important for proper functioning of the CNS.

Nutrition and Development of the Central Nervous System

Malnutrition affects development of the brain. One of the pioneers in this field has been Myron Winick, a pediatrician specializing in embryology and growth development [200]. In the 1960s, he spent several months in Chile, where he noticed at the time of autopsy that malnourished children had a reduced number of brain cells. Later his group published similar results from Jamaica. Studies among Korean orphans less than 1 year old with adequate nutrition or malnourishment have shown that malnourishment is associated with poor functional outcome at the age of 12 years. In developed countries, the most important nutritional factor for early disturbance of brain development is alcohol (i.e., fetal alcohol syndrome). Children with fetal alcohol syndrome have low birth weight, retarded growth, dysmorphic facial features, and learning deficits. In developing countries, many other types of significant intrauterine and early postnatal malnutrition may affect brain development. In these countries, malnutrition is usually associated with poor living conditions, poor hygiene, and poor socioeconomic status.

Nutrition plays an important role in the development of the human CNS. Prenatal malnutrition affects the developing brain in many ways. Adequate intake of proteins, minerals, and vitamins is necessary for proper brain development, including brain growth, neurogenesis, cell migration, and cell differentiation. Are some nutrients more important than others? Folate deficiency is associated with disturbances of neural tube development during early gestation. There is evidence that malnutrition may result in various types of minimal brain dysfunction, disorders of attention, and learning disabilities [200]. There is also evidence that malnutrition during pregnancy is associated with an increased incidence of some behavioral and psychiatric problems, including mental retardation and schizophrenia. Studies have shown that malnutrition may cause diffuse lesions and functional disturbances in connections between neurons and glia, axonal and dendritic circuits, and the development of various neurotransmitter systems [201]. Fortunately, the human brain is plastic, and the effects of malnutrition may be at least partly reversed by proper nutrition later in childhood [200]. In addition, genetic effects, living environment, possible infections, and many other factors are important. Pascual and collaborators have published their results on neuroglycopenia, a syndrome caused by insufficient glucose availability during brain development in the early years of life [202]. The cause of neuroglycopenia may be nutritional energy deficiency or a genetic mutation of the cerebral glucose transporter type 1 (*GLUT1*). In the latter case, children with neuroglycopenia may suffer from a combination of epilepsy, motor dysfunction, and neuropsychological abnormalities.

During gestation and early postnatal life, the PUFAs linoleic acid, α-LA, EPA, and DHA are necessary for proper development and functioning of cell membranes. DHA is present in high concentrations in retinal and cerebral cortical brain lipids. It is particularly necessary for development of the brain and retina and is normally supplied via the placenta and milk. By which mechanism do omega-3 fatty acids act in the CNS? Neuronal cell membranes contain phospholipids, and dietary omega-3 fatty acids are needed for proper constitution and functioning of these membranes. There is evidence that a sufficient amount of dietary omega-3 relative to omega-6 fatty acids is needed for proper CNS function. Too much omega-6 relative to omega-3 fatty acids may be harmful. Omega-6 fatty acids are metabolized to prostaglandins with higher inflammatory potential compared with those generated from omega-3 fatty acids. Sufficient tryptophan and tyrosine intake are needed for production of the serotonin and catecholamines. The omega-3/omega-6 ratio is also linked to proper functioning of serotoninergic and catecholaminergic neurotransmission. Several studies have shown that the ideal ratio of omega-3/omega-6 fatty acids is about 1:4. In many countries, this ratio is close to 1:30, which means that people have much more omega-6 acids relative to the important omega-3 acids. The ratio of membrane omega-3 to omega-6 PUFAs can be modulated by nutrition. This is also probably true for proper sleep–wake regulation, but more studies are needed to prove this. These results do not directly prove that malnutrition during early childhood causes problems in the development of the sleep–wake cycle. It is, however, very possible.

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Sleep Duration, Morbidity, and Mortality

31

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Introduction

Over a span exceeding 50 years, more than 50 epidemiologic studies have demonstrated a U-shaped association of sleep duration with mortality, with the lowest mortality associated with approximately 7 h of self-reported sleep [1–4]. Figure 31.1 illustrates data from the Cancer Prevention Study I, perhaps the first study to clearly demonstrate the U-shaped mortality association with sleep duration [5, 6]. Similar U-shaped epidemiological associations have been found between sleep duration and multiple morbidities, including cardiovascular disease [7, 8], stroke [8], hypertension [9], diabetes [10], depression [11], metabolic syndrome [12], dyslipidemia [13], and inflammation [14].

The pressing questions today are whether these associations are causal and whether they are remediable through sleep interventions. If short or long sleep are truly causal factors in mortality and morbidity, then modest changes in time in bed (TIB) or total sleep time (TST) might have significant benefits for health and possibly for survival.

This review will begin by discussing how epidemiologic data provide evidence of causality. Then, we will briefly review epidemiologic studies linking sleep duration with mortality and morbidity. We will also briefly discuss experimental sleep restriction studies and implications for health. Since the epidemiologic evidence linking mortality with long sleep is stronger and more consistent than that associated with short sleep [15], yet long sleep is not addressed as much in the literature, we will focus more on long sleep. We will discuss possible mechanisms mediating risks associated with long sleep. Finally, we will consider future research which could begin to resolve the causal elements of sleep duration in morbidity and mortality.

Epidemiologic Principles and Designs

Epidemiologic research involves studies of associations of risk factors with mortality or morbidity, for example, the associations of short or long sleep with mortality and disease. Epidemiologic data cannot entirely prove a causal association between risk factors and mortality or disease. However, various designs provide stronger evidence of a possible causal association. Moreover, in some literatures, such as that linking smoking with mortality, associations are so strong and consistent that assumptions of causality are virtually beyond dispute.

Cross-Sectional Studies

Cross-sectional studies measure risk factors and the presence or absence of disease simultaneously. For example, many cross-sectional studies have shown a higher prevalence of various diseases among short and long sleepers compared with average-duration sleepers [15]. An advantage of cross-sectional studies is that they can be performed relatively rapidly and inexpensively.

Potentially confounding factors (e.g., age, demographics, diet, medications, exercise, other diseases) which might explain the association of interest are typically statistically controlled in the analyses. However, in cross-sectional

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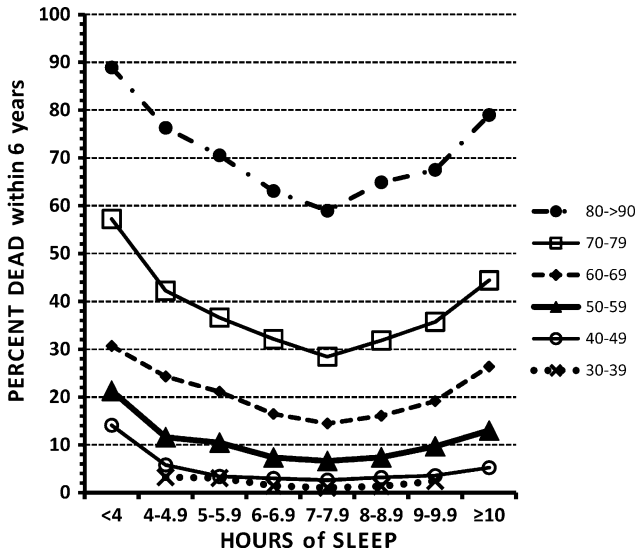

Fig. 31.1 Percent mortality (within 6 years) versus hours of sleep for different age groups, showing U-shaped distributions in every age group. Data were for over 400,000 participants in the Cancer Prevention Study 1 (Redrawn and adapted from Fig. 6 of Kripke et al. [6])

studies, the adequacy of control of confounders is often questionable. Even when dozens of factors are controlled, doubts can remain about whether the associations between risk factors and disease might still be explained by other factors which were not assessed or by complex interactions between potentially confounding factors, which are rarely assessed.

There are also limitations to the measurement of confounders. For example, questions pertaining to health could be limited to self-reports, and information about health-related behaviors such as diet and physical activity could be limited to brief questions for which validity has not been adequately established.

Another limitation of cross-sectional studies is an inability to show a temporal sequence between the risk factor and disease. For example, cross-sectional studies showing associations of depression with short sleep and long sleep cannot delineate whether a deviant sleep duration preceded depression or vice versa. Thus, cross-sectional studies do not provide strong evidence of causality.

Case–Control Studies

In case–control studies, a sample of subjects is selected for developing a disease or for dying, and a control sample, matched on age, sex, and other factors presumed to be relevant, is also selected. Then, the degree of exposure to potential risks factors and the odds of having the risk factor are compared retrospectively between the case sample and the control sample. Risk factors are determined from medical records and/or interviews of the participants or perhaps family members. For example, a recent case–control study identified infants who had died of sleep-related deaths (e.g., sudden infant death syndrome) and a control group and compared potential socioeconomic risk factors between the groups [16].

Case–control studies are most suitable for diseases which are rare and for diseases for which there is a long time period between exposure to a risk factor and onset of death or disease. One disadvantage of case–control studies is the difficulty in finding a control group which is adequately matched to the case group in factors which could influence the association. Another limitation is that interviews are susceptible to recall biases in case subjects or family members. For example, if poor sleep were assessed as a risk factor, case subjects might be biased to report that they had experienced poor sleep prior to the disease, a serious problem in studies of sleep duration.

Prospective Cohort Studies

Prospective cohort studies involve the selection of a group at random from a defined population, or the selection of groups exposed or not exposed to a risk factor, e.g., long or short sleep, versus 7 h sleepers. At baseline, the groups are carefully assessed on multiple potential risk factors for disease and mortality. The cohort and control group are then followed over time, and the incidence of disease or mortality is assessed.

An advantage of the prospective design is that risk factors can be carefully assessed at baseline, which leaves less potential for bias compared with retrospectively assessing risks after disease status is known. Prospective studies also allow for assessments of changes in risk factors over time, and for assessment of disease more accurately as it occurs. Temporal sequences between the risk factor and disease or mortality can also be assessed. Thus, prospective studies are generally regarded as the strongest epidemiologic evidence that a risk factor might cause a disease. However, causality can still not be definitively established in studies for which risk factors are not experimentally manipulated. There could be unrecognized or inadequately controlled confounders which could explain the association of interest, for example, a factor that was not adequately assessed at baseline.

Disadvantages of the prospective approach include its relatively high cost and time required to complete the study. However, a large proportion of studies that report prospective associations of risk with disease have involved retrospective analyses using baseline data that were previous collected, often many years beforehand, e.g., using electronic medical records.

Epidemiologic Evidence Linking Short and Long Sleep with Mortality

Associations of short and long sleep with mortality have been demonstrated in prospective studies involving >1 million participants, statistical control for over 30 potential covariates, and follow-up durations as long as 10–20 years [15]. Moreover, the patterns have been noted for men and women and all adult age strata. As reviewed elsewhere, there have been a large number of studies from all over the world demonstrating morbidity and mortality associated with long and short sleep. Although the possibility of confounding factors in these associations can still not be rejected, statistically, the chances that the associations are random are vanishingly small.

Kurina et al. [17] have provided an excellent critique of the literature. They highlight inconsistencies among studies: Of 55 findings, 30 supported an association of mortality risk with long sleep (including the largest studies), but only 16 supported an association of mortality risk with short sleep (including the two largest studies). Only two smaller studies reported scattered contrary findings. Despite the inconsistencies, in our view, the large consensus of studies encompassing millions of participants provides quite strong evidence that long sleep is associated with elevated mortality risks, and short sleep is less consistently associated with mortality as well. As reported several times previously, the evidence for association of long sleep with increased mortality is considerably stronger than the evidence for association with short sleep, but both are indicated by overwhelming trends among the results.

As noted by Kurina et al., the definitions of reported "long sleep" and "short sleep" durations have varied across studies, but we would think that such inconsistencies would be more likely to produce false negatives than false-positive findings of association. One suspects that many of the inconsistencies of definition arose from the use of samples too small to examine sleep durations in units of 1 h or less. Smaller samples also would have lacked adequate data and power for the extremes of short and long sleep. Smaller samples may require longer follow-ups to record enough deaths for statistical power, and the test–retest reliability of reported sleep durations drops off as the intervals between ascertainments increase. Over intervals as long as 20 years, the reliability of a single ascertainment of sleep duration decreases, so one might expect regression to the mean sleep duration to become increasingly important, tending to cause false-negative results.

Kurina et al. noted that sleep durations estimated from polysomnography or actigraphy are consistently shorter than those reported by questionnaire surveys. Moreover, questionnaires frequently neglect to distinguish between usual sleep durations on work days versus weekends and off-work times and frequently neglected the issues of napping and shift work. Although objective sleep durations are indeed usually shorter than questionnaire reports, the two are very significantly correlated. There is also evidence for a U-shaped associated of mortality with objective actigraphic sleep duration, however, with actigraphic recording, the optimal survival seems associated with 5.0–6.5 h [18], not with the 7.0 h (±0.5 to 1.0 h) frequently described as associated with optimal survival in questionnaire data. Accordingly, in actigraphic studies, we anticipate that both long sleep and short sleep will encompass ranges of duration shorter than the consensus from questionnaire studies, but that will in no way obviate the associations of sleep duration with mortality and morbidity. We do not find it plausible that widespread objective recording will negate the enormous evidence relating sleep duration to mortality and disease. Fortunately, just recently, low-cost wrist actigraphs with cloud-based data storage have become available to millions of customers, who purchase these actigraphs largely to keep track of exercise. As yet, we have seen no validation of sleep estimation algorithms for these popular consumer actigraphs, but surely it is only a matter of time until objective multi-year sleep recording will become available for tens of thousands of research participants, simply by analyses of data already being collected. Because modern polysomnography (especially with the intrusive instrumentation used for clinical apnea assessments) is well known to disturb sleep, and because multi-day and multi-year polysomnographic monitoring of tens of thousands of research participants is currently inconceivable, we do not anticipate that polysomnography will offer a superior objective measurement methodology compared to actigraphy.

In summary, although several wise critiques by Kurina et al. remind us of needed refinements of epidemiologic studies of sleep duration, we regard it as unlikely that better methodologies will negate the associations of sleep duration with mortality and various morbidities. However, it is important to concede that confounding which may not negate observations of association may negate association as definitive evidence of causation.

Arguments Advanced Against the Idea that Long Sleep Is Harmful

In epidemiologic studies, the risk of long sleep has typically been at least as great, and often greater than, the risk of short sleep, and more likely to persist following control for various confounds. Nonetheless, in contrast with the vast literature devoted to studying the risks of short sleep and speculation regarding potential underlying mechanisms, the risks of long sleep have been largely overlooked or dismissed as some type

of artifact. Several lines of arguments against the notion that long sleep is harmful are addressed below.

An "Epidemic" of Insufficient Sleep?

Limited data from selected epidemiologic studies have indicated that sleep duration has declined by about 1 h over the last few decades [19]. Such data, combined with evidence of risks of experimental sleep restriction (see below), have led to speculation—at times reaching hysterical proportions—that there is a modern epidemic of insufficient sleep. In particular, some scientists [20] as well as public relations advocates for sleep-focused businesses have been reluctant to accept evidence that 8 h sleep and beyond are associated with more mortality risk than 7 h. Such advocates of long sleep look back to a mythical time in the past when everybody slept 8 h, when women did not have to awaken to care for infants in the night, men did not have to guard the home, farmers did not have to tend to their livestock and fields, and nobody had to feed the fire. Of course, historical records fail to support these myths [21]. To the contrary, recent comprehensive reviews have indicated that there is no consistent temporal decline in nighttime or 24-h sleep duration, nor is there compelling evidence of increased prevalence of short sleep (<6 h/night) [22–24].

It is often also argued that the common phenomenon of sleeping extra amounts on weekends and holidays represents compensation for cumulative sleep debt during the week [25]. However, surveys suggest that sleeping extra amounts on weekends might be analogous to holiday overindulgence in food [26], and not necessarily indicative of harmful sleep debt. It makes no more sense to argue that people should always sleep to satiety than to argue that they should always eat to satiety. Just as being a bit hungry at times may be good for us, some daytime sleepiness could have had an adaptive role in evolution. In particular, midday napping in hot climates may be adaptive. Remarkably, both contemporary national questionnaire surveys and actigraphic studies indicate that since the year 2000, the U.S. adult population has had a median weekday sleep duration of about 6.0 h, consistent with the optimal actigraphic sleep duration associated with survival [18]. Since life expectancy has been increasing and health improving as sleep durations allegedly decrease, it requires a bold disrespect for evidence to insist that most of the population is sleeping too little.

Association of Long Sleep with Risks Could Be Explained by Other Factors

As discussed above, epidemiologic evidence cannot prove causality because of potential confounding of causes. Multiple psychobiological and sociobehavioral factors have been associated both with long sleep and health problems, including sleep apnea [27], depression [28], low socioeconomic status [29], unemployment [30], race [31], and low physical activity [4]. It is important to note that the same might be said of the risks of short sleep. Although epidemiologic studies have controlled for all of these factors, doubts still remain about how well these factors have been controlled or whether other factors have been overlooked.

Two lines of evidence resist concerns with a reverse direction of causality, i.e., moribund state or illness causing long sleep. First, epidemiologic studies that have excluded mortality data for the first several years to exclude moribund subjects at baseline have observed similar association of long reported sleep with excess mortality [15]. Second, associations of long sleep with risk have been found in prospective studies, including studies in which good health of subjects was apparent at baseline [32]. Indeed, a recent study of healthy children at baseline found a clear increased incidence of lifetime mortality among the long and short sleeping children at baseline [33].

Long Total Sleep Time or Long Time in Bed?

Research suggests that self-reported long sleepers [34], as well as average sleepers [35], tend to overestimate their TST by about 60 min compared with objective data. Thus, reported sleep durations tend to be closer to objective TIB than TST [35]. Mortality and morbidity risks associated with self-reported long sleep might be at least partly attributable to long TIB, which would have advantages for both research and therapeutic modification since TIB is far more modifiable than TST. However, given the high correlations of TIB with TST, reported long sleep is likely to be indicative of long physiologic sleep in epidemiologic studies. Recent research has confirmed risks associated with objectively long sleep [18, 36]. Studies that have discriminated between TIB and TST have found very similar mortality associations with both measures [18, 37, 38]. Moreover, studies which consider 24-h sleep report similar associations of sleep duration with risks.

Plausible Mechanisms of Risks of Long Sleep

Skeptics have argued that there is not a biologically plausible mechanism to explain how long sleep could cause negative health effects [20]. Yet, many healthy behaviors are hazardous in excessive amounts, including exercise, water intake, and sunlight exposure. Abundant self-report evidence suggests that sleep is not unique in this respect. People often feel lethargic after sleeping extra amounts on holidays or weekends [39] or following experimental sleep extension [40].

Clearly, there are hazardous effects of the extreme condition of excessive sleep produced by bed rest. Indeed, just 2–5 days of bed rest can elicit significant impairments in insulin sensitivity and cardiovascular function [41, 42]. More prolonged bed rest elicits profound deficits in bone density [43], muscle function [43], and mood [44]. In view of these findings, hospitals have increasingly attempted to minimize patient bed rest. During bed rest, young healthy adults display fragmented sleep patterns similar to that of nursing home residents, with extreme amounts of napping throughout the day and night [45], which might partly mediate the risks.

A similar hazard associated with habitual long sleep (or long TIB) is plausible via several potential mechanisms. First, extra TIB or sleep represents more completely sedentary time, and even an extra hour per day of other sedentary behaviors (e.g., television watching) has been associated with mortality and morbidity [46]. Long sleep has been associated with low levels of daytime physical activity [4], which could be explained by feelings of lethargy associated with long sleep [39, 40], as well as simply having less time available for physical activity [47]. Second, as with bed rest, long sleep is associated with increased sleep fragmentation, which has been significantly associated with poor health outcomes both in epidemiologic research [48] and in studies of experimentally induced fragmentation [49]. Third, long sleep duration could elicit metabolic changes that could lead to dyslipidemia [13]. Fourth, long TIB is associated with less exposure to light, which could result in depressed mood [50] and less robust synchronization of the circadian system. Fifth, lethargy and malaise, noted after acute sleep extension and in long sleepers, could potentially reflect cytokine imbalance elicited by long sleep.

Experimental Sleep Deprivation and "Short Sleep"

Negative effects of experimental sleep restriction have been well documented in dozens of short-term studies spanning over a century. Continuous sleep deprivation kills animals in a matter of weeks [51]. In humans, sleep restriction can elicit impairments in glucose tolerance [52], resistance to illness [53], mood [54], alertness [55], and cognitive performance [56]. Nevertheless, most sleep deprivation studies have had several limitations which make it difficult to draw definitive inferences with respect to relevance to public health. First, studies have mostly involved profound sleep deprivation, which might have little relevance to population variation in sleep duration. Second, most sleep deprivation studies have involved short-term manipulations (e.g., usually ≤ 5 days). Although negative effects might accumulate chronically, it is also plausible that people can adapt to sleep restriction. Indeed, several earlier studies found that TIB in young 8-h sleepers could be reduced to 4.5–5.5 h over several months with no impairments in performance or mood [57–60]. Third, double-blind designs are nearly impossible to accomplish in human sleep deprivation studies. Usually, the research observers are aware of the treatment, which could lead to subtle expectantly influences and interpretative biases. Participants invariably also know whether or not they are receiving sleep restriction. Fourth, laboratory sleep deprivation studies also tend to have almost-abusive aspects sensed by the participants and thus are susceptible to biases of participant expectancy and demand pressures related to easily deducible research hypotheses. Sixth, laboratory studies have examined participants subjected to exceptionally boring and meaningless tasks while deprived of bright light, caffeine, and usual levels of ambulation.

Some elegant laboratory studies have demonstrated cognitive deterioration when participants were randomized to spending 4 h in bed (i.e., sleeping less than 4 h) versus 6 h in bed (i.e., sleeping less than 6 h) versus 8 h in bed (i.e., sleeping less than 8 h). The dramatic disparity was between 8 versus 4 h in bed, with the deterioration associated with 6 h TIB being statistically marginal [56]. The relevance of such laboratory sleep deprivation studies to ordinary life is undocumented; they have not realistically simulated the variety of causes of short sleep found in the population.

Nonetheless, a recurrent illogic in discussions of short sleep is indiscriminant use of the term "sleep deprivation." In the laboratory, research participants may indeed be deprived of sleep. Nevertheless, it would appear that the short sleep associated with morbidity and mortality in most epidemiologic studies is usually not frankly coerced. Voluntary social factors may also be an element, as well as family demands. Sometimes a person restricts his/her sleep to comply with a bed partner's pattern. It is unknown to what extent short sleep in the population is attributable to external "deprivation," forms of voluntary self-restriction, genetic influences, insomnia, delayed and advanced sleep phase disorders, restless legs syndrome, or other medical disorders.

Genetic Causality

As much as 50 % of reported variation in sleep duration may be heritable [61, 62]. Two interesting genetic polymorphisms associated with sleep duration are a potassium channel variant [63] and short telomere length [64]. There are presumably other polymorphisms, such as those associated with delayed sleep phase disorder, which may also cause variations in sleep duration. The extent to which genetic variations might produce increased mortality mediated by variant sleep durations per se or alternatively by independent causal pathways is unknown.

Recently, a form of epidemiologic and genetic analysis utilizing Mendelian randomization has presented a new strategy for evaluating causal effects of short and long

sleep. Presumably, when one or both parents are heterozygous, Mendelian inheritance of a genetic polymorphism is essentially random. To the extent that a genetic polymorphism may cause lifelong habitual sleep duration to vary, the causal effects mediated by sleep duration can be evaluated by assessing the genetic association with sleep duration and thus with the outcome compared with the genetic association with the outcome directly. For example, if a potassium channel polymorphism is associated with short sleep (usually genetic associations are assumed causal because reverse causation cannot occur) and short sleep is associated with excess mortality, we determine the association of the potassium channel polymorphism with excess mortality. We could then estimate the association of the potassium channel polymorphism with control for the mediation by short sleep. From these data, it would be possible to determine the percentage of potassium channel polymorphism causal effect on mortality mediated by short sleep, and from this, the causal component of short sleep upon mortality could be inferred.

An increasing number of databases combining genome-wide association data with mortality data are being developed. As whole-genome sequencing becomes rapidly more widely utilized, whole-genome databases will be similarly developed. If data on sleep duration (whether questionnaire-based or objective) can be added to these databases prospectively, then follow-up for mortality and morbidity will permit Mendelian randomization analyses to be computed at the small cost of obtaining questionnaire or actigraphic records of sleep duration. The Mendelian randomization strategy will offer a highly feasible and efficient method of exploring the causality of sleep duration effects on mortality and upon various morbidities.

The Need for Controlled Trials

Ultimately, the causal element of sleep duration in mortality and morbidity must be explored through controlled trials, the gold standard experimental method of determining causality and treatment benefits. If sleep duration per se is a causal element in morbidity or mortality, then it should be demonstrable through the experimental method by randomly relieving the deviation from optimal duration. The problems of controlled trials of extending short sleep and curtailing long sleep are quite different. Ultimately, these problems must be mastered, if we are to have controlled-trial data to justify clinical interventions upon sleep duration.

The majority of controlled trials of extending short sleep have used hypnotic drugs. It is noteworthy that there are no controlled trials of hypnotic drugs which demonstrate objective long-term improvements in major health parameters, much less prolongation of survival. To the contrary, a large epidemiologic literature has demonstrated that use of hypnotics is associated with increased mortality and morbidity, as summarized by Kripke et al. [65] and Weich et al. [66]. Available controlled trials on hypnotic drug effects have generally been limited to studies of a year or less in duration and fewer than 1000 participants, study sizes which are too small to evaluate major hypnotic effects upon morbidity or mortality. The pharmaceutical industry is perfectly capable of performing trials of tens of thousands of participants followed for years, which should be adequate to assess major morbidity and mortality risks, but the industry has not yet made the effort to evaluate major risks of hypnotics, nor has government contributed with its regulatory role or by performing such studies with governmental support.

Fortunately, we do have useful data available from shorter term trials combined in meta-analyses by research groups without financial interests in hypnotics. In perhaps the most comprehensive meta-analysis to date, Buscemi et al. [67] found that hypnotics do not increase sleep durations even 1 h subjectively, and the objective sleep increments are much less. Indeed, the analysis questioned whether the "z" drugs (including zolpidem) produce any significant objective increase in sleep at all, certainly not enough to favorably impact mortality or morbidity. Were hypnotics able to relieve morbidity, we might expect to see fewer adverse medical effects reported in the hypnotic-administered groups than in the controls, but to the contrary, the randomized hypnotic groups had significantly more morbidity. Similar conclusions were reached in an independent meta-analysis of hypnotic effects on elderly patients (among whom most mortality associated with short sleep is concentrated) [68].

A couple of examples may be instructive. Mayer and colleagues reported a randomized controlled trial of ramelteon in which, at the end of 6 months, the ramelteon group was objectively found to be sleeping only about 1 min more than the placebo group [69]. The placebo group slept better than the hypnotic group after drug withdrawal.

In another randomized controlled trial of eszopiclone given to older insomniacs, the placebo group improved about 3 min more in actigraphic sleep duration than the eszopiclone group after 12 weeks, and the eszopiclone group slept slightly worse for three weeks after drug withdrawal [70], as reported on the ClinicalTrials.gov web site (http://www.clinicaltrials.gov/ct2/show/results/NCT00386334?term=eszopiclone&sect=X015_0b#outcome42 accessed February 19, 2014). In summary, the clinical trial literature does not suggest that hypnotics are a useful approach to reducing morbidity and mortality associated with short sleep. It remains to be seen whether exhortation is an effective method of lengthening self-restricted sleep durations, and whether such an approach can relieve the associated morbidity and mortality.

In the converse problem of curtailing long sleep, moderate changes are being proven feasible. Youngstedt et al. [71] completed an 8-week randomized controlled trial of willful self-restriction of long sleep with some objective improvements in sleep quality and no significant adverse effects, and a multi-center group is now expanding this strategy with objective monitoring [72]. Expanding preliminary iterations of this approach further will be needed before willful self-restriction could be tested in a randomized controlled trial large enough and long enough to explore whether restricting long sleep reduces the associated morbidity and mortality.

Summary

A strong epidemiologic literature has reported a U-shaped association of self-reported sleep duration with mortality and various morbidities. There is room for much extension and improvement in epidemiologic studies, but it appears that the epidemiologic findings encompassing millions of participants on several continents make a strong case for association of reported sleep durations with mortality and morbidity. The epidemiologic questionnaire findings are to a limited extent supported by objective sleep measurements, but larger objective studies are needed and now feasible. Unfortunately, causality cannot be inferred from the associations in these data, nor can it be inferred that extending short sleep will improve health or that restricting long sleep will improve health. The need for studies focused on causality is becoming more evident. Since sleep duration is to a considerable extent heritable, a genetic strategy based on Mendelian randomization offers a new pathway to exploring causality. To obtain a gold standard of causal evidence and to supply a basis for clinical interventions to modify sleep durations, we will need to develop large controlled trials which might demonstrate the possibilities of clinical benefit in modifying sleep durations.

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Obstructive Sleep Apnea Syndrome

32

Rachel Korson and Christian Guilleminault

Introduction

Obstructive sleep apnea syndrome (OSAS) is a common, often under recognized, medical disorder characterized by repeated episodes of upper airway closure during sleep. The Wisconsin Sleep Cohort data listed prevalence figures of moderate-to-severe OSAS (defined by an apnea-hypopnea index of ≥ 15 events per hour all accompanied by excessive daytime sleepiness) at 10 % in men and 3 % in women among the ages of 30–49 years but 17 % in men and 9 % in women among the ages of 50–70 years) [1]. OSAS is associated with a constellation of symptoms and objective findings [2]. The most common presenting complaints are loud, disruptive, interrupted snoring, associated with unrefreshing sleep and excessive daytime sleepiness (EDS), or fatigue. OSAS may long remain undetected because the breathing disturbances occur at night, but the consequences are reflected in impairment of daytime function. Amazingly, many patients with even severe sleep apnea of many decades duration remain unaware of the cause of their difficulties. Bed partners are invaluable informants, describing frightening long pauses of breathing, choking sounds, and stridorous gasps when breathing resumes. The course is a slowly progressive one. Thus, the patient's daytime performance becomes insidiously more impaired, until the patient eventually decompensates and presents to the healthcare system, either volitionally or as a result of one of the complications of sleep apnea. Sleepiness is typically misperceived as a natural consequence of aging. There is a disparity between the prevalence of OSAS in the community and recognition among medical professionals of the frequency and impact of OSAS; this disparity is particularly sizable among primary care providers and health system managers [3].

Complete obstruction of the upper airway is termed *obstructive apnea* and partial closure is referred to as a *hypopnea.* When measured by polysomnographic (PSG) recording, obstructive apneas are defined as a total cessation of airflow at the nose and mouth, lasting at least 10 s, associated with ongoing thoracic and abdominal efforts to inspire. As per the American Academy of Sleep Medicine (AASM) Guidelines, last updated in October of 2012, hypopneas are defined as a greater than 30 % decrease in nasal airflow, lasting at least 10 s, associated with continued respiratory efforts, and either a 3 or more second arousal or with a drop in blood oxygen saturation of 3 % or greater [2, 4, 5]. In a recent modification of the manual, the AASM confirmed the 3 % or more desaturation (cg). More advanced technology has shown that a small decrease in tidal volume (V_T) may involve only one breath (or respiratory cycle) and lead to a transient, electroencephalography (EEG)-defined arousal, when associated with increased respiratory efforts while asleep. The current, noninvasive method of measuring oxygen saturation in arterial blood (Sao_2) does not indicate a recognizable drop in Sao_2 in association with this V_T decrease. If repeated, however, the short arousal will have an impact on sleep continuity—that is, lead to sleep fragmentation. In the strictest sense of the term, a reduction of airflow with a short arousal is a hypopnea, and some sleep specialists do not limit the term *hypopnea* to the definitions outlined earlier. This may be appropriate, given that very short events can have pathophysiologic consequences and impair well being, as with upper airway resistance syndrome (UARS) [6–9]. Both apneas and hypopneas are terminated with a large inspiratory breath.

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Central apneas are seen on PSG as episodes of cessation of thoracic and abdominal respiratory efforts as well as nasal-oral airflow, lasting at least 10 s. Long-standing obstructive apnea may result in disturbances of central and peripheral respiratory reflexes, in turn causing central apneas. Moreover, the presence of inspiratory effort that distinguishes obstructive from central apneic events may be detectable only with esophageal manometry. Because this diagnostic tool is not in common use in sleep laboratories, these events are often misinterpreted as central apneas. Mixed apneas are composed of both central and obstructive components. The term *complex* or treatment-emergent central apnea refers to central apneas that are induced by the introduction of positive airway pressure (PAP) therapy. Treatment-emergent central apneas may dissipate with time as the body's chemoreceptors are thought be become readjusted to the normalized oxygen concentrations. Treatment-emergent central apneas, however, may persist.

The number of apneas and hypopneas are separately totaled and then divided by the hours of total sleep time to yield an apnea index (AI) and hypopnea index (HI). The AI and HI are summed to determine the apnea-hypopnea index (AHI), which is the average number of apneas and hypopneas per hour of sleep [10].

The minimum AHI and AI required to constitute a mild disorder is debated [11]. The symptomatology that is produced by a given objective amount of respiratory disturbance varies from individual to individual. Some people with severe OSA complain of very few symptoms, while other individuals with very mild OSA have severe symptoms. The correlation between AHI severity and long-term morbidity is not precisely delineated. This complex relationship is confounded by nightly fluctuations in the AHI, the amount of oxygen desaturation, and the percentage of time spent with reduced oxygen saturation. For clinical purposes, an AHI higher than 5 events/h is most commonly considered to be in the pathologic range [12, 13]. The term sleep-disordered breathing (SDB) has been given multiple definitions that render usage of this term difficult. It was initially created to report on the presence of abnormal breathing events that did not qualify for the definition of "hypopnea" that requires SaO_2 drop or visual EEG arousal and a set decrease in airflow. It became obvious over time that patients may have an impairment without having the required Sao_2 drop or that the visually scored EEG arousal was difficult to recognize. Also, introduction of the nasal cannula pressure transducer mode of recording led to recognition of flow limitation, and usage of an esophageal pressure (P_{es}) sensor to detect the presence of abnormal respiratory effort has changed the way breathing events are scored. Tabulation of these extra events led to calculation of a respiratory disturbance index (RDI) that includes respiratory event-related arousals (RERAs) as well as apneas and hypopneas. Others used "sleep-disordered breathing" as equivalent to AHI, rendering the value of the term at that time very questionable.

Obstructive sleep apnea syndrome lies along a continuum of SDB. There are controversies about the linearity of this continuum: It appears from recent data that there could be a point of "no return" where lesions in the upper airway leave permanent traces that may continuously impact on upper airway motor control during inspiration. Some (and we are part of this group) want to subdivide this reported "continuum" in two segments: First stage of chronic snoring and upper airway resistance (and there is no clear demonstration that chronic snorers do not always present some degree of upper airway resistance) with limited symptoms and usually no daytime sleepiness, and finally entering second stage through an increasing clinical severity, with progressive degrees of obstructive apnea based on RDI and oxyhemoglobin desaturations with clear sympathetic activation (cg). (This second stage has for some been always associated with a variable degree of upper airway neurologic lesions that may leave permanent sequelae.) Upper airway resistance syndrome (UARS) may be present without associated snoring but with associated daytime sleepiness or fatigue [6, 7].

The specific pathophysiology of these syndromes is discussed later in this chapter. As the incidence and prevalence of UARS have not been well characterized up to very recently, most of the presentation focuses on the well-known OSAS.

Epidemiology

The risk of developing OSAS increases with age, and the PSG pattern of obstructive apnea is strongly correlated with abdominal and neck obesity and male gender (however, when android obesity is present, subjects present with a combined syndrome: upper airway impairment and restrictive chest bellows impairment due to obesity) [14–17]. Prevalence of OSA reaches a maximum between the fifth and seventh decades [18]. Menopausal women develop OSAS at a rate similar to that of men. The Wisconsin Sleep Cohort Study evaluated the association between premenopause, perimenopause, and postmenopause and SDB in a group of 589 women. Using multivariate regression analysis adjusted for age, body habitus, smoking, and other potential confounding factors, Young et al. calculated the odds ratios for an AHI greater than 5 events/h of sleep to be 1.2 for perimenopause, and 2.6 (range 1.4–4.8) for postmenopause [19]. These results suggest that the menopausal transition is significantly associated with an increased risk of SDB independent of known confounding factors. However,

a recent study comparing younger (<30 years old) to older premenopausal women, found that with increasing age alone, came an increased risk of severe OSA (11 % vs. 21 %) [20]. Another important finding of this study was that, of the younger women, 20 % had UARS and 50 % had mild OSA. These mild presentations, although not often accompanied by the classic symptoms of snoring, witnessed apnea, and nocturnal gasping, did lead to significant daytime complaints of excessive daytime sleepiness, depression, and unrefreshing sleep [20].

Some minority populations appear to have a higher prevalence of SDB, indicating that race may be a risk factor. Three such populations are Pacific Islanders [21, 22], Hispanic Americans [23, 24], and Far East Asian [25], though there have been no studies that control for comorbid conditions found more frequently in these populations than in whites. As data from the Cleveland Family Study indicate, African-Americans may be at increased risk for sleep apnea [23]. In this study, the increased prevalence was not accounted for by differences in exposure to alcohol or tobacco or differences in body mass index (BMI). Moreover, this effect was most apparent in individuals younger than 25 years of age. Variable age of puberty, speed of development of secondary sexual characteristics, and mucosal enlargement associated with hormonal surge may have biased these findings. In contrast, a study in New Zealand comparing sleep apnea severity among Maoris, Pacific Islanders, and Europeans reported that race was not an important predictor of severity when adjusted for factors such as neck size, BMI, and age [24]. Familial aggregates of OSAS clearly indicate that risk factors for the development of this condition may exist very early in life [26–29].

Initial studies that attempted to define rates of OSAS were limited by biases that tended to underestimate actual prevalence. Early studies by Lavie [29] in Israel and Gislason et al. [30] in Sweden assessed the prevalence of OSAS in the adult male population to be 7 and 1.3 %, respectively. More recent studies of large, comprehensive population samples suggest a prevalence rate of OSAS at least two times higher than those early estimates [1, 31, 32]. In 1993, Young and colleagues published a large community-based study of adults 30–60 years of age that calculated, if OSA was defined as having an AHI greater than 5 events/h, a prevalence of 9 % in women and 24 % in men [13]. If the AHI of greater than 5 events/h was associated with symptoms of excessive sleepiness, however, the prevalence was 2 % and 4 % in women and men, respectively [13]. These studies are limited as they looked mainly at whites.

Obstructive sleep apnea syndrome has been associated with mortality both from vascular complications and from highway and industrial accidents. Two retrospective studies by Partinen et al. [33] and by He and colleagues [34] found an increased mortality rate for patients with OSAS, particularly in those younger than 50 years of age. As previously stated, OSAS is underdiagnosed. Untreated OSAS is a cause of death, as already shown by the study of Partinen et al. [33], and serious injury on the road and in the workplace [35–38]. Work by Findley et al. [38] suggests that the accident rate for OSAS patients is seven times that of the general population. Other studies have shown similar findings [39, 40].

Morbidity: Cardiovascular System

Over the past several decades, obstructive sleep apnea (OSA) has been shown to play a central role in hypertension, cardiovascular and cerebrovascular risk, metabolic syndrome, and longevity.

Hypertension

Systemic and pulmonary hemodynamics undergo acute and chronic changes as a consequence of obstructive apnea, most of which reverse on successful treatment of the upper airway obstruction. During normal sleep, blood pressure dips as compared to that during wakefulness. In subjects with OSA, nocturnal blood pressure remains elevated during sleep, with significant fluctuations in systemic arterial pressure occurring cyclically with episodes of apnea. During obstructive apneic events, there is an initial decline of blood pressure followed by an elevation that becomes maximal after ventilation resumes. In a study of 10 moderate-to-severe apneics, systolic and diastolic pressures rose approximately 25 % from their baseline values during apneas (i.e., from 126 to 159 mm Hg systolic and from 65 to 83 mm Hg diastolic) [41]. When apneas occur continually throughout the night and are associated with very severe oxygen desaturations, elevations may be extreme, exceeding 200 mm Hg systolic and 120 mm Hg diastolic [42].

Evidence implicates several mechanisms that contribute to cyclic increases in blood pressure. A fall in partial pressure of arterial oxygen and an increase in acidosis signal the carotid chemoreceptors to trigger vasomotor center-mediated arteriolar constriction, which leads to increased systemic vascular resistance. Increased ventilatory effort against a closed upper airway in the face of air trapping leads to significant right-to-left bowing of the interventricular septum and decreased cardiac output [43, 44]. Left ventricular collapse can occur with very negative inspiratory pressures [43]. With resumption of ventilation, and the abrupt shift from sleep to wake, there is a release of vagal parasympathetic predominance and heightened sympathetic tone.

Pulmonary stretch reflexes induce tachycardia, which increases cardiac output. Changes in preload and afterload due to repetitive Müller's and, at times, Valsalva maneuvers also contribute to the changes in cardiac output. Evidence of elevated sympathetic nervous system activity can be measured by increased urinary catecholamine levels, which return to normal after treatment of apnea [45, 46].

Investigation of OSA subjects using microneurography on the peroneal nerve in the popliteal fossa during wake and sleep has further enhanced our knowledge about sympathetic activity in people with OSA. In healthy individuals, muscle sympathetic nerve activity (MSNA) at the popliteal level shows low sympathetic activity, particularly at rest during daytime wakefulness in experimental conditions. OSA patients have elevated MSNA during wakefulness, with a very significant increase in discharge rate [47–49]. It is believed that the repetitive hypoxemia associated with apnea and hypopneic events leads to important changes in the autonomic nervous system neuronal network, with a resetting of the sympathetic receptors [49]. This resetting leads to the continuous discharges that persist during the daytime when hypoxemic events are not present. The abnormal waking sympathetic activity is thought to lead to vascular changes, including progressive endothelium impairment involving the nitric oxide system [50, 51], which has been strongly implicated in the development of plaques and atherosclerosis [52, 53]. These are some of the mechanisms believed to be responsible for developing hypertension with OSA.

Independent of the associated mechanisms, OSA is a risk factor for hypertension [54]; other factors are difficult to tease out as, unfortunately many studies have been performed on obese OSA patients and it is impossible to completely dissociate the role of obesity from the role of upper airway obstruction during sleep. Hypertension is also a frequent comorbid condition with sleep apnea [54–57]. Approximately 30 % of patients with systemic hypertension have sleep apnea, whereas 50 % or more of patients with sleep apnea have systemic hypertension, and the percentage of those with refractory hypertension is even higher. The Sleep Heart Health Study, in a cross-sectional analysis of over 6000 subjects, showed an independent association between OSA and hypertension. The most compelling evidence that OSA is an independent risk factor for hypertension comes from the Wisconsin cohort group. This population study involved over 700 government employees and collected medical and sleep data via detailed questionnaires, physical examinations, and PSG. Peppard et al. found that having OSA (diagnosed by PSG) significantly increased the risk of developing hypertension 4 years later compared to the risk in subjects without SDB, independent of known confounding factors [57]. This increased risk was greater in those subjects with more severe disease. Subjects with mild obstructive sleep apnea (AHI of 5–14.9 events/h) were 2.03 times (95 % confidence interval [CI], 1.29–3.17) more likely to have hypertension than normals, and subjects with an AHI of 15 events/hr or more were 2.89 times (95 % CI, 1.46–5.64) more likely to have hypertension. Even those with mild SDB (AHI of 0.01–4.9 events/h) were not immune from the negative effects of disordered sleep and were more likely to develop hypertension 4 years later, with an odds ratio of 1.42 (95 % CI, 1.13–1.78) compared to subjects without SDB [57].

Hypertension may be generated by sympathetic overactivity triggered by intermittent hypoxemia, large negative fluctuations in intrathoracic pressure, and repetitive arousals from sleep [56, 58, 59]. Hypertension may improve after treatment of apnea [60]. The ameliorative effect of treatment has been found after upper airway surgery [61] and nasal continuous positive airway pressure (CPAP) [62]. Moller et al. [63] performed 24-h blood pressure monitoring and measured plasma levels of vasoactive hormones in 24 OSA patients and 18 control subjects. Compared with the controls, OSA patients had significantly higher blood pressure and heart rate, and the sleep-related nocturnal blood pressure drop was reduced [63]. Thirteen OSA patients re-examined after 14 months of CPAP therapy demonstrated reduction in blood pressure, which correlated with a decrease in both plasma renin and plasma angiotensin II concentrations [63]. However, many patients with hypertension and OSA do not go back to normal blood pressure.

Sin et al. reported that 40 % of 301 patients with congestive heart failure had OSA and systemic hypertension. After controlling for other risk factors, OSA patients were 2.89 times (95 % CI, 1.25–6.73) more likely to have systolic hypertension than those without OSA. The degree of systolic blood pressure elevation was directly related to the frequency of hypopneas and apneas [64].

In OSA patients, there is evidence the body tries to compensate for hypertension. Increased release of atrial natriuretic peptide (ANP) during sleep has been found in sleep apnea, with concomitant increases in urine and sodium output [65]. ANP suppresses the renin–angiotensin–aldosterone system, and plasma renin activity curves have been found to be abnormally flattened in apneics during sleep [66]. These changes lower blood volume and blood pressure and may play a protective or compensatory role against blood pressure elevations in OSA. Treatment of apnea normalizes ANP, thereby diminishing diuresis and natriuresis, and increases renin and aldosterone release.

Accumulating data indicate that OSA is an independent risk factor for gestational hypertension and preeclampsia contributing to adverse maternal and fetal outcomes.

High-risk pregnant women should be screened and treated appropriately for any sleep-disordered breathing given the possible benefit that CPAP use may have on health outcome.

Heart Failure

Heart failure also appears to occur as a consequence of OSA. The Sleep Heart Health Study reported that OSA is associated with a relative odds ratio of 2.38 for heart failure independent of other known risk factors [67]. OSA is also prevalent in patients with heart failure. Javaheri et al. [68] performed PSG in 81 ambulatory men with stable, treated systolic heart failure. Fifty-one percent of the patients had moderate-to-severe sleep apnea with an AHI of 15 events/h, and the group had an average of AHI of 44 events/h [68]. Chan et al. reported in a series that about 50 % of patients with isolated diastolic heart failure had an AHI of at least 10 events/h [69].

Whether heart failure patients with SDB benefit from CPAP treatment is unclear. Several studies have shown that short-term use of CPAP in patients with heart failure and obstructive sleep apnea improved left ventricular ejection fraction, blood pressure, and ventricular systolic volume [70, 71]. CPAP is recommended for heart failure patients with clear-cut OSA [70, 71]. However, in addition to obstructive events, heart failure patients may present with a variety of abnormal respiratory activities while sleeping. They may have central events; mixed events, Cheyne–Stokes respirations, and repetitive diaphragmatic pauses; or a combination of mixed, obstructive, and rare central events. This last subgroup may derive some benefit from nasal or bilevel CPAP. However, a careful analysis of the PSG pattern is needed, and an in-laboratory titration for pressure is mandatory, evaluating the appearance of dyspnea reported during the titration night. Bradley et al. reported the first studies and concluded that nasal CPAP is not a recommended treatment for heart failure patients who suffer from central sleep apnea (defined as >50 % of apnea episodes central in etiology) as treatment did not improve quality of life, number of hospitalizations, or survival [72]. Kasai et al. reported that following CPAP therapy patients with heart failure and moderate-to-severe OSA were less likely to die or be hospitalized than untreated patients, though those who were poorly compliant with CPAP were most likely to reach these unwanted end points [73].

Pulmonary Hypertension

Moderate-to-severe increases in pulmonary arterial pressure occur with each apneic episode. Maximal pulmonary pressures are generated during rapid eye movement (REM) sleep. They coincide with maximal hypoxemic and hypercapnic values [60] and probably reflect hypoxic pulmonary vasoconstriction. When pressure gradients between the pulmonary artery lumen and thoracic cavity are evaluated, transmural pulmonary arterial pressure decreases during the first 25 s of apnea and then increases until breathing returns and transiently rises more rapidly [74]. Another hemodynamic change consists of reductions in cardiac output of up to one-third of baseline values in apneas longer than 35 s [43].

The development of persistent pulmonary hypertension during wakefulness and cor pulmonale may be caused by severe hypoxemia during sleep [73, 74], but is more likely in daytime hypoxemia [75]. There has again been controversy regarding the persistence of daytime pulmonary hypertension. Earlier studies estimated the prevalence of pulmonary hypertension in OSA patients to be as high as 20–41 % [76–78]. However, these studies were small and did not control for other risk factors for pulmonary hypertension. There is, however, agreement that a subgroup of OSA patients present with pulmonary hypertension, usually moderate, during the day associated with their sleep-related problem. The American College of Chest Physicians recommends that evaluation for OSA should be part of the initial workup in patients with pulmonary hypertension [79]. Possible mechanisms thought to cause pulmonary hypertension include hypoxemia-induced endothelial cell dysfunction and pulmonary artery remodeling [80]. The reversal of pulmonary hypertension in OSA patients is reported to be poor after treatment [81].

Cardiac Arrhythmias

Cardiac arrhythmias that occur exclusively during sleep are common in apneics. Sinus arrhythmia accompanies each obstructive respiratory cycle, in which rate diminishes with the cessation of airflow and accelerates when breathing resumes. These changes can be mild or severe, resulting in repetitive cycles of bradycardia and tachycardia fluctuating from fewer than 30 to more than 120 bpm [82]. Severe sinus bradycardia (fewer than 30 bpm) affects approximately 10 % of sleep apneics and is usually seen with severe hypoxemia [83–85]. These aberrations of rate combined with hypoxemia predispose to conduction defects, malignant arrhythmias, and perhaps sudden death. Asystoles of up to 13 s, second-degree atrioventricular (AV) block, premature ventricular contractions (PVCs), and runs of ventricular tachycardia are among documented apnea-related abnormalities [86]. A prospective study of 147 consecutive patients demonstrated significantly higher prevalence of nocturnal paroxysmal asystole in OSA patients and increased episodes of bradycardia and pauses that correlated with the severity of the sleep apnea [87].

Proposed mechanisms for bradycardia, Mobitz type I AV block, and asystole involve vagal nerve activation due to both Müller's maneuver and hypoxemic carotid body stimulation. Electroencephalographic arousal with airway reopening and lung expansion triggers cardiac acceleration. Increased sympathetic tone due to hypoxemia and acidosis may be expressed after vagal influence is withdrawn, leading to PVCs, sinus tachycardia, and ventricular tachycardia. PVC frequency and other ventricular arrhythmias have been shown to correlate with severity of oxygen desaturation, increasing threefold with desaturations lower than 60 % (as compared to 90 %) [87].

From a global perspective, many of these physiologic changes in response to asphyxia may be viewed as an attempt to preserve perfusion to the critical cerebral and coronary systems. Increased systemic pressure selectively perfuses these critical central vessels, whereas bradycardia decreases myocardial oxygen consumption. As bradycardia becomes more profound, however, myocardial perfusion may become more impaired, because the perfusion gradient drops as diastole is prolonged. Coronary ischemia may result in ventricular arrhythmia. On return of ventilation, cardiac rate and output rise in the setting of sympathetic dominance and decreased systemic resistance. The demand for myocardial oxygen to accomplish this work outweighs the supply of reperfused blood, rendering the myocardium vulnerable to malignant arrhythmias [87].

Obstructive sleep apnea may increase one's risk of developing atrial fibrillation (AF) and its recurrence after cardioversion. In one study, consecutive patients who underwent cardioversion for AF were compared to patients without AF who were referred for management of cardiovascular disease at a tertiary medical facility. The prevalence of OSA was statistically higher in patients with AF (49 %) compared to those without AF (32 %) [88]. Kanagala et al. showed that the recurrence rate of AF at 12 months after cardioversion in patients with untreated OSA was nearly twice that of untreated OSA patients (82 % vs. 42 %, respectively) [89].

Coronary Artery Disease, Myocardial Infarction, Stroke, and Early Death

Sleep apnea and even snoring have been epidemiologically linked to increased incidences of myocardial infarction and stroke [90, 91]. Spriggs and coworkers [92] looked at risk factors for stroke in approximately 400 individuals with OSAS who had been matched with controls for sex and age and found an odds ratio of 3.2 for symptoms of snoring. Another study found an increased odds ratio even after adjustment for ethanol use, hypertension, and heart disease. The ratio increased approximately fourfold if obesity, observed apneas, and a subjective sense of EDS were present [90]. A study of over 1000 patients showed an increased hazard ratio in OSA patients of 2.24 for stroke or death from any cause over a several-year period [93]. After adjustment for multiple risk factors (age, sex, race, obesity, hypertension, etc.), the hazard ratio remained significant at 1.97 (95 % CI, 1.12–3.48). Furthermore, analysis indicated that those with more severe OSA were more likely to reach these end points. Though this study strongly suggests OSA increases the risk of stroke or death, it may statistically underestimate its risk in the development of these end points as many of the OSA patients were treated surgically or with CPAP during the study period [93].

The increased incidence of stroke is likely secondary to multiple reasons. During apneic events, there is a greater chance of hypoxemia, hypercapnia, increased frequency of cardiac arrhythmias, increased coagulation, and paradoxical embolism through a patent foramen ovale. Cerebral blood flow may be variable during apneic events as evidenced by transcranial Doppler studies. However, Yaggi et al. [93] presented convincing data indicating that OSA is an independent risk factor for stroke.

Stroke and transient ischemic attacks are also a risk factor for OSA. Over half of patients with acute strokes or transient ischemic attacks have OSA [94, 95]. Stroke patients who have OSA appear to have higher mortality as well [94]. One study has shown that successfully treating stroke patients who have OSA with CPAP significantly decreased the risk of subsequent vascular events [96]. However, larger studies suggest that only a minority of stroke patients with OSA are able to tolerate CPAP [97].

Obstructive sleep apnea may be a predisposing factor to atherosclerosis and plaque formation, as discussed earlier, due to its action on the arterial endothelium and the nitric oxide system. Kaynak et al. [98] preformed ultrasonographic examination of both carotid arteries to evaluate intima-media thickness and the presence of plaque in 114 male patients referred for evaluation of SDB. Patients with OSA had significantly increased intima-media thickness compared with habitual snorers. Age and BMI were significantly associated with intima-media thickness, whereas age and RDI were most predictive for plaque [98].

Obstructive sleep apnea has been linked to other risk markers for cardiovascular disease, including increased levels of leptin, C-reactive protein, and homocysteine, and insulin resistance syndrome [99]. However, some of the abnormalities observed have been determined not to be related to OSA but to the frequently associated obesity; as an example, C-reactive protein is not elevated in OSA patients with a maximum BMI of 25 kg/m^2 despite a mean AHI of 30 events/h [100]. Abnormal levels of leptin and ghrelin seen in these subjects seem to be related more to the severity of the sleep fragmentation (or total sleep loss) induced by the

syndrome that directly results from apnea and hypopnea [101]. Leptin and ghrelin levels can normalize in patients once their sleep apnea has been treated [102].

Several studies have shown decreased mortality associated with OSA patients treated with tracheostomy or CPAP [33, 103]. He et al. [34], comparing cumulative survival after 5 years of untreated versus treated patients with an AI greater than 20 events/h, showed that cumulative survival was approximately 75 % in the untreated group as compared to almost 100 % for the treated group was criticized due to the large number of subjects lost at follow-up. A study by Partinen et al. comparing mortality in OSA subjects 5 and 8 years following tracheostomy or no treatment showed decreased mortality in treated subjects [33]. A large study from Spain involving over 800 patients showed that OSA patients compliant with CPAP, compared to those who were not treated, were more likely to survive over a several-year period. The survival rate was positively associated with increased CPAP usage [103]. Marin et al. [104] published a study involving several hundred Spanish men and showed that fatal and nonfatal cardiovascular events occurred more frequently in untreated OSA patients compared to treated OSA patients. Furthermore, treated patients with sleep apnea had a frequency of fatal and non-fatal cardiovascular events similar to that of simple snorers [104].

Earlier studies showed an increased incidence of proteinuria in OSA patients [105, 106]. However, more recent studies have not shown this correlation [107, 108].

Pathophysiology

Sleep-disordered breathing is caused by increased resistance while breathing secondary to narrowing at one or more sites of the upper airway. Locations of narrowing include the nose, retropalatal region, retroglossal region, or, less commonly, the hypoglossal region.

The size of the pharyngeal upper airway is dependent on a balance of forces between the upper airway dilators, which maintain upper airway patency, and the negative pharyngeal intraluminal pressure created during thoracic expansion as a result of inspiration. Skeletal factors also play a role. Bernoulli's principle dictates that narrowing of any segment while airflow is maintained causes an increased velocity of airflow in that segment. This decreases intraluminal pressure and further narrows the segment, favoring upper airway collapse. In sleep, the stage (REM vs. non-REM [NREM]) also influences upper airway patency as REM sleep is associated with atonia. Lack of coordination between inspiratory muscles and upper airway dilators leads to upper airway occlusion during sleep. This was reported as early as 1978 by Guilleminault and Motta [109] in an investigation of patients with postpoliomyelitis syndrome who had been treated with a cuirass ventilator. These patients developed a negative intrathoracic pressure that could not be counteracted by the upper airway dilators and that led to the development of OSAS. These findings were later confirmed by Hyland et al. [110] and by Simmonds and Branthwaite [111].

More recent studies have shown abnormal activity of the dilatory pharyngeal muscles (genioglossus and tensor palatine) in OSA patients. During the waking state, the activity of these muscles is increased compared to controls [112]. With sleep onset, there is normally an increase in resistance due to a decrease in upper airway muscle tone. In OSA patients, there is a greater diminution in muscle tone compared to controls as measured by electromyography (EMG) [112, 113]. A working model for OSA may be that, in the presence of a susceptible airway (one that is already narrowed by obesity, a small chin, enlarged tonsils, etc.), the factors that act to maintain upper airway patency and minimize increases in upper airway resistance during sleep are inadequate, with consequent SDB. Recent studies have suggested that a potential upper airway stabilizing mechanism may be initiated by the flow of air into the pharynx during inspiration. Although the complete details of this reflex have not been described, it appears that a reflex loop is activated once inspiration starts causing a flow of air into the upper airway with the following sequence of events: (1) Sensory neurons in the upper airway are activated; (2) sensory afferents travel to the brain stem, which subsequently activates the efferent hypoglossal nerve that innervates the genioglossus and geniohyoid; and (3) genioglossus and geniohyoid contraction keeps the pharynx open during inspiration. This reflex may be altered in OSA patients because of damage to the muscle and nerves from the vibratory trauma of snoring. This theory is supported by the findings of abnormal sensory nerves and nerve function seen in both histologic preparations and neurophysiologic studies of upper airway muscles in OSA patients [114–116].

At sleep onset, there is an increase in resistance due to a decrease in upper airway muscle tone [113, 117]. This increase in upper airway resistance has no known consequences in normal subjects. In snorers, however, there is a further increase in each snore. In response to this increased resistance, many subjects are able to increase their inspiratory effort and maintain normal V_T. Increased effort is demonstrated by P_{es} monitoring, which may reach peak inspiratory nadirs of −12 to −15 cm H_2O. The effort is constant over time, and in some patients does not negatively impact sleep architecture or oxygen saturation. However, in other cases, the upper airway dilators are unable to oppose the negative pharyngeal intraluminal pressure sufficiently to maintain minute ventilation and normal gas exchange [118].

In these cases, inspiratory effort is increased as reflected by an increase in P_{es} nadir. With increasing inspiratory efforts, there is a decrease in the width of the upper airway, as upper airway dilators are unable to exactly match the inspiratory negative pressure. At some point, an abnormally negative P_{es} pressure is reached, V_T is reduced for one to three breaths due to the further narrowing of the upper airway passage, and an arousal response is triggered. This response is transient and short lived (as short as 2 s with visual EEG scoring). Changes in sympathetic and parasympathetic tones vary depending on the degree of adjustment done by the upper airway muscles in relation to the increase in inspiratory efforts. The results of this delicate balance may lead to a chronic low blood pressure and even some small physical signs of chronic hyperactivity of vagal tone (cold hands, cold feet, slight dizziness when abruptly getting up particularly when getting out of bed just after waking up) [119].

It is notable that a large percentage of OSAS patients have subtle craniofacial abnormalities, such as a highly arched hard palate, a long soft palate with low placement and redundant tissues, and moderate retroposition of the mandible [120, 121]. It has been suggested that these abnormalities are responsible for obstructive apnea during the first weeks of life in certain subjects [122]. These abnormalities are related to genetic factors, and we have investigated several families in which a small upper airway has been passed down for generations [123].

As stated previously, the upper airway begins at the nares and includes the nasal vestibule, nasopharynx, oropharynx, and hypopharynx. The pharynx is an especially vulnerable portion of the upper airway because it serves both digestive and respiratory functions. It must be sufficiently floppy to contract and guide food into the esophagus, while alternately maintaining sufficient muscle dilation to keep from being sucked closed.

Nasal obstruction from any cause, including allergic congestion, inflamed lymphoid tissue, or septal deviation, can initiate obstructive nocturnal respiratory pathology by converting breathing from the nasal to the oral route. Oral breathing predisposes to abnormal airway dynamics favoring pharyngeal collapse and backward displacement of the base of the tongue. The dilating genioglossus and geniohyoid muscles become mechanically disadvantaged, and airway resistance is increased.

The next potential level of obstruction arises at the nose and oropharynx due to enlarged adenoidal, tonsillar, and soft palate tissues. Enlargement of these tissues is secondary to hereditary and acquired factors. Allergies and recurrent upper respiratory infections can cause hyperplasia and scarring of lymphoid tissue. Snoring renders the uvula more edematous due to suction and trauma, which further compromises the small oropharyngeal space. Macroglossia may be due in part to obesity and is implicated in OSAS [119].

A constellation of jaw malformations is associated with OSAS, including a highly arched hard palate and class II dental occlusion (overjet). The position of the mandible relative to the maxilla determines the posterior extension of the tongue. Because the genioglossus muscle inserts on the mandible, with retrognathia or micrognathia, the genioglossus originates on a backwardly displaced mandible and thus extends further posterior, predisposing to hypopharyngeal obstruction. During sleep in the supine position, gravity pulls the tongue further into the pharyngeal lumen, and varying degrees of decreased muscle tone additionally relax the tongue dorsally.

Chronic nasal obstruction during childhood that results in oral breathing may induce craniofacial changes predisposing to sleep apnea later in life. This has been shown in rhesus monkeys with experimentally partially occluded nostrils that developed mandibular deficiency relative to paired controls. Oral breathing changed EMG activity in facial muscle groups, leading to altered forces on the developing facial skeleton [124–126]. Partial improvement in these changes occurred if the obstruction was relieved early enough. Upper airway obstruction from enlarged adenoids in children has been shown to lead to decreased mandibular size and retrognathia, among other craniofacial changes (see below) [127–131].

Pathological hypotonia of the tongue muscles has been shown to lead to the development of a high and narrow hard palate which is associated with increased risk of sleep-disordered breathing. Understanding the continuous interaction between muscle activity of the tongue and the development of a normal palate and other anatomical structures supporting the upper airway highlights the role of myofunctional therapy in the treatment of sleep-disordered breathing [132].

Adiposity compromises the upper airway not only because the “double chin” externally compresses the pharynx in the supine position, but also through internal infiltration of parapharyngeal structures (i.e., the adipose tissue alters and reduces airway space). Pharyngeal dilator muscle mechanics may be compromised by this loading [133]. Additionally, upper airway imaging studies have shown that patients with OSA have narrow airways due to adipose tissue in the lateral walls of the pharynx.

Testosterone may contribute to obstruction by inducing more parapharyngeal muscle bulk and more centripetal fat distribution. This might explain the fact that snoring often begins at puberty or during the immediate postpubertal period. Even a few kilograms of excessive weight can tip the balance toward upper airway obstruction in anatomically vulnerable patients.

Morbid obesity degrades waking and sleeping ventilation in addition to its impact on upper airway dynamics. Adipose deposition around the abdomen, diaphragm, and ribs reduces

thoracic cage compliance, requiring increased work of breathing [134]. Functional residual capacity is decreased, and atelectasis of dependent airways may create ventilation-perfusion mismatch with hypoxemia [135]. In the supine position, the abdominal weight creates additional load, which increases hypoxemia [136]. During REM sleep, muscle atonia renders accessory respiratory muscles such as the intercostals and upper airway dilators functionally paralyzed. Thus, the diaphragm contributes mostly to inspiration against the load created by the heavy chest mass, leading to the profound oxygen desaturations seen during REM sleep in some obese patients.

Summary

Partial or complete upper airway occlusion is related to the development of greater subatmospheric intrathoracic pressure during inspiration. This subatmospheric pressure is transmitted to the pharyngeal region, creating "suction" on the soft tissues, which are the major constituents of the pharyngeal airway. To prevent closure, reflexes are normally activated at least 500 ms before the beginning of inspiration to activate the contraction of upper airway dilator muscles in opposition to this subatmospheric intrathoracic pressure.

During sleep, many of the upper airway dilator muscles have much less contractile power than the diaphragm. The genioglossus and geniohyoid muscles are particularly affected. The motor activity of these muscles is abnormal in OSA patients, with heightened contraction during the daytime and decreased contraction at sleep onset. This physiologic change allows the development of abnormal inspiratory upper airway resistance, which may result in partial or complete occlusion. If abnormalities of the upper airway due to anatomic, physiologic, or neurologic causes reduce size to a level lower than critical or limit the capabilities of upper airway dilator muscles, a more or less pronounced collapse will occur during sleep in this very flexible region. The obesity hypoventilation syndrome with increased arterial partial pressure of carbon dioxide (P_{CO_2}) has been described during the awake state. It is thought to result from reduced hypoxic and hypercapnic ventilatory drives and is not attributed to weight-related mechanical factors [137].

Neural factors that relate to state changes from wakefulness to sleep, as well as changes across sleep stages, play an adjunctive role in the anatomic considerations of the genesis of OSAS. During sleep, the wake-related contribution to ventilatory drive is lost. This wakefulness stimulus [138] consists of factors that are independent of metabolic and voluntary components. With sleep onset, autonomic integration of acid-base and oxygen homeostasis is believed to occur in the medulla. Inputs to this regulator include peripheral chemoreceptors for PCO_2 and partial pressure of oxygen (PO_2); central chemoreceptors for pH and PCO_2; and stretch receptors in the lung, thoracic wall, and upper airway. Ventilatory responses to both hypercapnia and hypoxia are decreased in all stages of sleep [139, 140], with more profound decrements usually occurring during phasic REM than in NREM sleep states. REM sleep-related decrements in muscle tone leading to changes in thoracoabdominal mechanics with distortion of the thoracoabdominal wall will be further increased in obesity. During sleep, PO_2, V_T, and minute ventilation are decreased, whereas PCO_2 increases by 2–6 mm Hg. These changes are attributed to a resetting of the CO_2 set point and a depressed ventilatory drive per given level of PCO_2 compared to wakefulness. For unknown reasons, males have a reduced ventilatory response to CO_2 compared to females [141].

With sleep onset, sensitivity of the central CO_2 set point to the peripheral chemoreceptors is reduced. This results in a central apnea or a reduction in diaphragmatic effort and a decrease in tidal volume (central hypopnea), which allows P_{CO_2} to rise. If resumption of breathing induces obstruction by the mismatched timing mechanism discussed earlier, or if the dilatory muscles of the oropharynx have decreased tonicity, then a brief arousal may be triggered. Arousal resets the P_{CO_2} to the awake set point and increases ventilation. With the resumption of sleep, a cycling of central apnea, obstructive apnea, and arousal will occur [142]. This is commonly observed in the mixed apneas typically seen in obstructive sleep apneics. Any cause of sleep fragmentation, such as periodic limb movements, may bring about the unstable respiratory state in predisposed individuals that produces this common type of sleep onset apneas.

In addition to the chemoreceptor influences described earlier, pressure-sensitive reflexes exert a more rapid influence on upper airway patency. Located throughout the upper airway [142], pressure-sensitive reflexes coordinate the interplay of forces between inspiratory pump muscles and dilator muscles in a breath-to-breath fashion. When suction pressure produced by the diaphragm is registered, these reflexes increase genioglossus muscle activity, moving the tongue anteriorly and prolonging the duration of inspiration. Longer inspiratory times reduce the peak suction pressure, facilitating patency of the airway.

These reflexes are normally reduced during sleep but may be defective or ineffective in patients with sleep apnea. Issa and Sullivan [143] found upper airway closure to occur at abnormally low inspiratory pressures in patients with sleep apnea during a study in which the nasal airway was occluded. Even when peripheral chemoreceptor drive was added, which should facilitate patency, there was no augmentation in activation of the dilator muscles, as measured by closing pressure.

The degree of hypercapnia in sleep apnea is influenced by input from the peripheral chemoreceptors on upper airway

dilators and the inspiratory pump as well as the ability of these reflexes to trigger arousal with resumption of ventilation. Most OSAS patients are normocapnic while awake. However, a limited population of severe sleep apneics displays hypercapnia while awake that is not attributable to pulmonary disease or obesity. The hypercapnia in these patients indicates hypoventilation due to downward resetting of chemoreceptor reflex sensitivity. Sullivan's group [144] showed that these patients had decreased carotid body responses to hypoxemia and failed to develop normal augmentation of response to superimposed arterial hypercarbia. Elevated levels of CO_2 were required to produce a ventilatory response. These patients demonstrated long periods of obstructive apnea or hypopnea, concomitant with sustained arterial oxygen desaturations and arterial CO_2 elevations.

Resetting of chemoreceptors may allow the endurance of longer apneic events while asleep without producing arousals. Because the chemoreceptor responses are depressed, they do not lead to increased inspiratory efforts—as would normally occur with sensitive reflexes—thereby preventing the partially occluded upper airway from being sucked entirely closed. Diminished inspiratory efforts through a narrow upper airway cause reduced total ventilation, with oxyhemoglobin desaturation and CO_2 elevation. Tracheostomy or nightly treatment with nasal CPAP normalizes awake hypercapnia, suggesting that sleep apnea is a major factor in its development.

Snoring

Snoring is a noise produced when vibration occurs at several levels of the upper airway. It may be associated with various degrees of upper airway resistance. It may be heard after a complete airway obstruction; with a significant hypopnea; or with hypoventilation, leading to a cohort of symptoms. It may be associated with a limited and intermittent drop in V_T and be associated with isolated sleepiness. It may cause sleep fragmentation or present with no other clinical symptoms. The notion that snoring itself may engender cardiovascular risk is in question. Studies that suggested this probably failed to separate out subpopulations with UARS (discussed later), or situational apneics based on such behavior elicitors as alcohol or sedative use. Although more research is required, it is likely that chronic heavy snorers eventually become patients with clinically significant syndromes of obstruction. The diagnosis of "benign snoring" may not truly exist, as data from the Wisconsin cohort study showed that people that snored and did not have obstructive sleep apnea (an AHI below 5 events/h) had an elevated risk of developing hypertension over several years [57].

Vibration from snoring may damage the tissue and nerves of the upper airway, decreasing compensatory mechanisms that maintain airway patency. Snoring, however, is not a prerequisite for partial upper airway occlusion leading to clinical symptoms.

Upper Airway Resistance Syndrome

Upper airway resistance syndrome [6–9] may cause a chronic complaint of EDS that is objectively confirmed by abnormal scores on the Multiple Sleep Latency Test (MSLT). It was first described in patients who suffered from EDS. A retrospective study selected 54 patients previously diagnosed at Stanford University with idiopathic hypersomnolence based on pathologic MSLT scores, who were also snorers [6]. The mean group MSLT score was 6.1 min, with abnormal scores defined as less than 8 min. These patients did not fit standard criteria for OSAS in terms of RDI, significant oxygen desaturations, or both.

In 14 patients (9 women, 5 men), nocturnal sleep showed fragmentation with repetitive 3- to 14-s alpha rhythm EEG arousals, with a mean of 49 ± 11 arousals per hour of sleep. When studied by esophageal balloon manometry (a technique reflecting intrathoracic inspiratory efforts as negative "suction" pressure) and a pneumotachometer with face mask to quantify airflow, a pattern emerged. Increasing inspiratory efforts were demonstrated by excessively negative P_{es} nadirs between -13 and -51 cm H_2O (normal is greater than -8), accompanied by decreasing peak flows and V_Ts one to three breaths before the arousals. These sequences were punctuated by repetitive arousals. Because the arousals and snoring would have been the only abnormalities identifiable by standard PSG recordings, these patients would not have met standard criteria for OSAS based on oxygen desaturation or apneas and hypopneas as measured by nasal–oral thermistor.

These 14 patients underwent CPAP titration to eliminate the snoring and alpha arousals. At a 3-week follow-up, subjective complaints of EDS were eliminated in all 14 patients, MSLT scores normalized to a group mean of 13 ± 3 min, and arousals were reduced to eight per hour of sleep.

In a series of 93 UARS patients, Guilleminault and Chowdhuri [9] reported that 56 % were women, 32 % were of East Asian origin, and the mean age was 38 ± 14. Thus, sex, race, and age distribution differs from the typical OSA patient demographics. UARS patients frequently complain of insomnia, sleep fragmentation, and fatigue. Their psychological profile often reveals high anxiety. Other clinical features of UARS patients include cold extremities, postural hypotension, history of fainting, a low systemic arterial blood pressure (below 105 mm Hg), orthostasis on tilt-table testing, myalgias, and functional somatic complaints [9]. During sleep, UARS patients demonstrate an increase in

alpha rhythm and a relative increase in delta sleep, unlike OSA patients, who show a predominance of stages 1 and 2 NREM sleep with a decrease in delta sleep. Additionally, NREM sleep has been shown to be more disturbed in UARS patients than controls, with an increase in EEG cyclic alternating pattern (CAP) rate that correlates to symptoms of fatigue and sleepiness [145]. Despite the recognition of UARS as a distinct disorder, many patients remain untreated and experience worsened symptoms of insomnia, fatigue, and depressed mood over time [146].

The difference between UARS and OSA patients is hypothesized to be caused by genetically predetermined and environmentally altered pharyngeal receptors, particularly mechanoreceptors. Patients with UARS may have intact, sensitive, peripheral pharyngeal function, or hyperfunction, whereas OSA patients may have primary pharyngeal receptor dysfunction. Patients with UARS awaken in response to relatively small increases in respiratory effort compared to OSA patients, whose arousal threshold requires much higher inspiratory pressures (up to −40 to −80 cm H_2O).

Secondary Apnea

A variety of medical conditions and craniofacial malformations are commonly associated with OSAS. Patients with congenital conditions including micrognathia, such as Pierre Robin, Hunter's, and Treacher Collins syndromes, and Crouzon's disease, present in childhood; children with cleft palates repaired by a pharyngeal flap have developed iatrogenic obstruction. Cranial base abnormalities associated with OSAS include achondroplasia and Klippel-Feil syndrome malformations. Down syndrome patients have large tongues and retrognathia, predisposing to upper airway obstruction. Children with Prader–Willi syndrome may suffer OSAS due to morbid obesity. Treatment of Prader–Willi syndrome with growth hormone may worsen OSA, which may even lead to death [147]. Endocrine abnormalities causing OSAS include hypothyroidism with myxedema, which causes macroglossia and parapharyngeal tissue infiltration. Acromegaly is a known cause of macroglossia.

Neurologic disorders associated with OSAS include the Shy-Drager syndrome of multisystem degeneration (central and obstructive apnea) and neuromuscular diseases involving facial and thoracoabdominal musculature such as poliomyelitis and myotonic and muscular dystrophies. Patients with acquired or hereditary neuropathies (such as Charcot–Marie–Tooth disease) and those with amyotrophic lateral sclerosis are also at a higher risk for developing OSA. History of stroke or transient ischemic attacks significantly increases risk of OSA. Secondary kyphoscoliosis will worsen nocturnal respiratory function. Lesions of the temporomandibular condyle leading to retrognathia (developmental or acquired due to rheumatoid arthritis, osteomyelitis, or trauma) may predispose to OSA.

Evaluation

History: Nighttime Symptoms

Pertinent symptoms of OSAS fall into daytime and nocturnal categories. Loud guttural snoring, at its worst in the supine position, punctuated by choking sounds and followed by cessation of breathing, is virtually pathognomonic. Although snoring commonly starts around the time of puberty, presentation to a physician is typically prompted by a recent increase in snoring intensity associated with weight gain. The sleep of the bed partner is compromised by the patient's high-amplitude snoring and restless sleep. The volume may be so loud as to exceed standards set by the Occupational Safety and Health Administration for workplace safety [148]. The apneic phase can last from seconds to more than a minute. These respiratory cessations may frighten bed partners, who often remain vigilant to wake the patient to resume breathing. Commonly, partners begin sleeping in separate rooms, which may create stress in the relationship.

Restless sleep in large part stems from sleep fragmentation caused by airway obstruction. Repetitive EEG arousals lasting seconds may terminate apneic episodes, thereby causing a regain of "wakeful" muscle tone observed on the chin EMG. This facilitates a restorative breath, allowing the cycle to repeat. Behavioral arousals accompany some of these EEG arousals, resulting in position changes, abrupt rising of the upper torso from the bed, and large flailing limb movements. Some of these movements appear to be agitated, with concomitant groaning or crying out of short dysphoric phrases. The vast majority of brief arousals are not consciously recalled on awakening, although the patient may appreciate that the quality of sleep has been poor. Clues to restless sleep are obtained by asking the patient how disturbed are bedcovers by morning, and how many times he or she awoke during the night.

It is surprisingly infrequent for the patient to awaken with actual awareness of an asphyxial sensation such as choking or gasping. When this does occur, it may be accompanied by a "feeling of dying," and the patient may run to the window or sit up at the edge of the bed. Rarely, patients are still unable to draw an inspiratory breath upon awakening, but usually can do so after coughing. It is believed that this may be due to adhesion of the uvula to the posterior pharynx.

There appears to be a subpopulation of sleep apneics in whom the presenting complaint is sleep maintenance insomnia. Some of their arousals trigger full awakenings that last at least several minutes. Because they remain unaware of

the respiratory antecedents of these awakenings, OSAS should be considered among the differential diagnoses in evaluating patients with chronic difficulties maintaining sleep.

The clinician should ask about symptoms related to snoring, such as the presence of a dry mouth or sore throat on awakening. Asking the patient if he or she drinks water overnight may also elicit information on a dry upper airway. Morning headaches that resolve within an hour of awakening should also be asked about, as they may be clues to nocturnal hypercarbia and increased intracranial pressure. These headaches are typically generalized or bifrontal in nature. The occurrence of nocturnal confusional spells, such as watering the houseplants with milk, may be due to either hypoxemia or slow-wave sleep (SWS) parasomnias triggered by respiratory-induced arousal.

Multiple episodes of nocturia have been related to elevated plasma levels of ANP and catecholamines [149, 150]. After the first night of treatment with nasal CPAP, a return to normal levels with concomitant decrease in urinary volume to approximately 50 % of pretreatment amounts has been reported. This helps explain why enuresis is more common in children with OSAS and was reported in 7 % of 120 apneic adults seen successively at Stanford in 1992 [151]. Confusion and increased intra-abdominal pressure from inspiratory attempts against a closed upper airway may also contribute to enuresis.

Symptoms of nocturnal esophageal acid reflux and heartburn are facilitated when excessively negative intrathoracic pressure exerts upward suction on abdominal contents, and increased abdominal pressure expels the contents. The patient may also complain of nocturnal aspiration. Bruxism may be noted and may be a clue to dental malocclusion resulting from the common jaw misalignment etiologically related to OSA. A history of orthodontic treatment to correct an overjet is common. The patient may have a history of wisdom tooth extraction secondary to impaction. These individuals may also manifest morning headaches or dysfunction of the temporomandibular joint.

History of seasonal or environmental allergies should be sought, as these are common causes of nasal obstruction in adults and adenotonsillar enlargement in children. Studies of rhesus monkeys with chronic and temporary nasal obstruction suggest that nasal obstruction with mouth breathing during childhood is etiologically related to subsequent mandibular growth insufficiency [126, 127]. We have documented craniofacial abnormalities with cephalometric radiography that were not appreciated on clinical examination [128].

Nocturnal diaphoresis of the face and chest may be seen in association with the increased effort required to inspire against resistance during the night. Increased caloric expenditures to breathe may also account for a subpopulation of sleep apneics who have difficulty gaining weight.

Ethanol or other sedatives used before bedtime worsen OSAS by at least two mechanisms. They greatly diminish the contraction of the upper airway dilators, as well as interfering with the organization of reflexes coordinating upper airway dilators with the contraction of inspiratory muscles [152]. They may also increase the cortical arousal threshold, allowing more prolonged apneas and severe oxygen desaturations. A history of increased snoring or development of any of the symptoms discussed earlier in association with sedating substances should raise the index of suspicion for OSAS. In elderly patients with AI greater than 5 events/h, sedative use or sleep deprivation may escalate the AI into the pathologic range [153].

History: Daytime Symptoms

The cardinal daytime symptom of OSAS is EDS, which manifests as a tendency to inadvertently fall asleep during quiet or passive activities, to take intentional naps, or to experience short but repetitive attention lapses while doing monotonous tasks. Such sleepiness is the consequence of sleep fragmentation. Patients usually misperceive the act of dozing off as being caused by the characteristics of the situation (i.e., boredom), rather than by their abnormal intrinsic degree of somnolence. It helps to inform patients that quiet settings do not produce sleepiness, but merely unmask it. Patients often forget or deny episodes of daytime sleepiness, which may better be elicited from household members who frequently observe the patient dozing while watching television or reading. Momentary lapses into sleep while driving are a potentially lethal consequence of somnolence, and history of these lapses should always be sought by inquiring about motor vehicle accidents due to sleepiness or inadvertently dozing at the wheel or swerving into another lane. Such incidents are particularly likely on long or monotonous trips. Affirmative answers require rapid treatment interventions.

Symptoms of fatigue, tiredness, and lack of energy are frequently reported by patients with OSA and must be enquired about during the clinical interview. These symptoms are more frequently reported and emphasized by OSA patients than sleepiness [154].

Cognitive complaints resulting from EDS are common and may be the only clue to OSA in those who misperceive their sleepiness. Automatic behavior, when an action is performed without subsequent recall, is an extreme manifestation of such cognitive impairment. Increased errors and poor judgment may place patients at risk of losing their jobs [12]. Severe morning confusion and disorientation, termed *sleep drunkenness,* may be a sequela of preceding hypoxemia. Studies have shown OSA patients have problems with attention, executive behavior, visuospatial learning, motor

performance, and constructional ability [155]. A meta-analysis showed a trend for improved performance of cognitive outcomes in OSA patients treated with CPAP compared to placebo [156]. Larger studies are currently underway evaluating the impact CPAP has on cognitive performance.

Sleep fragmentation may produce personality changes that are often first noted by family members. These include moodiness, irritability, anxiety, aggression, and depression. More marked personality changes involving irrational behavior, jealousy, and paranoia have been reported. Sleepy patients report less enjoyment from previously engaging activities. They are typically misperceived as unmotivated or lazy, descriptors they come to believe if the underlying etiology remains undiscovered.

Diminished libido or impotence is not an uncommon complaint, even in nonelderly OSA patients. Fanfulla et al. reported abnormal bulbocavernosus reflex in 68 % of 25 male OSA patients with AHI greater than 10 events/h [157]. These abnormalities correlated significantly with the severity of OSA and the severity of gas exchange alterations, but did not vary with age. With treatment of OSA, sexual function may improve [158–164].

In taking the medical history, inquiries regarding systemic sequelae must be sought. These include the existence and duration of borderline or elevated blood pressure; angina; symptoms of right heart failure, including peripheral edema; and transient cerebrovascular ischemic symptoms.

Physical Examination

Patient evaluation begins with observing the patient in the waiting room for sleeping or snoring. Obesity (BMI $\geq$ 30 kg/m^2) and neck circumference greater than 40 cm have shown a sensitivity of 61 % and specificity of 93 % for OSA regardless of gender [165]. The distribution of weight should be noted, as more midline depositions favor nocturnal respiratory pathology. In particular, adiposity or muscularity of the neck predisposes to upper airway obstruction, and severe abdominal obesity may also predispose to alveolar hypoventilation. A nasal voice is a clue to nasal obstruction, and mild hoarseness is often noted in heavy snorers. The lateral facial profile should be inspected for retrognathia or micrognathia, keeping in mind that the relevant site is the indentation below the lip that identifies the genial tubercle, where the tongue makes insertion on the mandible. The patient should bite down to demonstrate dental occlusion. Overjet is recorded in millimeters, and underbite should be noted as well. Palpate the temporomandibular joint while the patient opens the jaw widely for subluxation or a click as evidence of jaw misalignment. The oral cavity is inspected for dental prostheses, size of tongue, and soft palate tissue size and appearance. Soft palate edema and erythema may be due to snoring. A soft palate inferiorly positioned behind the tongue may be due to stretching from chronic excessive suction as a result of snoring. Tonsillar hypertrophy is noted. The hard palate is checked for a high arch, which has been found to correlate with OSAS.

Evidence of upper airway obstruction is obtained by evaluating breathing in the supine position with the jaw slackened slightly open and the nares occluded, to simulate oral breathing during sleep. If snoring or labored breathing results, this is good evidence that even greater difficulties will occur during sleep. The nose should be assessed for septal deviation, polyps, flaring of the nostrils, collapse of the internal valves, and patency of either vestibule with the opposite naris occluded. The thyroid should be examined for evidence of enlargement.

Blood pressure and pulse are measured and a general physical examination is performed, bearing in mind signs of dysrhythmia or heart failure. Lung auscultation provides clues of pulmonary pathology that would exacerbate oxygen desaturation caused by upper airway obstruction. A complete neurologic evaluation may uncover neuromuscular disorders impacting on upper airway patency and respiratory muscle function. A complete physical examination can eliminate the presence of generalized diseases, particularly those causing lymph node enlargement or mucosal infiltration, which may reduce the upper airway lumen.

The history and examination should reveal secondary causes of OSAS, including searching for a local tumor in the upper airway. Suspicion is raised in the presence of rapid emergence of obstructive symptoms not associated with weight gain, throat pain, constant hoarseness or other vocal cord dysfunction, prominent difficulties swallowing, or nasal regurgitation. Such symptoms should prompt otolaryngologic evaluation.

Laboratory Evaluation

Polysomnography

A full-night PSG study in the sleep laboratory is the main method of evaluation (level 1 study). The study devotes various channels to the recording of the EEG (i.e., F3–M1, C4–M1, C3–M1, 01–02), electro-oculogram (EOG), chin and limb (usually anterior tibialis) noninvasive EMG, qualitative measurements of oral-nasal airflow, thoracic and abdominal respiratory efforts, electrocardiogram (ECG), and pulse oximetry. An entire night of study is generally recommended, as opposed to a partial night, because substantial changes in respiratory disturbance typically occur from one sleep cycle to another across the night. Because REM sleep

predominates toward the end of the night, REM sleep-related respiratory disturbances might easily be missed without a full night of study.

However, in some circumstances, a split-night study can be considered. The split-night study requires the recording and analysis of the same parameters as a standard diagnostic full-night PSG. Recent guidelines from the American Academy of Sleep Medicine (AASM) state that a split-night study may be considered in patients if four criteria are met [156]. The first is that an AHI of at least 40 events/h be documented during a minimum 2-h diagnostic PSG. Split-night studies may be considered at an AHI of 20–40 events/h, based on clinical judgment (e.g., if there are also repetitive long obstructions and major desaturations). The second criterion is that CPAP titration be carried out for more than 3 h as respiratory events can worsen as the night progresses. The third criterion is that PSG documents that CPAP eliminates or nearly eliminates respiratory events during REM and non-REM sleep, including REM sleep with the patient in the supine position. The last criterion is that a second full-night PSG with CPAP titration be performed if the diagnosis of a sleep-related breathing disorder is confirmed but the second and third criteria are not met [165, 166].

A monitored level 1 PSG allows quantification of various factors that are disturbed in sleep apneics, including the RDI, oxygen desaturation, sleep stage percentages, and sleep efficiency. Sleep fragmentation can be assessed as variable-length awakenings or EEG arousals lasting only several seconds. CAP can be sought in non-REM sleep as a subtle indication of cortical arousals [167]. PSG helps determine whether the arousals are due to apnea or unsuspected factors such as periodic limb movements or primary insomnia. Associations between sleep stage and positional influences on respiratory disturbance can be made. Cardiac arrhythmias and their relationship to oxygen desaturation and sleep stage can be identified. Relatively invasive techniques to measure upper airway pressure may have circumscribed clinical usefulness. UARS (discussed earlier) may only be suspected based on transient alpha rhythm EEG arousals on the standard PSG, warranting additional investigation using esophageal manometry. Catheter systems allowing measurement of differential pressures at different levels of the upper airway may also help in determining the level of collapse at which surgical intervention should be addressed [168–170].

Pulse transit time measures the transmission time for the arterial pulse pressure wave to travel from the aortic valve to the periphery; it increases during arousal-induced increases in blood pressure. Pulse transit time has a high sensitivity and specificity in distinguishing between central and obstructive apnea-hypopnea and may be used if P_{es} monitoring is not available on attended PSG [171].

Technologies that allow in-home sleep monitoring are rapidly emerging. Portable units range from study levels 2–4. Level 2 units contain a minimum of seven channels, including EEG, EOG, chin EMG, ECG or heart rate, airflow, respiratory effort, and oxygen saturation. Level 3 units contain a minimum of four channels, including ventilation or airflow (with at least two channels of respiratory movement, or respiratory movement with airflow), heart rate or ECG, and oxygen saturation. Level 4 units measure a single parameter or two parameters, such as oxygenation and heart rate.

Although portable studies are a more convenient and less expensive alternative to standard PSG, there are significant limitations. The absence of trained personnel to intervene in the event of technical difficulty or medical emergency is one of the primary shortcomings. Concern has also been raised about the precision and accuracy of some portable units for the evaluation of more subtle cases of SDB, such as those with a predominance of hypopneas or UARS [172]. The most recent practice parameters published by the AASM approve the use of level 3 unattended portable monitoring units for the diagnosis of OSA in a limited setting [173, 174]. The guidelines state that these unattended studies can be performed only in conjunction with a comprehensive sleep evaluation by a board-eligible or board-certified sleep medicine specialist. A sleep medicine specialist must also interpret the study. Portable testing should only be performed on adult, nonelderly patients with a high pretest probability of having moderate-to-severe OSA without other sleep disorders, including central sleep apnea, periodic limb movement disorder, insomnia, parasomnias, circadian rhythm disorders, or narcolepsy. Furthermore, patients are not eligible for portable testing when they have comorbid medical conditions that may degrade the test accuracy, such as chronic obstructive pulmonary disease (COPD) or peripheral vascular disease. These recommendations further state there is insufficient evidence to use level 2 or 4 devices in an unattended setting [174].

Multiple Sleep Latency Test

The MSLT [175] is considered to be an objective measure of EDS. A series of daytime naps (usually five) of 20-min duration at 2-h intervals is performed to determine time to sleep onset. These sleep latencies are averaged. Scores under 8 min in the absence of confounding factors (e.g., insufficient preceding nocturnal total sleep time, use of hypnotic medication) are generally regarded as abnormal. REM occurrences during naps are also noted.

Because the demonstration of EDS is not required for the diagnosis of OSAS, MSLTs are not mandatory in the

evaluation of OSAS. If a PSG for suspected OSAS is negative, however, MSLT performed the subsequent day may help diagnose a different sleep disorder of excessive somnolence, though 5–15 % of OSA subjects can have MSLT findings consistent with narcolepsy. When complaints of sleepiness persist after adequate treatment is instituted, an MSLT may reveal an unsuspected second sleep disorder, requiring a separate treatment approach.

In large clinical populations, the severity of OSA based on AHI was not particularly predictive of sleepiness as objectively measured by the MSLT [175, 176].

Imaging Studies

As an adjunct to clinical evaluation, particularly when surgical treatment is contemplated, various imaging procedures can help identify the site(s) of upper airway obstruction. For a comprehensive review, the interested reader is referred to papers by Shepard et al. [177] or Faber and Grymer [178]. Imaging is also imperative when the history raises suspicion of a mass lesion as the cause of upper airway obstruction. It should be kept in mind that procedures performed on an awake patient do not reveal the actual anatomy during sleep, when postural and state-related changes in muscle tone alter the awake relationships.

Cephalometric radiographs provide a midline view of relevant cranial base and facial bones with their soft tissue appendages. Maxillary or mandibular deficiency can be calculated, and awake posterior airway space measured as the distance between the base of the tongue and posterior pharyngeal wall. Soft palate and lymphoid tissue extent is identified.

Fiberoptic endoscopy of the upper airway down to the vocal cords performed in the seated and supine positions provides further assessment of the possible sites of collapse. The patient can perform Valsalva and Müller's maneuvers to elicit collapse, although the predictive value for identifying candidates for surgical success after uvulopalatopharyngoplasty (UPPP) is limited [179–181]. Fiberoptic endoscopy should be systematically performed to eliminate secondary causes of upper airway obstruction if signs and symptoms are consistent with them.

Computed tomography (CT) scanning provides detailed surveys of cross-sectional levels of the upper airway, and magnetic resonance imaging (MRI) can be used to image multiple planes. CT and MRI have mainly been used as research tools due to their expense. Newer techniques such as fast CT scanning may prove to have prognostic clinical usefulness in selecting candidates for successful surgical outcomes. The 50-m s scan time, as compared to 2–5 s for conventional CT, is sufficiently rapid to show dynamic dimensional changes across various levels of the upper airway during the respiratory cycle. It can potentially be used in a sleeping patient.

Videofluoroscopy of the pharynx in anteroposterior and lateral directions offers another means for observing dynamic anatomic changes in the upper airway during ventilation. It is of limited clinical usefulness in view of its significant radiation exposure.

Other Studies

Pulmonary function tests, including spirometry and arterial blood gases, are a useful adjunct in investigation. Diminished vital capacity has been identified as a risk factor for SDB both in the Cleveland Family Study and in the elderly [22, 182]. Although associated with excess cardiovascular morbidity, a lowered vital capacity may be a marker for central obesity or an indicator of the presence of OSAS [183, 184]. Patients with daytime hypoxemia or CO_2 retention due to intrinsic lung disease might be expected to show severe oxygen desaturations with the addition of obstructive sleep pathology and may require cautious addition of low-flow oxygen to nasal CPAP. Those with restrictive pulmonary dynamics based on morbid obesity might require special treatment with bilevel positive airway pressure (BIPAP) or intermittent positive pressure ventilation delivered by nasal mask. Arterial blood gases provide the most relevant information for a sleep evaluation if obtained after the patient remains supine for 20 min. This aids in detection of insufficient ventilation associated with the supine position.

Thyroid function screening will exclude hypothyroidism as a cause of apnea and daytime somnolence. Polycythemia without known lung disease should lead to a consideration of sleep apnea.

Treatment

Behavioral Recommendations

Once OSAS is diagnosed, treatments can be suggested based on evaluation of contributing factors and disease severity. It has long been known that weight loss in obese patients is effective in the reduction of the number of apneas, sleep fragmentation, and the extent and number of desaturations. In overweight patients without obvious fixed anatomic considerations such as retrognathia, weight loss may result in eventual cure. For most patients, nasal CPAP should be instituted along with weight loss measures. These measures include weight reduction surgery, diet with or without pharmacologic intervention, and exercise. When applicable,

a program of exercise may be facilitated after daytime somnolence is ameliorated by CPAP. For those who are not completely cured by weight loss, the significant reduction in weight often allows a lower CPAP pressure requirement or increases the likelihood of a surgical cure. Patients with large losses should be re-titrated to the lowest effective pressure.

Elimination of central nervous system depressants such as ethanol or sedatives from the bloodstream at bedtime decreases the severity of OSAS. If a strong positional relationship is discovered, with obstruction limited to the supine position, recommendation to remain in a lateral or prone position can be made. A sock filled with a golf or tennis ball and sewn onto the back of the pajamas or T-shirt may help patients learn to avoid the supine position. A full-length wedge pillow may also be helpful in this respect. In mild cases, attention to position may suffice.

Pharmacologic Treatment

Currently, there are no US Food and Drug Administration (FDA)-approved medications that treat OSA. Tricyclic antidepressants such as protriptyline have been used to increase muscle tone and diminish REM sleep time in cases of mild or REM sleep-related OSAS. Progesterone acts as a respiratory stimulant in obese patients but has no impact on an obstructed airway. Paroxetine has been shown to mildly decrease apneas during NREM sleep [185]. Provigil has an FDA approval to treat residual daytime sleepiness of treated OSA patients, with statistical improvements in Maintenance of Wakefulness Test, Epworth Sleepiness Scale, and quality-of-life scores compared to controls [186]. Unfortunately, to date, pharmacologic approaches designed specifically to treat SDB have been largely unsuccessful.

Continuous and Bilevel Positive Airway Pressure (See also Chap. 34)

An enormous advance in the treatment of OSAS began in the early 1980s with the first commercially available continuous positive pressure generators. These bedside machines compress room air and channel it through a soft vinyl or silicone nasal mask, a full-face (nasal-oral) mask, or endonasal cushions at a given pressure. CPAP serves as a pneumatic splint to keep the upper airway patent. Pressure requirements must be established during sleep for each patient. Optimum pressure is the lowest one that completely eliminates obstructive apneas, hypopneas, snoring, and mask flow limitation and normalizes arterial PO_2. Patients who routinely consume ethanol in the evening are most accurately titrated to CPAP after consuming their usual intake, which raises the pressure requirement.

BIPAP differs from CPAP by using separate inspiratory and expiratory pressures. BIPAP machines time themselves to patient-initiated breathing. By reducing the pressure on expiration, BIPAP lowers the resistance against which the patient must exhale. This is advantageous for patients with severely restrictive pulmonary dynamics, such as those with emphysema, the morbidly obese, and those with neuromuscular weakness. Patients with normal lungs who could not tolerate CPAP might feel more comfortable on BIPAP, especially those requiring higher CPAP pressures (approximately 13 cm H_2O). Those with severe discomfort due to drying of the mucosa could benefit from BIPAP because of the overall decrease in airflow relative to CPAP. BIPAP also offers a higher range of inspiratory pressures than CPAP, with maximum pressures of 30 cm H_2O. The newer devices with extended pressure range also have the ability to control inspiratory time (flow) and are therefore more appropriate for patients with isolated neuromuscular disease. Intermittent positive pressure ventilation may be more useful in some patients with sleep-related hypoventilation who cannot be maintained on bilevel units.

A PSG study to titrate CPAP or BIPAP pressure should be performed for one entire night to allow adequate assessment. A second titration night can be done if an adequate pressure was not identified the first night. Ideally, the optimum pressure is checked for adequacy throughout all stages and positions. It is especially critical to evaluate the patient in the supine position, when the maximum pressure requirement occurs. Unfortunately, financial constraints increasingly dictate that split-night studies be performed. This method of diagnosis and treatment tends to underestimate the severity of disease because treatment takes place in the latter half of the night when apnea is usually at its worst. In patients with severe apnea, a rebound of unusually long REM sleep and SWS that may be out of circadian phase occurs once adequate airway patency is attained. REM sleep rebound shows unusually prominent phasic activity, whereas the SWS episodes may show exceptionally high voltage EEG activities. Rare but dangerous sequelae of REM rebound have been seen in severe apneics with CO_2 retention under slightly suboptimal pressure. Arousal is suppressed during a long rebound, and if partial upper airway closure persists, dangerous hypoxemia may result [182].

Auto titrating positive airway pressure (APAP) devices offer a theoretical advantage of foregoing a traditional CPAP titration study by delivering the lowest pressure needed to prevent respiratory disturbances. These devices may decrease side effects of traditional CPAP such as air swallowing and abdominal bloating and are theoretically able to accurately record flow leaks, hypopneas, and apneas. They detect snoring, apneas, hypopneas, flow limitation, and changes in airway resistance or impedance, which are then interpreted by a central processing unit based on specific

diagnostic algorithms to determine the resultant voltage for the APAP blower in response to these signals [187]. Studies have shown significant variability between different APAP devices, with undertreatment of 13–60 % of patients using the devices (residual RDI > 5 during treatment) as usually the APAP device is set between 4 and 20 cm H_2O, a setting that should not be used: Based on clinical evaluation, a minimum setting should be selected by the specialist [188]. There is insufficient evidence to use these devices to diagnose OSA [189].

The 2007 AASM practice parameters on APAP devices give sleep specialists the option to use these devices in an unattended setting to treat uncomplicated OSA patients [189]. Potential patients include those with moderate-to-severe OSA without significant comorbidities such as congestive heart failure, COPD, central sleep apnea syndromes, or hypoventilation syndromes. Sleep specialists have the option of treating these OSA patients with APAP devices either left in the self-adjusting mode or set at the prescribed 90th or 95th percentile pressure and utilized during a several-week trial period. Patients prescribed APAP devices should be closely followed by a sleep medicine specialist to ensure adequate treatment. A standard CPAP titration should be performed in patients whose symptoms do not resolve with APAP [189].

A severe limitation of APAP devices is that they determine pressures differently, and there are few studies comparing various APAP devices to each other and to set CPAP devices. APAP is not superior (and many would argue not even equivalent) to a fixed CPAP pressure determined by an attended titration. Therefore, AASM guidelines state "polysomnography directed CPAP titration is still the standard method for determination of effective CPAP pressure" [189]. With improvements in technology, greater clinical experience, and growing literature on the subject, APAP devices will likely be more widely used in the future.

Treatment with nasal CPAP or BIPAP offers advantages of safety and assured efficacy over surgical approaches. They offer immediate and complete treatment for OSAS and are less costly than extensive surgical approaches. They can be used temporarily while weight loss is pursued or surgery is pending. Positive pressure eliminates risk factors for associated morbidity along with daytime somnolence. Modern CPAP units are small, portable, and quiet. Most have a ramp feature that gradually adjusts the pressure upward to the preset pressure, allowing sleep onset to occur at more comfortable lower pressures.

Disadvantages of CPAP lie in psychological resistance to ongoing nightly reliance on a machine. Poor compliance is the main obstacle to this treatment modality. Patients may feel claustrophobic and intolerant of the restriction of their movement and may perceive the treatment as an obstacle to intimacy with their bed partner and as a reminder of their mortality. The devices are annoying to some patients, although they are continually improved. Those traveling frequently may find it inconvenient. Generally, young adults and patients who are dating find this treatment to have an unacceptable social impact.

Common physical difficulties encountered include reactive nasal congestion or rhinitis, sinusitis, epistaxis, drying of the nasal-oral mucosa, discomfort or skin trauma from a poorly fitting mask, and an allergic reaction such as contact dermatitis from the mask interface. Nasal symptoms usually subside after the first few months and can be ameliorated with heated humidification, daily nasal rinses, and a nasal steroid inhaler. Comfort issues and dermatitis should be closely supervised and addressed with trials of various mask adaptors and styles or by altering the mode of delivery via nasal pillows or other mask types. Psychological distress is minimized by support from the entire sleep laboratory team, with reassurance and understanding at the time of initiation and close follow-up. Sleep apnea support groups exist in many areas to help with coping and compliance. Occasionally, a brief course of bedtime hypnotics is required, with the patient's full understanding that the severity of apnea will worsen if the medication is used without the CPAP device. Flow leaks through an open mouth can be minimized by use of a chin strap.

Long-term compliance has been only fair, with an estimate of 60–85 % of patients using their machines regularly after one year [190, 191]. Compliance has been associated with the severity of daytime hypersomnolence before CPAP, but not with pretreatment disease severity as indicated by the RDI or oxygen saturation nadir. Intellectual understanding of the benefits of nightly use (i.e., to decrease cardiovascular risk factors) appears insufficient to motivate long-term compliance. Cognitive behavioral interventions may improve compliance [192]. In one study, use of a C-flex device was shown to significantly increase patient compliance [193].

In patients who do not wish to undergo the extensive surgeries that might be required to produce a complete cure, selective surgery to relieve nasal obstruction can reduce pressure requirements and improve CPAP tolerance. In patients with more than mild oxygen desaturation on diagnostic testing (i.e., <85 %) who choose surgical treatment, CPAP initiation may be contemplated preoperatively to decrease the postoperative risk of further desaturation due to edema. Preoperative CPAP also reduces soft palate edema due to snoring and improves overall health status. Weight

loss before surgery while using CPAP increases the chance of successful cure by creating more airway space through parapharyngeal tissue reduction.

Surgical Approaches (See also Chap. 36)

The first surgical treatment for OSAS was tracheostomy. This intervention is rarely needed now, because of the pervasive use of positive pressure therapy. Although used infrequently, tracheostomy provides immediate profound improvement for some individuals with severe OSAS. Maintenance of a tracheostomy is associated with some morbidity and psychosocial implications.

Surgery is individually tailored to overcome upper airway obstruction after a thorough analysis of the three main levels of potential obstruction: the nose, soft palate, and base of the tongue or hypopharynx. Often, more than one level must be treated, either sequentially or simultaneously. Patients must understand that surgical treatment is an extensive and more costly process with greater risks than medical treatment. In addition, surgery carries no guarantee of cure in an individual patient, with only statistical cure rates available.

Nasal obstruction can be corrected with septoplasty, polypectomy, or radiofrequency turbinate reduction. Though these procedures can improve nasal breathing and SDB, nasal surgery alone successfully treats only a minority of OSA patients.

Soft palate resection via UPPP or uvuloflap surgery has an approximately 40 % response rate in individuals but is much less successful in obese patients [194–203]. However, the success rate can be as high as 80 % in properly selected patients [195–201]. Depending on how "success" is defined, these rates may be altered considerably. Most surgeons consider OSA surgery as success if a 50 % reduction of the AHI achieved. The most common postoperative adverse sequelae include severe pain for approximately two weeks, transient nasal reflux and nasal speech due to palatal incompetence, minor loss of taste, and tongue numbness. Major complications involve permanent nasal reflux or nasal speech due to permanent velopharyngeal incompetence and scarring with retraction leading to palatal stenosis.

Because UPPP ameliorates snoring due to vibration of the uvula without addressing potential obstruction behind the base of the tongue, a major sign of ongoing residual obstruction may be masked. It is therefore imperative to follow up all surgeries with a postoperative sleep study. Ideally, this study should be delayed at least four months after surgery to allow thorough resolution of edema and readjustment of respiratory reflexes. Those patients with moderate-to-severe apnea can be maintained on CPAP in the interim and withdrawn two weeks before study to allow expression of airway changes from potential residual obstruction.

Genioglossus advancement via inferior sagittal osteotomy is a technique pioneered at Stanford University [204] that addresses the retroposition of the tongue by advancing the insertion point of the genioglossus, the geniotubercle. The surgeon makes a small mandibular incision at the geniotubercle, pulls the bone segment through the jaw, and allows the fracture to heal. This is usually performed in conjunction with UPPP. The success rates have been variable, ranging from 23 to 77 % [204–210]. Common complications are minor and consist of transient dental nerve anesthesia. Mandibular fracture may occur if the incision extends into the alveolus.

Hyoid advancement can expand the airway by moving the tongue base and pharyngeal musculature forward. This is achieved by attaching it to the thyroid cartilage. This procedure is usually performed in conjunction with genioglossus advancement to improve OSA, but some surgeons will combine it with UPPP alone [207, 209, 211]. The success rate of hyoid advancement is variable and ranges from 17 to 65 % [210, 211]. This surgery requires an external incision on the neck.

Maxillomandibular advancement (MMA) is another surgical option to improve OSA. It is generally reserved for patients for whom other treatments have failed and who do not want to be treated with nasal CPAP. This procedure expands the entire airway, including the nasopharyngeal and hypopharyngeal airway. Patients undergoing MMA who have previously undergone the earlier discussed surgeries can have excellent improvement of OSA. Generally the jaws must be advanced 8–14 mm for adequate treatment of OSA. MMA is currently the most effective sleep apnea surgical procedure, with success rates generally between 75 and 100 % [206, 212–215]. MMA shows promising cure rates long term, but weight gain is associated with the recurrence of OSA [215].

Tongue base suspension suture is thought to reduce the collapsibility of the tongue during sleep [213]. It is often performed in conjunction with UPPP, with variable success rates reported [217, 218]. Radiofrequency reduction of the base of the tongue may also improve OSA by increasing the retropharyngeal airway space. Though this procedure does improve OSA when performed alone, it does not appear to be as successful in the long run [219]. Many surgeons perform this procedure in conjunction with UPPP or MMA.

Bariatric surgery with significant weight loss has been shown to improve and even cure OSA in morbidly obese patients [220–222].

Oral Appliances (See also Chap. 36)

Various types of dental devices have been used to treat OSA. They work by increasing airway space, providing a stable

anterior position of the mandible, and advancing the tongue or soft palate, and possibly by changing genioglossus muscle activity [223]. The devices are worn only during sleep. There are a variety of oral appliances; some are prefabricated and are relatively inexpensive, while others are custom-made by dentists. The advantage over surgery is that there is no permanent change of anatomy and no surgical risk involved.

The most effective devices are those that cause the mandible to protrude forward. A meta-analysis concluded that oral appliances mildly improved subjective daytime sleepiness and SDB compared with controls, but less well than CPAP [224]. Though patients tend to be more compliant with wearing oral appliances than using CPAP, these devices tend not to be as effective in treating OSA [189]. Patients are more likely to achieve success with an oral appliance if they have less severe OSA, are nonobese, have positional OSA, and are able to significantly protrude their jaw from baseline [225, 226].

According to AASM guidelines, oral appliances can be used in patients with mild-to-moderate OSA who prefer them to CPAP therapy, or who do not respond to, are not appropriate candidates for, or fail treatment attempts with CPAP [227]. The success rate of oral appliances often mirrors the severity of OSA, with patients with mild OSA more likely to achieve success than those with severe OSA. Referral to a dentist who is adequately trained and has understanding of SDB is paramount. Minor tooth movement and cg changes in occlusion can develop in some patients after prolonged use 212a.

Obstructive Sleep Apnea in Children

Obstructive sleep apnea occurs in premature and full-term infants as well as in children (see also Chap. 52). Although this disorder in children was neglected for a long time, it is a common disorder affecting 3 % of children 2–8 years of age [228–232]. In very young patients, the apnea usually becomes apparent as a result of color change and bradycardia. In most children, a constellation of daytime and nighttime clinical symptoms signals the condition. At different ages, different symptoms are more common. Postpubertal teenagers do not differ from young adults, but younger children often present a different clinical picture.

Clinical Features

Obstructive sleep apnea syndrome can be associated with a series of daytime and nighttime signs and symptoms that may not be obvious at an initial evaluation [229, 230]. The daytime symptoms include EDS so severe that school authorities suggest medical consultation, and abnormal daytime behavior ranging from aggressiveness and hyperactivity to pathologic shyness and social withdrawal. Children may exhibit more subtle symptoms including inattention, daytime fatigue, learning problems, morning headaches, frequent upper airway infections, failure to thrive, and obesity. Nocturnal symptoms seen at all ages include difficulty breathing while asleep, heavy snoring, apneic episodes, restless sleep, nocturnal sweating, nightmares, and SWS parasomnias. The absence of normal growth or failure to thrive can be seen at most ages [227, 230–237].

Reasons for seeking consultation vary with age. Before 12 months of age, children may present with noisy nocturnal breathing, disturbed nocturnal sleep, and repetitive crying, or a poorly established day–night cycle may be the presenting features of OSA. OSA may also contribute to the occurrence of an apparent life-threatening event due to abnormal autonomic cardiovascular control and an increased arousal threshold [238, 239].

In toddlers, nocturnal crying spells or sleep terrors may prompt an evaluation for OSA. Grouchy or aggressive behavior, daytime mouth breathing, and difficulty waking up may be seen. Difficulty breathing while asleep, heavy snoring, apneic episodes observed by parents, restless sleep, nightmares, and night terrors are the most frequent reasons for consultation. This may be partly due to the parents' ability to evaluate a young child's sleep often and the fact that young children fall asleep early, allowing parents to note abnormal sleep behavior.

In children older than 5 years, EDS (associated with complaints of tiredness and daytime fatigue), abnormal daytime behavior, learning disabilities, frequent morning headaches, nocturnal enuresis, and major discipline problems are common reasons for consultation. A few children are referred at a late stage of the syndrome [240]. These children not only present significant failure to thrive but also may have been hospitalized for unexplained acute cardiac failure or unexplained development of systemic hypertension. The cardiac failure often will have occurred after the child had contracted a cold or bronchopneumopathy, which may not have been severe but, in combination with the chronic nocturnal problem, nevertheless led to the acute failure.

Symptoms of attention-deficit/hyperactivity disorder (ADHD) have been positively associated with SDB in children. Chervin et al. showed that children diagnosed with ADHD had a threefold increase in snoring compared with controls [237]. Other studies have shown similar findings [230, 235, 236]. What is even more interesting is that snoring on its own has been shown to be a strong risk factor for future emergence or aggravation of ADHD symptoms [237].

Classically, the pediatric patient presenting with OSA has large tonsils and is underweight and having difficulty increasing his or her weight, despite a normal appetite. He or she also may be shorter than expected. Nocturnal secretion of growth hormone in children with repetitive apneas has been shown to be abnormally low. We have noted a similar decrease with heavy snoring, due to decreased growth hormone levels released during sleep and elevated caloric expenditure from increased work of breathing. In addition, childhood obesity is becoming an epidemic, more obese patients are presenting with OSA and the incidence of pediatric OSA will likely rise. It is estimated that up to one-third of obese children have OSA [231, 241].

The clinical evaluation of children should be as thorough as for adults, and suspicion of OSAS should lead to PSG monitoring during sleep.

Polysomnographic Testing

Although repetitive apneas may be seen in children with equal frequency as in adults, most commonly the PSG indicates only intermittent apneas. Sometimes no apneas are monitored, even when a florid symptomatology exists [242]. A pediatric sleep study is evaluated differently than an adult record. The criterion for an apnea or hypopnea duration is equal to two breaths for the patient or 10 s, whatever is shorter. An AHI greater than 1/h is considered abnormal in the pediatric population [243]. Pediatric OSA patients have fewer cortical arousals with breathing events and their sleep architecture tends to be better preserved compared to adult OSA patients.

Prepubescent children have a greater tendency to present complete apneas during REM sleep. During NREM sleep, prepubescent children with OSAS present as loud snorers. Documented by a sonogram, snoring is commonly associated with an increase in respiratory rate. The degree of tachypnea is variable within a given age group and sometimes within a given subject during the night. The increase in breathing frequency compensates for the decrease in V_T and allows maintenance of normal minute ventilation with an appropriate level of oxygen saturation. However, partial upper airway obstruction leads to great enhancement of respiratory efforts, which is obvious when one observes the laborious, noisy mouth breathing during sleep. P_{es} measures demonstrate the increase in respiratory efforts. P_{es} nadir may reach −35 to −40 cm H_2O without induction of a complete collapse of the upper airway in children 5–6 years old. Increased efforts may also be demonstrated by monitoring of intercostal-diaphragmatic EMG. Surface electrodes placed 10 mm apart near the eighth right intercostal space, between the anterior and posterior axillary lines, permit collection of the EMG activity of the inspiratory muscles. The signal can be integrated, and, depending on the calibration procedures used, semi-quantitative or quantitative measurements may be obtained. Measurement with surface electrodes and integration of abdominal muscle activity during expiration may demonstrate the degree of active expiratory effort that some of these children have to perform.

Despite the increase in respiratory efforts associated with snoring and increased upper airway resistance, children may not present with very fragmented sleep. The short alpha rhythm EEG arousals seen with increased upper airway resistance in adults may be uncommon in children. Breathing may appear laborious, however, and increased efforts are often demonstrated by perspiration (at the head and neck or generalized). This suggests that the daytime sleepiness observed in these children despite near-normal sleep structure and the absence of microarousals cannot be explained by sleep fragmentation alone. Polygraphic monitoring must thus focus not only on the presence or absence of apnea (with the knowledge that the absence of apnea may be very misleading) but also on increase in respiratory effort and breathing frequency, as well as the importance of thoracoabdominal mechanical changes.

The repetitive inspiratory efforts expended during complete or, more often, partial upper airway obstruction lead to abnormal septal motion with leftward shift of the interventricular septum and the development of pulsus paradoxus [244]. Cardiac arrhythmias, particularly asystole and secondary AV block, may be seen, and intermittent increase in systolic blood pressure may be noted. Finally, systemic hypertension has been observed in association with OSAS. Systemic hypertension in prepubertal children completely disappears with tracheostomy. The only cases of systemic hypertension found to be clearly idiopathic and for which treatment of OSAS led to complete and long-term normalization of blood pressure were in prepubertal or pubertal children [245].

Asthma and Upper Airway Obstruction During Sleep

In children, a relationship exists between asthma and upper airway obstruction. Allergic reactions very early in life lead to mucosal swelling and enlargement of the pharyngeal region. There is a well-known interaction between the size of the upper airway and craniofacial development, particularly development of the mandible, during early childhood. The presence of upper airway allergies will thus limit maxillomandibular growth and cause a decrease in the size of the upper airway. Small upper airways are often associated with increased upper airway resistance during sleep, leading to increased respiratory efforts and the development of snoring during sleep. Increased upper airway resistance and

nocturnal snoring worsen asthma, causing increased risk of a nocturnal asthma attack.

Orthodontic Complications and Upper Airway Obstruction During Sleep

Children with partial or complete upper airway obstruction during sleep frequently have maxillomandibular growth retardation. Abnormal orthodontic features are common. Class II malocclusion is frequently seen but is not the only orthodontic problem. As 60 % of facial development is complete by 4 years of age and 90 % by 11 years of age, it is important to recognize orthodontic involvement. It is also important to understand that inappropriate orthodontic treatment that further impairs maxillomandibular growth may catalyze the appearance of snoring and significantly increase upper airway resistance during sleep. Abnormal maxillomandibular development may be responsible for the nocturnal occurrence of snoring and bruxism. Further understanding of the development of abnormal breathing during sleep came from studies of children submitted to adenotonsillectomy, the most common treatment in childhood OSA (see below).

Treatment

Nasal obstruction is rarely the only factor in the development of apnea in children, but it can be a contributing factor. In rare cases, correcting the obstruction can alleviate, if not cure, the OSAS.

Tonsillectomy and Adenoidectomy

Tonsillectomy alone or tonsillectomy with adenoidectomy is standard treatment of pediatric OSA. Early studies showed that this procedure can cure over 80 % and improve the vast majority of pediatric OSA cases. However, later studies suggest that OSA may persist in up to 70 % of postoperative patients [246–249]. Too often not enough attention is paid to problems that may be associated with enlarged tonsils and adenoids (i.e., abnormally long soft palate, retroposition of the mandible, or soft tissue infiltration behind the base of the tongue), which may explain residual apnea after tonsillectomy. Furthermore, if tonsillectomy and adenoidectomy are performed during the prepubertal years in boys, there is a chance that the extensive soft tissue growth that occurs during puberty may cause a reappearance of OSAS in those whose airway space is already compromised by a malocclusion such as a mild-to-moderate retro-position of the lower mandible [250]. A recent study comparing cephalometrics in children with OSA previously cured with tonsillectomy and adenoidectomy showed that there was a significant reduction in posterior airway space that developed at a mean age of 14 years compared to the same patients at a mean age of 11 years. This was associated with a return in sleep-disordered breathing [251]. Fiberoptic endoscopy must be performed systematically in association with one imaging test to determine the extent of soft tissue surgery needed to treat OSA. Systematic follow-up of OSA children post-T&A between 6 months and 3 years shows that abnormal breathing during sleep reoccurs [252]. The reasons why there are re-occurrences are not fully understood. It is known, however, that increased patient age at time of T&A, obesity, and the initial severity of the OSA are all factors associated with increased risk of reoccurrence. Some recurrences occur during puberty. Others occur at an earlier age, particularly in children who do not undergo myofunctional reeducation.

Factors that increase the risk of developing sleep-disordered breathing include prematurity, [252] a positive family history of OSA, [24–28] and cartilage lesions as seen in Ehlers Danlos Syndrome [253]. Other risk factors include infantile rheumatoid arthritis involving temporal mandibular articulation, posttraumatic lesions of the same articulation, and heritable neuromuscular disorders, such as Myotonic Dystrophy, that induce abnormal growth of the maxilla and mandible, a short anterior frenulum, and abnormal tongue positioning.

Research from 1972 to 1980 on a monkey model with experimentally induced increased nasal resistance largely contributed to our understanding of how increased nasal resistance may lead to abnormal craniofacial growth and to the development of sleep-disordered breathing. The infant monkeys showed changes in EMG firing, mouth breathing associated with abnormal muscle tone, oral facial hypotonia, and secondary changes in maxillary-mandibular growth [124, 126, 130]. In children, any cause of increased nasal resistance may lead to sleep-disordered breathing through these same mechanisms.

Orthodontic and Maxillomandibular Surgery

Pediatric OSAS is a complex problem. Changes in maxillary and mandibular growth, including retroposition of the mandible, a steep mandibular plane, and an abnormally narrow, high-arched palate, often result from abnormal mouth breathing. These features are not always obvious. No one can overlook Pierre Robin syndrome, but specialists do not always appreciate a mandibular problem, and orthodontists may not be aware of the negative impact that a moderately abnormal mandible has on the upper airway. Relatively noninvasive orthodontic approaches using rapid maxillary expansion in conjunction with traditional orthodontic treatments have been shown to effectively treat sleep apnea in children with lasting positive results [254, 255]. Maxillary distraction results in widening of the palate

and the nose, thereby improving nasal occlusion. Rapid maxillary distraction is usually preformed in pediatric patients whose OSA persists despite tonsillectomy and adenoidectomy. Bi-maxillary distraction is also performed depending on the orthodontic findings and degree of involvement of the mandible. Novel orthodontic techniques may be used when maxillary retrusion is important.

Recent investigations analyzing the results of post-T&A alone and post-T&A followed by orthodontic cases have shown that the above treatments may not be sufficient to prevent recurrence of SDB. This may be in part because these therapies do not address upper airway muscle activity and do not re-entrain normal nasal respiration in the place of mouth breathing. Myofunctional therapy has been used in conjunction with orthodontic treatment since the 1960s in different countries particularly western Europe and Brazil [256]. The efficacy of such associated treatments has been well documented since the 1990s. But it is only recently that myofunctional therapy has been used in adults with OSA with limited results [257]. In children, this treatment, in combination with the other treatment modalities, has been shown to result in a return of normal breathing 3–4 years post-treatment [132]. The advantage of myofunctional therapy is twofold. First, it leads to a noticeable improvement in upper airway muscle tone, and second, in many cases, it eliminates mouth breathing [257]. Mouth breathing in and of itself can be symptomatic. In a recent evaluation [258], children with residual symptoms of sleep-disordered breathing despite T&A ± orthodontics and aggressive allergy management were shown to have mouth breathing during polysomnography for more than 1/3 of the total recorded sleep time, while children without symptoms had less than 5 % of mouth breathing.

In addition to consideration of T&A, pediatric OSA patients should have an evaluation of their oral facial growth and tongue and lip muscle activity. The simple exercises indicated at http://www.myofunctionaltherapy.blogspot.com [257] should normally all be easily performed. Limitation of response indicates functional muscle impairment of the oral facial region that should be corrected with myofunctional rehabilitation. Post-treatment polysomnography with usage of a mouth thermistor protected from nasal flow by a "cup" cg [24] should demonstrate absent or based on Stanford data less than 5 % of mouth breathing. The presence of functional regional muscle impairment and/or a large amount of mouth breathing at post-treatment recording with mouth thermistor with cup should lead to systematic myofunctional therapy and nasal breathing reeducation. This should be done in conjunction with aggressive nasal allergy management and appropriate correction of any high-arched palate and narrow nasal cavity with rapid maxillary expansion.

At times, such approaches are insufficient and a more aggressive treatment approach is needed. Maxillofacial abnormalities are clearly related to the presence of OSAS in children. When present, maxillofacial surgery may be considered. Piecuch [259] reported a child treated with maxillofacial surgery for OSAS. Kuo et al. [260] have reported two cases and Bear and Priest [261] reported three cases of OSAS that were resolved by maxillofacial surgery. Bell et al. reported a 50 % success rate in treating eight cases of OSA with maxillomandibular advancement (MMA) [262]. The most extensive series of patients (teenagers and adults) treated with maxillofacial surgery was reported by Riley et al. [213] and Holty and Guilleminault did a meta-analysis of all published MMA cases including teenagers [263]. It is recommended that MMA is performed only after facial growth and development has peaked. Prior to this, allergy management, myofunctional therapy, and the orthodontic approaches described above are recommended to obtain as much benefit as possible. If symptoms persist, nasal CPAP may be used while awaiting MMA.

Ethnicity may render surgical protocols different. Taiwanese surgeons have proposed a specific protocol for Chinese individuals. The meta-analysis performed has shown that MMA success is significantly lower if at least a 12 mm advancement of the maxilla measured at the cut-point is not achieved. Given the ethnic differences in facial anatomy between Far East Asians and Caucasians, maxillary advancement will usually have a larger impact on Asian facial esthetics. Masking techniques such as counter-clockwise rotation may not be as successful in Far East Asians as in Caucasians if no other approach is taken at the time of surgery. MMA will always involve changes in facial presentation, but computer simulation based on cranio-facial CT of the subject can provide information on the post-surgical presentation. In the hands of well-trained surgeons, this procedure is often quite successful. However, adults after 40 years of age have a 30 % decrease in MMA success rates. Excessive weight gain and the development of lung diseases are two additional health problems that clearly decrease efficacy of MMA surgery at long-term follow-up [263].

Maxillomandibular advancement drawbacks include the assumption of surgical and anesthesia risk, a possibly esthetically displeasing facial outcome, as well as a prolonged postoperative recovery time of 8–12 weeks [262–264]. Again nasal breathing re-learning may be needed. It is recommended that all other treatment modalities be investigating prior to consideration of this major surgery.

Mandibular distraction osteogenesis, used in conjunction with orthodontics, has also been used to successfully treat six pediatric OSA patients [265]. Distraction osteogenesis has been used regularly in infants and young children with syndromic presentations such as Pierre Robin, Crouzon, and other cranial-facial syndromes. Its application is different here as individuals are not syndromic and usually the

sleep-disordered breathing has been diagnosed during the peri-pubertal period and orthodontic approaches such as rapid maxillary expansion cg or bimaxillary treatment have not been sufficient.

European orthodontists will often perform further maxillary widening through the use of palatal implants. This allows for avoidance of applied molar forces in addition to facilitation of nasal passage opening by more posterior implant placement. Such an approach allows re-opening of the palatine suture in teenage individuals most commonly 14–17 years of age. By making a surgical cut in the mandibular bone and applying a distractor, mandibular widening may also be performed. Such an approach is reserved for patients with lateral narrowing and no antero-posterior involvement, an uncommon presentation. The cost of implants in some countries limits its use.

Tracheostomy

In the past, tracheostomy was a frequent treatment when tonsillectomy and adenoidectomy were insufficient. Tracheostomy resolves the OSAS, but often causes secondary problems such as unexpectedly challenging stoma management, devastating psychosocial effects, and infection. Nevertheless, tracheostomy is clearly beneficial in many cases. The need for tracheostomy can be alleviated by the use of other treatment modalities.

Nasal Continuous Positive Airway Pressure

Children as young as 6 months old have been treated with nasal CPAP at Stanford since 1984, and long-term treatment has been successful [265, 266]. Several manufacturers currently supply nasal CPAP for young children, and Respironics provides masks for infants and very young children.

The complications and problems associated with this treatment have been related to (1) the fact that the children (many of whom were mentally handicapped) had difficulty understanding how the mask and CPAP equipment functioned; (2) problems with the parents' collaboration with the medical team to train the child to keep the nasal mask on his or her face; (3) air leaks at the edge of the mask causing reappearance of apnea and eye irritation; and (4) skin allergy to the masks in small children. The first two problems resulted in some children abandoning nasal CPAP treatment; the other problems, although occasionally bothersome, never led to interruption of therapy. The theoretical risk of stomach dilation due to incorrect administration or other problems has never been reported. In very young children, hand restraints during sleep may be necessary to adapt the child to the apparatus.

Pediatric patients using CPAP should be re-evaluated for mask fit every 6 months because of rapid craniofacial growth. An annual visit with a craniofacial specialist should occur to affirm that the headgear and mask do not worsen a maxillary growth deficiency [9, 26].

Summary

Obstructive sleep apnea syndrome is surprisingly common and must be recognized as a disease with diverse, adverse, systemic consequences, including cardiovascular risk. The associated sleep fragmentation, excessive daytime sleepiness, and fatigue can be disabling and degrade quality of life. As such, inquiries regarding symptoms of snoring and excessive daytime sleepiness should be routinely screened for as part of preventative health care. A high index of suspicion for this condition must be maintained, as the sequelae of the disease can be devastating. Fortunately, OSAS is easily treatable, with CPAP therapy being the gold standard of care. Recommendations can also be tailored to the patient's problems, taking into consideration individual preference, age, personality, lifestyle, and objective findings with PSG.

Advances in awareness of the presence and pathophysiology of pediatric SDB along with new understanding of reasons for incomplete or transient treatment success give hope that routine screening, early recognition, and aggressive treatment early in life will be performed. Evaluation will require systematically checking that nasal breathing has truly been restored. This is rarely performed today due to the limited understanding of many specialists of the impact of "loss of usage" of an organ such as nasal breathing during sleep. Functional therapies taught by a trained specialist to regain nasal breathing and proper muscle tone should be employed. This is only done in some limited places around the world today. However, such systematic approaches may decrease the frequency of OSA. In Brazil, a state law has made it mandatory for neonatologists to evaluate for the presence of an abnormal frenulum at birth. At Stanford, retrospective analysis of 6 years of pediatric referrals revealed that 1 out of 30 children with SDB has a short frenulum on ENT evaluation.

Some final considerations include the following: Ehlers Danlos syndrome, which is a risk factor for OSA, is quite common, yet under recognized. Symptoms such as abnormal tendencies for twisted ankles and knee or shoulder dislocations need to be more aggressively screened for. Also, aggressive treatment of nasal allergies, including desensitization shots, is also required to avoid intermittent and incomplete treatment of a chronic problem. Furthermore, early recognition of abnormal oral facial growth in young infants needs to be evaluated. Bottle-feeding with soft nipples that do not require the same strong sucking action as breast-feeding, or the same continuous effort from the upper airway muscles and tongue further predispose infants to

SDB and should be avoided. Such simple screening and precautions could dramatically impact pediatric SDB. Lastly, pediatric obesity is a growing epidemic and major cause of OSA. It leads to fatty infiltration of the tongue and other soft tissues of the upper airway. Abnormal adipocyte secretions of many peptides including leptin and obesin induce further metabolic and inflammatory consequences. Obesity and OSA may both cause some of the same symptoms, such as fatigue, and both can lead to major negative cardiac consequences later in life. In conclusion, when treating OSA, it is important not to forget to treat the underlying contributing factors such as obesity, which may have independent devastating health consequences. Recognition early in life of risk factors that may lead to abnormal breathing during sleep requires screening by not only pediatricians, but also by allergists, pediatric dentists, and orthodontists. Early intervention may halt disease progression, improve outcomes, and change lives.

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Central Sleep Apnea, Hypoventilation Syndrome, and Sleep in High Altitude

33

Bernardo J. Selim, Virend Somers, and Sean M. Caples

Introduction

The International Classification of Sleep Disorders (ICSD-3) has grouped the sleep-related breathing disorders into central sleep apnea syndromes (CSAS), obstructive sleep apnea (OSA) disorders, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorder [1]. This nosological classification encompasses a heterogeneous group of sleep-related breathing disorders with diverse pathophysiological mechanisms, which can be divided into two groups based upon their effect on CO_2 concentration, those with and those without elevated arterial carbon dioxide tension ($PaCO_2$). Sleep-related hypoventilation disorders are associated with hypercapnia ($PaCO_2 \geq 45$ mm Hg), and they are the result of either increased respiratory load (chest wall and lung elastic loads), decreased respiratory drive (ventilator control abnormalities), or inadequate respiratory muscle strength (neuromuscular unit impairment and neuromuscular disorders). In contrast, central sleep apnea (CSA) associated with eucapnic or even hypocapnic arterial carbon dioxide tension levels, during wake and sleep time ($PaCO_2 \leq 40$ mm Hg), are characterized by intermittent reduction (central hypopnea) or cessation of airflow concomitant with the absence of respiratory efforts (central apneas) (Table 33.1).

Some of these diverse disorders could be primary (e.g., congenital central hypoventilation syndrome [CCHS]), or secondary to medications (e.g., opiates) or medical conditions. When the underlying condition is reversible, the associated sleep-related breathing disorder may improve or resolve. However, when the correction of the underlying medical illness is not possible, long-term supportive treatment options are available.

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General Considerations in CSA and Alveolar Hypoventilation Pathophysiology

Neurophysiologically, a central apnea event is the result of absent pontomedullary pacemaker activity to generate a neural output with subsequent activation of the inspiratory thoracic muscles. Considering the mechanism(s) and the resulting tension of carbon dioxide in blood ($PaCO_2$), central apneic events can be grouped into the following: (1) physiologic CSA, (2) non-hypercapnic CSA, and (3) hypercapnic sleep apnea. These mechanisms are explained below with subsequent emphasis later in each disorder (Table 33.2).

1. Physiologic central apnea: sleep-onset and post-arousal central apneas.

When falling asleep, the usual influence of wakefulness on the drive to breathe is lost, facilitating the subsequent development of sleep-onset apneas. These are considered physiologic, and they are observed in healthy individuals during the transition from awakening to superficial stages of NREM sleep (e.g., N1 and N2). This transition shows highly sensitive dependence of the respiratory control system on $PaCO_2$-driven chemoreceptor input during the shift of eucapnic levels from awake to sleep state and vice versa [2, 3]. When falling asleep, a new eucapnic level (2–6 mm Hg) above awakening $PaCO_2$ level is set as a result of a physiologic decrease in tidal volume [4, 5]. During sleep, the previous awake eucapnic $PaCO_2$ level will become the new apneic threshold ($PaCO_2$ level below which a central apnea will occur). The apnea will endure until the $PaCO_2$-level increases back to the sleep eucapnic level, with subsequent reinitiation of breathing. Therefore, breathing instability at sleep onset is commonly observed (Fig. 33.1). In contrast to

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Table 33.1 Etiologies of central sleep apnea syndromes and alveolar hypoventilation

(I) **Physiologic central apneas**
1. Sleep-onset central apneas
2. Post-arousal central apneas
3. Phasic REM sleep
(II) **Sleep-related disorders associated with normal nocturnal carbon dioxide**
(A) *Central sleep apnea syndromes*:
1. Primary central sleep apnea
2. Central sleep apnea with Cheyne–Stokes breathing
3. Central sleep apnea due to high-altitude periodic breathing
(III) **Sleep-related disorders associated with high nocturnal carbon dioxide**
(A) *Ventilatory control abnormalities with normal pulmonary function test*:
1. Congenital central alveolar hypoventilation syndrome
2. Idiopathic central alveolar hypoventilation
3. Central sleep apnea due to a medication or substance (narcotics)
(B) *Neuromuscular disorders with abnormal pulmonary function test*:
1. Cervical spinal cord injury
2. Amyotrophic lateral sclerosis
3. Guillain–Barre syndrome
4. Myotonic and Duchenne dystrophies
(C) *Chest wall and lung disorders with abnormal pulmonary function test*:
1. Kyphoscoliosis
2. Thoracoplasty
3. Chronic obstructive lung disease
4. Advanced restrictive lung disease
5. Obesity hypoventilation syndrome

NREM, REM sleep is less dependent on the $PaCO_2$-driven chemoreceptor input, likely related to an increase in the central inspiratory neural drive as the main driver of respiratory function [6].

During cortical arousals, the chemoreceptor sensitivity is reset back to the awake eucapnic level, making the sleeping eucapnic $PaCO_2$ relatively hypercapnic in comparison with the awake eucapnic level. This will trigger an increased ventilatory response, facilitated by the increase in flow from dilation of upper airway muscles. When the sleep resumes, the recently reached arousal $PaCO_2$ level will cross the sleep apneic threshold with subsequent development of a central apnea, commonly called post-arousal apnea [7].

2. Non-hypercapnic CSA:

This is typically characterized by awake $PaCO_2$ less than 45 mm Hg. Apneic events are the result of over-response or under-response of the respiratory control system to minimal changes in nocturnal $PaCO_2$ (high "loop gain") [8]. The loop gain is an engineering term that describes the degree of response, in this case of the respiratory control system, after a ventilatory disturbance. The higher the loop gain, the higher the overventilation or underventilation response. Loop gain is comprised of three components: (1) the controller gain, the chemoreceptor-driven ventilatory response to changes of $PaCO_2$ and PaO_2 above and below the eucapnic level; (2) the plant gain, ventilatory response to changes in pulmonary capillary $PaCO_2$ and PaO_2; and (3) the mixing gain which is the circulatory time needed for changes in $PaCO_2$ and PaO_2 in pulmonary capillaries to be detected by the chemoreceptors (effective circulatory time) [9]. Disorders such as idiopathic CSA, Cheyne–Stokes breathing (CSB), and CSA due to high altitude are considered to be the result of this high "loop gain" of the respiratory control system. Because of the dependence on $PaCO_2$ described above, these breathing disorders are generally exclusive to NREM sleep.

3. Hypercapnic CSA:

This group of disorders is generally known as "alveolar hypoventilation" and is defined by an elevated nocturnal $PaCO_2$ level (>45 mmHg), which may extend during the daytime. The main respiratory abnormality resides anywhere along the brainstem respiratory control center (e.g., congenital central alveolar hypoventilation syndrome), throughout the respiratory motor output unit, from the motor neuron to the innervated respiratory muscle.

Overlap exists between obstructive sleep apnea and CSA in the obesity hypoventilation syndrome (OHS). In obese patients (body mass index >30 kg/m^2), an extension of nocturnal alveolar hypoventilation into daytime defines OHS. The pathophysiology is not completely understood, but it may include the interaction of the following: (1) high upper airway tone, (2) impaired respiratory mechanics (increased work load), and (3) decreased ventilatory drive (blunted respiratory response) [10–14].

Specific Considerations by Disease Entity

Central Sleep Apneas Syndromes

Primary Central Sleep Apnea

In the group of non-hypercapnic CSAs, primary CSA is an idiopathic disorder (ICSA) characterized by recurrent central apneas associated with polysomnographic criteria of 5 or more events of central apneas and/or central hypopneas per hour of sleep, representing more than 50 % of the total number of apneas and hypopneas. There are common complaints of sleep fragmentation (e.g., excessive daytime

Table 33.2 Central sleep apnea syndromes and alveolar hypoventilation

Categories	Disorders	Pathophysiology
Central sleep apnea syndromes associated with normal nocturnal carbon dioxide	*Primary central sleep apnea*	Idiopathic. Probably, the combination of increased ventilatory response to $PaCO_2$ changes by chemoreceptors (high loop gain system) and a failure of expiratory to inspiratory switch in central respiratory controllers
	Central sleep apnea with Cheyne–Stokes breathing (*CSB*)	Commonly seen in systolic and diastolic heart failure. CSB is the result of an increased ventilatory response to $PaCO_2$ changes (high loop gain system), a narrow difference between the apnea threshold and the sleeping eucapnia, as well as an impaired cerebrovascular reactivity to CO_2
	Central sleep apnea due to high-altitude periodic breathing	Periodic breathing is the result of hypoxia-mediated increase in controller gain, with subsequent narrowing of the difference between eupneic PaCO2 and apneic threshold, as well as the oscillation in cerebral blood flow
	Central sleep apnea due to a medication or substance (narcotics)	Cluster or ataxic breathing is the result of opioid effects on the pre-Bötzinger complex with subsequent suppression of respiration rate and respiratory drive
Sleep-related hypoventilation disorders associated with high nocturnal carbon dioxide	*Ventilatory control abnormalities:* • Congenital central alveolar hypoventilation syndrome (CCAHS) • Idiopathic central alveolar hypoventilation	For CCAHS, ventilatory control is blunted by mutations in the PHOX2B gene For idiopathic central alveolar hypoventilation, the etiology is unknown
	Neuromuscular disorders: • Spinal muscular atrophy • Myotonic dystrophy • Cervical spinal cord injury	Ventilatory control blunted by inability to translate ventilatory center output into appropriate neuromuscular action
	Chest wall abnormalities: • Kyphoscoliosis • Thoracoplasty • Obesity hypoventilation syndrome	Increased work of breathing due to thoracic cage abnormalities with subsequent chronic respiratory failure
	Lung disorders: • Chronic obstructive lung disease • Advanced restrictive lung disease	In obstructive and restrictive disorders, ventilatory drive remains high, but effectiveness is reduced by gas exchange abnormalities secondary to increased airway resistance and pulmonary parenchymal damage

sleepiness, frequent nocturnal awakenings, or insomnia). By this definition, the presence of an alternative diagnosis, such as Cheyne–Stokes breathing or evidence of sleep-related hypoventilation would automatically exclude the diagnosis of ICSA [1].

Epidemiology:

ICSA is a rare disease, with an estimated prevalence reported to be 4–7 % of patients referred to a sleep center [15].

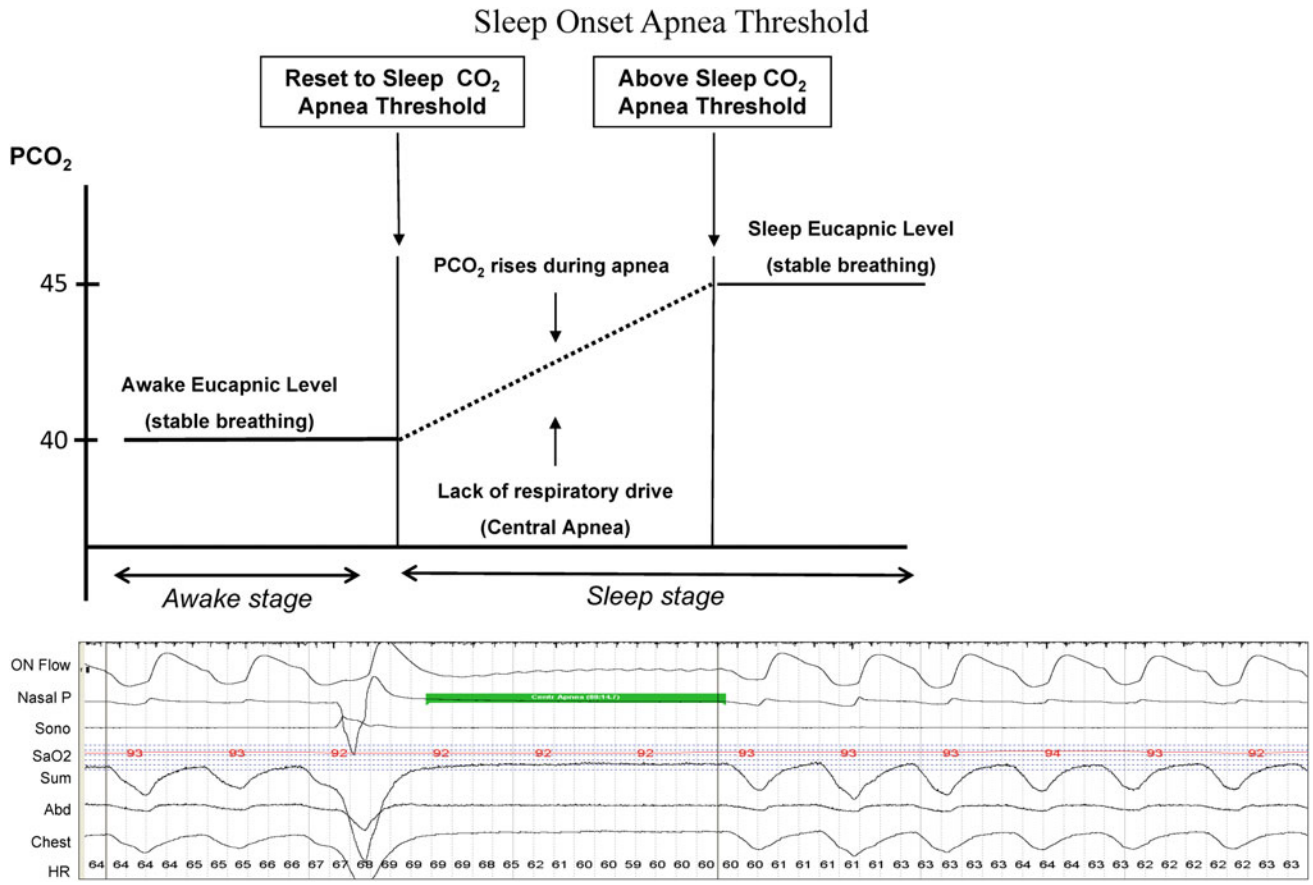

Fig. 33.1 At sleep onset, there is breathing instability, often in the form of central sleep apnea. The set point of the apnea threshold is different in wakefulness and sleep. When falling asleep, the awake eucapnic level falls below the set point sleep apneic threshold resulting in lack of respiratory drive (apnea) until the new sleep eucapnic level is reached and the respiratory drive is reinstituted

Clinical characteristics:

ICSA patients may present with complaints of snoring, witnessed apneas, restless sleep, insomnia, and/or excessive daytime sleepiness [15, 16]. It is more common in older males and in patients with cardiovascular disease [17, 18].

Pathophysiology:

The underlying mechanism is not well understood. Like in Cheyne–Stokes breathing due to congestive heart failure (CSB-CHF), idiopathic CSA patients have an increased hypercapnic ventilatory response during arousals, likely the result of high controller and plant gain, facilitating the crossing of the apnea threshold [7, 8, 19]. This mechanism can be supported by the clinical response of ICSA to acetazolamide, with the subsequent increase in systemic $PaCO_2$ [20]. However, the absence of the crescendo–decrescendo ventilatory pattern in ICSA and a shorter breathing cycle length, likely from the absence of effective circulatory time delay, may point to alternative pathways from those of CSB.

Polysomnography:

Idiopathic CSA is characterized by repetitive episodes of CSA frequently found during N1 and N2 sleep (NREM). Different from CSB, the periodic breathing cycle length in CSA is shorter (20–40 s), and the apnea event terminates with a large breath, concomitant with the presence of an arousal. No crescendo–decrescendo ventilatory pattern is present in this periodic breathing pattern [1, 21] (Fig. 33.2).

Management:

1. *Pharmacological treatment*:

Limited data support a trial of acetazolamide, zolpidem, and triazolam in ICSA treatment. In a non-randomized treatment study, DeBacker and colleagues have found that the

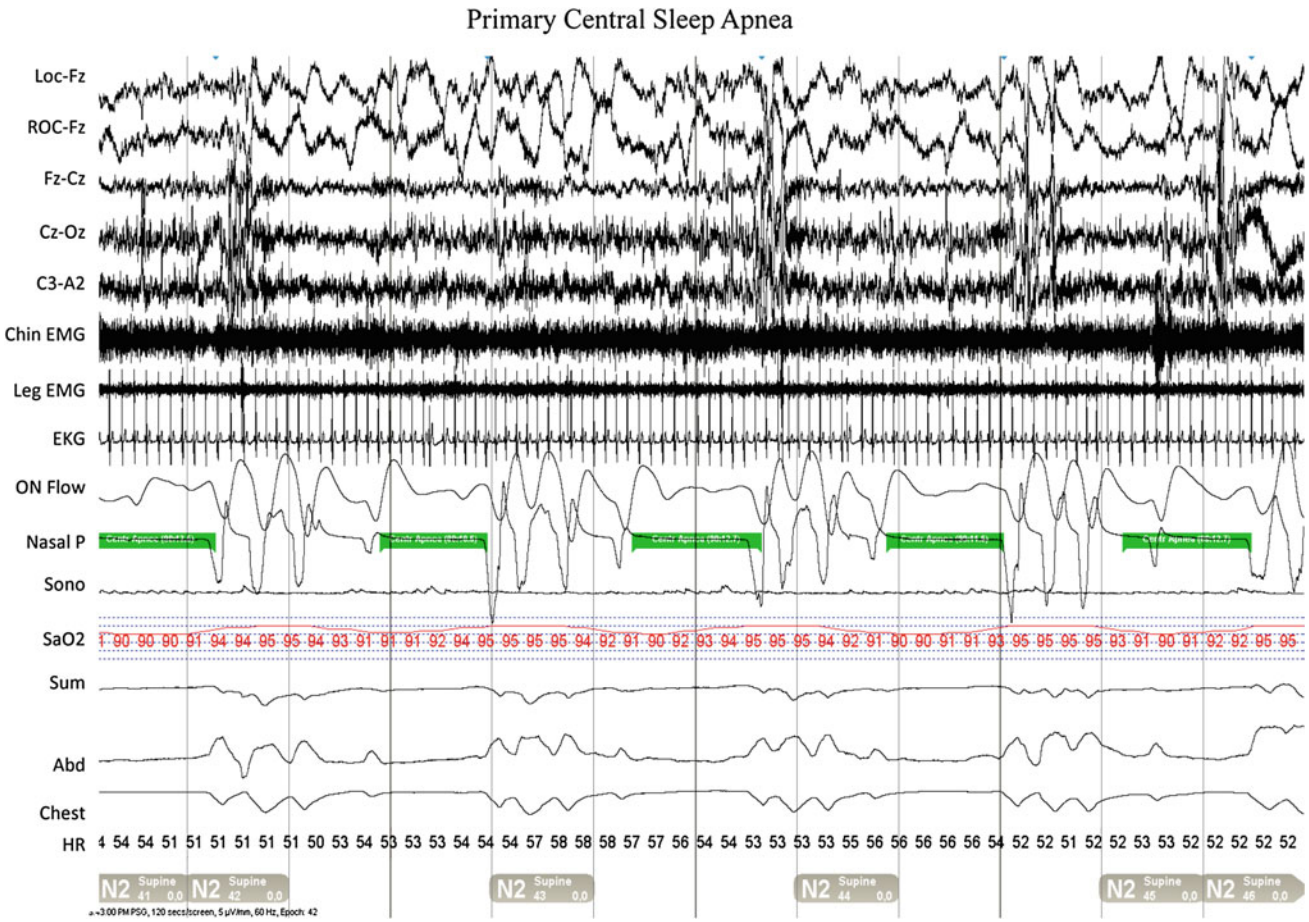

Fig. 33.2 This polysomnographic segment obtained from a patient with primary central sleep apnea shows 4 epochs of 30 s with cyclical central apneic events. Each heavy vertical line demarks 30 s. The thermal sensor channel (ON flow) shows a drop of ≥ 90 % of peak thermal sensor signal from baseline. The nasal pressure signal (Nasal P) denotes episodes of central apneas (*green bars*) separated by a normal ventilation with a cycle length of 20–40 s

administration of acetazolamide at low doses can decrease the apnea–hypopnea index (AHI) at one-month follow-up, with concomitant decrease in daytime sleepiness [15, 20]. Effective reductions of AHI and central apnea index (CAI) were also reported with administration of zolpidem, and triazolam, with the improvement in daytime sleepiness in the zolpidem intervention group [22, 23]. Due to limited available evidence and the potential of side effects, pharmacological intervention in ICSA should be individualized until further studies are available.

2. *Assistive devices*:

There is also limited supporting evidence regarding the use of positive airway pressure (PAP) in the form of Continuous PAP (CPAP), Bilevel PAP with backup rate (BPAP-ST) or Adaptive servo-ventilation (ASV) in patients with ICSA [24]. Current CSA practice parameters recommend a trial of positive airway pressure therapy for the treatment of ICSA until further studies define the best treatment strategy [25].

Central Sleep Apnea Due to Cheyne–Stokes Breathing Pattern in Congestive Heart Failure (CSB-CHF)

Epidemiology:

Congestive heart failure (CHF) is a highly prevalent chronic disease, affecting around 2 % of the general population (5–6 million Americans) and up to 10 % of those above age 65 [26]. CHF is the most commonly recognized cause of CSA. Although the existing literature is limited by referral and participatory bias, it is estimated that in heart failure patients with reduced left ventricular ejection fraction (<45 %), as

much as 31 % have CSA [27–29]. In those patients with preserved ejection fraction (diastolic dysfunction), the prevalence of CSA may reach up to 23 % [30].

Clinical characteristics:

Classic signs and symptoms such as paroxysmal nocturnal dyspnea (PND) and orthopnea in those with heart failure might be explained in many instances by CSA-CSB. Even though patients with heart failure and sleep-disordered breathing do not commonly report sleep-related complaints such as excessive daytime sleepiness, presenting clinical characteristics of patients with CSA-CSB may be otherwise undistinguishable from those with OSA [31]. Patients in CHF with CSB are more likely to have atrial fibrillation and poorer functional status (NYHA class), supporting the notion that CSB is a consequence of progressive heart failure and possible indicator of higher morbidity and mortality [29]. Although found more frequently in CHF patients, CSB is not pathognomonic as it can also be observed in stroke and in chronic renal failure patients [32].

Pathophysiology of CSB due to heart failure with/without preserved systolic function:

Non-hypercapnic central apnea in heart failure patients with ventricular dysfunction are the result of the interaction of the following factors: (1) low awake steady state of $PaCO_2$, (2) lack of increase of $PaCO_2$ at sleep onset, with subsequent reduced difference between the apnea threshold and the sleeping eucapnic level (reduce PCO_2 reserve), (3) increased response to $PaCO_2$ changes (high loop gain system), and (4) impaired cerebrovascular reactivity to CO_2.

- In heart failure patients, a low awake steady state of $PaCO_2$ has a direct correlation with severity of the heart failure and high wedge pulmonary pressure in comparison with eucapnic heart failure patients. By stretching J-receptors (afferent C fibers), minute ventilation is increased with subsequent low steady level of wake $PaCO_2$ [33–35].
- The awake $PaCO_2$ does not increase at sleep onset as expected by the physiological development of sleep-related hypoventilation in eucapnic individuals. In these patients, the increase venous return while in supine position translates into an elevated capillary pulmonary pressure with subsequent increase in respiratory rate and ventilation. This will prevent the expected rise in $PaCO_2$ during sleep stage, narrowing the difference between the sleep eucapnic level and the apnea threshold $PaCO_2$ level, with propensity to develop central apneas [36, 37].
- Increase response to $PaCO_2$ changes (high loop gain system) is the result of increased gain in the three components of the respiratory control system: controllers, plant, and mixing gain. In heart failure, the controller gain is increased by acute lung vascular receptor stimulation of the atrial and pulmonary vasculature and by increased carotid chemoreceptor sensitivity. The plant gain is increased mainly by a low functional residual capacity. Finally, the mixing gain is increased by a prolong arterial circulation time as a result of pulmonary congestion, ventricular enlargement, and decreased stroke volume [37, 38] (Fig. 33.3).
- Impaired cerebrovascular reactivity to CO_2 has been noted in CSA patients with CHF, affecting the stability of the breathing pattern by causing ventilatory overshooting during hypercapnia and undershooting during hypocapnia [39].
- *Polysomnography*:

The classification of sleep disorders as obstructive sleep apnea (OSA) or CSA is important when determining treatment options in CHF. In CSA with CSB, the polysomnography during diagnostic or positive airway pressure titration should show at least 5 or more central apneas and/or central hypopneas per hour of sleep, representing more than 50 % of the total number of apneas and hypopneas. The characteristic periodic breathing pattern of heart failure, known as Cheyne–Stokes breathing, is defined polysomnographically by cycles of ≥ 3 consecutive central apneas and/or central hypopneas separated by a crescendo–decrescendo shape tidal volume [40]. It is commonly found during transition

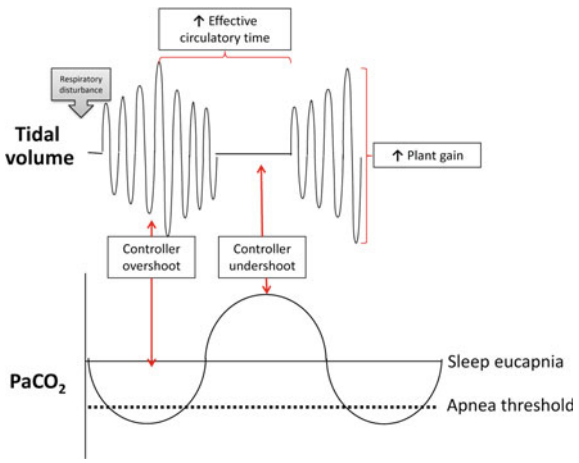

Fig. 33.3 Schematic of respiratory control response in Cheyne–Stokes breathing (CSB). The loop gain is the respiratory control system's degree of response to a ventilatory disturbance. It is comprised of (1) the controller gain, (2) the plant gain, and (3) the mixing gain (effective circulatory time)

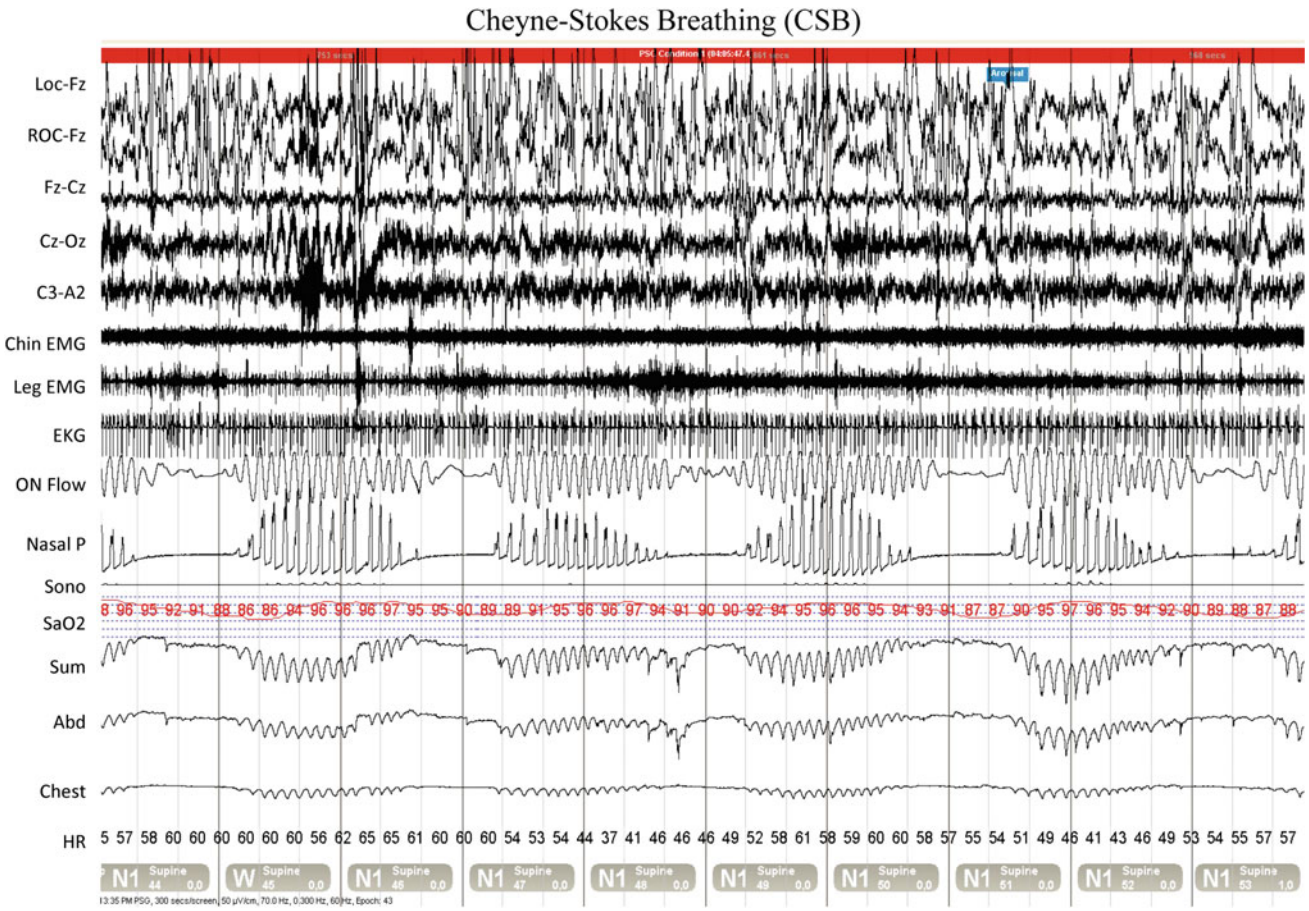

Fig. 33.4 This polysomnographic segment obtained from a patient with compensated systolic heart failure shows 10 epochs of 30 s. Each heavy vertical line demarks 30 s. The thermal sensor channel (ON flow) shows the presence of apneic events as a drop of ≥ 90 % of peak thermal sensor signal from baseline. The nasal pressure signal (Nasal P) denotes episodes of ≥ 3 consecutive central apneas separated by a crescendo and decrescendo change in breathing amplitude with a cycle length of ≥ 40 s

from wakefulness to NREM sleep (N1 and N2), dissipating in N3 and REM. The cycle length, measured from the beginning of a central apnea to the end of the next crescendo–decrescendo respiratory phase, averages ≥ 40 s, and it likely reflects a prolong circulatory time (high mixing gain) [8]. Central apneas that occur within a run of CSB are reported to be associated with less marked oxygen desaturation than similar obstructive and mixed apneas [41]. Arousals, usually located during the ventilatory period, have not shown to have any critical role in termination of apneas or protective mechanism as in obstructive sleep apnea [42] (Fig. 33.4).

Management:

1. *Cardiovascular pharmacological therapy*:

Optimization of cardiovascular pharmacotherapy should be the first intervention in the management of CSA due to CHF. The use of beta-blockers, ACE-inhibitors, angiotensin II receptor blockers (ARB), aldosterone antagonists, and diuretics will have a salutary effect in the neurohormonal physiopathology of heart failure, with potential benefits in Cheyne–Stokes breathing. For example, β-blockers are known to influence hypoxemic chemosensitivity (controller gain) [43]. Also, ACE-inhibitors and diuretic therapy may influence the occurrence of CSB by lowering the intracardiac filling pressures [44]. Despite current efforts to optimize cardiovascular therapy in severe CHF, no significant change of Cheyne–Stokes prevalence could be appreciated in small observational studies [29, 45, 46].

Even though not commonly used, other pharmacological therapies are theophylline and acetazolamide. Acetazolamide, by respiratory stimulation and diuretic effect, may decrease the plant gain and widen the difference between the sleep eucapnic levels and the sleep apneic threshold [47]. Clinically, this translates into a reduction in AHI and improvement in patient's perception of sleep quality [48, 49]. However, side effects associated with acetazolamide, such as paresthesias, tinnitus, metabolic acidosis, electrolyte

imbalance, and dizziness, should be considered at time of prescription. Theophylline, by competing with adenosine at a central level, stimulates respiratory centers resulting in a 51 % reduction in the apnea–hypopnea index, mostly because of a reduction in the number of episodes of central apnea. It also shows a decrease in the duration of arterial oxyhemoglobin desaturation during sleep [49–51]. However, the benefits of theophylline should be weighed against the narrow therapeutical range and stimulant effect.

2. *Gas therapy*:

CO_2 supplementation and dead space therapy:

Because the pathophysiology of Cheyne–Stokes breathing is thought to be related to increase chemosensitivity to $PaCO_2$ at the central controllers (high controller gain), avoiding relative hypocapnia may stabilize the respiratory system. This can be reached by CO_2 supplementation (gas modulator) or by increasing anatomic dead space (DS). Low CO_2 supplementation can be bled from a positive airway pressure gas modulator into a positive airway pressure device. However, limitations relate to cost of the gas modulator, supply of CO_2, and side effects of treatment have affected the practical application of this therapy in the clinical field [52]. Increasing physiologic dead space during positive pressure therapy has been reported to control CSAs in those with CHF [53, 54]. Low levels of CO_2 inhalation mildly raise the sleep eucapnic level, increasing the difference with the $PaCO_2$ apneic threshold. This is achieved by the sequential connection of a non-vented oronasal mask to 4–6 in. of tubing (rebreathing space), an exhalation valve, and a conventional positive pressure circuit. This expiratory rebreathing reservoir represents an increase of $PaCO_2$ in the order of 2–3 mm Hg. Unfortunately, pressure leaks and sleep fragmentation are common [55]. When compared to ASV therapy (discussed later) in patients with CHF, DS and ASV caused a similar reduction in the apnea–hypopnea index (AHI), but total sleep time was significantly decreased by DS, attributed to a high arousal index and disruption of sleep architecture [56].

Oxygen therapy:

Uncontrolled studies of oxygen supplementation via nasal cannula report a decrease in the AHI, as well as an increase the left ventricular ejection fraction (LVEF) at 3–12-month follow-up without clinically significant adverse effects [57, 58]. These effects may be achieved by different pathways: (1) by reducing the controller gain, (2) by increasing the difference between the eucapnic $PaCO_2$ level and the $PaCO_2$ at apneic threshold, and 3) by increasing cerebral CO_2 levels [59, 60]. Even though oxygen supplementation cannot replace CPAP treatment benefits, oxygen supplementation could be considered in those patients with poor compliance with noninvasive ventilation [25].

3. *Assistive devices*:

Several assistive devices modalities have been studied in patients with CHF. Continuous positive airway pressure (CPAP), bilevel positive airway pressure without backup rate (BPAP-S) and with respiratory backup rate (BPAP–ST), and adaptive servo-ventilation (ASV) have been investigated.

Continuous positive airway pressure (CPAP) therapy:

There are a number of beneficial effects on the cardiovascular system when continuous positive airway pressure is applied to the patient with CHF. CPAP can affect the response of the respiratory control system by several pathways. It may decrease the circulatory time (mixing gain) and increase the difference between the eucapnic sleep levels and the apneic threshold. Positive airway pressure may also increase the functional residual capacity (decrease in plant gain) and overcome resistance to airflow in the congested upper airway.

Despite these effects, a large multicenter controlled trial named the Canadian Continuous Positive Airway Pressure for Patients with CSA and Heart Failure Trial (CANPAP), failed to show survival benefit with CPAP treatment in advanced HF and CSA at interim analysis, leading to early termination of the study. Worth noting in this study, CPAP implementation showed attenuation of CSA, improvement in nocturnal oxygenation, and an increase in the ejection fraction [61]. This negative result in survival benefit might be attributed to a lack of PAP titration to achieve a therapeutical reduction in AHI or limited compliance with the device. The authors suggested the lower than expected prevalence of CSA led to under-powering, possibly as a result of better medical management in the era of beta-blockers. However, in a subsequent subgroup analysis, CPAP showed positive effect on LVEF and transplant-free survival when CPAP therapy was able to normalize the apnea–hypopnea index to less than 15 events per hour [62, 63]. Subsequent studies have also shown CPAP to increase the LVEF by 6 % and decrease the AHI between 21/h [95 % CI 17–25] and 30/h [95 % CI 23–37] [25]. In conclusion, CPAP may be appropriate therapy for selected patients in whom respirator events are controlled [25].

Bilevel positive airway pressure (BPAP) therapy:

There is paucity of publications regarding the impact of bilevel positive pressure ventilation in patient with CHF. The data available up to now discourage the use of BPAP-S mode in this population, as it may aggravate central apneas/periodic breathing by hyperventilation. It has been shown that CPAP and BPAP-ST are equally effective in lowering the AHI and NYHA class [64]. BPAP-ST could be an effective alternative to those patients with high residual AHI while on CPAP, benefiting from an increase in LVEF of up to 12.7 ± 10 % [65].

Adaptive servo-ventilation (ASV) therapy:

The adaptive servo-ventilation is a feedback control system targeting minute ventilation or peak respiratory flow, adding a component of ventilation that is anticyclic to the patient's own respiratory drive periodicity. Short-term studies have shown ASV to effectively suppress the Cheyne–Stokes breathing pattern seen in CHF patients with CSA, with improvements in some sleep-related outcomes, as outlined below. When compared to CPAP, compliance may be better with ASV [66]. However, as final results of ongoing large clinical trials are awaited, and in the context of an unexpected increase in mortality associated with ASV as detailed below, the role of the device in the management of CSA in patients with CHF remains to be defined.

Patients with systolic CHF-CSB on treatment with ASV show improvement in polysomnographic parameters (normalization of number of respiratory events), cardiac function (left ventricular ejection fraction, LVEF, and N terminal pro B-type natriuretic peptide NT-proBNP), NYHA functional class, and cardiopulmonary exercise tolerance parameters (VO_2-ATOxygen consumption at anaerobic threshold or peak exercise, VO_2 peak, and 6-min walking distance) [67]. One observational study reported a decrease in the number of cardiac events (cardiac death and rehospitalization) at 6-month follow-up [68, 69]. Even in cases of coexistence of obstructive sleep apnea (OSA), CSA, and Cheyne–Stokes breathing (CSB) in patients with and without heart failure, ASV reduced the central apnea hypopnea index and BNP levels significantly more effectively as compared with CPAP over an eight-month and twelve-month follow-up period [70, 71]. A similar profile of improvements has also been shown in patients with diastolic CHF-CSB on ASV, as well as CHF patients with obstructive and CSA occurring concurrently within the same night, independent of the severity of the sleep-disordered breathing [72–74]. Limited published data are available to infer the impact of ASV on mortality [69, 74]. Recently, preliminary results of the SERVE-HF trial, which assessed the effects of treatment of CSA with ASV on mortality and morbidity in patients with symptomatic chronic heart failure (NYHA 2–4) with reduced ejection fraction (LVEF $\leq$ 45 %), showed an increased risk of cardiovascular mortality for those treated with ASV in comparison with those with best medical care alone. The increased risk appears to be greatest in those with pure CSA with more severe ventricular dysfunction. However, additional analysis of the phase IV SERVE-HF data and further longitudinal studies are needed to accurately identify the long-term impact of ASV in CSA-CHF patients with varies left ventricular ejection fractions, as well as those with preserved ejection fraction.

There are few published studies with direct comparison of ASV with CPAP, BPAP-ST, and oxygen supplementation. At one night study, ASV suppresses CSA and/or CSB (CSA-CSB) in heart failure and improves sleep quality better than CPAP or 2 L/min of oxygen supplementation. In comparison with BPAP-ST, ASV performs better in CSB-CHF but equivalent to CPAP [75, 76].

Other devices and interventions:

Some smaller case series show improvement in the AHI when atrial overdrive pacing (AOP) is used to improve cardiac function in patients with CSA-CHF in comparison with those without AOP [77]. This may be attributed to an increase in cardiac output with subsequent decrease in pulmonary wedge pressures and circulatory time. Similar to AOP, cardiac resynchronization therapy (CRT) reduces the AHI without altering sleep stages [78]. When both AOP and CRT are combined, a minor additional improvement in the AHI is obtained by decrease in the central AHI [79]. Of note, preliminary data from unilateral transvenous phrenic nerve stimulation in patients with CSB–CHF showed a trend toward stabilization of breathing and improvement in oxygen saturation [80].

In those patients with CSA secondary to impaired cardiac function from valvular disease, surgical treatment has been shown to improve sleep-disordered breathing. Even though improved, CSB may persist even after post-transplant normalization of cardiac function [81].

Central Sleep Apnea Due to a Medication or Substance, Opioids

Epidemiology:

A projected 201.9 million opioid prescriptions were dispensed in the USA in 2009 [82]. As the quantity of opioid prescription in the USA has grown rapidly in recent years, the number of patients on opioids presenting to the sleep

clinic for evaluation of sleep-related breathing disorders has also increased. It is estimated that the prevalence of CSA among opioid users, on at least six months therapy, is about 24 %. In methadone maintenance therapy, CSA is identified in up to 30 % of patients [83]. A direct relationship between the total daily dose of opioid and the AHI is found only among methadone users and not among other opioid users including oxycodone, hydrocodone, morphine, hydromorphone, and tramadol [84]. Sleep-disordered breathing has been reported to be reversed with discontinuation of methadone [85].

Clinical characteristics:

Opioid-related breathing disorders in sleep can present in the form of obstructive sleep apnea, CSA, alveolar hypoventilation, or a combination of them. Although symptoms of excessive daytime sleepiness, sleep fragmentation, and insomnia are common complaints, it is difficult to disentangle independent effects of the sleep disorder from the influences of the underlying pain syndrome and non-sleep-related influences of narcotics.

Pathophysiology:

Opioids are naturally occurring or synthetic agents which bind to a class of four G protein-coupled receptors in the central and peripheral nervous systems and respiratory tract, leading to decreased neuronal excitability [86]. These receptors fall into four classes: δ, μ, nociception/orphanin, and the κ receptor. Opioid medications, mimicking endogenous ligands (endorphins, enkephalins, dynorphins, etc.), act through these receptors at different levels of the peripheral and central nervous system. Ligands that stimulate μ and κ receptors particularly suppress central respiratory pattern generation, resulting in decreases in respiratory rate and tidal volume. Both naturally occurring and synthetic opioids may exhibit preferential receptor affinity and may act as agonists, mixed agonists/antagonists, or antagonists.

Animal research, supported by limited work in humans, describes opioids acting on medullary respiratory neurons with the suppression of respiration rate and respiratory drive (pre-Botzinger complex), central chemoreceptors' response to hypercapnia, peripheral response to hypoxemia (glomus cell of carotid body), and depression of the arousal system. Generally, in humans, opioids tend to decrease hypoxic and hypercapnic ventilatory responsiveness. Opioid agonists, particularly fentanyl, tend to decrease upper airway muscle tone and the compensatory response to resistive loading. In addition, some agents have been associated with increased rigidity of accessory respiratory muscles, further limiting ventilation.

These influences suggest that opioids may increase susceptibility to sleep-related breathing disorders. The effect of opioids on human ventilatory control is influenced by dose and ligand specificity. At lower doses, respiratory depression occurs secondary to a decrease in tidal volume, and at higher doses, secondary to a decrease in respiratory rate [86]. A decreased ventilatory response to hypercapnia/hypoxia also occurs [83].

Polysomnography:

Polysomnographic effects on sleep during acute opioid administration include decreases in slow-wave and REM sleep with decreased sleep efficiency and increases in arousals and N1 and N2 sleep. Other studies have shown a decrease in slow-wave sleep with increased N2 sleep and no change in sleep efficiency or total sleep time in patients receiving either morphine or methadone during polysomnography [87]. During chronic opioid administration, the decreases in slow-wave and REM sleep may normalize with improvement in sleep efficiency [88].

As mentioned in the pathophysiology section, a decreased ventilatory response to hypercapnia/hypoxia will develop CSAs in two characteristic patterns of breathing: the cluster period breathing pattern and the ataxic/Biot's breathing pattern. The cluster breathing is characterized by cycles of hyperventilation with tidal volumes of stable amplitude, separated by central apneas of variable duration. The ataxic/Biot's breathing pattern is characterized by variable amplitude and rate of tidal volume as well as variable central apnea duration (Fig. 33.5)

Management:

The literature assessing treatment of CSAS due to drugs or substance is limited. As the effect of opioids on central apneas is probably dose-dependent, discontinuation or a decrease in opioid dose to the lowest tolerated by the patient is recommended [89]. Only limited data support use of PAP devices. CPAP may reduce the AHI, generally by controlling obstructive respiratory events, but not CSAs. In fact, the use of CPAP may aggravate CSA [90]. Regarding intervention with ASV, there are conflicting data from small studies about its role in this group of patients. Further study is needed before routine use of PAP devices can be recommended in the setting of chronic opioid use [90, 91].

Central Sleep Apnea Due to High-Altitude Periodic Breathing

After a high-altitude ascend to approximately 3500 m above sea level or greater, most healthy individuals will develop a

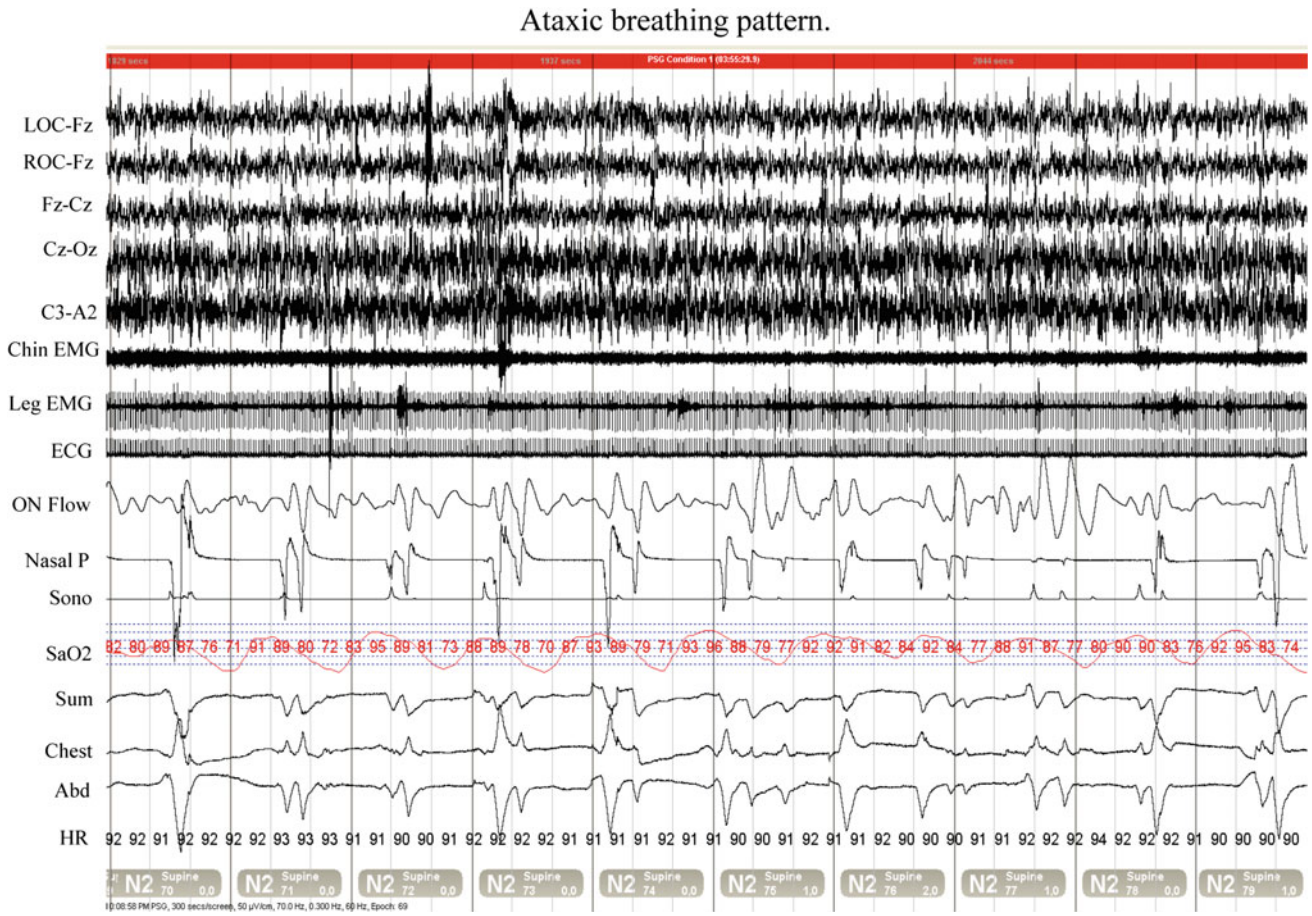

Fig. 33.5 This polysomnographic segment obtained from a patient on chronic opioids shows 10 epochs of 30 s. Each heavy *vertical line* demarks 30 s. The thermal sensor channel (ON flow) and the nasal pressure signal (Nasal P) denotes ataxic or irregular breathing

periodic breathing pattern driven by acute alveolar hypoxia [92–94]. This typically develops during ascension itself, immediately after or during the acclimatization period. Development of CSA due to high altitude will depend not only on altitude itself, but also on speed of ascension as well as on individual variability to hypoxic responsiveness.

Clinical characteristics:

Arousal events increase with altitude. This increase in total arousals will translate into sleep fragmentation which may result in subsequent complaints of fatigue and excessive daytime sleepiness [95, 96]. Despite the fact that the number of arousals is higher in periodic breathers at different altitudes, periodic breathing pattern itself is not associated with a poorer subjective sleep quality when compared to non-periodic breathers [92, 97].

Pathophysiology:

The major effects of high altitude on humans relate to the changes in barometric pressure (PB) and its consequential changes in the ambient pressure of oxygen (O_2). Since the fraction of inspired oxygen remains constant at approximately 20.93 % during ascension, the most important determinant of inspired PO_2 and subsequent arterial PO_2 (PaO_2) at any altitude is the barometric pressure. For example, at an altitude of 3000 m, the barometric pressure and inspired PO_2 are only about 70 % of that at sea level. During ascension, as arterial PO_2 falls due to a low atmospheric pressure (hypobaric hypoxia), ventilation will be stimulated, with resultant hypocapnia and respiratory alkalosis. Despite high individual variability in acclimatization to the increasing hypoxia at high altitude, sustained hypoxic stimulus during ascension will trigger a periodic breathing

pattern in clusters during the night [97]. It is the hyperventilation triggered by hypoxia, with subsequent fall in $PaCO_2$ below the apneic threshold, that results in central apneas [98]. With breathing cessation, $PaCO_2$ increase will trigger a subsequent hyperventilation period based on high tidal volumes, in which the PaO_2 rises and $PaCO_2$ falls to near wakefulness level. In high altitude, periodic breathing is the result of the hypoxia-mediated increase in controller gain, with subsequent narrowing of the difference between eupneic $PaCO_2$ and apneic threshold, as well as the oscillation in cerebral blood flow, which elevates the cerebrovascular responsiveness to hypercapnia and hypocapnia [99–101]. Even though acclimatization to high-altitude results in an overall increase in saturation of oxygen, periodic breathing may increase in duration and persist in time, consistent with progressive increase in loop gain of the respiratory control system [96, 102, 103].

Polysomnography:

In healthy individuals, sleep architecture changes at high altitude with concomitant development of periodic breathing. When altitude starts increasing from 3500 m above sea level, duration in N1 stage increases, at the same time slow-wave sleep decreases. However, the time spent in REM sleep is well preserved along ascension up to 5000 m above sea level. Total arousal events increase as altitude increases, as a result of an increase in spontaneous arousals, as well as an increase in arousal related to periodic breathing and/or obstructive sleep apnea [95, 97, 104]. A periodic breathing pattern can develop at any altitude above 3500 m. In comparison with those individuals without periodic breathing, periodic breathing subjects experience an increase in the total arousal index, without a disruption of sleep architecture or sleep oxyhemoglobin saturation [92, 97].

At high altitude, periodic breathing is characterized by recurrent central apneic events in cycles of 12–34 s. It is usually associated with mild oxygen desaturation. Worse in NREM sleep, it stabilizes during REM sleep. As noted in different studies, there is high individual variability in intensity of periodic breathing to hypoxia at any certain altitude [94]. Because it is considered an adaptation to high altitude, there are no established polysomnographic criteria regarding the frequency of apneic events above which it is considered abnormal.

Management:

Slow ascension and acclimatization are crucial interventions to ameliorate the development of sleep and breathing disorders. By physiologic adaptation of oxygen content and carrying capacity to high altitude, slow ascent can decrease respiratory drive triggered by hypoxia. Unfortunately, at elevations above 3500–4000 m, acclimatization does not restore normal sleep, even for healthy individuals born at high altitude [96, 105].

At this time, limited data support pharmacological interventions, such as theophylline, temazepam, and acetazolamide for the prevention and treatment of high-altitude periodic breathing. If pharmacological intervention is contemplated, side effects and limitations of the intervention should be cautiously considered. Theophylline and acetazolamide have being shown to normalize the sleep-disordered breathing at high altitude. Different from theophylline, acetazolamide significantly improves basal oxyhemoglobin saturation during sleep, with no major side effects. The effect of temazepam on periodic breathing, overnight SaO_2, and next-day cognitive performance has also been studied. Even though temazepam has shown to reduce periodic breathing, it has also been associated with a small but significant decrease in overnight SaO_2. If pharmacological intervention is considered, theophylline and acetazolamide are recommended to be started 3 days before ascension [106]. On the other hand, temazepam is recommended to be taken on two consecutive nights soon after arrival at 5000 m [107].

Since all of the deleterious effects of high altitude are caused by the low inspired PO_2, supplementary oxygen can improve the inspired PO_2, thereby decreasing respiratory drive and ensuing central apneas. Unfortunately, implementation of this intervention is challenging at high altitude, and data in oxygen supplementation are limited to intervention in acute high-altitude illness such as acute mountain sickness [108, 109].

Sleep-Related Hypoventilation Disorder, Central in Origin Versus Due to Medical Disorder

Classification:

In pulmonary physiology, arterial tension of carbon dioxide ($PaCO_2$) is calculated by the alveolar equation, in which alveolar tension of carbon dioxide (Pa CO_2) is proportional to CO_2 production (VCO_2) divided by alveolar ventilation.

$$PaCO_2 = K \times \frac{VCO_2}{\left(V_t \times RR \times \left(1 - \frac{V_d}{V_t}\right)\right)}$$

In this equation, the alveolar ventilation results from the product of tidal volume (V_t), respiratory rate (RR), and the dead space-to-tidal volume ratio (V_d/V_t) Assuming a constant

CO_2 production from our body, hypoventilation is mainly the result of decrease in minute ventilation ($V_t \times$ RR) or the increase of dead space volume (V_d), as a volume of gas that does not eliminate CO_2, or a combination of both [110]. Because the causes of alveolar hypoventilation are multiple, a clinical classification based on the patient's pulmonary function can help to differentiate abnormalities of the ventilatory drive (autonomic/metabolic respiratory control system) associated with normal pulmonary function versus abnormalities of pulmonary mechanics with subsequent abnormal pulmonary function. Pulmonary function is commonly evaluated based on the information obtained in a pulmonary function test (PFT), further narrowing the differential diagnosis in hypoventilation. Pattern of volume and flow changes observed in the spirometry and lung volumes can support an obstructive (e.g., COPD) or restrictive physiology (e.g., interstitial lung disease and neuromuscular-skeletal diseases). Information from the diffusion capacity of carbon monoxide (Dlco) can point to changes in the surface of gas exchange (e.g., emphysema) or vasculature (e.g., pulmonary hypertension). When neuromuscular diseases are in question, a maximal respiratory pressures test can reflect changes in inspiratory and expiratory respiratory muscles' strength (Table 33.1).

Alveolar Hypoventilation Syndrome with Decrease in Ventilatory Drive (Normal Pulmonary Function)

This group of disorders is characterized by nocturnal chronic alveolar hypoventilation and hypoxemia despite normal neuromuscular and pulmonary function. Either idiopathic (e.g., non-obstructive alveolar hypoventilation), genetic (e.g., CCHS), or acquired disorders (e.g., lesions in brainstem, respiratory depressant medications) share the common feature of nocturnal failure of the autonomic/metabolic breathing pathway with subsequent profound nocturnal hypoventilation. In general, these conditions may be attenuated during the daytime when the wakefulness/voluntary drive to breathe is dominant.

(a) Congenital Central Alveolar Hypoventilation Syndrome

Congenital central hypoventilation syndrome (CCHS), formerly referred as Ondine's curse, is a rare disease identified by an autosomal dominant genetic mutation in the PHOX2B gene located in the chromosome 4p12, the role of which in the disease has yet to be identified [111–114].

Epidemiology:

Reports of incidence of CCHS vary widely from 1 in 10,000 to 1 in 200,000 live births [115]. The spectrum of hypoventilation severity is varied, and although most cases present in newborns, mild phenotypes can also be identified in adults (primary hypoventilation syndrome) [116]. Unfortunately, the mortality rate is calculated to be around 38 % and median age of death is about 3 months [117].

Clinical characteristics:

During wakefulness, non-respiratory behavioral influences will modulate the ventilatory activity. However, during sleep, nocturnal shallow breathing, or cyanosis and apnea, is commonly found in perinatal sleep. Apart from alveolar hypoventilation, with subsequent signs and symptoms of profound nocturnal hypercapnia and hypoxia, this disease has been associated with Hirschsprung disease (aganglionic megacolon), neural crest tumors (e.g., neuroblastomas), and ocular abnormalities (e.g., strabismus) [118]. If untreated, death may occur as a complication of cor pulmonale and severe hypercapnia-hypoxemia.

Pathophysiology:

Even though the pathophysiology of the abnormal control of breathing in CCHS remains unclear, a unifying hypothesis is that the abnormality is located in areas of the brain involved in integration of chemoreceptor afferent pathways for ventilation. Patients with CCHS typically have adequate ventilation while awake followed by profound alveolar hypoventilation during sleep ($PaCO_2 > 45$ mm Hg), mainly due to decreased tidal volume and respiratory rate [119]. Depending on the severity of the disease, hypoventilation may extend into wakefulness.

Polysomnography:

After NREM sleep is established, failure of automatic–metabolic control of breathing will manifest as a severe hypoventilation, with or without central apneas, associated with sustained desaturations. Contrary to NREM sleep, ventilatory function becomes more stable during REM sleep [120].

(b) Brain stem, diencephalic regions, and spinal cord disorders

Independent of the mechanism of brainstem lesion, namely compression, edema, ischemia, infection, or infiltration, the

compromise of central chemoreceptors as well as the respiratory centers in the brain stem will result in hypoventilation and sleep apnea. Also, lesions of the descending pathways associated with the respiratory center, such as anterior cervical spinal artery syndrome or cervical cordotomy, will also translate into an ultimate failure of the autonomic/metabolic breathing pathway with subsequent profound hypoventilation. In these patients, the respiratory mechanics are normal with consequent normal pulmonary function.

Alveolar Hypoventilation Syndrome with Abnormal Respiratory Mechanics/Gas Exchange

Neuromuscular Disorders and Chest Wall Syndromes

Based on the neuroanatomical location of these lesions, from the upper motor neurons down to the neuromotor axis and up to the respiratory muscles, they can be grouped into motor neuron disorders (e.g., amyotrophic lateral sclerosis (ALS), post-polio syndrome), demyelinating disorders (e.g., multiple sclerosis, Guillain–Barre syndrome), neuromuscular junctional disorders (e.g., myasthenia gravis, Eaton Lambert syndrome), and respiratory muscle disorders (e.g., muscular dystrophies, mitochondrial myopathies). They are associated with hypercapnia ($PaCO_2 \geq 45$ mm Hg) as a result of increased respiratory load (chest wall and lung elastic loads). Functionally, these altered mechanics will not only reduce the minute ventilation but will also increase the dead space volume (higher V_d/V_t). In general, these disorders have an abnormal pulmonary function test characterized by restrictive physiology, with concomitant decrease in maximum inspiratory pressures as a marker of inspiratory muscle weakness.

Lower Airways Obstruction, Pulmonary Parenchymal Disease, and/or Vascular Pathology

Lower airway obstruction diseases, of which chronic obstructive pulmonary disease (COPD) is the most common, will limit the airflow with constraint of maximal minute ventilation. Alveolar hypoventilation will occur when the reduced maximal minute ventilation falls below the minimal minute ventilation threshold needed to maintain eucapnia. On the other hand, advanced stages of intrinsic restrictive pulmonary diseases, such as interstitial lung disease (ILD), will impair minute ventilation by reducing tidal volumes (V_t) and increasing dead space fraction (V_d/V_t). Finally, disorders that obliterate pulmonary vascular flow, such as pulmonary hypertension, will decrease the number of alveolar units able to participate in gas exchange (gas exchange disorders), with subsequent increase in dead space volume (V_d/V_t) and hypoventilation. Abnormalities in the pulmonary function test are characterized by obstructive physiology, a restrictive physiology, or a combination of both. Concomitant decrease in diffusing capacity of carbon monoxide (DLco) in the pulmonary function test may support a pulmonary parenchymal and/or vascular pathology.

Polysomnography:

If upper airway tone is not compromised, the polysomnographic study is characterized by sustained nocturnal desaturations without significant presence of respiratory events. The diagnostic criteria for scoring hypoventilation requires that a polysomnography or a sleeping arterial blood gas should be performed, showing at least one of the following criteria: (1) an overnight oximetry with less than 90 % for more than five minutes with a nadir of at least 85 %, and/or (2) more than 30 % of total sleep time at a saturation of oxygen less than 90 %, and/or (3) $PaCO_2$ that is $\geq$45 mm Hg or higher than during wakefulness [1]. It is worth noting that with diaphragmatic compromise (e.g., diaphragmatic paralysis), ventilatory efforts will be maximally affected during REM, with subsequent generation of "pseudo" central apneas.

Management:

Noninvasive ventilation (NIV), in the form of positive airway pressure ventilation (PAP), is the first-line therapy in nocturnal alveolar hypoventilation independent of etiology. In patients with neuromuscular diseases such as amyotrophic lateral sclerosis (ALS) with preserved bulbar function, BPAP-ST has been shown to improve median survival as well as quality of life at 1 and 6 months. Unfortunately, in those ALS patients with moderate-to-severe bulbar dysfunction, NIV may improve sleep-related symptoms, but has not been shown to prolong survival [121].

Limited data exist in average volume assured pressure support in alveolar hypoventilation. However, it could be an alternative to BPAP-ST for alveolar hypoventilation in progressive neuromuscular diseases due to its ability to self-adjust pressures for a target tidal volume.

The role of oxygen therapy in cases of alveolar hypoventilation syndrome is limited to those cases with persistent oxygen desaturations despite optimal control of hypercapnia by PAP devices. Its implementation as monotherapy should be avoided in patients with alveolar hypoventilation due to neuromuscular diseases or chest wall deformity as it may facilitate carbon dioxide retention [122].

Alveolar Hypoventilation Due to Obesity Hypoventilation Syndrome

Obesity hypoventilation syndrome (OSH) is defined as a body mass index >30 kg/m^2 combined with findings of daytime hypercapnia ($PaCO_2$ > 45 mm Hg at sea level) and hypoxemia (PaO_2 < 70 mm Hg at sea level), not otherwise explained by other known causes of alveolar hypoventilation, such as neuromuscular, restrictive, or obstructive pulmonary disorders (e.g., COPD) [123]. In the current obesity epidemic, this entity is often unrecognized and treatment is frequently delayed without a high clinical suspicion, despite the increased morbidity and mortality associated with this disease. While blood gas analysis is confirmatory, clues to the diagnosis may come from pulse oximetry and serum bicarbonate levels. In one study, a calculated bicarbonate cutoff of more than 27 m mol/L provided a sensitivity of 85.7 %, and a specificity of 89.5 % for the diagnosis of OHS, with 68.1 % positive and 95.9 % negative predictive value [124].

Epidemiology:

Large population-based studies are lacking, but the estimated prevalence of OHS is about 0.15–0.3 % in the general population, 11–20 % in sleep clinic referral cohorts for suspicion of OSA, and 8 % in bariatric surgery clinics with an increase up to 50 % of those hospitalized patients with BMI greater than 50 kg/m^2 [125–127].

Clinical characteristics:

OHS patients tend to be extremely obese and often present with complaints indistinguishable from OSA patients, such as excessive daytime sleepiness, morning headaches, and poor concentration [128]. Pulmonary function tests are characteristics of a restrictive physiology. Different from OSA patients, OHS patients have a lower SaO_2 during the daytime, peripheral edema, and pulmonary hypertension [125–127, 129]. In comparison with OSA, pulmonary hypertension is more common and more severe probably due to more chronic hypoxemia with concomitant endothelial dysfunction [125, 130].

Unfortunately, there is a significant delay in the diagnosis of this disorder with subsequent higher numbers of hospitalization and intensive care admission, in comparison with those obese patients without OHS [127, 131–133]. In general, the mortality rate in patients with untreated OHS is high [134]. Mortality is also elevated in this population in comparison with non-OHS obese individuals (23 and 9 %, respectively, at 18-month follow-up), as most patients are discharged without therapy [127]. Cardiovascular morbidity is also higher than non-OHS obese individuals, and OHS patients are more likely to develop CHF, angina pectoris, and cor pulmonale [133, 135].

Pathophysiology:

Daytime hypercapnia separates OHS from OSA. In approximately 90 % of patients with OHS, the sleep-disordered breathing is obstructive in nature [125]. The remaining 10 % of patients with OHS have an AHI of less than 5 events per hour, and their sleep-disordered breathing consists of sustained nocturnal hypoventilation, defined as a nocturnal increase of $PaCO_2$ of at least 10 mm Hg over wakefulness levels. In these patients, the predominant abnormality is a sustained hypercapnic–hypoxemic state ($SaO_2 \leq 90$ %), which extends during daytime. The physiopathology of OHS is not completely understood, but it may relate to interactions of the following: (1) impaired respiratory mechanics (increased work load), (2) reduced upper airway tone, and (3) decreased ventilatory drive (blunted respiratory response) [136].

Impaired respiratory mechanics:

In comparison with obese individuals without daytime hypercapnia, OHS patients have more impairment of respiratory mechanics based on low lung volumes (e.g., vital capacity and functional residual capacity), with the reduction in respiratory system compliance, increased airway resistance, and subsequent increased work of breathing associated with reduction in inspiratory muscle strength [10, 12, 137–139].

Reduced upper airway tone:

In patients with predominant upper airway obstruction, hypercapnia is considered to be the result of a combination of an elevated AHI with prolonged apnea duration and a short ventilatory duration between respiratory events. The subsequent development of metabolic compensation with high bicarbonate levels may further blunt the chemoreceptor-mediated ventilatory response to CO_2, resulting in the extension of hypercapnia into the daytime [13, 140–142].

In those OHS patients without upper airway obstruction, alveolar hypoventilation with sustained hypoxemia may occur and is strongly associated with development of awake hypercapnia [140]. In these patients, minute ventilation decreases by the reduction in tidal volume of approximately 21 % during NREM sleep and 39 % during REM sleep [143].

Decrease in ventilatory drive:

To compensate for the increase in respiratory load, obese individuals without OHS maintain eucapnia by increasing respiratory drive. Leptin, a circulating protein produced mainly by adipose tissue (adipokine), may contribute to this adaptation [144]. However, in OHS patients, despite increases in leptin levels, the respiratory drive and the responsiveness to hypoxia and hypercapnia are diminished [14, 145, 146]. It is suspected that a "central leptin resistance" may play a role in this phenomenon [14].

Polysomnography:

OHS patients may present different polysomnographic patterns. Those with predominant obstructive sleep apnea physiology will present cyclical airflow limitation (e.g., obstructive apnea and obstructive hypopnea) and desaturations indistinguishable from other non-OHS OSA patients. The second typical respiratory abnormality taking place during sleep in OHS patients is REM sleep hypoventilation. REM sleep hypoventilation is aggravated in OHS, as impaired respiratory mechanics combined with REM-related respiratory drive reduction will result in the absence of compensatory increases in work of breathing [128]. After adequate CPAP therapy with resolution of upper airway obstructive physiology, persistent central sustained hypoventilation may be present with sustained oxyhemoglobin desaturation [123, 147].

Management:

Weight loss is an important goal in the management of obesity hypoventilation syndrome (OHS). Bariatric surgery is an effective intervention to achieve substantial weight loss; however, obstructive sleep apnea and the need for PAP therapy for this may still be considered after surgery [148, 149].

Together with weight loss, positive airway pressure is considered the first-line therapeutic modality for nocturnal hypoventilation [25]. In most cases of OHS, when obstructive apnea–hypopnea is predominant, CPAP is highly effective in improving gas exchange and sleep-disordered breathing at ≤ 3 months, as well as improving lung volumes and central respiratory drive ≥ 4 weeks [150–152].

If sustained desaturation and elevated $PaCO_2$ levels persist despite the elimination of respiratory events by CPAP therapy, BPAP therapy is indicated. Even though it is estimated that 20–50 % of patient with OHS will fail CPAP with requirement of BPAP therapy, BPAP is not superior to CPAP if titration is successful [151]. During bilevel therapy, the difference between the inspiratory positive airway pressure (IPAP) and expiratory pressure (EPAP) should be targeted to improve ventilation by increasing tidal volume. Although BPAP treatment in OHS patients significantly improves blood gases (reduction in hypercapnia and hypoxemia), as well as sleep architecture, it does not show changes in inflammatory (IL and cytokines), metabolic (glucose and lipid metabolism), and cardiovascular (endothelial function and arterial stiffness) markers at one-month follow-up [153]. Although improved mortality has been shown with noninvasive positive pressure ventilation treatment when compared with historical controls, no prospective controlled trials are available at this time [135].

Limited data are published regarding average volume assured pressure support devices (AVAPS). In stable OHS patients on AVAPS, even though nocturnal hypoventilation is better controlled, their objective and subjective sleep quality and comfort of ventilation are slightly lower in comparison with those on BPAP [154, 155].

In addition to PAP therapy, and despite effective nocturnal ventilation, up to 40 % of OHS patients may need oxygen supplementation [147]. Even though supplemental oxygen therapy may worsen respiratory status of uncontrolled hypercapnic respiratory failure, persistent daytime hypoxemia after initiation of PAP therapy has been shown to be an independent predictor of poor survival in OHS patients [156, 157].

If noninvasive mechanical ventilation fails, tracheostomy for mechanical ventilation may be required without guarantee of complete daytime CO_2 normalization [158].

Treatment-Emergent Central Sleep Apnea

Treatment-emergent CSA, formerly known as complex sleep apnea syndrome (CompSAS), has been a topic of considerable controversy. It has been recently added into the group of CSAS by the International Classification of Sleep Disorders Task Force [1]. The diagnosis is based on the presence of 5 or more predominantly obstructive respiratory events during a diagnostic polysomnography, followed by a positive airway pressure titration polysomnography showing significant resolution of obstructive events and emergence or persistence of CSA events. The CAI should be more or equal to 5 events per hour, and the number of central events should represent more or equal to 50 % of total number of apneas and hypopneas. However, the presence of any alternative diagnosis associated with CSA, such as heart failure (CSA-CSB) or opiate use, would automatically exclude the diagnosis of treatment-emergent CSA [159, 160].

Epidemiology:

Depending upon the patient population being tested and the definition being used, the prevalence of treatment-emergent CSA ranges from 3 to 15 %. The persistence of treatment-emergent CSA while on positive airway pressure without a backup rate has been a controversial topic in the field of sleep medicine. Some authors assert that treatment-emergent CSA is a transient phenomenon related to sleep fragmentation and sleep stage shifts that occur while on initial CPAP therapy, results from inadequate titration, or from overtitration of positive airway pressure resulting in the Hering–Breuer reflex effect [161, 162]. Indeed, after 2–3 months of appropriate CPAP treatment in treatment-emergent CSA patients, eliminating obstructive but not central events, Dernaika and colleagues showed that treatment-emergent CSA patients had a 92 % (14 out 21 patients) complete or near-complete resolution of CSA events by polysomnography [163]. However, other authors have found that nearly fifty percent of patients have persistent central events despite compliance with CPAP therapy for a mean of 3 months [164]. Unfortunately, most of these studies are limited by their retrospective design, small sample sizes, and follow-up time. Nonetheless, a prospective study published in 2011 showed that the prevalence of treatment-emergent CSA fell from 12.2 % at time of diagnosis to 6.9 % (95 % CI 4.5–9.3 %) in comparison with those with only OSA while on fixed CPAP treatment for 3 months [165].

Clinical Characteristics of Treatment-Emergent Central Sleep Apnea:

Patients with treatment-emergent CSA tend to be older and have more coronary artery disease, and more fragmented sleep than those patients with OSA [160, 165]. The tendency to develop central apneas during PAP titration may be associated with additional cardiovascular comorbidity as well, including CHF and Cheyne–Stokes breathing pattern, arterial hypertension, and coronary artery disease [165, 166]. However, up to one-third may have no identifiable risk factors.

Pathophysiology:

Treatment-emergent CSA shares physiologic phenotypic features of both obstructive (OSA) and CSA. Like OSA, it is characterized by increased upper airway resistance with elevated critical closing pressure (P_{crit}), accompanied by increased ventilatory effort. Once on CPAP, with stabilization of critical closing pressure, a CSA physiology will predominate or emerge with the absence of ventilatory effort during apneic events likely driven by chemoresponsive ventilatory dysregulation (high "loop gain").

Polysomnography:

During the polysomnographic diagnostic study, treatment-emergent CSA is characterized by predominantly obstructive respiratory events (obstructive or mixed apneas, obstructive hypopneas) with an apnea/hypopnea index (AHI) ≥ 5 events per hour. During positive airway pressure titration, resolution of obstructive events follows the emergence or persistence of central apneas or hypopneas such that the central disordered breathing index is ≥ 5 per hour with >50 % central events. In comparison with those with OSA, and during the diagnostic portion of the polysomnographic study, treatment-emergent CSA patients may possess a mildly elevated central apnea index, particularly during NREM supine sleep, or higher arousal index [160, 167] Regarding other polysomnographic findings, in a finding of uncertain significance, periodic limb movements have been noted to be less frequent on PAP therapy in those with treatment-emergent CSA when compared to those with OSA [168].

Management:

Under the diagnosis of treatment-emergent CSA, different investigators have recruited heterogenous group of subjects with not only obstructive sleep apnea physiology during the diagnostic polysomnographic study but also with concomitant presence of CSAs ("mixed sleep apnea"), Cheyne–Stokes respiration, or ataxic breathing. Therefore, the outcomes used to measure a successful response to treatment with continuous positive airway pressure devices (CPAP) and noninvasive ventilation (NIV) will be tightly linked to the natural history of the disease and its baseline treatment. If we focus in those patients with baseline elevated apnea–hypopnea index but with low central apnea events (CAI < 5/h), in whom implementation of CPAP or BPAP-S shows emergence of CSA, the following conclusions can be drawn about treatment based on current evidence:

Continuous positive airway pressure (CPAP) therapy:

By definition, patients with treatment-emergent CSA have emergent CSAs while on positive airway pressure, associated with increased total arousals, wake time after sleep onset (WASO), and sleep stages shift, making them a susceptible population for fragmented sleep and possible intolerance to CPAP therapy [163]. Treatment-emergent CSA patients have also shown greater difficulties in adapting to CPAP treatment [169]. As mentioned above, although

most treatment-emergent CSA patients tend to improve with long-term CPAP use, there is a substantial group with persistent elevated CSA who may likely benefit from noninvasive ventilation. Unfortunately, no clinical or polysomnographic predictors are yet available to differentiate this subgroup of non-CPAP responders.

Adaptive servo-ventilation (ASV) therapy:

The adaptive servo-ventilation is a feedback control system adding a component of ventilation that is anticyclic to the patient's own respiratory drive periodicity [75, 170].

In comparison with CPAP and BPAP-ST, ASV treatment targeting minute ventilation in treatment-emergent CSA patients has not only been shown to have a significantly greater decrease in the AHI in all positions and stages of sleep, but also a lower residual arousal index, and a higher percentage of REM sleep [76, 171]. This beneficial effect should not be attributable to treatment-emergent CSA patients with occult CHF, as ASV has been proven to be an effective treatment for treatment-emergent CSA in patients with normal BNP, excluding possible confounding of CSA-CSB cases [172].

Two forms of servo-ventilation are currently available in the USA, one targeting a peak respiratory flow and the other targeting minute ventilation. Both devices have comparative acute efficacy in control of AHI, with no significant difference in residual CAI, and improvement in ESS score. The compliance with them is also high at 4–6-week follow-up [173]. Notwithstanding these apparent short-term improvements in sleep associated with ASV, there remains a need for larger, longer-term trials as well as exploration of cost efficacy before ASV can be routinely recommended for treatment-emergent CSA.

Summary

In conclusion, CSA syndromes comprise a wide spectrum of unstable breathing associated with important comorbidities. Identification of treatable conditions, such as CHF and use of opioids, is crucial in the management of these diseases. Even though the mechanism of instability of the respiratory metabolic control system is well established in patients with CHF and high-altitude periodic breathing, the mechanism underlying CSA in other pathologies remains to be investigated. Mounting evidence supports the general use of positive airway pressure devices in these disorders, with different degrees of therapeutic success depending on the underlining etiology and pathophysiology of the CSA.

Sleep-related hypoventilation–hypoxemic diseases are a heterogenous group of sleep-related breathing disorders with diverse pathophysiology, ranging from failure of the central automatic control of breathing to impaired lung function or chest wall mechanics. They are characterized by an elevation of arterial carbon dioxide tension and/or reduction of oxygen saturation during sleep, which may extend into the daytime. The current evidence supports the treatment of these disorders with different modalities of noninvasive ventilation (NIV), titrated to a specific minute ventilation.

While significant progress has been made in understanding CSA syndromes (CSAS) and sleep-related hypoventilation disorders, a paucity of research in these areas still exists. Further clinical trials are needed to expand our knowledge of pathophysiologic mechanisms, associated comorbidities, and the impact of positive airway pressure in the natural history of these diseases.

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Positive Airway Pressure in the Treatment of Sleep Apnea–Hypopnea

34

Charles W. Atwood and Patrick J. Strollo

Introduction

The application of nasal continuous positive airway pressure (CPAP) for the treatment of obstructive sleep apnea in adults was first described in 1981 [1]. Since then, it has become the medical therapy of choice for obstructive sleep apnea (OSA). Fundamentally, conventional positive airway pressure (PAP) systems that are employed to treat OSA patients consist of a generator that directs airflow downstream to the patient via tubing and an interface (e.g., nasal mask, oral-nasal mask, nasal cannula or prongs, or oral interface; discussed later in this chapter). Air, under the clinician-prescribed degree of positive pressure, is then introduced into the upper airway. The air pressure pneumatically splints the upper airway, thereby maintaining patency of this conduit and minimizing resistance to airflow. The splinting effect constitutes the primary mechanism of therapeutic action [2, 3]. An additional mechanism of action is the direct relationship between lung volume and upper airway patency mediated through traction on mediastinal and upper airway structures created during lung inflation; [4, 5] it has been postulated that at least part of the effect of CPAP in maintaining upper airway patency is mediated through augmentation of lung volume, although the magnitude of the effect is relatively small [2, 3, 6].

Regardless of the mechanism, nasal CPAP has documented effectiveness in eliminating obstructive and mixed apneas [7]. Some "central" apneas, particularly those observed in patients with predominantly obstructive events, are also eliminated by nasal CPAP [7, 8]. This finding supports the contention that the central portion of mixed apneas and many central apneas may actually represent delayed inspiratory effort due to prolongation of the preceding expiration related to expiratory upper airway instability with augmented upper airway resistance and slowing of expiratory airflow [9, 10]. It is also consistent with stabilization of oscillating ventilatory control during CPAP administration [11–14].

Positive Pressure Modalities Used to Treat Obstructive Sleep Apnea/Hypopnea

Continuous Positive Airway Pressure

The first PAP modality described to treat adults with OSA was CPAP [1]. CPAP may also be conceptualized as *constant* PAP, reflecting the fact that, by conventional definition, this modality delivers the same magnitude of pressure to the patient during inspiration and expiration (i.e., the pressure delivered during the patient's exhalation equals that delivered during inhalation). Fixed-pressure CPAP (i.e., the same pressure is delivered throughout the sleep period) is the standard to which all other modalities are compared.

Bilevel Positive Pressure

Studies of the pathogenesis of OSA have indicated that upper airway resistance increases during expiration despite the absence of negative intrapharyngeal pressure during this phase of the breathing cycle [9, 15, 16]. Sanders and coworkers speculated that instability of the upper airway during expiration is the initial event in the sequence leading

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to obstructive apnea [10]. Moreover, it was conceptualized that the splinting action of positive pressure in the upper airway, during both inspiration and expiration, was necessary to eliminate obstructive events, *but* less pressure is required to maintain adequate upper airway patency during expiration than during inspiration. This was based on the hypothesis that, during expiration, inherent upper airway instability represents the primary factor that favors airway closure, whereas during inspiration inadequate upper airway patency is related to two factors: the collapsing influence of negative intraluminal pressure and the inherent instability of the airway. The importance of expiratory events was subsequently demonstrated by computed tomography and magnetic resonance imaging to observe expiratory narrowing of the upper airway [17–20]. Application of expiratory positive airway pressure by Mahadevia et al. [21] was associated with a reduction in apnea frequency, although these investigators postulated that the improved upper airway function was related to increased oxyhemoglobin saturation secondary to increased functional residual capacity.

Bilevel positive airway pressure (bilevel PAP) provides the ability to independently adjust the inspiratory and expiratory pressure such that the pressure delivered during exhalation need not be as high as that delivered during inhalation [22–26]. By allowing independent adjustment of the inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP), bilevel PAP provides the potential to treat OSA patients with expiratory pressure that is lower than inspiratory pressure [22]. Setting the EPAP at a level that prevents upper airway occlusion during or at end-expiration permits the patient to generate inspiratory airflow or volume at the initiation of inspiratory effort, and this triggers delivery of IPAP, which supports upper airway patency during the inspiratory phase of the breathing cycle. Over and above preventing complete upper airway occlusion, delivery of a sufficient level of IPAP augments upper airway patency and eliminates partial obstructions (hypopneas) as well as upper airway obstruction-related desaturations and arousals from sleep. If the airway were to become occluded during expiration (e.g., EPAP not set sufficiently high), IPAP would not be triggered and the apnea would become apparent.

In an investigation of 13 patients with OSA in which optimal settings of nasal CPAP and bilevel PAP were compared, Sanders and Kern [22] observed that the EPAP delivered during bilevel PAP was significantly lower than the level of CPAP, and the mean value of EPAP for the group was 37 % lower than the required level of CPAP ($p < 0.001$). In contrast, there was no difference between the level of IPAP during bilevel PAP administration and the level of CPAP. There was comparable relief of OSA/H using both modalities. Several subsequent studies have confirmed the effectiveness of bilevel PAP in the treatment of OSA in adults [24–27].

Most bilevel PAP devices can be used in three modes. In the "spontaneous" mode, IPAP is delivered in response to a patient "trigger." In the "spontaneous-timed" mode, the patient may trigger the delivery of IPAP, but in addition, the physician may set the device so that IPAP is delivered at prescribed intervals if a spontaneously triggered delivery does not occur within that interval. This backup feature is infrequently needed in treating patients with OSA, although it has been helpful in providing nocturnal ventilatory assistance to other patient groups such as those with ventilatory muscle dysfunction resulting from neuromuscular disease and those with nocturnal hypoventilation due to chest wall deformities such as kyphoscoliosis. The spontaneous-timed mode may be beneficial in patients with Cheyne–Stokes breathing (CSB) and those who develop problematic central sleep apnea on CPAP in the context of complex central sleep apnea (see later in this chapter). In these patients, the capability for spontaneous triggering facilitates tolerance of the device by the awake patient, whereas during sleep the timed bilevel PAP "breaths" delivered at prescribed intervals prevent the long breathing pauses between lung inflations that are characteristic of central sleep apnea. Additionally, it is now recognized that, at least in some patients, central sleep apnea events may be associated with a closed upper airway [28–30]. Thus, it may be necessary to provide a critical level of EPAP to facilitate delivery of IPAP to the patient. CPAP and bilevel PAP are discussed in the context of complex central sleep apnea, CSB, and cardiovascular disease later in this chapter. There is also a "timed" mode for bilevel PAP devices in which IPAP is delivered with a clinician-set frequency and the patient cannot initiate delivery. In general, we have not found this mode to offer benefit over the "spontaneous-timed" mode.

Autotitrating CPAP and Bilevel PAP

Autotitrating CPAP (APAP) and bilevel PAP devices employ proprietary algorithms to detect impending collapse or instability of the upper airway and adjust the amount of pressure that is delivered in order to maintain patency. Following a period of upper airway stability, the pressure gradually decreases (according to each manufacturer's algorithm) until impending collapse or instability is again detected. The delivered pressure is then increased per the algorithm. Thus, the pressure "floats" throughout the night with the intention of meeting the patient's requirements in real time (Fig. 34.1).

At least in part, the putative advantages of the autotitrating devices (APAP and auto-titrating bilevel PAP) are to reduce the pressure to which patients are exposed and thereby to increase comfort, satisfaction, and adherence to

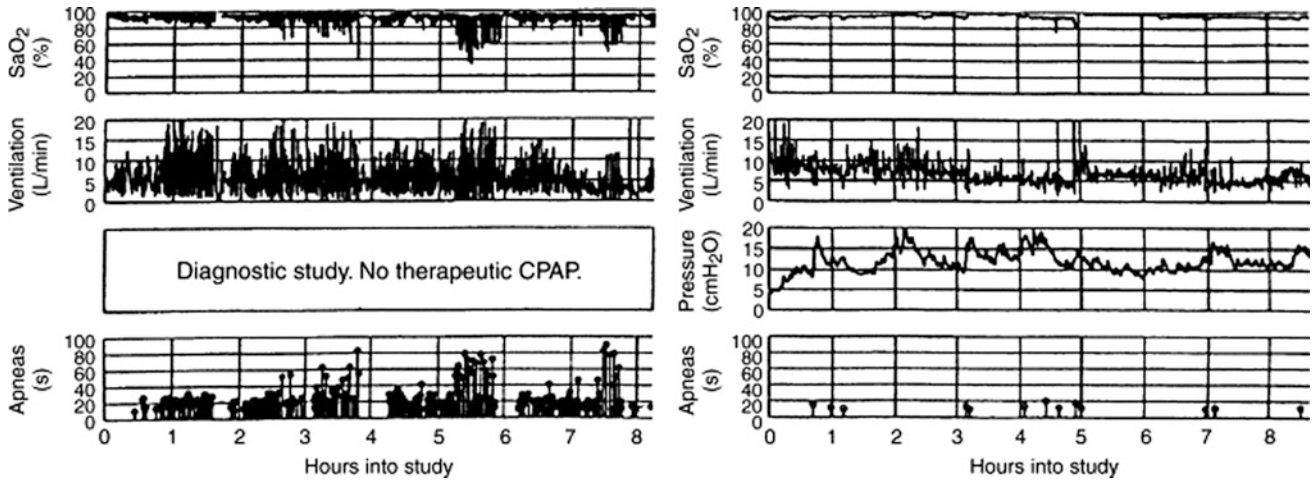

Fig. 34.1 Arterial oxyhemoglobin saturation (SaO_2), minute ventilation, CPAP mask pressure, and apneic events recorded with an oximeter and a prototype of an intelligent CPAP machine in a patient with sleep apnea. *Left* Diagnostic study with repeated episodes of obstructive apnea. *Right* Autotitrating CPAP with pressure levels that vary across the recording (Reproduced with permission from Polo [239])

therapy. Bilevel PAP also is capable of assisting or augmenting ventilation by virtue of the gradient between end-expiratory and inspiratory pressures. The autotitrating devices attempt to respond to concern that the optimal therapeutic PAP prescription may vary across the night (e.g., across various body positions) and across nights. Indeed, investigators recently reported that a notable proportion of patients receiving a prescription of fixed-pressure CPAP were subsequently found to have an apnea–hypopnea index (AHI) >10 on the same prescription [31]. However, the patients with AHI >10 did not differ significantly from those without persistent OSA with regard to quality of life, mood, vitality, or Epworth Sleepiness Scale score.

A review and a meta-analysis of APAP reveals that these devices may provide comparable alleviation of OSA and perceived daytime sleepiness, compared with fixed-pressure CPAP with a mean pressure that is about 2 cm H_2O lower. This does not appear to translate into improved adherence to therapy, however [32, 33]. It is important to note that studies that examined APAP efficacy excluded patients with underlying cardiopulmonary disease as well as other comorbidities. Further studies are needed before recommending routine use of this modality in patients with these comorbidities. Issues related to CPAP, bilevel PAP, and APAP modalities are discussed later in the chapter.

"Pressure-Relief" CPAP and Bilevel PAP

"Pressure-relief" CPAP and bilevel PAP have recently been introduced [34, 35]. These provide expiratory pressure relief that is proportional to expiratory airflow, while pressure increases rising to the prescribed EPAP level at end-expiration. In expiratory pressure relief, the pressure-relief bilevel PAP device provides relief of pressure at end-inspiration [34]. Plausibly, this is facilitated by the high lung volume at end-inspiration that contributes to upper airway patency as well as the fact that, as inspiration reaches its end, airflow diminishes with consequent reduction in collapse-promoting negative intrapharyngeal pressure. Pressure-relief CPAP was as effective in reducing sleep-disordered breathing events and improving sleep continuity as conventional CPAP [35]. Gay and coworkers [34] demonstrated comparability between pressure-relief and convention bilevel PAP in alleviating OSA; however, there are too few studies of these modalities on which to base conclusions.

Adaptive Servo-Ventilation

Although CPAP and bilevel PAP therapy may be associated with improvement in Cheyne–Stokes breathing (CSB) and central sleep apnea, sometimes there is no improvement or worsening [36, 37]. Adaptive servo-ventilation (ASV) has introduced into clinical practice primarily to address CSB in the context of heart failure as well as idiopathic and complex central sleep apnea or treatment-emergent central sleep apnea (central sleep apnea that becomes clinically problematic during application of conventional CPAP or bilevel PAP during treatment of OSA). In general, these devices provide a variable degree of inspiratory pressure support that stabilizes the patient's ventilation over time. Thus, if there is a reduction in the patient's spontaneous ventilation, the degree of inspiratory positive pressure support will increase proportionately to minimize a decrement in ventilation [38]. A backup rate of IPAP delivery may also be set by the clinician.

Teschler et al. [38] evaluated the effects of supplemental oxygen, CPAP, bilevel PAP, and ASV in patients with CSB (with primarily central sleep apnea) due to heart failure and reported that ASV provided the greatest reduction in AHI, slightly but statistically significantly lower than on bilevel PAP. Sleep continuity, sleep efficiency, percent slow-wave sleep, and percent rapid eye movement (REM) sleep were comparable on ASV and bilevel PAP. The ASV settings in this investigation included a backup rate of 15 breaths/min, and the backup rate on the bilevel PAP was set at the patient's awake spontaneous breathing rate, less 2 breaths/min (for the study group, the range of backup rate was 13–18 breaths/min). It is not possible to determine how much improvement in CSB was specifically due to the ASV or bilevel PAP algorithm as opposed to the presence of a backup rate on both modes in this study. A subsequent case series by Banno et al. [36] reported improved CSB on ASV that had failed to improve on CPAP. These authors indicated that they employed the same default settings as Teschler et al. [38], and therefore a backup rate may also have been used.

A small case series of heart failure patients with CSB who failed CPAP and bilevel PAP (with a backup rate) reported a beneficial effect of ASV [39]. The ASV employed in this study included a default backup mode. A randomized 4-week crossover trial of ASV prescribed at therapeutic settings (including a backup rate) versus ASV prescribed at subtherapeutic settings (with a backup rate of 15 breaths/min) was performed on patients with heart failure and CSB [40]. The results demonstrated significantly greater improvement of the AHI during the intervention with ASV at therapeutic settings. Although the active intervention resulted in a substantial reduction in objectively assessed sleepiness compared with subtherapeutic ASV, there were no statistically significant changes in the secondary outcome measures of the study, including subjective sleepiness, questionnaire assessment of health status, and performance using a driving simulator with either therapeutic ASV or subtherapeutic ASV. However, plasma brain natriuretic peptide and urinary metanephrine excretion fell on the active intervention, suggesting a favorable physiologic impact of ASV. These results suggest that ASV results in physiologic improvements, but the absence of subjective improvement in sleepiness is disappointing.

Despite initial enthusiasm for ASV therapy in heart failure patients, the use of this mode has been questioned recently on the basis of a randomized examining the role of ASV in central sleep apnea with systolic heart failure, the SERVE-HF trial. In a study with 1325 subjects with a left ventricular ejection fraction of 45 % or less and clinical heart failure, there was no difference in AHI between the ASV group and the treatment-as-usual control group at 12 months after starting ASV therapy. Furthermore, there was a statistically significant increase in mortality in the ASV therapy group compared to the control group (hazard ratio for ASV was 1.28 (90 % CI 1.06–1.55). This study result has resulted in a questioning of the role of this mode of therapy in systolic heart failure. Further studies being conducted presently may clarify the results of SERVE-HF.

The general features of various PAP modalities are summarized in Table 34.1. It is important to note that algorithms and modes of operation vary across manufacturers and models. This table is not intended to represent definitive features of specific brands and models but rather to describe general features.

Effectiveness of PAP in Treating Patients with OSA

There is abundant evidence that, when applied in sufficient pressure, PAP effectively eliminates OSA events as well as respiratory effort–related arousals. Following initiation of CPAP therapy during sleep, most OSA patients with daytime sleepiness at baseline report increased subjective alertness [41–43]. There is, however, variability across studies. In a meta-analysis of randomized trials, Marshall and coworkers [44] reported that, after controlling for placebo effects, the Epworth Sleepiness Scale score [45] increased significantly, but only by 1.2 points in patients with mild to moderate OSA. The effect of CPAP on objective metrics of sleep propensity during the day (e.g., Multiple Sleep Latency Test [MSLT] or Maintenance of Wakefulness Test) is less clear, with only some studies showing an effect and a less compelling impact in patients with mild OSA [42–47]. The meta-analysis by Marshall et al. examined the ability to remain awake under soporific conditions, assessed by the Maintenance of Wakefulness Test and observed that, over the three randomized trials in which this assessment was performed, sleep latency increased significantly but only by 2.1 min, and there was no significant change in the sleep latency during the MSLT in the four trials in which it was assessed [44]. The investigators called into question the clinical significance of their changes. Another meta-analysis [48] reported a significant reduction in the Epworth Sleepiness Scale score by an average of approximately 3 points, with relatively greater reductions in patients with severe OSA. These investigators also observed only a marginal improvement in the MSLT after introduction of CPAP therapy.

In the context of vigilance and alertness, a critically important functional outcome to examine is the effect of OSA

Table 34.1 General features of positive pressure delivery modalities

Positive pressure modality general features	
Continuous positive airway pressure (CPAP) The clinician may prescribe the CPAP level	
Positive pressure delivered during inspiration equals that delivered during expiration	
"Pressure-relief" CPAP	The clinician may prescribe the CPAP level
• Positive pressure delivered during expiration decreases in proportion to the increasing expiratory airflow early in expiration and increases back to the prescribed CPAP level as the patient's expiratory airflow decreases with the approaching end of exhalation	
The clinician can set the degree of pressure relief	
Bilevel positive pressure	The clinician may prescribe the level of inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP)
• EPAP may be set independent of IPAP, but EPAP may not be higher than IPAP	
Some models permit prescribing a timed backup rate	
Pressure-relief bilevel positive pressure	Same as for bilevel positive pressure except the clinician may also prescribe inspiratory and expiratory pressure relief
Autotitrating CPAP	CPAP level fluctuates over the period of use according to a manufacturer-designed algorithm
The clinician may prescribe the minimum-maximum range within which the pressure may fluctuate	
Autotitrating bilevel positive pressure	IPAP and EPAP levels fluctuate over the period of use according to a manufacturer-designed algorithm
• The clinician may prescribe the minimum EPAP and maximum IPAP within which the pressure may fluctuate	
The clinician may prescribe the maximum IPAP-EPAP gradient ("pressure support") up to a manufacturer-designed limit	Adaptive servo-ventilation The clinician prescribes an EPAP level
• Different brands have different algorithms for establishing the minimum and maximum IPAP level and minimum level of pressure support	
In general, the pressure support varies to maintain a target ventilation or a target airflow; there is a default timed backup rate	

Algorithms and modes of operation vary across manufacturers and models. This table is not intended to represent definitive features of specific brands and models but rather to describe general features

and subsequent therapy on motor vehicle crashes [49]. In this regard, a number of studies employing driving simulators have demonstrated improved performance following initiation of CPAP therapy [50–53]. Similarly, a comparison of the number of accidents per driver per year over the 3 years before and following CPAP therapy in OSA patients demonstrated a notable reduction, reaching levels that were comparable to those in individuals without OSA [54] (Fig. 34.2).

Turkington et al. [52] reported that benefits on driving performance, assessed using a simulator, may be evident within 7 days of initiating therapy, while, more recently, Orth et al. observed improvement after only 2 days [53]. This is consistent with earlier data indicating that there may be a reduction in subjective daytime sleepiness after just 1 night of nasal CPAP therapy [55], and that progressive reduction in objective daytime alertness (assessed by the MSLT) may occur over 2 weeks following initiation of therapy [56]. The progressive nature of the improvement in symptoms and the apparent variability in response, as reflected in the previous discussion of the meta-analyses of CPAP effectiveness, highlights the importance of recognizing that patients may not be sufficiently alert to resume full activities (especially those that require vigilance, such as operating vehicles or potentially dangerous tasks) within the first several days of treatment. In addition, although studies have concluded that driving simulators may provide insight into on-the-road driving performance, differences do exist [53, 57]. It is important for clinicians to recognize that in general, studies examining treatment effect on motor vehicle crashes have been uncontrolled. To better assess the improvement in symptoms of daytime sleepiness, it is essential that the healthcare team make follow-up contact with the patient soon after the initiation of therapy. Close follow-up will facilitate evaluation of the patient's ability to perform activities that require alertness as well as to assess therapeutic adherence (see discussion below).

PAP often has a beneficial impact on other symptoms of OSA. Studies have reported relief of tiredness, reduced snoring, decreased nocturnal awakenings with perceived choking or gasping, and a reduction in nocturia [46, 58–64]. It

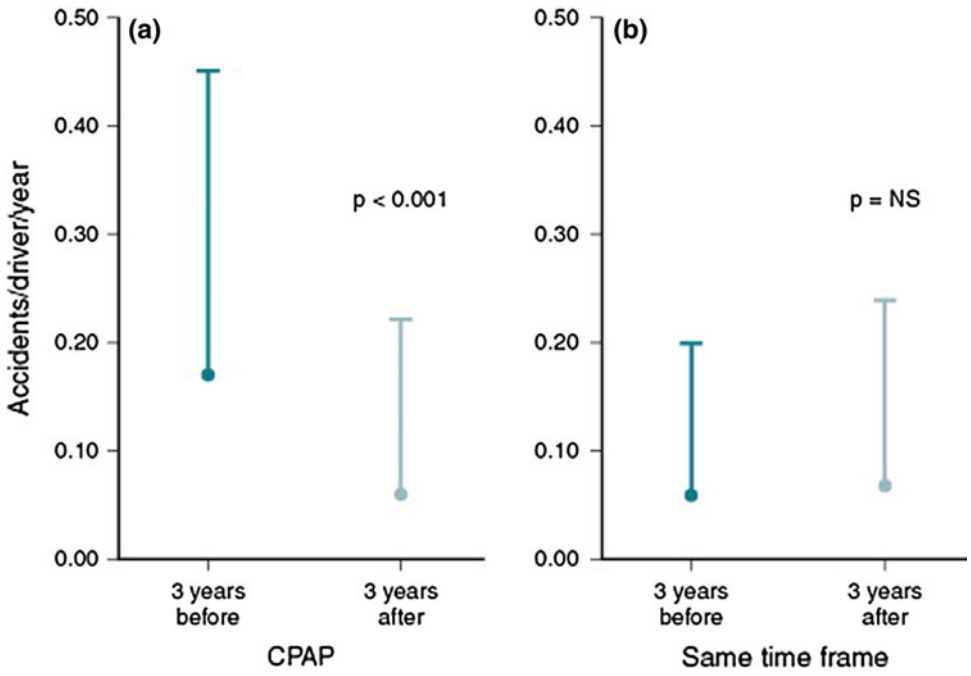

Fig. 34.2 **a** Accident rates (mean ± SD) for patients with OSA over the 3 years before and after initiation of CPAP therapy. **b** Accident rates (mean ± SD) for control subjects over the same time interval (Reproduced with permission from George [54])

is appropriate to note at this point, however, that nocturia—at least in conjunction with benign prostatic hypertrophy—has been reported to negatively influence adherence to PAP therapy [65], probably due to the inconvenience of removing and replacing the interface. It may be possible to extrapolate this finding to OSA patients with nocturia that is unassociated with prostatic hypertrophy. In light of the potentially beneficial effect of PAP use on nocturia, patients should be counseled to stick with the PAP therapy to achieve a favorable outcome, and the etiology of residual nocturia should be investigated and treated.

The impact of PAP on quality-of-life measures and neurocognition has also been assessed. Engleman and co-investigators reported the results of a placebo-controlled trial of CPAP in patients with mild OSA; use of CPAP for >2.5 h/night was associated with improved visual-motor skill, social function, and vitality (using the Medical Outcomes Short Form-36 [SF-36]). In addition, the Hospital Anxiety and Depression Scale Depression Score was reduced. In a non-placebo-controlled study comparing "conservative" management and CPAP for moderate to severe OSA, McFayden et al. [66] examined the results of the disease-specific Functional Outcomes of Sleep Questionnaire (FOSQ) as well as the SF-36 and found that CPAP was associated with improved psychosocial function and the patient's (but not the spouse's) marital satisfaction. Conversely, Barnes et al. found no effect on neurobehavioral function or quality-of-life metrics on the SF-36 or the FOSQ [46]. These investigators speculated that differences in the study population, particularly related to gender, may explain the disparate results. Studies of patients with moderate to severe OSA (e.g., the most symptomatic individuals prior to treatment) indicate the largest effect sizes are in the contexts of sleepiness and vitality. Studies have suggested that patients with moderately impaired pretreatment cognitive performance experience modest improvements [42, 43, 67]. Moreover, data suggest that daily use of PAP for at least 6 h over 3 months is associated with clinically relevant improvement in verbal memory in some, but not all, OSA patients [68]. The most definitive data to date concerning neurocognition in sleep apnea comes from the Apnea Positive Pressure Long-Term Efficacy Study (APPLES) in which 1204 adults with OSA were randomly assigned to effective CPAP vs. sham CPAP and had neurocognitive testing performed. After adjusting for confounders such as baseline education level, gender and ethnicity, the investigators found no significant relationship between OSA (as quantified by AHI) and neurocognitive performance. The small association between OSA and neurocognition that was detected was largely associated with degree of hypoxemia [69].

Side Effects of Pap Therapy

Like most treatment interventions, PAP is often associated with a variety of generally minor, but troublesome side effects (Table 34.2) [16, 19, 25, 45–50, 58, 61, 70–75]. Side effects may be attributable to either the patient-device interface or the sensation of high airflow or pressure. Some patients simply perceive the lifestyle and other challenges associated with nasal PAP to be unacceptable [3, 46, 48, 61, 73, 76–78]. Such individuals are often, but not invariably, younger patients who are unable to envision indefinite nasal PAP therapy. Although some studies have concluded that

Table 34.2 Side effects of nasal CPAP

Side effect	Management measures
Mask related Skin abrasion or rash Conjunctivitis from air leak • Protective skin covering • Customized mask • Reinforce hygienic care of device Eye patch	Optimize mask fit from wide selection of commercially available types of masks, select nonallergenic material
Pressure or airflow related Chest discomfort Aerophagia Sinus discomfort Smothering sensation Difficulty exhaling Difficulty initiating and/or maintaining sleep Pneumothorax or pneumomediastinum Pneumocephalus • Reduce pressure with bilevel positive airway pressure Try to reduce requisite pressure using oral appliance + CPAP (no published data)	Pressure ramp
Problems related to the nasal route Rhinorrhea Nasal congestion, nasal and/or oral dryness Epistaxis (may be massive, especially in anticoagulated patients) • Saline nasal spray • Topical nasal steroid preparation • Consider trial of nasal aerosol of ipratropium bromide solution • Chin strap for oral dryness Oral-nasal mask interface Desensitization over time	Heated humidification
Other Noise Cumbersomeness or inconvenience Spousal intolerance Longer tubing to move device further from bedside (consult device manufacturer for permissible lengths) • Intensify education of patient and spouse Recommend attending a patient support group (A.W.A.K.E Network of the American Sleep Apnea Association)	

side effects do not impact on adherence to therapy [61, 74], others have concluded the converse, citing side effects as a reason for nonadherence [79].

Claustrophobia

Not uncommonly, patients complain of claustrophobia in conjunction with enforced breathing through a nasal mask or nasal prongs system, or with CPAP in general [47, 48, 51, 72, 73, 80, 81]. For those patients who are uncomfortable breathing exclusively via the nasal route, an oral-nasal mask that permits breathing through either the oral or nasal route may be a useful alternative [82, 83] (see later). Clinicians should be aware of one study demonstrating that, when patients were randomly assigned to either nasal or oral-nasal interface, adherence was lower while using the latter [84]. This study did not examine adherence to CPAP when an oral-nasal mask was prescribed as a "salvage" intervention for patients with complaints regarding a nasal interface. A desensitization program to promote acclimatization to nasal CPAP may be useful in some patients [81], and a study found that the sensation of claustrophobia diminishes over time with perseverance of treatment [80]. The investigators suggested that early identification of patients who are likely to be claustrophobic and institution of interventions targeted to address this issue (e.g., desensitization, education, and support) may be of considerable value [80, 85].

Problems Related to Nasal Route of Breathing

Problems with skin abrasion or leakage of air directed into the eyes, with or without consequent conjunctivitis [61, 86], may result from a poor mask fit. Other complaints related to the nasal route of breathing include nasal dryness, congestion, and rhinorrhea. The reported prevalence of such effects varies from 25 to 65 %. One study observed that use of nasal prongs or pillows was associated with better adherence to therapy than a nasal mask [87]. Although the percentage of days during which patients used CPAP was slightly greater when using the nasal pillows (94 % vs. 86 %), the time of CPAP use per night across all nights as well as specifically on those nights during which patients used CPAP was not statistically different between the two interfaces. There was no difference between the interfaces with regard to relief of sleep-disordered breathing and functional outcome assessed by the FOSQ. The authors reported that overall satisfaction was greater with use of the nasal pillows. In our experience, we have found that interface preference varies across patients. Moreover, preferences vary over time in individual patients, with many switching back and forth across interfaces. It may be reasonable to provide patients with several interfaces from which they may choose on any given night. Of course, follow-up is important to ensure ongoing success in alleviation of OSA and symptoms.

Nasal Dryness and Congestion

Nasal dryness and congestion can occasionally be treated simply with either administration of saline nasal spray at bedtime or a room humidifier. For some patients, a topical nasal steroid may be effective. Addition of a low-resistance humidifier to the PAP system may also be extremely helpful in certain patients, and heated humidification systems are now standard on most PAP systems. Richards et al. documented increased nasal resistance in the presence of high nasal flow, such as occurs when there is a mouth leak during nasal CPAP

application [88]. Incorporation of a heated, but not an unheated, humidifier into the CPAP system minimized the increase in nasal resistance, presumably by increasing the relative humidity of the inspired gas and reducing release of inflammatory mediators. The superiority of heated humidifiers to nonheated humidifiers in restoring relative humidity to inhaled air was confirmed in a study by Fleury et al. [89]. The issue of routine prescription of a heated humidifier at the time of the initial PAP prescription has been the focus of several investigations, often yielding conflicting results. In a setting more clinically relevant to OSA patients than that employed by Richards et al., Duong et al. [90] measured nasal airway resistance before and after a night of CPAP in patients randomized to receive heated humidification or placebo. There was no significant difference between the groups with regard to total nasal airway resistance in the evening before CPAP use or in the morning following CPAP use. There was also no difference between the groups with regard to the overnight percent change in nasal airway resistance.

Massie et al. [91] reported that, compared with a cold humidifier, heated humidification of CPAP-delivered air resulted in a statistically significant improvement in adherence, albeit by only an average of 0.6 h. While there were less frequent reports of dry mouth, throat, and nose during application of heated humidification, the global adverse side effect score did not differ by heated versus cold humidification. Three quarters of the patients preferred heated humidification, reflecting that a measurable minority did not. In a more recent study, Mador et al. [92] compared adherence and quality of life in a group of 49 OSA patients prescribed to receive CPAP with heated humidification versus 49 control patients who were not initially prescribed heated humidification but did receive it only if nasal symptoms occurred that were unresponsive to other measures. Six control patients crossed over to heated humidification. There was no difference in adherence or Calgary Sleep Quality of Life Index between the groups over 12 months. There was no improvement in adherence in control patients who crossed over to heated humidification, although nasal symptoms diminished. Similarly, in a randomized crossover trial, Neill et al. [93] observed that, compared with placebo humidification, heated humidification of CPAP was associated with fewer upper airway symptoms and a slightly greater degree of use initially following setup. However, by the end of week 3, there was no difference in adherence or in satisfaction with therapy. The authors concluded that heated humidification may be useful in addressing side effects but is not appropriate for routine prescription to all patients. Nevertheless, it appears that heated humidification may provide benefit to at least some patients. Rakotonanahary et al. [94] observed that chronic nasal mucosal disease, nasal septum deformity, and a history of uvulopalatopharyngoplasty predicted need for heated humidification of PAP.

Thus, there is considerable literature that does not support benefit to the *routine* prescription of heated humidification to all OSA patients at the time of initial setup, although there are selected subsets who benefit from such a prescription. It is reasonable to approach the issue of heated humidification from the perspective expressed by Brown in commenting, "If it's dry, wet it." [95]. In this context, the data indicate that patterns of adherence (or nonadherence) are established early on [96], so there is considerable wisdom in obtaining follow-up very soon after the patient receives the PAP unit in order to detect and address factors that may diminish the enthusiasm to be adherent to treatment.

Although routine use is to be discouraged, occasional administration of a vasoconstrictive nasal spray may be helpful when nasal congestion is related to a self-limited condition such as an upper respiratory tract infection.

Whereas nasal dryness is rarely a serious problem, massive epistaxis has been reported [97]. Mucosal dryness may be a contributory factor to the epistaxis, which did not recur after placement of a humidifier in the CPAP system. In light of this report, it seems prudent to follow patients with a history of bleeding tendencies, epistaxis, or coagulopathy who are on PAP with particular care, and to consider humidifying the delivered air from the outset of therapy.

Rhinorrhea

Rhinorrhea after initiation of PAP therapy, present in approximately 35 % of patients [61], is often a difficult problem to control. The cause of this untoward effect is likely to be related to inflammation, as in nasal congestion. Similarly, one study did not observe a beneficial effect from humidification, although it is uncertain if a heated humidifier was employed [61]. Therefore, it may be worth trying a heated humidifier, as described previously, for the treatment of rhinorrhea. Although we are unaware of published, systematically conducted research studies, we have found the administration of anticholinergic nasal sprays such as ipratropium bromide or Azelastine nasal spray (if used, care must be taken due to sedating potential) may be only variably effective among patients with rhinorrhea. However, as noted previously, nasal steroids have been observed to provide more consistent benefit.

When evaluating a patient with rhinorrhea, it is essential to consider the possibility of a cerebrospinal fluid leak. Kuzniar et al. [98] described two patients who developed rhinorrhea after initiation of CPAP therapy, which subsequently proved to reflect a cerebrospinal fluid leak that in one patient was complicated by meningitis. Clinicians should keep this uncommon but real possibility in mind when assessing rhinorrhea in CPAP users.

Barotrauma and Chest Discomfort

When providing positive pressure therapy, the clinician must always consider the potential for barotrauma. Although clinicians should be vigilant for pneumomediastinum and pneumothorax, these are uncommon in OSA patients receiving CPAP, at least as assessed by review of the literature. Pneumocephalus has been reported in a sleep apnea patient with a cerebrospinal fluid leak who was placed on nasal CPAP [99] and in a patient on nasal CPAP who presented with headache [100]. Pneumocephalus should be considered when any patient using CPAP therapy develops a nasal discharge, or neurologic signs and symptoms including headache, seizures, dizziness, or cranial nerve palsy.

A small number of patients complain of chest discomfort on nasal CPAP therapy [75, 101, 102]. This is probably related to the positive end-expiratory pressure and consequent elevation of resting lung volume [103], which stretches the chest wall muscles and cartilaginous structures, creating a sensation of chest wall pressure that may persist after awakening. Although the complaint of chest discomfort should be completely evaluated in any patient, if a cardiopulmonary workup in an OSA patient on CPAP is nondiagnostic, efforts should be made to reduce the expiratory pressure, if necessary by using bilevel PAP (discussed later). Similarly, a certain proportion of patients perceive discomfort when exhaling against positive expiratory pressure [58, 102]. If the level of CPAP cannot be satisfactorily reduced, a trial of bilevel PAP may be considered [104] (see later).

Effects on Arterial Blood Gases and Oxyhemoglobin Saturation

While it is usually beneficial to patients with OSA, administration of nasal CPAP may be associated with untoward effects on arterial blood gases and oxyhemoglobin saturation. Pépin et al. [61] reported severe oxyhemoglobin desaturation during nasal CPAP therapy in a hypercapnic sleep apnea patient with cor pulmonale. Similarly, Krieger et al. [105] reported persistent and notable desaturation despite CPAP administration *with* supplemental oxygen to hypercapnic OSA patients. Although the cause of this desaturation is not certain, it may be due to one or more of the following: (1) worsening hypoventilation related to the added mechanical impedance to ventilation associated with exhalation against increased pressure; (2) increased dead space ventilation [106]; and (3) that venous return and cardiac output decrease due to increased intrathoracic pressure during CPAP administration in patients with impaired right or left ventricular function and inadequate filling pressure. With regard to the potential contribution of alveolar hypoventilation to nocturnal oxyhemoglobin desaturation during CPAP therapy, Fukui et al. [107] noted that nasal CPAP failed to reduce sleep-related hypercapnia during non-REM sleep in OSA patients, and Piper and Sullivan [108] observed persistent sleep desaturation on CPAP in severe OSA and hypercapnia. Similarly, Resta et al. [18] reported that hypoventilation during sleep on CPAP was more likely to occur in more obese patients and those with higher arterial partial pressure of carbon dioxide ($Paco_2$). This highlights the prudence of conducting CPAP trials under monitored conditions in patients at high risk for nocturnal hypoventilation, including individuals with chronic ventilatory failure (awake hypercapnia) and morbidly obese individuals.

Despite these caveats and troublesome experiences, CPAP administration has also been reported to improve awake arterial blood gases in OSA patients with hypercapnia and cor pulmonale [109–111]. A study has demonstrated that CPAP therapy for OSA reduces pulmonary artery pressure in patients with mild pulmonary artery hypertension [112]. In this study, the pulmonary systolic pressure was related to both the AHI and diastolic dysfunction.

The mechanism responsible for augmented alveolar ventilation during wakefulness in hypercapnic persons has not been clearly defined. The literature is not consistent with regard to the effect of CPAP on the slope of the hypercapnic ventilatory response curve in OSA patients, with some of the differences related to measuring different parameters of ventilatory control and others perhaps related to differences in subject populations. Some investigations observed no change in the slope of the carbon dioxide/ventilation relationship in normocapnic patients [113, 114]. Mateika and Ellythy observed an elevation in the ventilatory recruitment threshold to CO_2 in normocapnic OSA patients compared with normal subjects, with no difference in ventilatory response above this threshold [115]. This may provide insight into the earlier observation by Berthon-Jones et al., who reported a leftward shift in the ventilatory response to carbon dioxide following initiation of CPAP therapy without a change in the slope of the line representing the relationship between carbon dioxide tension and ventilation [114]. These data are consistent with a reduction in the chemoreceptor(s) set point to $Paco_2$ following initiation of therapy.

Although the issue has not been systematically explored specifically in hypercapnic OSA patients, it is possible that alleviation of sleep-related hypercapnia with alleviation of apneas and hypopnea alters the hypercapnic threshold by reducing serum buffering capacity. Alternatively, enhanced chemosensitivity to carbon dioxide during wakefulness may be due to relief of hypoxic depression of central nervous system respiratory centers. While it had been previously believed that sleep deprivation reduces hypercapnic ventilatory responsivity [116], more recent data, collected over 24 h of sleep deprivation with electroencephalographic

documentation of wakefulness, refuted the earlier study [117]. These issues notwithstanding, studies indicate that CPAP often does not reduce $Paco_2$ during sleep and wakefulness in hypercapnic patients [18, 106, 107], and reliance on this modality to reduce awake hypercapnia may be problematic [108]; augmentation of ventilation after maintenance of upper airway patency may facilitate improvement in diurnal hypercapnia [104].

Acceptance of and Adherence to Pap Therapy

The most significant disadvantage to PAP therapy is that patients must actively participate in their own treatment both in terms of the number of nights used as well as the number of hours used per night. Although the optimal duration of nightly PAP use—or for that matter, the minimal amount of use that confers benefit—are unknown, recent studies suggest that use of at least 6 h/night confers greater cardiovascular mortality risk reduction compared with fewer hours of use per night [118] (Fig. 34.3). In addition, PAP use for >6 h/night over 3 months has been associated with a greater likelihood of normalized memory performance [68]. Viewed from the opposite perspective, sleeping for as little as 1 night without CPAP is associated with increased sleepiness [55, 119]. These data highlight the need for clinicians to facilitate maximal PAP use by patients.

Before adherence to a therapeutic PAP prescription can be considered, the patient must accept the opportunity to receive this therapy. The acceptance rate of CPAP varies across a number of studies, ranging from 62 to 92 % [71, 72, 120–125]. Among the reasons for nonacceptance are difficulty falling asleep, frequent nocturnal awakenings, and mask discomfort. In addition, those who accept CPAP therapy are generally more likely to complain of greater tiredness as well as episodes of falling asleep at undesirable times [121].

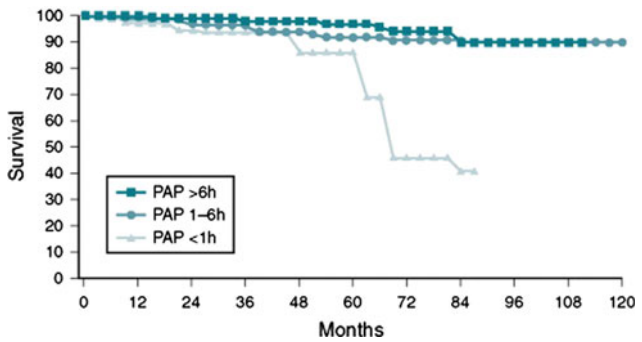

Fig. 34.3 Kaplan–Meier cumulative survival rates according to categories of PAP compliance. Survival rates in the patients using PAP > 6 h/night were significantly higher than in the patients using PAP < 1 h/night. Cumulative survival rates in patients using PAP 1–6 h/night were significantly greater than in patients using PAP < 1 h/night. Cumulative survival rates were not different in the patients using PAP > 6 h/night compared with patients using PAP 1–6 h/night (Reproduced with permission from Campos-Rodriguez et al. [118])

In recent years, there has been increasing interest in "split-night" polysomnography in which the initial portion of the night is spent in performing a diagnostic evaluation for OSA and the remainder of the night is devoted to establishing a PAP prescription [104, 124–131]. If the diagnosis of OSA is established during the initial portion of the night, a therapeutic titration of CPAP is undertaken. The impact of this paradigm has been explored and, in general, split-night studies provide an acceptable strategy for laboratory evaluation and initial PAP prescription without negatively impacting acceptance and adherence in patients with severe OSA [124, 125, 130–132]. Some data suggest, however, that long-term adherence may not be as high in patients with mild to moderate OSA as in patients with more severe OSA, thereby mandating particularly close follow-up in the former group [130]. Current recommendations of the American Academy of Sleep Medicine include that a CPAP titration may be conducted after observing an AHI of 40 (or AHIs of 20–40, based on clinical judgment) over at least 2 h of diagnostic polysomnography, and a CPAP prescription may be established based on a titration over at least 3 h of sleep that documents that CPAP eliminates or nearly eliminates the respiratory events during non-REM and REM sleep (including REM sleep in the supine position) [132]. Although a number of investigations have included bilevel PAP devices in assessing acceptance as well as adherence to therapy following split-night studies, neither these devices nor APAP modalities have been the specific subject of these studies.

Once a patient has "accepted" CPAP therapy, he or she must be adherent to it. In the last several years, investigators and clinicians have been able to objectively monitor daily use and patterns of use over time with meters and software that have been incorporated into the PAP devices. Such objective metrics are particularly important in assisting clinicians with management since subjective patient reports overestimate time of use [61, 71, 73, 123]. Objective adherence monitoring is now the standard of care, with its utility highlighted by the observation that suboptimal patterns of usage are established shortly after initiation of therapy, so that the clinician needs to recognize and address the contributory factors early on [76–78, 80, 96]. Moreover, information regarding the degree to which a patient is adherent to PAP is essential for assessment of a suboptimal clinical response. If a patient's symptoms are inadequately resolved after the initiation of PAP treatment, possible reasons other than poor adherence include delivery of insufficient pressure to maintain upper airway patency during sleep (perhaps due to an incorrect prescription or because of

technical issues such as air leaks through the mouth or skin-mask interface that impair delivery of the prescribed pressure), misdiagnosis of the etiology of the individual's symptoms, the contribution of comorbid elements to the patient's symptoms, or failure to use the device for a sufficient duration on a regular basis. Currently available software within PAP devices provides information regarding delivered pressure and the magnitude of leaks, as well as an estimate of the AHI on PAP therapy. This constellation of information can provide the clinician with important management insights.

Despite the availability of software providing objective adherence information to clinicians, there remain gaps in our knowledge in this regard. For example, although the clinician may know the average duration of daily PAP, the *total sleep time* is not known. This information is highly desirable for optimal interpretation of the machine-use data. For example, 4 h of PAP use may reflect acceptable adherence if the patient is asleep or at least in bed with intention to sleep for 4.5 h (e.g., a late night at work with an early appointment in the morning). On the other hand, 4 h of PAP use may reflect inadequate adherence if the patient is asleep for 8 h. It is evident that it is highly desirable for the clinician to have objective information about a patient's usual bed and sleep time during follow-up subsequent to initiation of PAP therapy.

In general, utilization of PAP ranges from 4 to 6 h/day, with considerable interindividual variability and a measurable proportion of patients with <2 h/night or complete nonadherence. As discussed earlier, >6 h of use per night is associated with reduced cardiovascular mortality and increased likelihood of normalizing memory function [68, 118]. The relative value of <6 h of use per night is unclear, as if there is a threshold of nightly use above which no further benefit is obtained in this regard as well as with respect to cardiovascular and cerebrovascular morbidities. Existing data suggests that optimal relief of daytime sleepiness requires nightly use of PAP. As also noted earlier, sleeping for as little as one night without PAP results in increased sleepiness [55, 119]—but is it necessary to use PAP during *all* sleep time? Hers et al. observed persistent benefit in oxyhemoglobin saturation and sleep continuity for the remainder of the night after CPAP was discontinued following 4 h of use [133]. The investigators postulated that the persistent improvement is related to greater sleep continuity while on CPAP, with increased upper airway stability during the latter portion of the night after CPAP was removed. This hypothesis is based on earlier data demonstrating increased upper airway collapsibility following a period of sleep fragmentation [134]. These investigators as well as others [135] speculated that duration of nightly use of CPAP by at least some OSA patients is determined by their perception of the amount of use required to obtain a satisfactory degree of symptomatic benefit.

It is intuitively evident that greater insight regarding the determinants of adherence would facilitate treatment modifications that would promote more universal and optimal utilization by patients. Unfortunately, our understanding remains incomplete. Some reports suggest that adherence improves as the patient's perception of sleep propensity increases [71, 79, 136, 137]. Notably, the patient's perception of daytime sleepiness, assessed using specific questionnaires such as the "hypersomnia score" [71] or the Epworth Sleepiness Scale [45], predicts adherence with CPAP more reliably than the MSLT, which is an objective measure of sleepiness [58, 73, 138]. Some studies have noted that, after adjusting for confounding factors, lower AHI is an independent risk factor for nonadherence [79, 136]. Conversely, several investigators have observed that adherent patients cannot consistently be differentiated from nonadherent patients by the frequency or variety of side effects of CPAP therapy, initial AHI, gender, weight, or the prescribed level of CPAP [58, 73, 75, 123, 138–140]. More recently, the contribution of "self-efficacy," including the patient's perception of the consequences of untreated OSA and expectations of treatment outcome [76], as well as psychologic factors such as coping strategies and willingness to modify behavior [77, 78], have been examined in the context of adherence. Stepnowski et al. [77] observed that adherence to CPAP was uninfluenced by baseline depression, stress, or anxiety but was significantly related to the patient's score on a Ways of Coping Questionnaire (Fig. 34.4). Additional important contributions to adherence

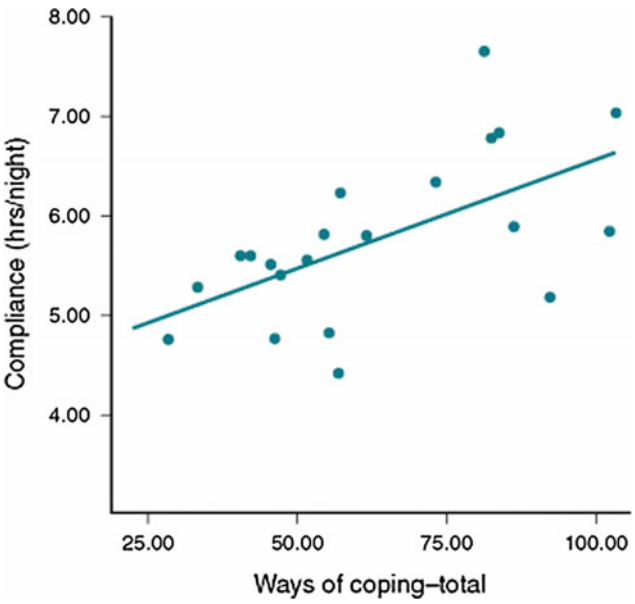

Fig. 34.4 Relation between the total ways of coping questionnaire score and adherence (average number of hours of CPAP use per night). Adherence = 4.38 + 0.02 * ways of coping (Reproduced with permission from Stepnowsky et al. [77])

include the response to therapy with regard to sleepiness, performance and mood, home/family environment/support, encumbrance on lifestyle (e.g., ease of travel, intimacy), and interface comfort.

As discussed earlier, patients commonly experience side effects in conjunction with PAP therapy. Although evidence regarding the impact of side effects on acceptance and adherence varies, it is reasonable and prudent for the clinician to make every effort to minimize if not eliminate them (see Table 34.2). It is likely that the perception of a given side effect varies across individuals and therefore may have a different degree of impact. Thus, a simple comparison of prevalence in compliant and noncompliant patients may be misleading and obscure the impact of a particular side effect on the compliance of individual patients. Several practices may enhance patient acceptance and compliance with CPAP therapy. These are outlined in Table 34.2 as well as later in this chapter. Appropriate patient selection for chronic PAP therapy is an important factor, and educating the patient, utilizing discussion and educational literature addressing the nature of OSA, the consequences of untreated OSA, and a detailed discussion of therapeutic options and implications, is essential [141]. It is intuitively obvious that patients who require "arm-twisting" to take a PAP unit home, even after efforts have been made to explain the need for the device and the manner in which it operates, are unlikely to use it conscientiously on a long-term basis. Therefore, PAP should be provided only to patients who are reasonably receptive to using it or who are sufficiently open minded to give it a reasonable home trial.

Patient–PAP Device Interface Options

Since the initial report in 1981 of CPAP therapy for adults with OSA, which described use of a customized nasal mask [1], there has been an appropriate and ever-growing cornucopia of interfaces from which patients and clinicians may choose in an effort to enhance comfort and convenience. These interfaces include commercially available nasal prongs/pillows or cannula systems, commercial and custom-made nasal masks, commercially available oral-nasal masks [82, 83], and an oral interface [142]. In a 3-week randomized crossover design study comparing nasal pillows and a nasal mask, Massie et al. [87] reported that, when using the nasal pillows, there were less frequent adverse effects and less air leak reported as well as less trouble initiating and maintaining sleep. However, there was no difference between the two types of interfaces with regard to the time of PAP use per night, Epworth Sleepiness Scale score, or FOSQ score.

Clinicians also have the option to prescribe an oral-nasal mask or oral interface for patients who are unwilling or unable to use an exclusively nasal interface or who are unable to keep their mouth sufficiently closed during sleep to permit maintenance of adequate positive intrapharyngeal pressure. In our experience, a chin strap is only variably helpful, and when necessary, the delivery of positive pressure via an oral-nasal mask should be considered. These interfaces also have the advantage of increasing humidity in the inspired air, independent of an external humidifier [93]. Oral-nasal interfaces have successfully reduced the AHI in a substantial majority of the patients in whom they have been applied [82, 83]. However, oral-nasal interfaces may be less acceptable than nasal interfaces to patients who have had an unsuccessful uvulopalatopharyngoplasty [84].

Particular care must be taken when employing an oral-nasal mask, owing to the potential risk of aspiration of gastric contents if the patient vomits. Although to our knowledge this complication has not been encountered in patients with OSA, it remains a concern. Accordingly, patients using an oral-nasal mask for nocturnal PAP should be instructed not to take anything by mouth to allow gastric emptying before applying the positive pressure. Furthermore, before initiating PAP therapy via an oral-nasal mask, patients should be routinely instructed to notify their physician if they are experiencing nausea or vomiting from any cause. They should also be provided with a nasal interface as a temporizing, if not long-term, option and counseled to sleep with the head of the bed elevated.

Coverage of both the nose and mouth by an oral-nasal mask also raises theoretical concerns regarding the potential consequences of machine failure, when airflow that can be entrained by the patient through a nonfunctional or dysfunctional device is limited or nonexistent. Safety valves should be incorporated in the circuit, close to the patient, to facilitate inhalation of fresh air and/or to minimize dead space in the event of machine malfunction. Optimally, an alarm should also be present to signal power failure.

There does not appear to be a significant effect of interface on the requisite positive pressure required to stabilize the upper airway during sleep [83, 87, 142]. Since patients may change their interface preference over time, they should be made aware that a choice remains open to them at all times during their treatment.

Variations and Modalities of PAP Therapy for OSA: Implications for Acceptance and Adherence

Clinical experience indicates that nasal CPAP maintains upper airway patency and acceptable oxygenation during sleep in the overwhelming majority of patients with OSA. Some patients find the administration of CPAP sufficiently bothersome to precipitate complete intolerance of therapy or

at least result in unsatisfactory adherence. Use of variations of CPAP and other PAP modalities have been explored to address patient complaints that appear to be specific to CPAP.

Pressure Ramping

For some patients, the sensation of positive pressure is sufficiently unpleasant to cause difficulty with initiating sleep. Pressure ramping of CPAP allows adjustment of the rate of rise in delivered pressure over time, from a clinician-specified level to the target therapeutic pressure. Thus, a window of time is created during which the delivered pressure is lower than the target pressure and the patient may find it easier to fall asleep. Because the level of positive pressure may be transiently below that required to maintain upper airway patency during sleep, pressure ramping may allow apnea, hypopnea, and oxyhemoglobin desaturation to occur for a variable period of time, until the pressure reaches the prescribed, optimal value. We are unaware of published studies that address the level of risk that the delay in optimal pressure delivery may present to patients, nor are any data available regarding the effectiveness of pressure ramping on patient adherence to CPAP therapy. In fact, Pressman et al. described a case of "ramp abuse" in which a patient repeatedly awoke to reactivate the ramp [143]. Although the published recordings may have been influenced by movement artifact, failure of sleep continuity and probable repetitive episodes of oxyhemoglobin desaturation (because the pressure was subtherapeutic during the time that the patient was asleep) were evident. As Pressman et al. pointed out, such abuse will not be detected if only CPAP machine run time is monitored as a reflection of adherence. Conversely, monitoring run time at the prescribed pressure gives the clinician insight into this activity.

Thus, although pressure ramping is a conceptually attractive feature, its degree of effectiveness and safety remain to be documented, and the specific patient populations for which it might provide maximal benefit have yet to be identified. Whether or not it should be routinely prescribed for all patients has not been systematically evaluated, but since it is available on most commercially available CPAP machines, clinicians may consider pressure ramping should a patient encounter difficulty in initiating sleep due to CPAP. A careful subsequent follow-up is essential.

Bilevel PAP Therapy

This modality has been discussed above. Because in many patients it permits PAP treatment of OSA using expiratory pressures that are not mandated to be as high as inspiratory pressures [22–25] bilevel PAP has been prescribed with the intent to reduce complaints or likelihood of complaints related to some side effects, including a smothering sensation, chest wall discomfort, and bothersome nasal or sinus pressure related to the sensation associated with breathing against a positive pressure. Additionally, some patients may be at increased risk for barotrauma by virtue of emphysema or bullous lung disease (though a review of the literature suggests that this is not a prevalent complication of CPAP therapy for OSA), while in others, elevated expiratory pressure may be associated with a tendency toward alveolar hypoventilation [24, 25, 27, 108].

The existing literature does not support routine prescription of bilevel PAP rather than CPAP with the intent to improve adherence [123]. There may be a subset of OSA patients who prefer the bilevel PAP, including but not limited to the very obese, those with higher $Paco_2$, and those with underlying pulmonary or neuromuscular disease [131]. Bilevel PAP may be a therapeutic alternative for patients who find nasal CPAP uncomfortable [104] or for those in whom the delivery of PAP represents an unacceptable degree of risk (i.e., patients with bullous lung disease). Prospective, controlled studies are required to determine if and to what degree bilevel PAP is successful as salvage therapy for OSA populations who are nonadherent to CPAP.

APAP and Auto-titrating Bilevel PAP

APAP devices have been previously described in this chapter. The capacity to provide a pressure that "floats" across the sleep period and varies in response to the physiologic requirements to maintain upper airway patency led to the assumption that this mode would improve adherence. To our knowledge, there have not been published, systematic trials of autotitrating bilevel PAP in this regard, but there has been a recent meta-analysis examining studies of APAP [33]. Although APAP was comparable to fixed-pressure CPAP in reducing the AHI and did so with a 2-cm H_2O reduction in mean pressure, this modality did not confer a benefit in adherence over fixed-pressure CPAP (Fig. 34.5). At this time, there is a general acceptance that APAP and fixed-pressure CPAP lead to essentially equivalent outcomes for patients with OSA. There may be subgroups which will either prefer or have a better result with one mode or the other but such groups have not been identified yet. Several studies which have compared lab-based CPAP titration vs. home-based APAP trials have found this and a nonsignificant trend toward better adherence in the home APAP group [144, 145]. However, it may be beneficial in improving comfort and tolerance in selected patients. Systematic studies are required to assess the impact of autotitrating bilevel PAP.

Pressure-Relief CPAP and Bilevel PAP

There are few studies addressing the effect of pressure-relief CPAP on adherence. One nonrandomized study demonstrated that adherence to pressure-relief CPAP over 3 months was significantly better than adherence to

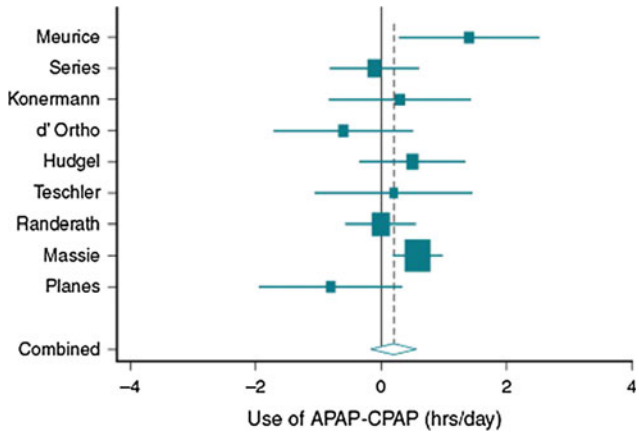

Fig. 34.5 Comparison of nightly adherence to autotitrating CPAP (APAP) versus fixed-pressure CPAP. A positive score indicates a better adherence to APAP than CPAP. *X axis* Nightly adherence with APAP minus adherence on CPAP. *Y axis* Investigations reporting adherence data. The *dashed line with the diamond* at the bottom represents the pooled effect though the mean of the estimate (Reproduced with permission from Ayas et al. [33])

conventional CPAP [141]. There was no difference between pressure-relief and conventional CPAP with regard to the degree of change in subjective sleepiness and FOSQ score. Another study, utilizing a randomized, 7-week crossover design comparing pressure-relief CPAP and conventional CPAP, confirmed the comparability between pressure-relief CPAP and conventional CPAP in alleviating sleep-disordered breathing but found no difference in adherence over 7 weeks [35]. Similarly, there was no significant difference with regard to complaints. To our knowledge there are no published systematic studies examining the impact of routinely prescribed pressure-relief bilevel PAP on adherence. However, a recent study suggested that pressure-relief bilevel PAP may provide some benefit as a salvage therapy for patients who are suboptimally adherent to CPAP despite intensive education and interventions to maximize comfort [146]. Thus, there are too few data on which to make conclusions about the role of pressure-relief CPAP and bilevel PAP. While these modalities may be useful in specific patients, there are no data to indicate benefit from routine prescription to all patients at initial setup.

Follow-up of CPAP Patients and Its Role in Enhancing Adherence

As noted above, it appears that an individual's pattern of CPAP use (or nonuse) is established very shortly after initiating home therapy [72, 73, 122, 147]. It is therefore reasonable to consider that enhanced adherence would result from early and consistent contact between the patient and the care provider in an effort to identify and resolve problems with therapy, provide encouragement, and give support. While this may be a reasonable line of thought, the literature provides conflicting information on this subject. One study indicated that positive reinforcement by periodic telephone contact does not favorably influence therapeutic compliance [74]. In contrast, considerably larger investigations have demonstrated improved adherence in conjunction with intensive educational and support measures after initiation of home treatment [85, 148]. Chervin et al. [141] reported that patients who had received educational literature regarding sleep-disordered breathing and CPAP or bilevel PAP use and patients who received follow-up telephone calls from healthcare personnel were more adherent than patients who had received neither of these interventions. In contrast, intensive follow-up of PAP patients in Hong Kong did not improve adherence when compared to standard care [149].

It is also essential that a physician and staff who are experienced in the care of OSA patients and the difficulties they encounter act as continuing support and educational resources to answer questions and provide reassurance when uncertainties arise. At our center and others, patient support groups serve a very important function in fostering a climate of openness and sharing of information as well as providing a forum for discussion of issues relevant to all types of sleep-disordered breathing (OSA, nocturnal ventilatory failure associated with neuromuscular and chest wall disorders, etc.) and overall health. Group meetings provide patients with the realization that they are not and should not be isolated by their disorder. This is crucial, since many OSA patients have been labeled by society as lazy or malingerers, resulting in social ostracism and low self-esteem. Many of the consequences of OSA are reversible by PAP therapy, with remarkable and gratifying results for all concerned. In our experience, there is no doubt that important benefits are obtained from support groups, judging from the excellent long-term attendance and favorable patient comments.

Summary

When all things are considered, adherence to PAP, which entails the presence of a relatively cumbersome box at or near the bedside and an equally cumbersome (if not unappealing) interface over the nose, is surprisingly good. Adherence to PAP compares favorably to therapies that most would consider substantially less noxious, such as metered-dose inhalers for treating asthma [150]. Without doubt, this relates to the remarkable symptomatic improvement experienced by the majority of users.

Traditional and Evolving Methods of Initiating Pap Therapy

Traditionally, patients have undergone an attended (by a technologist), monitored (by polysomnography) trial of PAP to establish therapeutic levels of pressure prior to initiating long-term therapy. Because the requisite level of PAP may vary according to body position and sleep stage, clinicians should be certain that the delivered pressure is effective in maintaining adequate upper airway patency and oxygenation during sleep in all positions, including and especially the supine position (and when possible during supine REM sleep). It also provides an opportunity for the patient to examine the PAP unit and various interfaces before home use. The most comfortable and leak-free interface with the device (i.e., nasal mask, prongs, or oral-nasal mask) can be selected. Then, while the patient is still awake, he or she may be provided with an opportunity to experience PAP across a wide range of pressures, to permit familiarization with the associated sensations. Another advantage of attended evaluation of the patient on PAP is the immediate availability of knowledgeable and caring healthcare professionals who can respond to questions and allay concerns. When wearing a PAP device for the first time, patients have been anecdotally reported to awaken in the middle of the night disoriented and perhaps frightened by the apparatus. Under these circumstances, albeit rare, reassurance is readily supplied by the laboratory personnel conducting the trial.

Several other benefits have also been attributed to polysomnographically monitored trials of CPAP therapy. Fry et al. [151] observed an increased frequency of periodic leg movements in sleep (PLMS), with and without accompanying arousals during nasal CPAP therapy. These investigators hypothesized that the improved sleep quality and architecture associated with relief of OSA by nasal CPAP "unmasks" PLMS. However, several subsequent studies observed that the Periodic Limb Movement Index was not appreciably different during a diagnostic polysomnogram and during CPAP therapy [152, 153], although arousals may diminish in conjunction with PLMS during CPAP therapy, at least acutely [152]. Nonetheless, periodic limb movement disorder may coexist with OSA and may persist after alleviation of OSA on CPAP, and a patient may not obtain symptomatic abatement of daytime sleepiness or fatigue. Thus, a monitored initial trial of CPAP addresses many issues and concerns that, if not considered, may lead to dismissal of this form of therapy as a viable therapeutic option. Attention to these factors at the outset of therapy will maximize the opportunity for a successful outcome.

Split-Night Diagnostic and CPAP Titrations

This paradigm for initiating PAP therapy has been discussed above in the context of acceptance and adherence. The current healthcare environment has fostered exploration of alternative means of establishing PAP therapy for OSA in order to facilitate access to limited diagnostic and therapeutic resources [154]. As noted earlier in this chapter, some clinicians are requesting that diagnostic and PAP titrations be conducted in single, split-night studies. Although this may lead to a satisfactory CPAP prescription for many patients [120, 124–130] there are a number of patients for whom the duration of time available for CPAP titration is too limited in the context of a split-night study to achieve a satisfactory prescription [129]. In particular, patients with milder degrees of OSA in whom the titration is initiated later in the night (because more prolonged monitoring was needed to establish the diagnosis of OSA) are more likely to have unsuccessful split-night titrations.

An American Academy of Sleep Medicine statement of practice parameters indicates that a split-night paradigm is an alternative to the 2-night diagnostic and therapeutic titration PAP strategy to develop a PAP prescription if the AHI is 40 over a diagnostic study duration of at least 2 h. A split-night study also may be warranted when the AHI is 20–40 in an appropriate clinical context and when PAP titration is conducted over more than 3 h, with elimination or near-elimination of disordered breathing events, including during REM sleep in the supine position [132]. It should be noted that some reimbursement guidelines mandate that the diagnostic study duration be at least 2 h *of sleep*. Clinicians should take care to check on local and current guidelines in this regard. Recent studies have also indicated that the split-night-PSG strategy and the traditional 2-night paradigm provide similar benefits, but the former is associated with lower cost [155, 156]. In addition, split-night studies may reduce the waiting time for initiation of therapy [157].

Home CPAP Titration

Some investigators have advocated in-home initiation of CPAP therapy employing both attended monitoring and unattended/unmonitored titrations [158, 159]. Waldhorn and Wood described titration of CPAP by a technologist in the patient's home using a portable 4-channel monitor recording heart rate, chest wall movement, CPAP pressure in the mask, and oxyhemoglobin saturation to guide CPAP adjustment [159]. The authors reported elimination of apneas, hypopneas, and snoring, but this was assessed by the 4-channel

monitor and not polysomnography. Self-reported adherence to CPAP therapy in this group of 17 patients was an average of 7.23 ± 1 h (mean ± standard deviation [SD]) per night, which is at least comparable to values obtained by conventional in-laboratory titration. Coppola and Lawee [158] reported their experience with unattended home CPAP titration in which 11 patients had increases in CPAP level in response to telephone interviews between the clinician, patient, and bed partner that revealed persistent snoring, apnea observed by the bed partner, and/or symptoms consistent with OSA. Good subjective outcome was reported in these studies, but the absence of objectively assessed adherence (which was unavailable at the time of these studies) is a significant limitation of these data.

Whether or not attended, in-home titration provides a cost-effective and efficient alternative to in-laboratory methodology remains to be determined, but clearly, committing a technician to spend a night monitoring one titration constitutes a measurable utilization of resources. In addition, the applicability of this paradigm across all home environments and social conditions, as well as for patients without bed partners, remains to be determined.

Use of Predictive Formulas to Estimate or Establish the CPAP Pressure Prescription

A CPAP prescription consists of the pressure that maintains satisfactory upper airway patency and oxyhemoglobin saturation during sleep, while providing satisfactory sleep continuity using a interface that is well-tolerated by the patient. Several investigators have suggested that the requisite level of CPAP can be estimated with sufficient clinical accuracy to obviate the need for monitored titration, thus providing a starting point at which titration may begin either in the monitored environment, in order to maximize the time available to "fine-tune" the final pressure prescription, or in the home setting, with further adjustments made on the basis of clinical guidelines or the results of home diagnostic evaluation [160–162]. Miljeteig and Hoffstein [158] reported that the three variables that best predicted the minimal therapeutic CPAP level (defined as that which reduced the AHI to <10) were body mass index (BMI), AHI, and neck circumference. In a subsequent data set from 129 patients, reported in the same paper, the minimal CPAP predicted from this equation was 8 ± 2.1 cm H_2O and the value obtained during laboratory titration was 8.1 ± 3 cm H_2O (mean ± SD). Seventy-one percent of patients had predicted values within 2.5 cm H_2O of the measured values, and 95 % had predicted CPAP levels within 5 cm H_2O of the measured values. The investigators indicated that their predictive equation may not be applicable to all patients due to variability in individual responses to a given level of CPAP.

In a subsequent study of 26 patients, Hoffstein and Mateika prospectively tested the predictive value of the previous equation [161]. For the group as a whole, there was no significant difference between the predicted and the polysomnographically titrated optimal CPAP levels defined as the lowest titrated pressure at which the AHI was less than 10. In 38 % of patients $CPAP_{predicted} = CPAP_{optimal}$; in 38 % of patients, $CPAP_{predicted}$ was within 1 cm H_2O of $CPAP_{optimal}$; in 15 % of patients, $CPAP_{predicted}$ was within 2 cm H_2O of $CPAP_{optimal}$; and in 8 % of patients, $CPAP_{predicted}$ was >2 cm H_2O of $CPAP_{optimal}$. In general, $CPAP_{predicted}$ underestimated $CPAP_{optimal}$, although $CPAP_{predicted}$ was grossly inaccurate in 8 % of the patients, being too high in one and too low in the other. It is important to recognize that the criteria for defining effective CPAP level did not include elimination of respiratory effort–related arousals, as may be seen in the upper airway resistance syndrome [163].

In an open randomized trial, Hukins examined prescription of a CPAP level based on the patient's BMI with that established during a polysomnographic titration [162]. In the formulaic group, CPAP was initially prescribed at 8 cm H_2O if the BMI was <30, 10 cm H_2O if the BMI was between 30 and 35, and 12 cm H_2O was prescribed if the BMI was 35 or more. If the patient could not tolerate the prescribed pressure, it was decreased. The pressure was increased if there was persistent sleepiness or snoring. The formulaic pressure was slightly but significantly higher than that established by polysomnographic titration (13 ± 2 vs. 11.8 ± 2.4 cm H_2O, $p = 0.04$). A sleep study was done after 3 months. Sleep efficiency was greater in the formulaic group, with comparable AHI and Arousal Index as well as percent slow-wave sleep and REM sleep. After 3 months, the polysomnographically prescribed pressure group tended to have a lower Epworth Sleepiness Scale score than the formulaically prescribed group (6.9 ± 3.6 vs. 9.2 ± 5.6, $p = 0.07$), but there was no difference in discontinuation of therapy, adherence, or quality of life as reflected by the SF-36. The average time to initiation of therapy was notably shorter in the formulaically prescribed group. Hukins concluded that the formulaic prescription strategy could be used when there would be an untoward delay in initiating CPAP treatment were the prescription to be developed through in-laboratory polysomnographic titration. Assessment of comparability of the two prescription strategies past the 3-month milestone remains to be done.

Along similar lines, a randomized, single-blind 5-week crossover trial compared a CPAP prescription based on an in-laboratory polysomnographic titration, determining a CPAP level that remained unchanged, and a prescription that was initially based on the formula described by Hoffstein et al. [161], with subsequent patient self-titration according to perception of effectiveness and comfort [164]. Participants

were provided with information regarding the indication for and how to adjust CPAP as well as interfaces. There was no difference between the two prescription strategies with regard to adherence, quality of life using disease-specific instruments, perceived sleepiness, and objective ability to maintain wakefulness under soporific conditions. The CPAP that was identified by patients to be optimal during the self-adjusting study arm was 10.1 ± 2.0 cm H_2O (mean ± SD) compared with the 9.7 ± 2 cm H_2O that was determined during the polysomnographic titration arm. On average, over the 5 weeks in the self-titrating arm of the study, patients made 5.7 changes in the CPAP level from the initial level determined according to formula. The investigators concluded that establishing an initial CPAP prescription using a formula with subsequent patient adjustment is as effective as more conventional methods and may enhance the efficiency with which limited resources are utilized. It should be noted that the duration of this study was only 5 weeks in each arm. Moreover, as the investigators indicated, this strategy may only be applicable in patients with an understanding of the self-titrating instructions and the ability to adjust their own CPAP devices. Clearly, regardless of the method employed to establish the PAP prescription, patient education and follow-up remains an essential element.

Use of APAP Devices

The general principles and use of APAP in the context of adherence have been previously discussed in this chapter. One potential venue for APAP is application in the sleep laboratory with subsequent examination of the data to identify a single "best" level of CPAP to prescribe for chronic therapy with a "fixed" CPAP device (e.g., the value at or below which the pressure is during 90 % of the study, or $CPAP_{90\%ile}$). This would enable titration in an attended environment but without obligating the technologist to manually adjust the level of CPAP. Thus, the technologist's responsibility would de-intensified, perhaps permitting a lower technologist-to-patient ratio (with resultant reduction in cost). Alternatively, in-laboratory titration may be bypassed and the patient sent home on an autotitrating device for a short period to establish the $CPAP_{90\%ile}$ on which a fixed-pressure CPAP device may be prescribed. Finally, the patient may simply be provided with an autotitrating device to use at home in the autotitrating mode.

In a randomized controlled study of 360 OSA patients, Masa et al. [165] compared standard polysomnographic titration with a formula-based prescription [160] and APAP. The evaluative period was 12 weeks. In the formula-based prescription group, the pressure could be increased by 1–2 cm H_2O if the patient's bed partner noted snoring or apnea, after which an "optimal" pressure was deemed to have been identified. There was no difference across the groups with regard to withdrawals. The autotitrating group had a lower response on the SF-36 physical and the EuroQuality of Life Scale than the standard titration group, but there was no difference between the improvement in the formula-based group and the standard titration group. There were no differences among the groups with regard to adherence, side effects, and complaints. The investigators concluded that titration of CPAP can be accomplished with an APAP device or in a paradigm using a predictive formula to establish an initial pressure prescription. It should be noted that this study excluded patients with chronic illnesses or conditions such as cancer, chronic pain, renal failure, moderate or greater chronic obstructive pulmonary disease, substance addiction, and CSB; individuals who had a previous uvulopalatopharyngoplasty; those without a partner; patients with "important" chronic nasal obstruction; and those who lacked sufficient skill in adjusting a nasal mask. Whereas the observations of Masa et al. [165] are of considerable interest, the numerous clinical exclusions reduce generalizability to a measurable proportion of OSA patients seen in sleep disorders centers at this time.

More recently, in a study similar to that of Masa et al., West et al. [166] compared 6 months of APAP; initial application of APAP to identify the $CPAP_{90\%ile}$, which was used to provide a fixed-pressure CPAP prescription; and a CPAP prescription based on neck circumference and the frequency of dips in oxyhemoglobin saturation during baseline sleep. Individuals were not excluded from this study based on comorbidities. At 6 months, data were available in 86 of the 98 randomized patients. The investigators observed that, after 6 months, there was no difference among the groups with regard to the hours used per night, Epworth Sleepiness Scale score, objective ability to maintain wakefulness, 24-h ambulatory blood pressure, health assessed using the SF-36, and the Sleep Apnea Quality of Life Index. The investigators concluded that more complicated treatment initiation and maintenance strategies using APAP offered no benefit to patients over a simpler, formula-based prescription strategy.

In summary, APAP has evolved as a technology, and is now considered an acceptable alternative to fixed-pressure CPAP prescribed on the basis of a sleep laboratory based titration. Treatment of patients with APAP left in the auto mode is commonplace. Some practitioners prefer to use APAP to determine a 90 or 95 % pressure level and use that pressure level in a fixed-pressure mode. Patient and clinician preference should determine which approach will be used for a given patient.

Effect of Positive Airway Pressure Therapy of OSA on Systemic Disorders

Effect of PAP Therapy on Cardiovascular Mortality in OSA Patients

As noted earlier in this chapter, several studies have documented increased cardiovascular mortality in OSA patients, with reduction following initiation of and subsequent adherence to PAP therapy [118, 167, 168]. Although these studies were not randomized controlled trials comparing the effects of PAP therapy with sham PAP, the results are reasonably compelling. In this light, Peker and colleagues [169] assessed incident cardiovascular events in middle-aged men with OSA over 7 years and noted that the incidence of cardiovascular events in patients who were adequately treated (by PAP, uvulopalatopharyngoplasty, or oral appliances) was about 7 % in contrast to about 57 % in patients who were inadequately treated.

Observations regarding the effect of PAP in patients with OSA should not be generalized to patients with central sleep apnea or CSB in conjunction with heart failure. A multicenter, randomized controlled trial of CPAP versus no CPAP in patients with central sleep apnea and heart failure associated with reduced left ventricular (LV) function was stopped early due to relatively higher mortality in the group receiving CPAP compared with the group not receiving CPAP, over the first 18 months of participation in the study [170]. It should be noted that after the initial 18 months, survival was better in the group receiving CPAP. Over the entire duration that the study was being conducted, there was no difference in transplant-free survival between the groups. The authors speculated that the early mortality in the group receiving CPAP may have been attributable to the effects of PAP in the clinical context of relative intravascular volume depletion. They concluded that CPAP is not indicated to improve transplant-free survival in heart failure patients with central sleep apnea.

Effect of PAP Therapy on Cardiac Rhythm Disturbances in OSA Patients

Cardiac rhythm disturbances are common in OSA patients [171–178]. There are several potential mechanisms through which OSA predisposes to rhythm disturbances, including sleep-related changes in sympathovagal balance as well as alteration in sympathetic nervous system activity in conjunction with sleep-disordered breathing events, changes in QT interval, hypoxemia, and the influence of carotid chemosensitivity [179–183]. The favorable response of arrhythmias to CPAP therapy, especially in the absence of structural heart disease, reinforces the linkage between OSA and rhythm disturbances [173, 175, 184–186]. A recent randomized controlled trial reported that, after 1 month, CPAP therapy reduces the frequency of premature ventricular beats by nearly 60 % in OSA patients with heart failure compared to patients who are not receiving CPAP, in whom there was no significant change [186]. The authors acknowledged that, despite randomization, the group receiving CPAP had less severe OSA at baseline. The importance of this study is highlighted by recognition that sleep [179–181] and OSA have been associated with increased QT interval and increased dispersion, which may predispose to serious and potentially fatal arrhythmias especially in the setting of ventricular irritability. In contrast to these studies, one study reported bradyarrhythmias (pauses >3 s and episodes during which heart rate was <40 beats/min) were more responsive to CPAP therapy than supraventricular arrhythmias [175]. The effect on ventricular tachyarrhythmias was not reported.

In summary, it is evident that nocturnal cardiac rhythm abnormalities are prevalent in patients with OSA and treatment with PAP often has an ameliorative effect on them. Clinical judgment is necessary to determine if other immediate interventions (e.g., reduction or elimination of β blockade in the case of bradyarrhythmias, antiarrhythmic medication, pacemaker) are indicated. Moreover, careful follow-up assessment is essential to determine if additional interventions are required.

Effect of PAP Therapy in OSA Patients with Heart Failure

A number of studies support the improvement in LV function after initiation of PAP therapy for patients with OSA and heart failure [167, 187–191]. The mechanisms by which PAP may improve LV function in OSA patients with heart failure include relief of sleep-related hypoxemia, elimination of cyclic increases in LV afterload, reduction in sympathetic nervous system activation [188, 192, 193], and reduced inflammation. Kaneko et al. [190] observed that OSA patients with a notably reduced LV ejection fraction at baseline experienced a significant improvement after one month of CPAP therapy (an average increase of approximately 8 % for the group). These observations were reinforced by Mansfield et al. [191], who conducted a randomized trial comparing a group of OSA patients with heart failure who were treated with CPAP for three months and a group who did not receive CPAP therapy. The group receiving CPAP experienced an improvement in LV ejection fraction by about 5 %, while the group who did not receive CPAP had an increase of approximately 1.5 % (Fig. 34.6). There was no change in systemic blood pressure during CPAP application to explain the beneficial effects, but there was a reduction in overnight urinary norepinephrine excretion, consistent with reduced sympathetic activity in the

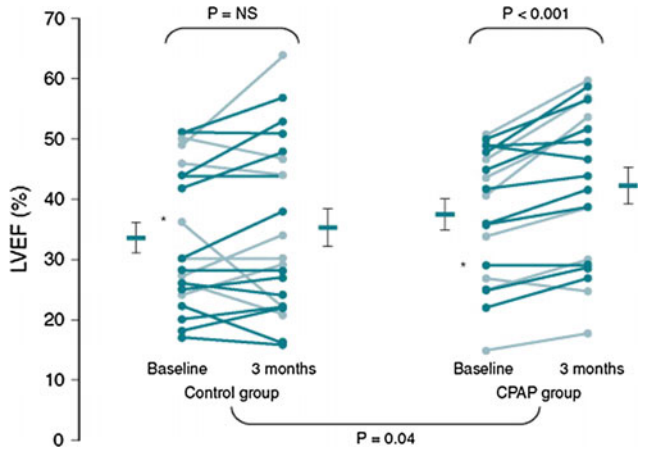

Fig. 34.6 Change in left ventricular ejection fraction over 3 months in OSA patients who were not (*left*) and who were (*right*) treated with CPAP. The *asterisk* indicates patients who were in atrial fibrillation at the indicated point in time (Reproduced with permission from Mansfield et al. [191])

group receiving CPAP. Although this trial did not apply a placebo or sham CPAP control, the consistent results with other studies as well as other aspects of the design support the credibility of the results.

In summary, LV dysfunction in OSA patients may be improved by PAP therapy of sleep-disordered breathing.

Effect of PAP Therapy in OSA Patients with Hypertension

Epidemiologic studies have provided compelling evidence that OSA is associated with increased risk for systemic hypertension (HTN) [194–200]. Sleep apnea has been identified by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure as a risk factor for HTN [201]. Although it is plausible that PAP therapy would ameliorate diurnal HTN by eliminating intermittent hypoxic exposure and sympathetic nervous system activation, and improve sleep continuity [192, 202–210] the literature provides conflicting data in this regard.

Using a randomized, placebo-controlled design to compare ambulatory blood pressure on CPAP and sham CPAP in subjectively sleepy (Epworth Sleepiness Scale score > 9) OSA patients, Pepperell et al. [211]. observed a small but significantly greater reduction in mean blood pressure during sleep in the active CPAP–treated group (93.7 ± 1.6 and 90.3 ± 1.4 mm Hg before and after one month of active CPAP, respectively; 96.2 ± 1.6 and 95.8 ± 1.5 mm Hg before and after one month of sham CPAP) and during wakefulness in the active treatment group (104.3 ± 1.3 and 101.9 ± 1.3 mm Hg before and after 1 month of active CPAP, respectively; 104.2 ± 1.4 and 106.1 ± 1.4 mm Hg before and after one month of sham CPAP). Although small, the reduction in blood pressure in the active CPAP group would have a notable public health impact on cardiovascular risk. A post hoc analysis however suggested that individuals in whom CPAP use reduced the AHI below 15 may experience improved left ventricular function and heart transplant-free survival time [211].

Similarly, in a randomized sham CPAP controlled trial in individuals with moderate to severe OSA, including notable oxyhemoglobin desaturation, Becker et al. [212] observed a reduction in mean blood pressure by approximately 10 mm Hg after about 9 weeks of active CPAP therapy, while no change was observed in the group receiving sham CPAP (Fig. 34.7). The observation of Becker et al. [213–215] may be the more noteworthy since the sham CPAP was associated with some improvement in OSA. Conversely, there are a number of well-designed studies of groups of OSA patients either with or without subjective sleepiness, and with HTN, that have failed to demonstrate a significant reduction in blood pressure with PAP therapy (Fig. 34.8).

In summary, it is evident that further research is required to define the effect of PAP on HTN in OSA patients. For example, a small case series of OSA patients with medically refractory HTN received benefit from CPAP in this regard [216]. Perhaps the heterogeneity of the data with respect to the effect of PAP on HTN should not be surprising. Hypertension is probably heterogeneous in etiology and duration, with varying degrees of vascular remodeling also potentially influencing therapeutic responsiveness. There may be subsets of hypertensive OSA patients with greater likelihood of deriving blood pressure improvement from PAP therapy, and identifying these patients is a challenge for the future.

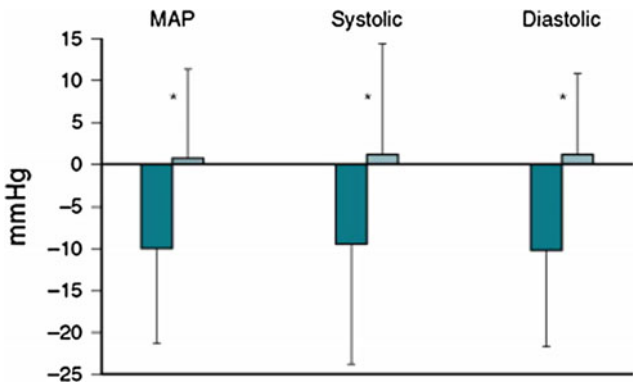

Fig. 34.7 Change in blood pressure in OSA patients receiving active CPAP (*closed bars*) and sham CPAP (*open bars*). Difference in mean arterial pressure (MAP) $p = 0.01$; systolic pressure, $p = 0.04$; diastolic pressure, $p < 0.005$. (Reproduced with permission from Becker et al. [212])

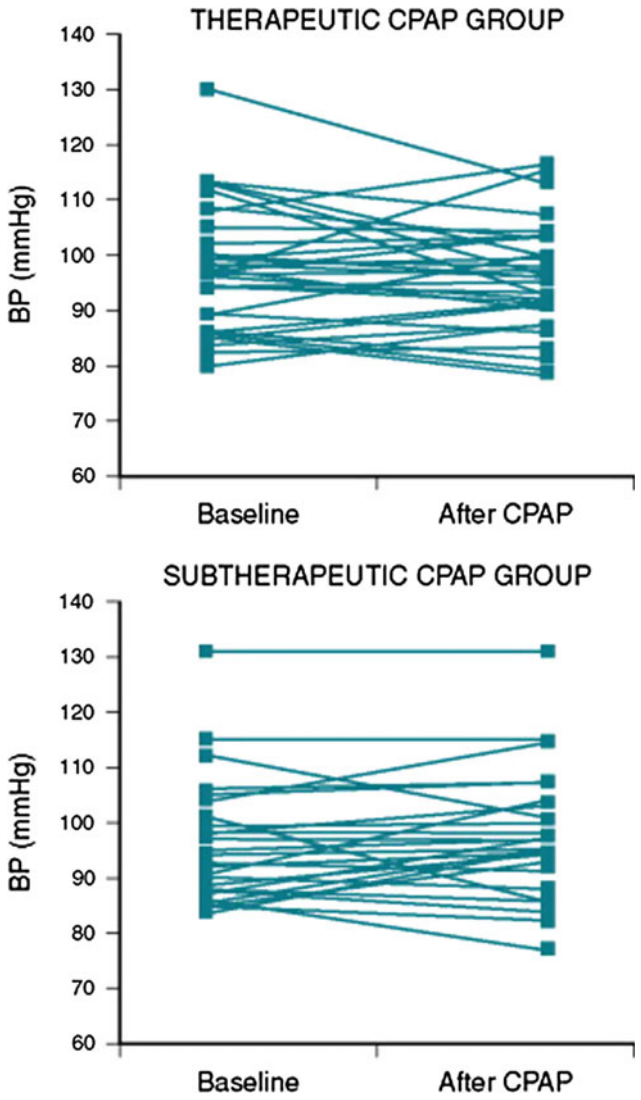

Fig. 34.8 Change in blood pressure in OSA patients receiving therapeutic CPAP (*top*) and sham CPAP (*bottom*) (Reproduced with permission from Campos-Rodriguez et al. [214])

PAP Therapy and Stroke

The association between sleep-disordered breathing, including OSA, and increased risk for stroke is increasingly recognized. Data from the Wisconsin Sleep Cohort indicate that, even after adjusting for age, gender, smoking, HTN, alcohol use, and BMI, sleep-disordered breathing is associated with increased risk for prevalent stroke [217]. There was also a suggestion of an association between sleep-disordered breathing and incident stroke, but this did not reach statistical significance, perhaps due to the study being underpowered to address this issue. Of comparable importance, sleep-disordered breathing following a stroke is a poor prognostic indicator of survival and function [218–223].

In a longitudinal observational cohort study, Yaggi et al. [221] reported the risk of first-time incident stroke or death from any cause over a median follow-up period of 3.4 years in OSA patients (mean AHI = 35) >50 years old compared with non-OSA patients (mean AHI = 2). There were 22 strokes in the OSA group and 2 strokes in the non-OSA group during the study interval. For the composite event of stroke or death, the probability of event-free survival was significantly less in the OSA group. These investigators observed a significant trend for increasing risk of stroke or death from any cause as the AHI increased, with the risk being threefold greater in OSA patients with AHI > 36 compared with the non-OSA group. OSA remained significantly associated with first-time incident stroke and death from any cause, even after adjusting for gender, race, age, smoking status, alcohol ingestion, BMI, and the presence of diabetes mellitus, hyperlipidemia, atrial fibrillation, and HTN. There are several limitations of this study. The study population was substantially male and Caucasian, an analysis of the probability of incident stroke alone in individuals with and without OSA was not performed, and the degree to which OSA was independently associated with first-time incident stroke (not combined with death from any cause) was not assessed. In addition, many of the participants in this study were prescribed treatment for OSA, and this factor, as well as adherence, was not assessed. It is therefore possible that first-time incident stroke and death from any cause were underestimated. The data are consistent with previous cross-sectional studies independently associating OSA with cardiovascular disease and death and therefore add to the concern regarding adverse outcomes from this disorder.

Consequently, the outcome of PAP therapy for sleep-disordered breathing following stroke is of substantial interest. This is a difficult issue to address, and the results of randomized placebo-controlled trials have not, to our knowledge been published. Martinez-Garcia et al. [224] observed that patients noted to have OSA following a first stroke and who were adherent to CPAP therapy had a significantly lower incidence of a second event compared to patients who were intolerant of CPAP. Of course, the possibility that the intolerant group were burdened by an unidentified additional risk for another cerebrovascular event cannot be excluded. Two randomized trials of CPAP versus no-CPAP therapy observed no benefit from CPAP therapy for severe OSA following stroke [225, 226], with the exception of improved depressive symptoms in the CPAP group in one of these studies [226]. Thus, to date studies provide conflicting data regarding the outcome of PAP therapy following stroke. However, a common theme is that there is a greater degree of nonadherence in these patients [149, 225, 226]. Altered cognitive function is probably at least partially responsible for the notable nonadherence in this population [226]. Further studies are required to

determine if PAP therapy of OSA reduces risk for incident stroke and to define patient groups who may benefit from PAP. If there are stroke patients who will benefit from PAP therapy, research is required to define specific measures and programs that will promote adherence.

PAP Therapy of Abnormal Glycemic Control and Type 2 Diabetes Mellitus

There is increasing awareness of the association between OSA, abnormal glycemic control, type 2 diabetes mellitus, and other features of the metabolic syndrome [227–234]. Since insulin resistance, the metabolic syndrome, and diabetes are known risk factors for cardiovascular disease, if causation is established between OSA and these metabolic perturbations, the former would provide an attractive interventional target through which the burden of cardiovascular disorders could be reduced. Interventional studies provide one avenue to determine if OSA contributes to abnormal glycemic control. Only limited data are currently available. Utilizing a hyperinsulinemic euglycemic clamp to assess insulin sensitivity, Brooks et al. [235] demonstrated that four months of CPAP therapy increased insulin sensitivity in very obese OSA patients with noninsulin dependent diabetes. This did not translate into improved fasting glucose, and the authors speculated that the effect of the substantial obesity in the subject population and residual severe insulin resistance masked translation of increased sensitivity to improved glycemic control. Along these lines, Harsch et al. [236] demonstrated that insulin sensitivity increased in nondiabetic OSA patients following three months of CPAP therapy, with the greatest response occurring in individuals with BMI < 30. More recently, Babu et al. [237] reported that diabetic patients with generally moderate or severe OSA who are adherent to CPAP, with use for >4 h/day, have a progressive reduction in hemoglobin A_{1c} (HbA_{1c}) over time after initiation of PAP therapy. No such effect was observed in patients who used CPAP < 4 h/day. Furthermore, the reduction in HbA_{1c} was greatest in those patients with baseline values >7 %. A strength of the study was that no adjustment of medication was permitted during the study interval. However, this was not a randomized trial, and data regarding weight at baseline at the end of the study interval were not described. Thus, the results should be taken in light of these limitations.

In summary, the data are far too limited to permit conclusions regarding the likelihood that PAP therapy of OSA will improve insulin sensitivity and glycemic control, independent of other factors. However, existing information provides cautious encouragement that, at least in less obese patients, treatment of OSA will confer metabolic benefit and perhaps downstream reduced cardiovascular risk. Moreover, a recent randomized controlled trial reported no difference between three months of active versus placebo CPAP with regard to insulin resistance or glycosylated hemoglobin in obese (mean BMI approximately 36) men with type 2 diabetes and OSA [238].

Summary

PAP constitutes a safe and effective treatment for OSA. There have been substantial modifications and developments over the last 25 years in an effort to provide greater patient comfort with regard to interface and modality. In addition, different modalities of PAP have been developed to better address subsets and nuances of sleep-disordered breathing. Notably, randomized controlled trials have demonstrated efficacy of PAP therapy in improving patients' perception of daytime function, and other studies have provided compelling evidence for improved outcomes with respect to systemic disorders, including but not limited to LV function and cardiac rhythm disturbances in OSA patients. Nonetheless, further work is required to identify the best target threshold for patient adherence, identify and address those factors that impede optimal adherence, and identify those subsets of patients who are most likely to obtain benefits from this form of treatment.

Sleep medicine has come a long way since the days when tracheotomy or no therapy was the only treatment options that caregivers could offer their OSA patients.

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Preoperative, Perioperative, and Postoperative Evaluation and Management of Sleep-Disordered Breathing

35

Edwin Seet and Frances Chung

Introduction

Sleep-disordered breathing constitutes an important public health issue. The economic cost of sleep-disordered breathing is considerable [1]. Sleep and anesthesia are inextricably linked. An appreciation of sleep physiology is critical to the understanding of the effects of anesthesia induced state of unconsciousness. Furthermore, sleep-disordered breathing has a significant impact on the perioperative surgical patient. The perioperative patient under anesthesia is vulnerable to the effects of arousal suppression and under the watchful protection of the anesthesiologists; it is the therefore also the responsibility of the perioperative physicians to ensure the return of the patients' protective responses in the postanesthesia recovery period. The subsets of sleep-disordered breathing influencing the use of anesthesia would include the following: obstructive sleep apnea (OSA), obesity hypoventilation syndrome, and central sleep apnea [2]—of which OSA is the preeminent and most pertinent.

Obstructive sleep apnea is caused by repetitive partial or complete obstruction of the upper airway, characterized by episodes of breathing cessation lasting more than 10 s during sleep. A consequence of this obstruction and oxyhemoglobin desaturation would be recurring arousals from sleep to restore airway patency, leading to increased sympathetic output, daytime hypersomnolence, memory loss, and executive and psychomotor dysfunction [3].

In this chapter, the authors propose stepwise algorithms based on available evidence from the published literature pertaining to the preoperative, perioperative, and postoperative management of patients suspected or diagnosed of sleep-disordered breathing. In those instances where peer-reviewed evidence is lacking, recommendations are made based on opinion and/or consensus. The algorithms suggested here serve as guides for the perioperative physician. Clinician discretion for the individual patient at the bedside is paramount and should take into account patient-specific and circumstantial factors [4].

OSA Prevalence, Associated Comorbidities, and Perioperative Complications

Obstructive sleep apnea is the most common sleep-disordered breathing disorder affecting 17 % of men and 9 % of women aged between 50 and 70 years [5]. Despite its prevalence, more than half of the patients with OSA were unrecognized and undiagnosed at the time of surgery, putting these patients at increased risks of perioperative and postoperative adverse events [6, 7]. Anesthesiologists and surgeons failed to identify significant number of patients with both preexisting OSA and symptomatic undiagnosed OSA prior to surgery [7]. A similar conundrum is seen even in the context of ambulatory surgery [8].

Obstructive sleep apnea is associated with myocardial ischemia, heart failure, hypertension, arrhythmias, cerebrovascular disease, metabolic syndrome, insulin resistance, gastroesophageal reflux, and obesity (Table 35.1). The prevalence of OSA was 78 % in morbidly obese patients planned for bariatric surgery [9]. Various craniofacial deformities (e.g., macroglossia, retrognathia), endocrine diseases (e.g., hypothyroidism, Cushing disease), demographic (male, age above 50 years), and lifestyle factors (e.g., smoking, alcohol consumption) predispose to OSA [10]. Perioperative physicians should be aware of the possible coexistence of these medical conditions—for the purpose of diagnosis, optimization, and risk stratification prior to the scheduled surgery.

In large population studies, unrecognized and untreated OSA has been associated with higher risks of all-cause

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Table 35.1 Medical conditions associated with obstructive sleep apnea

Category	Condition	Prevalence (%)
Cardiac	Treatment-resistant hypertension	63–83
	Congestive heart failure	76
	Ischemic heart disease	38
	Atrial fibrillation	49
	Dysrhythmias	58
Respiratory	Asthma	18
	Pulmonary hypertension	77
Neurological	1st ever Stroke	71–90
Metabolic	Type II diabetes mellitus	36
	Metabolic syndrome	50
	Hypothyroidism	45
	Morbid obesity	50–90
Surgical	Bariatric surgery	71
	Intracranial tumor surgery	64
	Epilepsy surgery	33
Others	Gastroesophageal reflux disease	60
	Nocturia	48
	Alcoholism	17
	Primary open-angle glaucoma	20
	Head and neck cancer	76

mortality, myocardial infarction, stroke, heart failure, and arrhythmia [11–16]. In the perioperative period, a meta-analysis by Kaw et al. which included 13 studies with 3942 patients showed that the presence of OSA significantly increased the odds of postoperative desaturation (odds ratio 2.3), respiratory failure (odds ratio 2.4), reintubations (odds ratio 2.1), cardiac events including myocardial infarction, cardiac arrest and arrhythmias (odds ratio 2.1), and intensive care unit transfers (odds ratio 2.8) [17]. A more recent large surgical cohort study including 14,962 patients noted that patients who had a diagnosed history of OSA and those who screened at high risk of having OSA on OSA screening tools (e.g., STOP-Bang, STOP questionnaires, Flemons) were associated with critical care admission postoperatively and at an increased cumulative one-year mortality [6].

In the context of a strong association between OSA and adverse perioperative outcomes, prudent risk mitigation strategies and perioperative precautions should be undertaken to reduce adverse events in the vulnerable surgical patients with a suspicion or diagnosis of sleep-disordered breathing.

Classical Diagnostic Criteria of OSA

The gold standard definitive diagnosis of OSA requires an overnight polysomnography reporting the Apnea Hypopnea Index (AHI). The AHI is defined as the average number of abnormal breathing events per hour of sleep. Apnea refers to airflow cessation for at least 10 s and hypopnea occurs when there is reduced airflow with desaturation of ≥ 4 % [18].

The American Academy of Sleep Medicine criteria for OSA diagnosis requires either an AHI ≥ 15, or AHI ≥ 5 with symptoms, such as excessive daytime sleepiness, unintentional sleep during wakefulness, unrefreshing sleep, loud snoring reported by partner, or observed obstruction during sleep [19]. The Canadian Thoracic Society guidelines for the diagnosis of OSA specifies the presence of an AHI ≥ 5 and either of (1) daytime sleepiness not attributable to other factors or (2) at least 2 other symptoms of OSA (e.g., choking or gasping during sleep, recurrent awakenings, unrefreshing sleep, daytime fatigue, or impaired concentration) [20]. The AHI also determines the severity of OSA. OSA is mild for AHI ≥ 5–15, moderate for AHI 15–30, and severe for AHI >30 [19].

Principles of Perioperative Evaluation and Management of OSA Patients

In an attempt to improve the perioperative care for OSA patients, various authors have constructed guidelines or clinical pathways [21–24, 10]. The authors of this chapter would like to propose and update functional algorithms for the preoperative, perioperative, and postoperative

management of sleep-disordered breathing, in particular for suspected and diagnosed patients with OSA [10].

Preoperative Evaluation of the Patient with Diagnosed OSA

During the preoperative clinical consultation, a relevant history of OSA symptomatology should be elicited, followed by a physical examination. Cardiopulmonary examination should be focused at eliciting signs of congestive heart failure (rales, S3, jugular venous congestion) and pulmonary hypertension (right ventricular heave, loud P2). Previous polysomnography results should be reviewed to confirm the diagnosis of OSA and evaluate the severity of the disease (Fig. 35.1).

Patients with long-standing OSA may present with a plethora of clinical signs and symptoms signifying the development of systemic complications, such as hypoxemia, hypercarbia, polycythemia, and cor pulmonale. The presence of significant comorbidities should be determined, especially morbid obesity, uncontrolled hypertension, arrhythmias, cerebrovascular disease, heart failure, and metabolic syndrome.

Obesity hypoventilation syndrome occurs in 0.15–0.3 % of the general population [25]. Pulmonary hypertension may complicate long-term untreated OSA, occurring in 15–20 % of patients [26]. Pulmonary hypertension is important in the perioperative period as certain physiological derangements may raise pulmonary artery pressures further and should be avoided intraoperatively. The American College of Chest Physicians does not recommend routine evaluation for pulmonary arterial hypertension in patients with known OSA [27]. Should there be anticipated perioperative triggers for acute elevations in pulmonary arterial pressures (e.g., high-risk surgical procedures of long duration), a preoperative transthoracic echocardiography may be considered [21]. The indication for additional testing of the cardiovascular system would be contingent on the surgical risk factors, active cardiac conditions, clinical cardiac risk factors, and the patients' functional capacity as per guidelines from the American Heart Association [28].

Bedside oximetry to determine baseline oxygen saturation and serum bicarbonate levels would be useful in risk

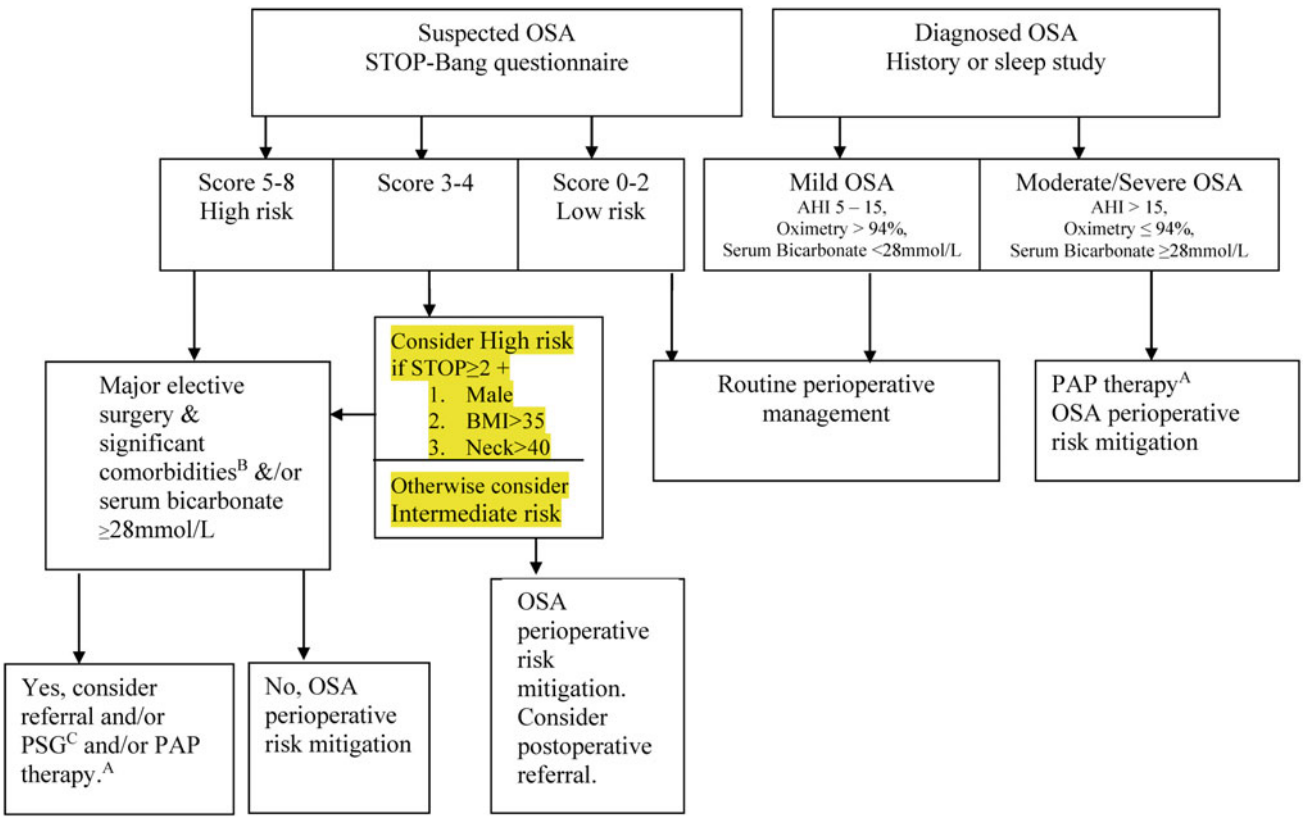

Fig. 35.1 Preoperative Evaluation of Diagnosed or Suspected Obstructive Sleep Apnea Patients. [A]Positive airway pressure (PAP) therapy—includes continuous PAP, bilevel PAP, and automatically adjusting PAP. [B]Significant comorbidities—heart failure, arrhythmias, uncontrolled hypertension, pulmonary hypertension, cerebrovascular disease, metabolic syndrome, obesity BMI >35 kg/m^2. [C]PSG (polysomnography)—includes level 1 to level 4 in-laboratory and portable polysomnography devices. Adapted from Seet and Chung [82]

stratifying the OSA patients (Fig. 35.1). In the absence of coexisting respiratory problems that may contribute to low baseline oxygen saturation, an oximetry reading of ≤ 94 % on room air is a red flag for severe long-standing OSA [29–31]. A raised serum bicarbonate level of 28 mmol/L or more may also be a harbinger for OSA with hypercapnia and may foreshadow perioperative and postoperative adverse events [32–34, 35].

Obstructive sleep apnea patients may be on positive airway pressure (PAP) therapy in the form of continuous PAP or bilevel PAP. These devices may have an automatically adjusting element which provides respiratory assistance based on airflow measurements, fluctuations in pressure, or airway resistance. The updated PAP therapy settings should be obtained. The OSA patients' compliance to the PAP therapy should be assessed. Indications for a reassessment by the sleep medicine physician would include patients who have defaulted follow-up, those non-compliant to PAP treatment, those who have experienced recent exacerbation of OSA symptoms, or those who have since undergone upper airway surgery. PAP therapy defaulters should be encouraged to resume therapy.

To date, there is insufficient evidence to prove conclusively the benefit of PAP therapy in the perioperative setting. The duration of therapy required to effectively reduce perioperative risks has not been delineated. Of note, a retrospective matched cohort study suggested that preoperative PAP therapy may possibly be beneficial based on the observation that OSA patients who did not use home PAP devices prior to surgery but required PAP therapy after surgery had increased complication rate [36]. Furthermore, a short period of 5 days of PAP therapy has been shown to improve gas exchange and sleep-disordered breathing [37]. Patients with moderate or severe OSA who are already on PAP therapy should continue preoperative PAP therapy prior to surgery [23]. Unfortunately, from an observational retrospective study in the surgical population, PAP therapy adherence was found to be extremely low with only a third of the patients using their PAP devices for more than 4 h per night [38].

The anesthesia team in charge of the patients during the perioperative period should be informed about the patient so that adequate preparation of beds with monitoring and risk mitigation measures may be carried out proactively.

Arising from the Busselton Health Cohort study, mild OSA was not an independent mortality risk entity in the general population [12]. It is still uncertain whether the corollary is true and that mild OSA may not be a significant risk factor for the perioperative surgical patient. Based on opinion, preoperative PAP therapy might not be indicated for mild OSA. Figure 35.1 puts forth an algorithm for the preoperative evaluation and management of the patient already diagnosed with OSA.

Preoperative Screening Tools for Evaluation of Suspected OSA

An in-laboratory level 1 polysomnography is the gold standard [19]. Ideally, all suspected patients of OSA should have a diagnosis made by a formal overnight polysomnography, and it may be the preferred modality if patient has significant comorbidities. However, routine testing with an in-laboratory sleep study is prohibitive when considering the cost, resource-intensity, and preoperative time constraints. OSA screening before surgery is therefore recommended as part of a pre-anesthesia and presurgical plan. Several bedside screening tools have been developed to meet the need for an economical and sensitive OSA screening test. These could include the STOP and the STOP-Bang questionnaires [39, 40], the Berlin Questionnaire [41], the American Society of Anesthesiologists (ASA) checklist [23], the Sleep Apnea Clinical Score [22], the Perioperative Sleep Apnea Prediction (P-SAP) score [42], etc.

The authors recommend the STOP-Bang questionnaire—which is a concise, validated and easy-to-use 8-point dichotomized-acronym (Table 35.2) [43]. Each question is scored based on the answer of "Yes" or "No." Patients with STOP-Bang scores of 0–2 may be considered to be at low risk, 3–4 intermediate risk, and 5–8 high risk of having OSA [39, 40, 29–31]. The STOP-Bang questionnaire has high sensitivity and negative predictive value at the expense of lower specificity, especially for patients with moderate-to-severe OSA [39, 40]. A STOP-Bang score of 0–2 is reassuring as the patient is unlikely to have moderate-to-severe OSA. For moderate OSA (AHI > 15) and severe OSA (AHI > 30), the sensitivity of STOP-Bang score is 93 and 100 %, respectively, while the specificity is 43 and 37 %, respectively [39, 40]. At higher cutoff values for STOP-Bang 5 or greater, the specificity of STOP-Bang questionnaire for severe OSA (AHI > 30/h) was increased to 74–95 % [29–31]. Furthermore, the presence of an increased serum bicarbonate level ≥ 28 mmol/L improves the specificity of the STOP-Bang score in predicting moderate-to-severe OSA [32–34].

An up-to-date study validating the performance of the STOP-Bang in obese and morbidly obese patients reported that for identifying severe OSA, a STOP-Bang score of 4 has high sensitivity of 88 %; and for confirming severe OSA, a score of 6 is more specific [32–34]. Another recent retrospective analysis of over 5000 patients demonstrated that the STOP-Bang score may be used to stratify the need for postoperative critical care; and a score of 6 or more was associated with a fivefold increase in critical care admissions versus a score of 2 or less [44]. In summary, the STOP-Bang questionnaire is useful in the preoperative setting for OSA prediction, triaging patients for confirmatory sleep testing, and excluding those without disease [45].

Table 35.2 STOP-bang: obstructive sleep apnea screening questionnaire

S	**S**noring: Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?	Yes	No
T	**T**ired: Do you often feel tired, fatigued, or sleepy during daytime?	Yes	No
O	**O**bserved: Has anyone observed you stop breathing during your sleep?	Yes	No
P	Blood **P**ressure: Do you have or are you being treated for high blood pressure?	Yes	No
B	**B**MI: BMI more than 35 kg/m^2?	Yes	No
A	**A**ge: Age over 50 years old?	Yes	No
N	**N**eck circumference: Neck circumference greater than 40 cm?	Yes	No
G	**G**ender: Male?	Yes	No

Low risk of OSA Yes to less than 3 questions
At risk of OSA Yes to 3 or more questions
High risk of OSA Yes to 5 or more questions

Preoperative Evaluation of the Patient with Suspected OSA

In any preoperative patients presenting for surgery, a high index of suspicion should be present for undiagnosed OSA. A clinical examination should be performed with emphasis on pertinent symptoms and signs of OSA. The bed partner's presence at the interview would be useful in the assessment of snoring and observed airway obstruction or apnea during sleep. The preoperative evaluation and management of the suspected OSA patient is dependent on the urgency of surgery. In the emergency situations, patients should proceed for surgery without extensive OSA workup. Perioperative risk mitigation measures should be undertaken based on the clinical suspicion of OSA.

Emergency surgery is in contrast to the elective operative setting, where referral to a sleep medicine physician, preoperative sleep studies followed by preoperative PAP therapy may be indicated in a subgroup of patients. An algorithm is suggested in Fig. 35.1. Specific considerations for further preoperative evaluation would include a high pretest probability of OSA based on the STOP-Bang score, the risk from major surgery, the presence of other significant comorbidities suggestive of chronic OSA or other forms of sleep-disordered breathing, and the need of postoperative opioids. These comorbidities include uncontrolled hypertension, heart failure, arrhythmias, pulmonary hypertension, cerebrovascular disease, morbid obesity, and metabolic syndrome. Patients with STOP-Bang score 5 or greater with comorbid diseases scheduled for major elective surgery should be considered for a preoperative assessment by a sleep medicine physician. Major elective surgery may have to be delayed to allow adequate time for preoperative PAP therapy. The eventual decision to evaluate a patient preoperatively should be made based on the clinical judgment of the attending physician, taking into account patient-related, surgical-related, and logistical factors.

A recent retrospective study found that patients at risk of OSA on screening had no significant increase in postoperative complications if managed on the OSA risk management protocol. Proceeding with elective surgery without delay for polysomnography was suggested to be clinically safe [46]. In our algorithm (Fig. 35.1), patients with a STOP-Bang score of 3–4 (intermediate risk of OSA) may proceed with surgery without further preoperative testing. The attending anesthesiologist should undertake perioperative risk mitigation measures. These intermediate risk patients may have difficult airway and/or recurrent postoperative postanesthesia care unit (PACU) respiratory events (desaturation, apnea, pain-sedation mismatch) [39, 40, 47]. Such red flags may warrant a subsequent sleep medicine physician referral cum polysomnography on discharge from the hospital. The STOP-Bang has high negative predictive value; therefore, patients who screen 0–2 are unlikely to have OSA. These patients may proceed with surgery with routine perioperative care (Fig. 35.1).

At present, there is inadequate scientific literature regarding the work-up of the suspected OSA and the preparation for surgery. Research is needed in this area to define the safe and cost-effective pathway.

Home Sleep Testing and Nocturnal Oximetry

Portable polysomnography or home sleep testing can be classified into level 2 (full unattended polysomnography with ≥ 7 channels), level 3 (devices limited to 4–7 channels), and level 4 (1–2 channels including nocturnal oximetry) devices. These may be viable alternatives to a level 1, in-laboratory, fully attended polysomnography. Home sleep testing can successfully identify OSA in 82 % of adult surgical patients [48]. Advantages of limited channel home sleep testing include accessibility, ease of use, potential cost-saving, and the ability to study patients in their

home environment. Portable devices may be considered when there is high pretest likelihood for moderate-to-severe OSA without other substantial comorbidities as suggested by the Portable Monitoring Task Force of the American Academy of Sleep Medicine [49]. The Canadian Thoracic Society recommends that portable monitoring devices may be used as confirmatory tests for the diagnosis and treatment of OSA so long as proper standards for conducting the tests and interpretation of results are met [20]. These devices should be used with caution in patients with comorbid diseases and for the diagnosis of other sleep-disordered breathing besides OSA [20].

In the perioperative context, level 2 multichannel home sleep testing has been shown to have a diagnostic accuracy similar to standard polysomnography [50]. In addition, nocturnal oximetry was found to be both sensitive and specific for detecting OSA in STOP-Bang positive surgical patients, and the oxygen desaturation index derived from nocturnal oximetry correlated well with the AHI obtained from polysomnography [29–31]. However, it should be recognized also that there may exist inconsistencies in how physicians interpret nocturnal oximetry tracings and results [51].

These portable devices are useful surrogates for preoperative OSA detection and diagnosis, especially if an in-laboratory polysomnography is not feasible. These home sleep testing helps with expedient risk stratification of suspected OSA patients, allowing preoperative PAP therapy to be instituted in selected cases, with the intention of reducing perioperative adverse events.

Perioperative Management Strategies for OSA Patients

A variety of perioperative risk mitigation strategies may be employed with the aim of ameliorating adverse outcomes for the suspected and diagnosed OSA patient. These are listed in Table 35.3 and elaborated in the section below. In the night immediately preceding the planned surgery, sedative premedication should be avoided [23]. In addition, preoperative multimodal preventive analgesic regimens may have a beneficial opioid-sparing effect.

Intraoperatively, the quintessential concern of the anesthesiologist would be the difficult airway. OSA is a predictor for difficult mask ventilation [52]. Difficult laryngoscopy and tracheal intubation was found to occur 8 times as often in OSA patients compared to those without OSA. Furthermore, patients with severe OSA showed higher prevalence of difficult intubation compared with those patients with lower AHI [53]. In a recent publication, obesity—which commonly coexists with OSA—was found to be a predictor of failed laryngeal mask airway insertion and ventilation [54]. Advanced planning for intraoperative airway management

Table 35.3 Perioperative Precautions and Risk Mitigation for OSA Patients

Anesthetic concern	Principles of management
Premedication	Avoid sedating premedication Consider alpha-2 adrenergic agonists (clonidine, dexmedetomidine)
Potential difficult airway (mask ventilation, tracheal intubation, and supraglottic airway device)	Optimal positioning (head elevated laryngoscopy position) if patient obese Adequate preoxygenation Consider continuous positive airway pressure preoxygenation Two-handed triple airway maneuvers Anticipate difficult airway. Personnel familiar with a specific difficult airway algorithm
Gastroesophageal reflux disease	Consider proton pump inhibitors, antacids, rapid sequence induction with cricoid pressure
Opioid-induced ventilatory impairment	Minimize opioid use Use of short-acting agents (remifentanil) Multimodal approach to analgesia (NSAIDs, acetaminophen, tramadol, ketamine, gabapentin, pregabalin, dexmedetomidine, clonidine, dexamethasone, melatonin) Consider local and regional anesthesia where appropriate
Carryover sedation effects from longer acting intravenous and volatile anesthetic agents	Use of propofol/remifentanil for maintenance of anesthesia Use of insoluble potent anesthetic agents (desflurane) Use of regional blocks as a sole anesthetic technique
Excessive sedation in monitored anesthetic care	Use of intraoperative capnography for monitoring of ventilation
Postextubation airway obstruction	Verify full reversal of neuromuscular blockade Extubate only when fully conscious and cooperative Non-supine posture for extubation and recovery Resume use of positive airway pressure device after surgery

Adapted from Seet and Chung [82]

with alternative intubation strategies in accordance with difficult airway algorithms would be prudent [55].

Preoxygenation using continuous PAP 3–5 min with a head-up tilt has been suggested to achieve higher end-tidal concentration of oxygen. This prolongs the time to desaturation [56]. Two-handed mask ventilation may be needed to attain adequate ventilation. OSA patients with obesity may benefit from being positioned in the head elevated laryngoscopy position to achieve optimal alignment for direct laryngoscopy and tracheal intubation [57]. The use of video laryngoscopes may increase intubation success and reduce intubation times compared to the traditional direct laryngoscope [58].

Gastroesophageal reflux disease secondary to hypotonia of the lower esophageal sphincter is common among patients with OSA [59]. Proton pump inhibitors, antacids, rapid sequence induction, and intubation with cricoids pressure may be considered to decrease aspiration risk. Several of the anesthetic agents result in respiratory depression, such as volatile agents, benzodiazepines, neuromuscular blockers, and most importantly opioids. OSA patients suffer from chronic sleep deprivation and have blunted responses to hypercarbia and hypoxia. These lead to increased sensitivity to the respiratory depressant effects of anesthetic agents. There may be benefits from the use of short-acting anesthetic agents, including propofol, desflurane, and remifentanil.

Opioid-induced ventilatory impairment (OIVI) may be described as central respiratory depression, decreased conscious level, and upper airway obstruction secondary to opioid administration, with the consequence of alveolar hypoventilation. OSA patients are more susceptible to this entity of OIVI. Patients with OSA who received opioids postoperatively were 12–14 times more likely to desaturate compared to those who were given non-opioid analgesic agents [60]. Perioperative opioid-sparing analgesics are therefore recommended. This would include multimodal analgesic agents such as NSAIDs, COX-2 inhibitors, paracetamol, and tramadol. Other novel adjuvants such as pregabalin, gabapentin, dexamethasone, ketamine, dexmedetomidine, clonidine, and melatonin also help with reducing postoperative opioid requirements [61–63].

Loco-regional anesthesia techniques avoid manipulation of the airway and reduce the need for perioperative opioids. Wound infiltrations, peripheral nerve block infusions, and epidural infusions of local anesthetic reduce opioid requirements postoperatively. These techniques may be recommended in OSA patients if the nature of surgery permits. A recent large sample size population-based analysis of database in the USA suggested that regional techniques, in particular neuroaxial techniques, conveyed benefits in reducing major complications, requirement for mechanical ventilation, and intensive care services in OSA patients undergoing joint arthroplasty [64]. The same principles may potentially be extrapolated to other regional techniques (e.g., peripheral nerve blocks, local infiltration anesthesia) in patients undergoing major surgeries; however, the paucity of evidence summons the need for more research in this area. Patients receiving sedation for surgical procedures under monitored anesthetic care should be monitored for adequacy of ventilation by capnography [23].

At the conclusion of the surgery, the extent of residual neuromuscular blockade should be verified and reversal done. Minute amounts of residual neuromuscular blockade can result in aspiration, airway obstruction, hypoventilation, hypoxia, and reintubation [65]. These risks are amplified in the OSA patient. Postextubation, patients should be nursed in a semi-upright or lateral position [23].

Due to the increased coexistence of pulmonary hypertension in OSA patients, many of which remained undetected, intraoperative triggers for elevation in pulmonary artery pressures should be avoided. These risk factors include hypothermia, hypercarbia, hypoxemia, and acidosis.

Postoperative Management Strategies for OSA Patients

The decision regarding the postoperative disposition of the OSA patient is dependent on several factors: OSA severity, postoperative opioid requirement, the nature, and extent of surgery. The main postoperative concern for the OSA patient is OIVI. Improved postoperative monitoring is crucial in mitigating the risk of OIVI; however, critical care and monitored beds are limited. The eventual decision of where the patient is to be monitored and the level of monitoring prescribed is at the discretion of the attending anesthesiologist. Recently, Swart et al. published a PACU order-based approach to facilitate postoperative decision making for patients with OSA. The orders prompt anesthesiologists to consider the baseline preoperative factors and perioperative events associated with higher risk of complications from OSA, diagnostic follow-up and possible sleep medicine consult [66]. We put forth a similar decision-tree aid and functional algorithm detailed in Fig. 35.2 and described below.

Firstly, all patients with previously diagnosed or suspected OSA who had received moderate sedation or general anesthesia should be subjected to an extended period of monitoring in the PACU (Fig. 35.2). An additional 60 min of continuous monitoring in a quiet environment after the modified Aldrete criteria for discharge has been met is suggested [10].

The occurrence of recurrent respiratory events in the PACU is an indication for continuous postoperative monitoring. PACU respiratory events include the following: (1) episodes of apnea for ≥ 10 s, (2) bradypnea <8

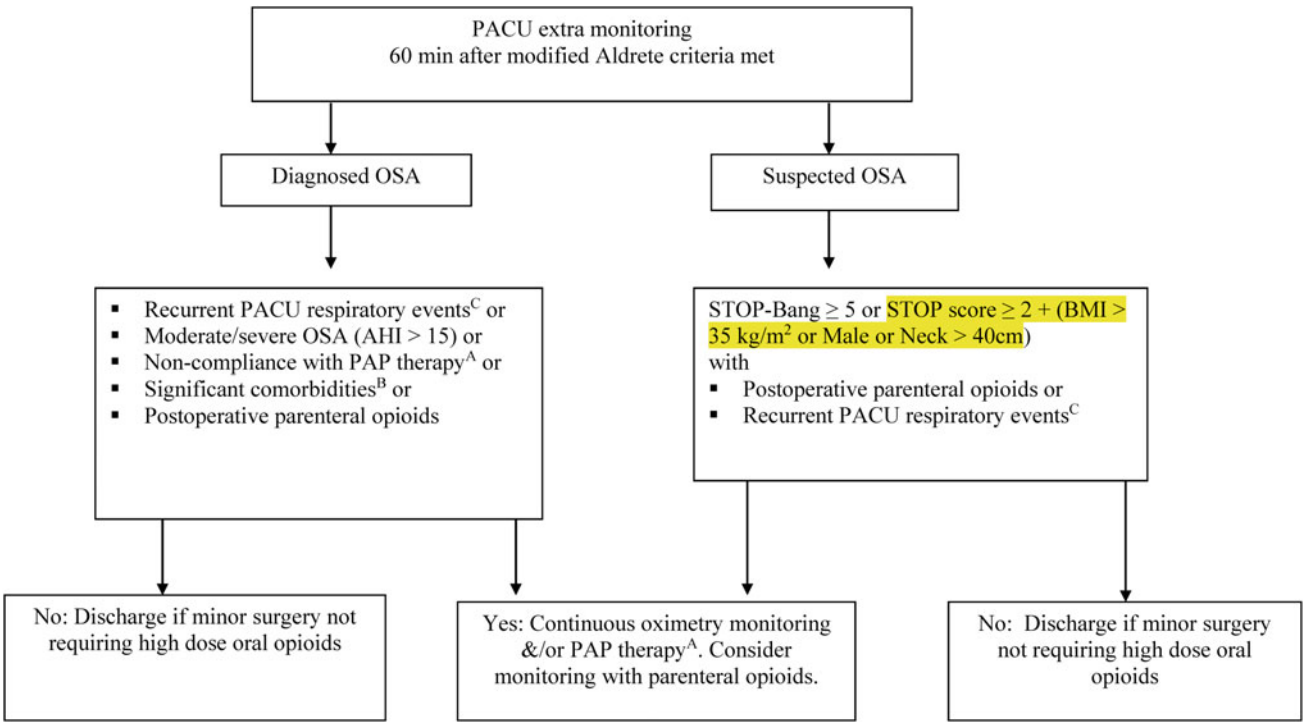

Fig. 35.2 Postoperative management of the diagnosed or suspected. Obstructive sleep apnea patient. [A]Positive airway pressure (PAP) therapy—including continuous PAP, bilevel PAP, or automatically adjusting PAP. [B]Significant comorbidities—heart failure, arrhythmias, uncontrolled hypertension, cerebrovascular disease, metabolic syndrome, obesity BMI >35 kg/m^2.[C] Recurrent postanesthesia care unit (PACU) respiratory event—repeated occurrence of oxygen saturation <90 %, or bradypnea <8 breaths/min, or apnea ≥ 10 s, or pain-sedation mismatch. Adapted from Seet and Chung [82]

breaths per minute, (3) repeated oxygen desaturation to <90 %, or (4) pain-sedation mismatch (high pain and sedation scores concurrently) [47]. Any of the above events occurring repeatedly in separate 30-min intervals may be considered recurrent PACU respiratory events. It was recently found that sedation level may be more reliable a predictor of OIVI than respiratory rate, because OIVI may not consistently be accompanied by bradypnea [67]. Patients with suspected OSA (i.e., scored as high risk on screening questionnaires) and who develop recurrent PACU respiratory events postoperatively are at increased risk of postoperative respiratory complications [47]. Therefore, continuous monitoring of these vulnerable patients with oximetry in an area with personnel trained to respond and intervene is advocated (Fig. 35.2). These areas may include the surgical ward outfitted with remote telemetry and oximetry monitoring. With continuous oximetry monitoring in the ward, care in intensive care units and step-down units are not needed.

For patients who have been previously diagnosed with OSA, red flags which may prompt the need for continuous postoperative oximetry monitoring would include known moderate or severe OSA, significant comorbidities, non-compliance to PAP therapy, and parenteral opioid administration (Fig. 35.2). For patients suspected of OSA with a STOP-Bang score of 5 or greater, and either requiring postoperative parenteral opioids or encountering recurrent PACU respiratory events, continuous oximetry monitoring may likewise be advised (Fig. 35.2).

Additionally, this same cohort of patients who require continuous oximetry monitoring may also benefit from postoperative PAP therapy. Patients with OSA and already on PAP devices should continue their PAP therapy postoperatively [23]. Limited literature suggests possible improved outcomes with postoperative PAP therapy in OSA patients. A retrospective review of 797 patients scheduled for bariatric surgery demonstrated that timely recognition and management of OSA with perioperative continuous PAP may mitigate the risk of postoperative complications [68]. A smaller case series of 14 patients with OSA reported that the use of CPAP continuously for 24–48 h after extubation may reduce the risk of postoperative complications [69]. PAP therapy was also found to decrease postextubation respiratory failure in severely obese patients admitted to the

intensive care unit with an absolute risk reduction of 16 % [70]. In a recent randomized controlled trial of 177 patients, it showed the feasibility of perioperative auto-titrating PAP for OSA patients. Perioperative auto-titrating PAP treatment significantly reduced postoperative AHI and improved oxygen saturation in the patients with moderate and severe OSA [71].

In contradistinction, the utility of postoperative auto-titrating PAP therapy in patients at high-risk for OSA failed to show benefit in reducing hospital length of stay and postoperative complications [72] in a recent study. Future research is necessary to discover the true utility of postoperative PAP therapy.

A multimodal approach to analgesia should be employed to minimize postoperative opioid usage. If postoperative parenteral opioids cannot be avoided, supplemental oxygen is commonly administered to prevent hypoxemia from OIVI. The Anesthesia Patient Safety Foundation further advises that ventilation should also be monitored (e.g., capnography) for the detection of hypoventilation when supplemental oxygen is delivered [73] (Fig. 35.2). Nurse training in detecting respiratory depression and rapid administration of naloxone is critical and can potentially prevent mortality and morbidity.

Recent research by Chung and colleagues uncovered an interesting but troubling phenomenon—the disturbances in sleep architecture were greatest on postoperative night one and breathing disturbances during sleep were greatest on postoperative night three [32–34]. Patients with a higher preoperative AHI were predicted to have a higher postoperative AHI. Preoperative AHI, male gender and 7w2-h opioid dose were positively associated with postoperative AHI [32–34]. Sleep architecture may normalize only after the 5th postoperative night. Therefore, the occurrence of late complications in OSA patients may be attributed to hypoxemia and sympathetic stress from upper airway obstruction in the first few postoperative nights. To date, recommendations on the most expedient duration to monitor OSA patients postoperatively remain controversial.

Ambulatory Surgery and the OSA Patient

There has been an increasing interest in ambulatory surgery for OSA patients. However, there remain concerns for OSA patients and their suitability for same day hospital discharge after surgery because of the risks of postoperative complication—including death from postoperative apnea and hypoxemia. Recent consensus statements from the Society for Ambulatory Anesthesia have been published to guide preoperative patient selection with OSA for ambulatory surgery [74].

On systematic review of relevant studies, the committee found that known OSA patients with well-controlled comorbid diseases and who will comply with postoperative PAP therapy may be considered for ambulatory surgery. Patients unwilling or unable to comply with PAP therapy may not be suitable candidates. Patients should be advised to apply their PAP devices when sleeping even in the day for several days postoperatively. Patients with suspected OSA and optimized comorbid conditions, and who will not require oral opioids postoperatively, may also be safely discharged after ambulatory surgery.

The author's proposed algorithm in Fig. 35.2 in similar fashion recommends that diagnosed or suspected OSA patients without significant comorbidities, recurrent PACU respiratory events or need for high dose oral opioids, be considered for discharge home after surgery at the discretion of the attending physician. Patients and their family should be educated regarding the use of PAP therapy when sleeping, and to avoid opioids due to the adverse effect on breathing.

Patients with severe OSA and uncontrolled comorbidities are not suitable for ambulatory surgery [61, 74]. The threshold for unanticipated hospitalization of the OSA patient should be lowered, for example, with the occurrence of postoperative respiratory events or exacerbation of cardiac comorbidities. Stand-alone ambulatory surgical centers that take care of OSA patients should have prearranged transfer agreements with inpatient institutions that are able to manage postoperative problems associated with OSA.

A judicious criteria for patient selection, detailed preoperative risk stratification and optimization of OSA and related comorbidities, in tandem with well-trained multidisciplinary medical personnel, experienced high volume facilities, and stringent discharge criteria adhering strictly to the protocol to a reliable escort are the essential system processes required for the safe delivery of care for the OSA patient presenting for ambulatory surgery.

Central Sleep Apnea

Central sleep apnea (CSA) is characterized by the lack of drive to breathe, resulting in repetitive periods of inadequate or absent ventilation and compromised gas exchange. CSA is contrasted to OSA, since in the former there is a lack of respiratory effort during airflow cessation. However, significant overlap exists in the pathophysiology of CSA and OSA. In some patients with what seems like apparent OSA, when treated with CPAP to eliminate upper airway obstruction, they emerge with CSA patterns. This unclassified clinical entity has been termed complex sleep apnea syndrome [75]. Typically, CSA can be considered the primary diagnosis when more than 50 % of the apneic episodes

are scored as central in origin (i.e., without respiratory effort).

The various manifestations of CSA include obesity hypoventilation syndrome (OHS), Cheyne–Stokes breathing, high altitude-induced periodic breathing, opioid-induced central apnea, and idiopathic CSA [76]. The former two conditions relevant to the surgical patient and their impact on the perioperative patient will be elaborated in greater detail.

Obesity Hypoventilation Syndrome

Obesity hypoventilation syndrome is characterized by a triad of features—body mass index ≥ 30 kg/m^2, sleep-disordered breathing, and daytime hypoventilation ($PaCO_2 \geq 45$ mm Hg, $PaO_2 < 70$ mm Hg) in the absence of other confounding causes of hypoventilation [77]. The pathogenesis of OHS may include impaired respiratory mechanics secondary to obesity causing increased mechanical load, leptin resistance resulting in central hypoventilation, and impaired compensatory response to acute hypercarbia in OSA [78].

OHS prevalence in the general population is 0.15–0.3 % [78]. It is a disease entity separate from OSA and obesity; however, there is considerable overlap. Distinguishing clinical feature of OHS includes more severe upper airway obstruction, restrictive pulmonary physiology, blunted central respiratory drive, and pulmonary hypertension; 90 % of patients with OHS also have OSA. The estimated prevalence of OHS in patients with known OSA is 11 %, and the prevalence of OHS in bariatric surgical patients is 8 % [25].

Surgical mortality rate was reported to be as high as 8 % in OHS patients undergoing bariatric surgery [79]. Therefore, there should be an increased awareness among perioperative physicians and anesthesiologists of the possibility of undiagnosed OHS in the surgical patient. Useful preoperative clinical predictors of OHS would include serum bicarbonate and room air oximetry. A preoperative raised serum bicarbonate level has a high sensitivity of over 90 % in predicting hypercapnia in OHS patients [35]. If serum bicarbonate is increased in the presence of hypoxemia on room air oximetry during wakefulness, a confirmatory test involving a measurement of arterial blood gases is recommended [25]. A highly sensitive serum bicarbonate threshold of 27 mmol/L is complemented by a highly specific AHI threshold of 100 in the diagnosis of OHS [35]. Preoperative echocardiogram may be considered in patients with OHS in view of the strong association of OHS with pulmonary hypertension of 30–88 % [25].

Perioperative management principles of OHS patients are similar to patients with OSA (Table 35.3). Additionally, the anesthesiologist should be cognizant of an increased mortality risk compared with normocapnic obese patients [80]. Continuous postoperative monitoring is essential to pick up OIVI early for intervention.

Cheyne–Stokes Breathing Syndrome

Cheyne–Stokes breathing syndrome is distinguished by the occurrences of cyclical crescendo and decrescendo breathing amplitude and the presence of a serious medical illness. These would include congestive heart failure, left ventricular systolic dysfunction, stroke, and Shy–Drager syndrome.

For the small subgroup of patients with Cheyne–Stokes breathing syndrome, the main concern to the anesthesiologist would be the associated medical condition—whether of cardiopulmonary or neurological origin. These associated medical conditions should be optimized in the preoperative period. For example, medical heart failure therapy should be the first step in the management of CSA with heart failure [20]. If CSA persists thereafter, there may be a role for PAP therapy in improving cardiovascular function [81]. Intraoperatively, special considerations and precautions for anesthesia relate to their underlying comorbid disease. The incidence of postoperative morbidity and mortality would be high and counseling of patient-specific perioperative risks should be undertaken.

Conclusion

Sleep-disordered breathing is a prevalent yet underdiagnosed condition. A significant number of patients with OSA are unrecognized when they present for surgery. OSA can lead to several systemic complications and is also linked to increased perioperative morbidity. This chapter reviewed the evidence supporting the perioperative management of patients with sleep-disordered breathing and lays out an approach to the screening, evaluation, and management of the known and suspected OSA patients, with the intention of mitigating the perioperative risks in this vulnerable group of patients.

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Oral Appliances and Surgical Techniques for Treatment of Obstructive Sleep Apnea Syndrome

36

John A. Fleetham and Fernanda R. Almeida

Introduction

This chapter is based on a recent overview of the treatment of the obstructive sleep apnea syndrome (OSAS) by oral appliances (OAs) and upper airway surgery [4] with additional figures and videos [3]. This treatment approach does not include lifestyle modifications or nasal continuous positive airway pressure (CPAP). Where possible, recommendations are based on data from randomized controlled clinical trials. In the field of OA therapy, there are currently 19 randomized controlled trials with OA compared to placebo (9 studies) or compared to CPAP (10 studies) and 9 randomized controlled trials between appliance designs. However, many of the surgical treatments for OSAS are not supported by such rigorous forms of evidence, and so to a considerable extent, treatment recommendations are based on data from uncontrolled studies, case series, consensus guidelines, and practice parameters. The treatment approach to OSAS should be individualized to each patient based on a careful risk–benefit analysis that takes into account their age, severity of symptoms, presence of associated comorbidities or safety critical occupation, etiology of upper airway obstruction, overnight sleep monitoring findings, the local expertise in terms of specialized treatments, and the ability to provide long-term follow-up. The primary goal of the treatment for OSAS is symptom improvement, so the need to establish effective treatment is more important in patients with marked daytime symptoms. Some treatments, such as CPAP, can be established in a more timely fashion compared to others, such as OA and corrective upper airway surgery. This is an important factor when the patient has a comorbidity/condition or a safety critical occupation. Relevant comorbidities and conditions are ischemic heart disease, cerebrovascular disease, congestive heart failure, refractory systemic hypertension, obstructive/restrictive lung disease, pulmonary hypertension, hypercapnic respiratory failure, and pregnancy. Safety critical occupations include patients working with machinery or employed in hazardous occupations and include truck, taxi, and bus drivers; railway engineers; airline pilots; air traffic controllers; aircraft mechanics; ship captains; and pilots. Car drivers who admit to have fallen asleep while driving within the last two years also require expedited treatment. The indications for the treatment of asymptomatic patients with OSAS are less clear. Treatment may be considered in asymptomatic patients with significant comorbid illness, who work in a safety critical occupation, or who have an apnea–hypopnea index (AHI) > 30 events/h. Certain physical factors limit the use of some treatments. Severe nasal obstruction may preclude nasal CPAP and may need to be addressed before these treatments are considered. Mandibular advancement devices, the most common type of OA used, require adequate dentition for their effective use, while tongue retaining devices can effectively treat edentulous patients. The presence of large tonsils should prompt referral to an otolaryngologist for consideration of tonsillectomy. Corrective upper airway surgery may not be a suitable option for patients who use their voice professionally. Long-term follow-up by either a primary care provider or sleep disorder specialist should be arranged in a similar fashion to other chronic diseases such

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as diabetes or hypertension. Patient education about the nature, complications, and treatment of OSAS by a trained healthcare professional (respiratory therapist/nurse/polysomnographic technologist) is an important component of all treatment strategies.

Oral Appliances

Oral appliances (OAs) are now widely used for the treatment of snoring and mild–moderate OSAS, both as primary therapy and as an alternative for patients who are unwilling or unable to tolerate CPAP (Video 1 Overview). OA is an appealing treatment option for patients as they are small and simple to use. There are a variety of synonyms for OA. In addition to dental, they may be called oral, intraoral, or mandibular, and instead of appliance, they may be called a device, splint, or prosthesis. OA therapy for OSAS remains underutilized despite several recent reviews [2] and recommendations from both the Cochrane Collaboration [7] and American Academy of Sleep Medicine [5].

Appliance Type

There are currently a large number of different OA available for the treatment of OSAS (Fig. 36.1) (Video 2–5, Appliance A, B, C, and D). OA increases the size of the upper airway by either advancing the mandible or the tongue. There are other minor design differences in the OA currently available that may also impact on their success and treatment adherence. Mandibular advancement OAs are most widely used and utilize traditional dental techniques to attach the OA to one or both dental arches. Construction usually requires dental impressions, bite registration (Video 6, Bite registration), and fabrication by a dental laboratory. Some OAs are available in a prefabricated form and are sometimes referred to as "boil and bite." These can either be fitted by the patient themselves or molded to the patient's teeth in an office setting. In a recent randomized controlled trial, a prefabricated device has shown to be ineffective and unable to predict efficacy of a titratable custom-fabricated OA. Some OA restricts mouth opening by means of clasps, whereas others allow relatively unhindered movement. More recently, OAs have been developed with an adjustable hinge that allows progressive advancement of the mandible, called titratable appliances, after initial construction until the optimal mandibular position is achieved (Video 7, Titration). The amount of anterior posterior mandibular movement and the speed with which this can be changed varies considerably between patients. Mandibular advancement OA normally requires at least 8 teeth in each of the maxillary and mandibular arches. Furthermore, the patient should be able to advance their mandible by at least 5 mm without discomfort. Severe temporomandibular joint disease and advanced periodontal disease are relative contraindications to mandibular advancement OA treatment.

The other major type of OA available is the tongue retainer that keeps the tongue in an anterior position during sleep by means of negative pressure in a soft plastic bulb. It fits over both the mandibular and maxillary arches and has a flange which fits between the lips and teeth, keeping the appliance anterior in the mouth. This appliance was one of the first to be developed and is available in both a fabricated and prefabricated form. It can be used in edentulous patients and is the OA of choice for patients with no teeth, limited anterior posterior mandibular movement or a extremely large tongue. In a recent study, tongue retaining devices have shown to improve the efficacy of mandibular advancement devices, improving its efficacy [1]. Patients should be assessed prior to OA treatment and not have major active periodontal disease, and dental restorations should ideally be completed prior to treatment (Video 8, Patient Assessment). Patients should be provided with information concerning the efficacy and side effects of OA, and written consent should be obtained (Video 9, Patient information). A combined medical and dental approach to OA treatment is important. OA therapy should be supervised by both medical and dental specialists with a major interest in the management of sleep-disordered breathing.

Mechanism of Action

The majority of OA is designed to maintain the mandible and/or tongue in a protruded posture, thereby preventing upper airway obstruction during sleep. Proposed mechanisms of action of OA include increased upper airway size, decreased upper airway collapsibility, activation of upper airway dilator muscles, and stabilization of mandibular posture. Several different upper airway imaging techniques have been used to assess changes in upper airway size and function with OA in patients with OSAS. These imaging techniques include cephalometry, computed tomography, magnetic resonance imaging, and video endoscopy, but most of these studies show poor reliability in predicting treatment outcomes. Voluntary mandibular and tongue protrusions have been shown to increase upper airway size and alter upper airway shape particularly in the velopharynx in subjects with and without OSAS. Several studies have demonstrated an

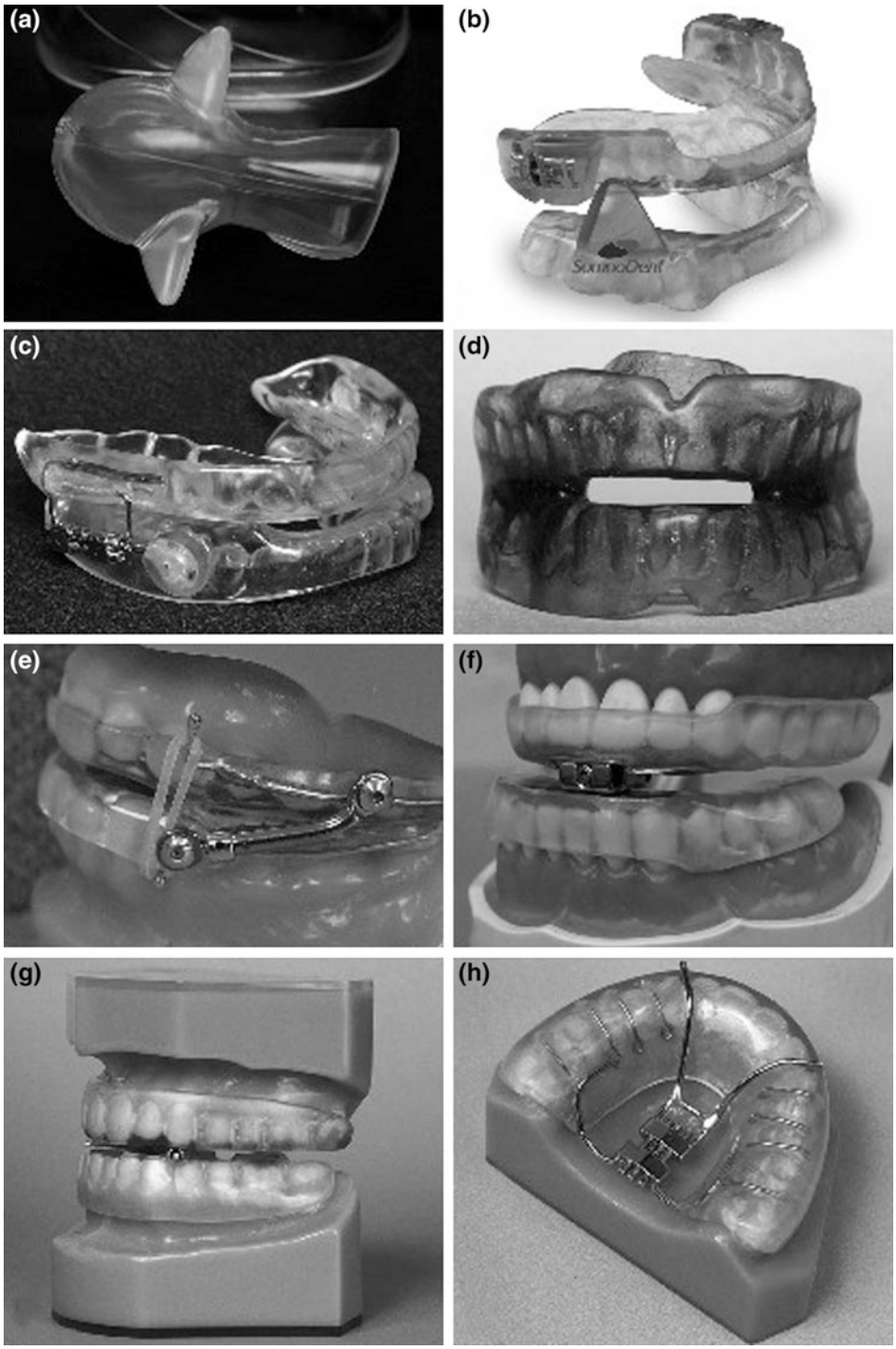

Fig. 36.1 Different types of oral appliances used for the treatment of obstructive sleep apnea syndrome. **a** AveoTSD (Innovative Health Technologies, New Zealand), **b** Somnomed (Denton, TX), **c** PM positioner (Tonawanda NY), **d** Monoblock (Courtesy of Dr. M Marklund), **e** Herbst (Tonawanda, NY), **f** MDSA (Medical dental sleep appliance, R.J. and V.K. Bird, Australia), **g** Klearway lateral view (Tonawanda, NY), **h** Klearway hinge view (Tonawanda, NY) (Reproduced with the permission from The European Respiratory Society [15])

increase in the anteroposterior diameter of the upper airway following OA insertion (Fig. 36.2). This increase was predominant in the oropharynx and hypopharynx, but some studies have also suggested an effect on the velopharynx (Figs. 36.3 and 36.4). Almost all of these upper airway imaging studies have been performed during wakefulness, and it is unknown whether the same changes occur during sleep. Mandibular advancement OAs have been shown to increase upper airway muscle tone, which may also contribute to increased upper airway patency.

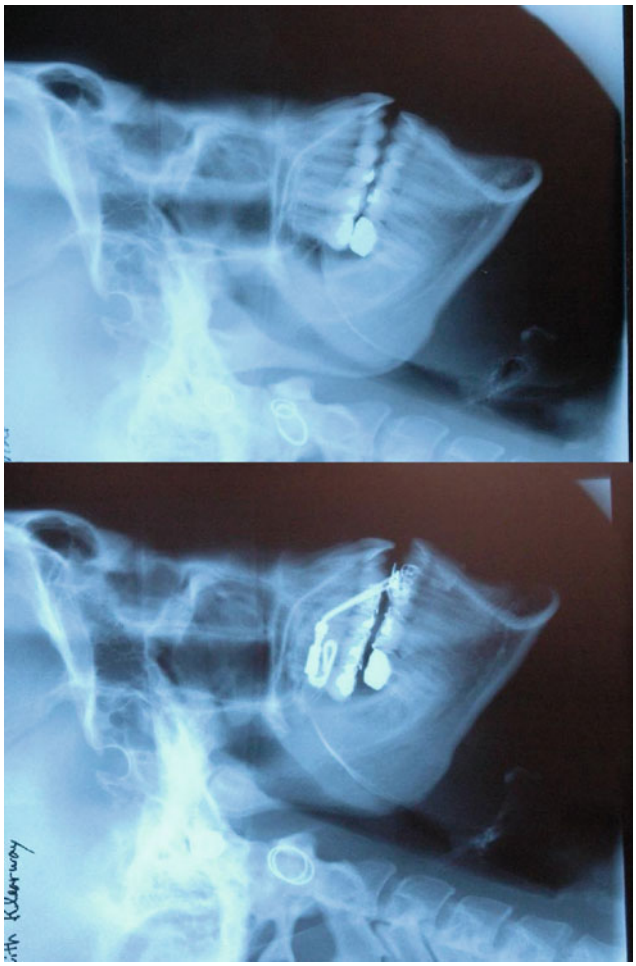

Fig. 36.2 Lateral cephalometry of a male patient without (2a) and with (2b) a mandibular advancement oral appliance. Note the advancement of the mandible and an increase in the size of the velopharynx with the mandibular advancement oral appliance (Reproduced with the permission from The European Respiratory Society [15])

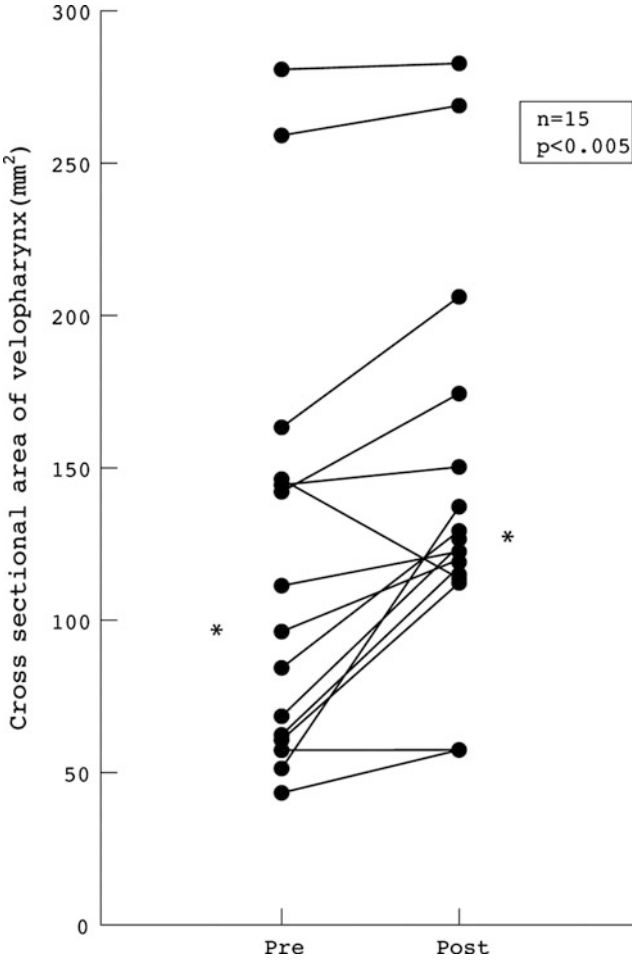

Fig. 36.3 Increase in cross-sectional area of the velopharynx after insertion of a mandibular advancement splint. *Asterisk* Median values (Reproduced with the permission from BMJ Publishing Group Ltd. Thorax [12])

Efficacy

The effectiveness of OA therapy can be influenced by the patient's body mass index, the severity of OSAS, the presence of positional OSAS, and the degree of mandibular advancement obtained with the OA. Until recently, the majority of the data concerning the efficacy of OA in the treatment of OSAS were from uncontrolled case series studies which were subject to study design issues such as regression to the mean, and selection and reporting bias. With about 18 randomized controlled trials comparing OA to placebo and/or CPAP, there is increasing evidence that OA significantly improve snoring, daytime sleepiness, quality of life, systemic hypertension, and indices of sleep-disordered breathing. A variety of prospective randomized trials have been performed to evaluate the efficacy, side effects, compliance, and preference of OA treatment in patients with OSAS. There are at least 9 randomized controlled trials comparing OA to an inactive control that demonstrate that OA improves daytime sleepiness, systemic hypertension, and indices of sleep-disordered breathing in patients with OSAS. Additional well-designed, large-scale randomized controlled trials comparing active and control OA are required to determine which groups of patients are most likely to benefit from OA treatment, how these patients can be identified, and how much benefit can be achieved and with what cost, side effects, and complications. There are at least 10 randomized controlled trials which have compared the efficacy and side effects of OA and CPAP. Although both CPAP and OA led to similar improvements in daytime sleepiness, health status, and blood pressure, conversely the magnitude of improvement in AHI was significantly more with CPAP. Some studies suggest that the higher efficacy of CPAP is counterbalanced by the higher adherence to OA

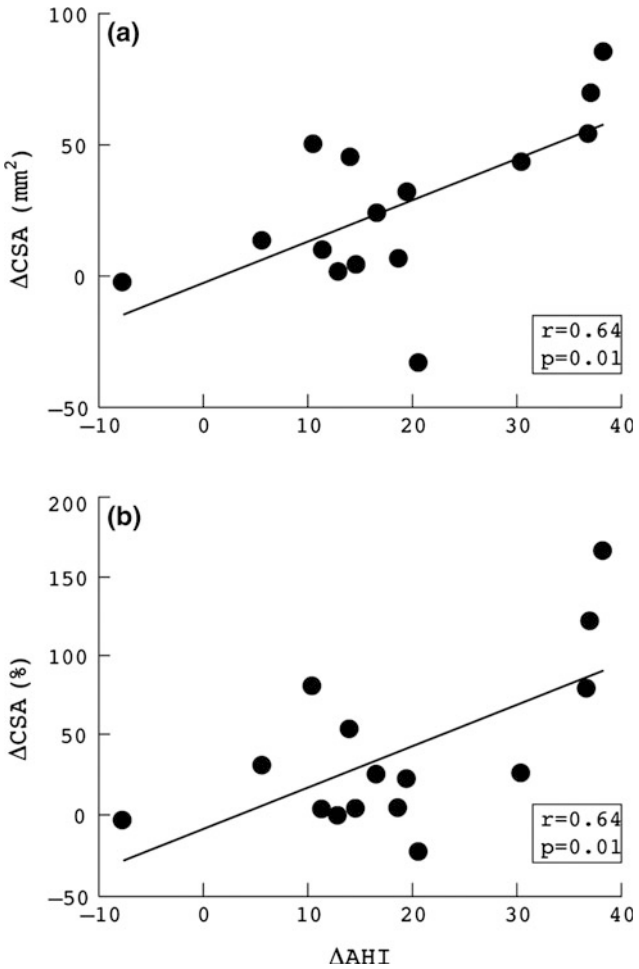

Fig. 36.4 Relationship between change in apnea + hypopnea index (ΔAHI) and **a** the absolute and **b** the proportional changes in cross-sectional area (ΔCSA) of the velopharynx after insertion of a mandibular advancement splint (Reproduced with the permission from BMJ Publishing Group Ltd. Thorax [12])

(hour per night and nights per week), resulting in a similar treatment effectiveness [16]. Furthermore, it takes longer to obtain optimal treatment with an OA than CPAP, which can be a major issue in patients with excessive daytime sleepiness. Patients who responded to both treatments tend to prefer the use of an OA to CPAP. All of the randomized controlled trials have been short-term studies over 3–6 months, but there are now several non-randomized studies establishing long-term efficacy over 4–5 years.

OA design has been proposed as an important determinant of treatment success, and there have been at least 9 prospective comparative studies evaluating different OA designs. Most studies using comparable mandibular protrusion with minimum vertical opening have shown that the differences were minimal. Some studies looking at vertical opening have shown a detrimental effect of the increase in the anterior vertical opening of these devices. There were varying degrees of patients' acceptance, but the incidence of long-term side effects with different OA is independent on the appliance design. Finally, there is one longitudinal parallel group study comparing the effectiveness of OA with uvulopalatopharyngoplasty in patients with mild to moderate OSAS over 4 years, which suggests that an OA was more effective than uvulopalatopharyngoplasty in improving indices of sleep-disordered breathing. However, the significance of this finding is questionable, as there is no definitive evidence of the effectiveness of this type of corrective upper airway surgery. OA therapy may also be indicated as an adjuvant to nasal CPAP when the patient is away from home or electrical power, or used in conjunction with CPAP, allowing patients who were unable to tolerate high CPAP pressures to use CPAP in combination with an OA with an average reduction of 2.5 cm of H_2O pressure. OAs have also been used as combination therapy in patients who have had an unsuccessful response to uvulopalatopharyngoplasty.

Predictors of Success

A variety of predictors of OA treatment success have been proposed. It has been suggested that younger, less obese patients, with smaller neck circumference and with OSAS that occurs predominantly in the supine position, may be more likely to obtain a successful response with an OA. Treatment success may be inversely related to pretreatment severity, but this relationship may just be a function of the definition of treatment success. Several upper airway skeletal and soft tissue measurements made from pretreatment lateral cephalometry have been shown to be associated with treatment success. These include a more micrognathic or retrognathic mandible and small soft palate and tongue. Upper airway fluoroscopy and, more recently, flow-volume curves and nasal resistance measurements have also been proposed as techniques to guide successful OA therapy. A primary oropharyngeal site of obstruction may be associated with a better treatment outcome. However, there is considerable overlap between good and poor treatment responses with all these variables. The utility of any treatment recommendation based on clinical features, OSAS severity, or upper airway anatomy requires prospective validation.

Treatment Adherence

Self-reported treatment adherence data for up to 5 years are available for OA therapy. Self-reported treatment adherence has been reported as high as 96 % patients using OA for >75 % nights and 80 % patients using OA >75 % of each night. Treatment adherence varies between OA type and appears better with mandibular advancement rather than

tongue retaining OA. Adherence rates appear to decrease with duration of use and have been reported as 60 % at one year and 48 % at two years. Previous experience with nasal CPAP suggests that self-reported treatment adherence tends to overestimate actual use. Recently, Vanderveken and colleagues (2012) have described an objective sensor to monitor OA compliance, which has recently been approved for commercialization. Future studies and clinical practice should now include objective OA compliance data.

Side Effects and Complications

Side effects are common, but generally minor. Excessive salivation, mouth dryness, morning-after occlusal changes, and discomfort in the gums, teeth, or jaw are common side effects in the first weeks of OA therapy, but usually resolve with time. More persistent side effects related to temporomandibular joint dysfunction and dental crown damage appear to be uncommon. Long-term common side effects include tooth movement and occlusal alteration (Video 10, Side effects). Small occlusal changes may be found in up to 80 % of patients after continuous five years of OA wear, independent of the appliance used. The clinical significance of these occlusal changes is uncertain. OA adjustment can decrease side effects by reducing pressure on the anterior teeth and excessive mandibular advancement. Side effect types vary between types of OA with tongue pain occurring in tongue retention OA and gagging associated with OAs that have a maxillary component to modify soft palate position.

Cost

The cost of OA therapy varies depending on the type of OA used and the extent and expertise of the dental supervision. Consensus opinion indicates that a prefabricated OA can range from $45 to 100 and custom-made OA ranges from $500 to over $1000. OA usually remains effective for two to three years and after that they can break and require either repair or replacement. OA treatment generally includes about ten dental appointments, and then, dentist service fees vary greatly between $200 per appointment or a fixed fee of $2500, depending on the time spent caring for the patient and geographic economic factors. Costs can equal or exceed those associated with nasal CPAP therapy. There is increasing evidence that OA is a cost-effective treatment for OSAS [10].

Treament Recommendations

A Cochrane systematic review [7] recently concluded that there was increasing evidence that OA improves subjective daytime sleepiness and sleep-disordered breathing compared with control appliances. However, it recommended that until there was more definitive evidence on the effectiveness of OA compared to CPAP, OA therapy should be restricted to patients with mild symptomatic OSAS and those patients who are unwilling or unable to comply with CPAP therapy. The American Academy of Sleep Medicine [5] reviewed similar data to the Cochrane Collaboration and recommended that OAs were indicated for use in patients with mild–moderate OSAS who prefer them to CPAP, or who do not respond to, or are not appropriate candidates for, or who fail treatment with CPAP. They recommended CPAP therapy as first-line therapy for patients with severe OSAS, but OA can also be prescribed for severe OSAS if patients can not tolerate CPAP. OA can have insufficient reduction in OSAS severity and has also shown a placebo effect on sleepiness; therefore, it is important to perform follow-up sleep monitoring to verify the efficacy of OA therapy. Patients treated with OA require long-term dental follow-up to monitor patient adherence, to evaluate OA deterioration or maladjustment, to evaluate the health of the oral structures, and to monitor occlusal changes.

Upper Airway Surgery

Upper airway surgery is the treatment of choice in less than 1 % of patients with OSAS who have a specific anatomic upper airway lesion such as adenotonsillar enlargement, antrochoanal polyp, or tumor. Tracheostomy was the primary treatment for severe OSAS prior to the introduction of CPAP. The long-term morbidity associated with tracheostomy led to the development of a variety of other upper airway surgical procedures for the treatment of OSAS. The goal of these procedures is to remove the site of upper airway obstruction by either increasing upper airway size or decreasing upper airway collapsibility. The procedures achieve this by (1) resection of redundant soft tissue (nasal surgery, uvulopalatopharyngoplasty, laser-assisted uvulopalatoplasty (LAUP), midline glossectomy); (2) induction of scar tissue formation (cautery or radio frequency ablation of soft palate, tongue, or epiglottis); or (3) displacement of bony and ligamentous attachments of upper airway soft tissue structures (maxillary and mandibular osteotomies, tongue, and hyoid suspensions). There are two detailed reviews of the literature on the surgery for OSAS [11, 14]. They identified only a few randomized or quasi-randomized trials comparing upper airway surgery with conservative management or other treatments for OSAS. Consequently, any recommendations regarding the role of upper airway surgery in the treatment of OSAS must take into account the weakness of the existing data. CPAP should be used to treat patients preoperatively and to protect against postoperative

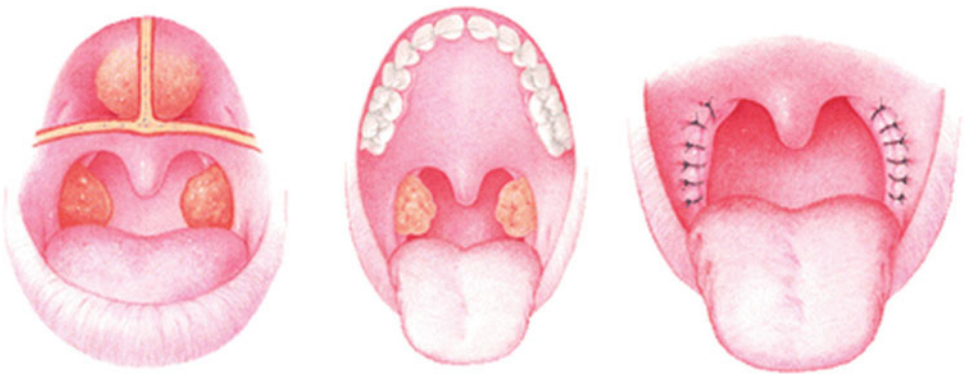

Fig. 36.5 Adenotonsillectomy is first-line therapy for obstructive sleep apnea in children. Both adenoid tissue and tonsillar tissue are removed, and the lateral pharyngeal walls are sutured to prevent collapse (Reprinted with the permission from the American Thoracic Society. Copyright © 2014 American Thoracic Society. Cite: Won et al. [19]. Official Journal of the American Thoracic Society

upper airway obstruction. Long-term follow-up is strongly recommended because the long-term efficacy of upper airway surgery has not been well established.

Tonsillectomy

Adenotonsillar hypertrophy is a common cause of OSAS in children. Adenotonsillectomy is first-line therapy for obstructive sleep apnea in children. Both adenoid tissue and tonsillar tissue are removed, and the lateral pharyngeal walls are sutured to prevent collapse (Fig. 36.5). Adenotonsillectomy is curative in 75–100 % of children with OSAS. Adenotonsillar hypertrophy is occasionally the primary cause of OSAS in adults. Eight of 9 patients had a reduction in AHI $\geq$ 50 % or to <20/h postoperatively in a prospective study of tonsillectomy in adult patients [18]. The presence of large tonsils in a patient with OSAS should prompt referral to an otolaryngologist for the consideration of tonsillectomy.

Uvulopalatopharyngoplasty

Uvulopalatopharyngoplasty (UPPP) is a procedure introduced over 25 years ago which has been widely used for the treatment of OSAS. This procedure reduces upper airway obstruction by shortening the uvula, trimming the soft palate, and suturing back the anterior and posterior pharyngeal pillars (Fig. 36.6). Tonsillectomy is performed at the same time if tonsils are found to be enlarged. Uvulopalatal flap is a modification of UPPP. Instead of removing the uvula and soft palate, the uvula is retracted and tucked superiorly under the soft palate (Fig. 36.7). The pharyngeal

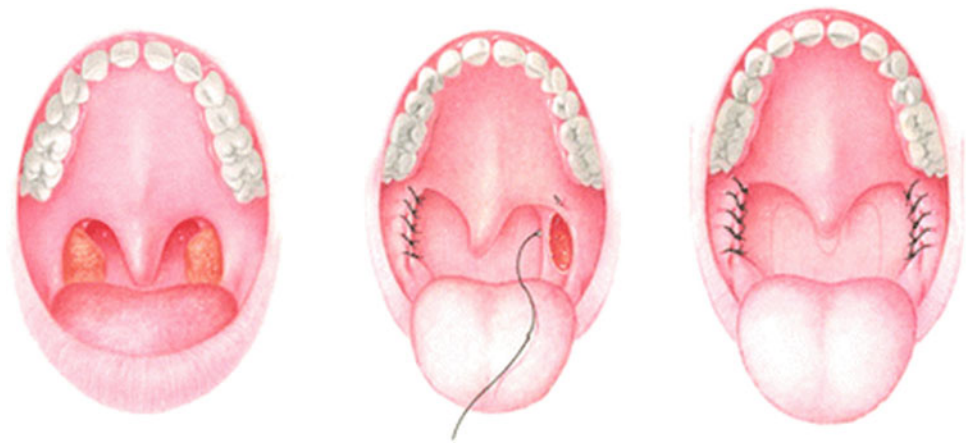

Fig. 36.6 Uvulopalatopharyngoplasty reduces upper airway obstruction by shortening the uvula, trimming the soft palate, and suturing back the anterior and posterior pharyngeal pillars. Tonsillectomy is performed at the same time if tonsils are found to be enlarged (Reprinted with the permission from the American Thoracic Society. Copyright © 2014 American Thoracic Society. Cite: Won et al. [19]. Official Journal of the American Thoracic Society

Fig. 36.7 Uvulopalatal flap is a modification of uvulopalatopharyngoplasty. Instead of removing the uvula and soft palate, the uvula is retracted and tucked superiorly under the soft palate. The pharyngeal pillars are sutured back, and tonsils are removed in this procedure as well (Reprinted with the permission from the American Thoracic Society. Copyright © 2014 American Thoracic Society. Cite: Won et al. [19]. Official Journal of the American Thoracic Society

pillars are sutured back, and tonsils are removed in this procedure as well. Sher and associates [13] performed a meta-analysis of 37 reports on UPPP for the treatment of OSAS published between 1966 and 1995. UPPP resulted in a mean 38 % reduction in AHI. A higher AHI was associated with a lesser improvement post-UPPP. A good response to UPPP, as defined by a 50 % decrease in AHI and a post-operative apnea index <10/h and AHI < 20/h, was obtained in 41 % of patients. There is one randomized controlled trial comparing UPPP with conservative management. Daytime sleepiness was improved in the surgical group, but there was no difference in oxygen desaturation index between the two groups at 12 months. The surgical complication rate was 22 %. Complications included infection, tracheostomy, and dysphagia. One patient had a myocardial infarction and one patient had a transient ischemic attack following surgery.

One randomized trial compared UPPP to lateral pharyngoplasty. Daytime sleepiness was improved in both groups, but AHI was only significantly reduced in the lateral pharyngoplasty group. Nasal regurgitation was noted with equal frequency in both groups. There is another randomized trial of UPPP versus laser-assisted uvulopalatoplasty (LAUP) for the treatment of snoring in patients with palatal flutter [9]. Eighty percent of patients had a subjective improvement in their snoring, and the objective snoring index was also significantly reduced with both procedures. Some of the LAUP patients had a higher snoring index after surgery. No postoperative complications were reported in the LAUP group, but bleeding, velopharyngeal insufficiency, and infection were reported in the UPPP group. Another study evaluated the short-term and long-term responses to UPPP or UPPP plus tonsillectomy [17]. Snoring was improved in the majority of patients at long-term follow-up. The oxygen desaturation index was improved in some patients at short-term follow-up. UPPP in combination with tonsillectomy was more effective than UPPP alone. UPPP can result in an increase in OSAS severity [13], and subjective outcomes do not always match objective outcomes. One study found the majority of patients reported reduced snoring and improved sleep despite lack of improvement in the AHI, and snoring intensity following UPPP surgery. Consequently, it is important to perform follow-up sleep monitoring to verify there has been an objective improvement in OSAS severity.

UPPP may be more effective in patients with retropalatal obstruction than in patients who also have a retrolingual obstruction. Five percent of patients with OSAS and retrolingual obstruction obtained a good response to UPPP compared with 52 % of patients with a retropalatal obstruction. The good responders had a lower mean AHI compared with the poor responders. A study was performed with cephalometry and upper airway CT scans on 20 patients before and after UPPP [6]. Thirty-five percent had a good response to UPPP, and these patients had an increase in the retropalatal oropharynx post-UPPP, whereas poor responders did not. The post-UPPP velopharynx was larger in good responders compared with poor responders. The change in the size of the narrowest segment of the oropharynx correlated with the change in the AHI, suggesting that failure to increase velopharynx size may be one of the causes of a failure to achieve a good response with UPPP. There is limited long-term follow-up on UPPP. In a study of 50 patients following UPPP for OSAS, the good response progressively decreased from 60 % at 6 months to 30 % at 21 months during the long-term follow-up which was associated with significant weight gain. Complication rates

are difficult to determine from the literature. Postoperative pain is common but self-limited. Velopharyngeal insufficiency may occur in up to 40 % of patients. Velopharyngeal stenosis has also been reported and may explain the worsening of OSAS in some patients post-UPPP. Postoperative upper airway obstruction has been reported in 10 % of patients, and some deaths have occurred. UPPP may interfere with the patients' ability to tolerate CPAP therapy. Patients with a prior UPPP develop a mouth leak at a lower CPAP pressures than patients with OSAS without prior UPPP. Furthermore, patients with prior UPPP have a lower adherence with CPAP than patients with OSAS without a UPPP. UPPP may be considered in selected patients with OSAS who have failed CPAP and/or OA treatment. Patients being offered UPPP should be informed about the limited efficacy, potential complications, and the risk of subsequent difficulty with CPAP treatment.

Laser-Assisted Uvulopalatoplasty

LAUP is a modified UPPP procedure with less radical resection of palatal tissue. LAUP is performed with a carbon dioxide laser as either a one-stage or multistage office procedure under local anesthesia. Although it was originally introduced for the treatment of snoring, more recently it has used to treat patients with OSAS. Two meta-analyses by Verse [17] and Littner et al. [8] reviewed over 70 articles published between 1980 and 2000. These meta-analyses revealed a small reduction in AHI post-LAUP. Applying similar criteria to those outlined earlier for UPPP, good response rates between 27 and 41 % were reported with LAUP. Twenty to thirty patients were objectively worse post-LAUP, which may be caused by palatal fibrosis and subsequent upper airway narrowing. Subsequently, in the only randomized controlled trial to date, 45 patients with mild OSAS were assigned to either LAUP or no treatment. AHI was reduced by a mean of 21 % in the LAUP-treated group, compared with no change in the control group. Less than 25 % of the LAUP-treated patients had a good response in terms of a reduction in AHI to less than 10/hr with an associated symptomatic improvement. There was no difference in the change in subjective sleepiness between the two treatment groups. Both snoring severity and frequency, based on visual analogue scales were reduced in the LAUP group. There was no difference between the two treatment groups in change in quality of life scores. Despite this limited efficacy, approximately 50 % of patients were satisfied with LAUP. Reported adverse effects include postoperative pain, nasal regurgitation, dysphagia, infection, change in vocal quality, and a sensation of dry throat. The development of postoperative upper airway edema and narrowing has raised concerns about the advisability of performing LAUP as an outpatient procedure in patients with OSAS. The long-term results of LAUP have not been defined, but there are some data to suggest that short-term improvements are not maintained over time. Practice parameters issued by the American Academy of Sleep Medicine advise that LAUP is not recommended for the treatment of OSAS [8].

Other Palatal Procedures

A variety of other surgical procedures which either stiffen or ablate palatal tissue have been described for the treatment of both snoring and OSAS. These include laser palatoplasty, laser cautery-assisted palatal stiffening, and temperature-controlled radio frequency tissue ablation of the tongue and soft palate (TCRFTA). A randomized controlled trial comparing TCRFTA with sham (placebo) surgery and nasal CPAP therapy has been performed in patients with mild–moderate OSAS [20]. There were no differences in outcomes between TCRFTA and CPAP. TCRFTA increased airway volume, reduced AHI, and improved quality of life. Compared with sham surgery, TCRFTA does not reduce the AHI sufficiently to be recommended as a treatment for OSAS.

Nasal Surgery

There are no randomized controlled trials of nasal surgery as a treatment for OSAS. It is rarely an effective treatment for OSAS. There was an improvement in OSAS following nasal surgery in a subgroup of patients without a narrow upper airway, which suggests that the failure of nasal surgery to improve OSAS may be related to the persistent upper airway narrowing. Relief of nasal obstruction may reduce snoring and may help to facilitate CPAP treatment. Nasal surgery is not indicated as a primary treatment for OSAS, but may play a role in improving CPAP adherence.

Maxillary and Mandibular Surgery

A variety of maxillary and mandibular surgical procedures have been developed to relieve upper airway obstruction distal to the velopharynx, in the retroglossal oropharynx and hypopharynx [19]. Inferior sagittal mandibular osteotomy with genioglossus advancement, hyoid myotomy and hyothyroidopexy, total subapical mandibular osteotomy, bilateral sagittal split mandibular osteotomy, and LeFort 1 maxillary osteotomy are performed in various combinations and are designed to advance the ventral wall of the pharynx. Genioglossus advancement enlarges the hypopharyngeal space by pulling forward the tongue base at the geniotubercle through a mandibular osteotomy (Fig. 36.8).

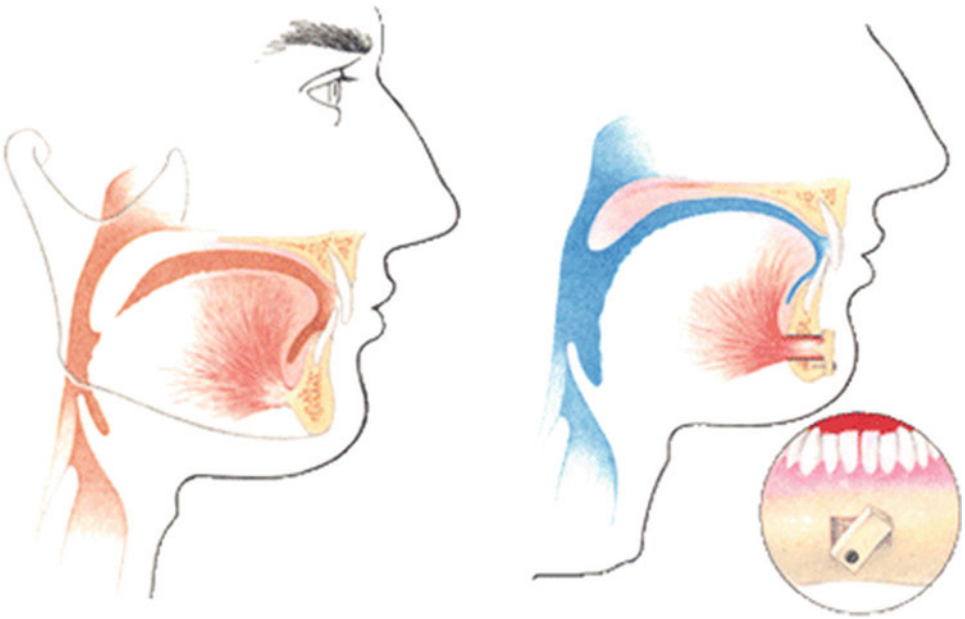

Fig. 36.8 Genioglossus advancement enlarges the hypopharyngeal space by pulling forward the tongue base at the geniotubercle through a mandibular osteotomy (Reprinted with the permission from the American Thoracic Society. Copyright © 2014 American Thoracic Society. Cite: Won et al. [19]. Official Journal of the American Thoracic Society

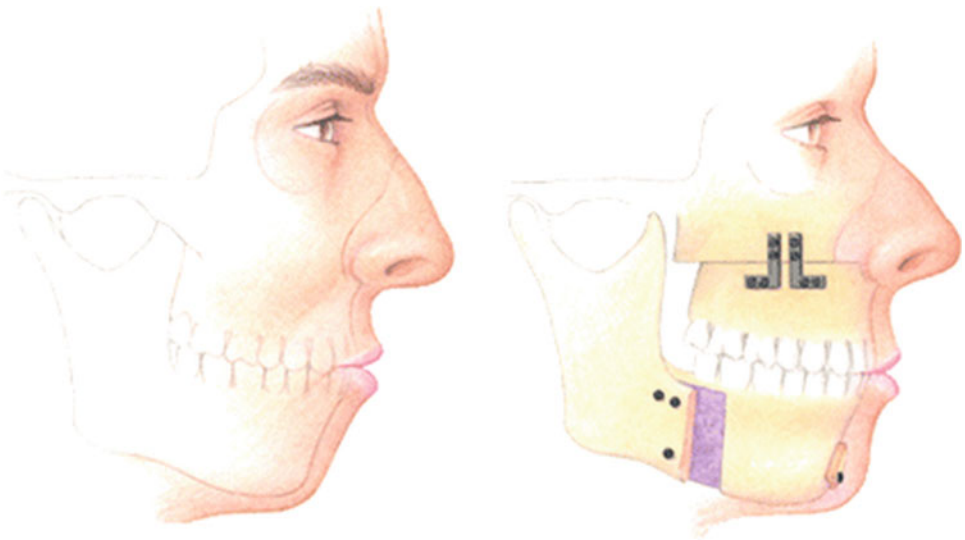

Fig. 36.9 Maxillomandibular advancement osteotomy, or phase II surgery, advances the maxilla and mandible to enlarge the retrolingual and retropalatal spaces (Reprinted with the permission from the American Thoracic Society. Copyright © 2014 American Thoracic Society. Cite: Won et al. [19]. Official Journal of the American Thoracic Society

Maxillomandibular advancement osteotomy, or phase II surgery, advances the maxilla and mandible to enlarge the retrolingual and retropalatal spaces (Fig. 36.9). There are no randomized controlled studies of this type of surgery for OSAS. The literature is difficult to interpret because of the different surgical procedures, the adjunct procedures used (e.g., hyoid suspension, septoplasty, and UPPP), the selection of patients with different skeletal types, confounding variables such as postoperative weight loss, and varying definitions of a good response. Three hundred and six patients with OSAS were treated in a two-phase surgical approach. Stage I procedures included UPPP for retropalatal narrowing, and inferior sagittal mandibular osteotomy with genioglossus advancement, and hyoid myotomy and suspension for retroglossal obstruction. Patients who failed to respond adequately to the Stage I procedure were offered the Stage II procedure consisting of maxillomandibular advancement. Good response rates to Stage I surgical procedures ranged between 23 and 67 %. Stage II procedures yielded good response rates between 75 and 100 %, whether as primary treatment or following Stage I surgery. More recently, maxillomandibular advancement has been proposed as the primary surgical treatment without a staged approach. Limited long-term follow-up suggests that good response rates of 80 % persist for at least 2 years. A combined surgical and dental approach is important to ensure satisfactory dental occlusion postoperatively. Complications of Stage I surgery include anesthesia of the lower lip in the

majority of patients and postoperative upper airway obstruction. Anesthesia of the cheek, lower lip, and chin is common after Stage II procedures, and a change in facial appearance is to be anticipated. Maxillomandibular surgery may be effective in carefully selected patients with OSAS who have failed CPAP and/or OA treatment.

Tongue-Base Surgery

Glossoplasty, laser midline glossectomy, lingualplasty, and tongue-base suspension have all been developed to remove excess lingual tissue and increase retrolingual oropharyngeal size in patients with snoring or OSAS. There is a randomized trial comparing tongue advancement done by a mandibular osteotomy in conjunction with UPPP, compared to tongue suspension with UPPP. AHI was not reported, but there were significant improvements in subjective daytime sleepiness in both treatment groups. There is insufficient data to recommend tongue-base surgery as a treatment for OSAS. Most forms of upper airway surgery have not been proven to have benefit for the treatment of OSAS in controlled clinical trials. New or unproven procedures should be considered experimental and be rigorously tested in research studies prior to widespread implementation in clinical practice.

Tracheostomy

Tracheostomy was commonly performed for severe OSAS prior to the introduction of CPAP. It is the only surgical procedure that consistently relieves OSAS by bypassing the recurrent upper airway obstruction during sleep. Central apneas and hypopnoea may occur after tracheostomy, but usually resolve within six months. Tracheostomy is associated with long-term morbidity related to granulation tissue and the cosmetic effect with its associated psychosocial morbidity. There are no randomized studies of tracheostomy for the treatment of OSAS. Tracheostomy should only be considered in carefully selected patients with OSAS when all other treatments fail.

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Nature, Evaluation, and Treatment of Insomnia

37

Charles M. Morin and Ruth M. Benca

Introduction

Insomnia is a prevalent complaint both in the general population and in clinical practice. Chronic insomnia can present as an independent condition or more often as a coexisting condition with another medical or psychiatric disorder. Insomnia diagnosis and therapeutic approaches have evolved over the last two decades. Whereas it used to be conceptualized predominantly as a symptom of other psychiatric or medical disorders, current diagnostic classifications now recognize insomnia as a disorder on its own [1–4]. In addition, there have been significant advances in the therapeutics of insomnia, from a predominantly symptomatic approach to more focused interventions on perpetuating factors with cognitive behavioral therapy and on more targeted brain receptors with pharmacotherapy [5].

Significance of Insomnia

Population-based estimates indicate that about 30 % of adults report insomnia symptoms, 9–12 % experience additional daytime symptoms, and between 6 and 10 % meet diagnostic criteria for an insomnia syndrome [6–8]. In primary care medicine, approximately 20 % of patients report significant sleep disturbances [9]. Insomnia is more prevalent among women, middle-aged and older adults, shift workers, and patients with medical or psychiatric disorders. Difficulties initiating sleep are more common among young adults, and problems maintaining sleep are more frequent among middle-aged and elderly adults. The incidence of insomnia is higher among first-degree family members (daughter, mother) than in the general population [10], although it is unclear whether this link is inherited through a genetic predisposition, learned by observations of parental models, or simply a by-product of another psychopathology.

Persistent insomnia can produce an important burden for the individual and for society, as evidenced by reduced quality of life, decreased work productivity and increased absenteeism and disability, and higher rates of healthcare utilization [9, 11, 12]. Increasing evidence suggests associations between chronic insomnia and long-term negative health outcomes such as increased risk of hypertension, diabetes, and even mortality [13–16].

Nature of Insomnia

Clinical Presentation and Objective Findings

Insomnia is characterized by a spectrum of complaints reflecting dissatisfaction with the quality or duration of sleep. These complaints may involve problems initiating sleep at bedtime, trouble staying asleep with middle-of-the-night awakenings and difficulty going back to sleep, or waking up too early in the morning with an inability to return to sleep [1–4]. In addition, daytime fatigue, cognitive impairments, and mood disturbances (e.g., irritability and dysphoria) are extremely frequent and often the primary concerns prompting patients with insomnia to seek treatment.

The diagnostic criteria of insomnia have recently been revised with the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders [4] (see Table 37.1) and the third edition of the International Classification of Sleep Disorders [3]. While the main diagnostic criteria for an insomnia disorder remain similar to those of previous DSM and ICSD editions, several important changes were made with the last editions of these classifications. For instance, nonrestorative sleep is no longer part of the insomnia

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Table 37.1 Diagnostic criteria for insomnia disorder (DSM5)

• The predominant complaint is a dissatisfaction with sleep quality or duration, associated with one or more of the following symptoms: 1. Difficulty initiating sleep 2. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings 3. Early morning awakening with inability to return to sleep
• The sleep disturbances cause clinical significant distress or impairments in daytime functioning
• The sleep disturbances occur at least 3 nights per week and is present for at least 3 months
• The sleep disturbances occur despite adequate opportunity for sleep • The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder • The insomnia is not attributable to the physiological effects of a substance • Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia

definition, mainly because this complaint is not well defined and not specific to insomnia. Other changes include the addition of a minimum frequency, i.e., 3 nights or more per week with sleep difficulties, and an increase in the duration threshold from 1 to 3 months for defining chronic insomnia. The most important change introduced in both classifications is that there is no longer a distinction made between primary insomnia and insomnia secondary to another medical or psychiatric disorder. When present, such comorbidities only need to be listed, but there is no requirement to make a causal attribution to determine whether insomnia is primary or secondary. This marked departure from previous nosology was based on increasing evidence that (a) symptoms and clinical features often overlap in primary and secondary insomnia, (b) when insomnia is comorbid with another disorder (e.g., major depression), it is often difficult to determine which condition is the cause and which is the consequence, (c) the direction of this relationship may change over time, and (d) treatment outcome is superior when treating both conditions concurrently than treating either alone.

While the DSM nosology has always recognized only one form of primary insomnia, the ICSD used to distinguish among different subtypes, up to the recent edition of ICSD-3. Psychophysiological insomnia, the most common subtype, is presumed to result from conditioned arousal, which is more likely to develop among individuals with an increased psychological and biologic predisposition to insomnia. The sleep of individuals with psychophysiological insomnia is more sensitive to daily stressors and is characterized by extensive night-to-night variability [17]. Paradoxical insomnia involves a genuine complaint of poor sleep that is not corroborated by objective findings. A patient may perceive very little sleep (e.g., 2–3 h per night), whereas PSG recordings show normal or near-normal sleep duration and quality. This condition is not the result of an underlying psychiatric disorder or of malingering, but it is likely to be mediated by psychological and cognitive (information processing) variables influencing the perception of sleep and wakefulness. To some degree, all insomniacs tend to overestimate the time it takes them to fall asleep and to underestimate the time they actually sleep. In paradoxical insomnia, however, the subjective complaint of poor sleep is disproportionate to objective findings. Thus, this condition may represent the far end of a continuum of individual differences in sleep perception. Idiopathic (childhood) insomnia presents an insidious onset during childhood, unrelated to psychological trauma or medical disorders, and is very persistent throughout the adult life. It does not present the variability observed with other forms of primary insomnia. Despite their heuristic value, these insomnia phenotypes have also been abandoned in ICSD-3 nosology, primarily for reasons of simplicity, lack of validity of these phenotypes, and, more important, the desire to harmonize criteria with the DSM-5 classification.

Polysomnographic (PSG) Findings

Polysomnographic (PSG) evaluation of self-defined insomniacs reveals more impairments of sleep continuity parameters (i.e., longer sleep latencies, more time awake after sleep onset, and lower sleep efficiency) and reduced total sleep time compared to self-defined good sleepers [18–20]. Sleep architecture shows increased amount of stage 1, reduced slow-wave sleep, and more frequent stage shifts through the night. A recent meta-analysis has also suggested that rapid eye movement (REM) sleep amount is decreased [20]. Notably, sleep disturbances recorded in primary insomniacs are similar to those observed in patients with generalized anxiety disorder or some affective disorders such as dysthymia [18, 19, 21], perhaps suggesting a common underlying thread to these conditions. In addition, there is a significant overlap in the sleep patterns of subjectively defined insomniacs and good sleepers such that some insomniacs may show better objective sleep than good

sleepers and some good sleepers more sleep impairments than insomniacs; subjective reports of insomnia are often far worse than objective evidence of sleep abnormalities. Investigations of the microstructure of sleep reveal increased beta activity in primary insomniacs relative to healthy controls, both around the sleep-onset period, during non–REM (NREM) sleep and, in some studies, during REM sleep [22–25]. Spindle activity, which is thought to have a sleep-protective role, is not reduced in insomnia, however [24, 26]. These data are consistent with psychological findings of hypervigilance and a ruminative, worry-prone cognitive style among insomniacs.

Daytime Complaints and Neurobehavioral Findings

Most patients with insomnia complaints also report impairments of daytime functioning, involving fatigue, mood disturbances, and difficulties with attention and concentration, with memory, and with completion of tasks [27]. Patients may initially report excessive daytime sleepiness, but a closer investigation usually reveals mental and physical fatigue rather than true physiological sleepiness, which is more likely among patients with insomnia comorbid with another medical (e.g., pain) or sleep disorders (e.g., sleep-related breathing disorders). Insomniacs have trouble sleeping at night, in part because of a chronic state of hyperarousal, which may also interfere with the ability or propensity for sleep during the day.

Despite significant subjective complaints, objective evaluation of daytime performance usually reveals fairly mild and selective deficits (e.g., attention) on various neurobehavioral measures [28, 29]. In general, impairments on these measures are more strongly associated with subjective than with objective sleep disturbances. Individuals with insomnia tend to perceive their performance as more impaired relative to how they should perform and as more impaired than that of normal controls. Discrepancies between subjective and objective performances are similar to those observed between subjective and objective measures of sleep, which may reflect a generalized faulty appraisal of sleep and daytime functioning among individuals with insomnia [30].

Course and Prognosis

The onset of insomnia can occur at any time in life, but the first episode is more common in young adulthood. It is often precipitated by stressful life events, such as marital separation, occupational or family stress, and interpersonal conflicts [31]. In a small subset of cases (e.g., idiopathic insomnia), insomnia begins in childhood, in the absence of psychological or medical problems, and persists throughout adulthood. Insomnia is a common problem among women during menopause and often persists even after other symptoms (e.g., hot flashes) have resolved with hormonal replacement therapy. Insomnia may also have a late-life onset, which needs to be distinguished from normal (age-related) changes in sleep; such late-life onset is often associated with other health-related problems.

Potential risk factors for insomnia include demographic factors (e.g., female gender and advancing age), psychological factors (e.g., a worry-prone cognitive style), hyperarousal, and a personal or familial history of insomnia. For most individuals, insomnia is transient in nature, lasting a few days, and resolving itself once the initial precipitating event has subsided. For others, perhaps those more vulnerable to sleep disturbances, insomnia may persist long after the initial triggering event has disappeared; other factors would then perpetuate sleep disturbances [32]. The course of insomnia may also be intermittent, with repeated brief episodes of sleep difficulties following a close association with the occurrence of stressful events. Longitudinal studies have shown that chronicity rates may range from 45 to 75 % for follow-ups of one to seven years [33–35]. Even in chronic insomnia, there is often extensive night-to-night variability in sleep patterns, with an occasional restful night's sleep intertwined with several nights of poor sleep [17]. The type of sleep difficulties (i.e., sleep-onset or maintenance insomnia) may also change over time. The prognosis for insomnia varies across individuals and is probably mediated by a combination of biologically related predisposing factors and psychological and behavioral perpetuating factors. It may also be complicated by the presence of comorbid psychiatric or medical disorders.

Etiology and Pathophysiology

Insomnia is most likely multifactorial in nature, but its precise etiology is not known. Hyperarousal is a central feature of insomnia, but it is not entirely clear whether this is a state that is conditioned to sleep-related stimuli or a more enduring trait present throughout the 24-h period. It is likely that both biologic and psychological factors contribute to increased arousal and interference with normal initiation and maintenance of sleep.

Biologic basis. Evidence of hyperarousal in insomnia is derived primarily from cross-sectional studies using different physiological, hormonal, and EEG markers (see Bonnet and Arand [36]; and Rieman et al. [37] for reviews). For instance, numerous studies have reported increased body temperature, galvanic skin response, heart rate, and metabolic rate, both near-sleep onset and during sleep, among

individuals with insomnia relative to healthy good sleepers. Investigations using quantitative EEG techniques and event-related potential (ERP) studies have also shown increased high-frequency (beta) activity during sleep (see "Polysomnographic Findings" above), higher amplitude of waking P300 responses [38], and evidence of decreased inhibition and/or increased sensitivity in response to auditory stimuli in insomnia [36, 37, 39]. Neuroendocrine studies have yielded more mixed results, with some findings suggesting increased cortisol and adrenocorticotropic hormone levels during sleep and throughout the 24-h period [40, 41] and other findings failing to reveal significant differences between insomniacs and good sleepers [42].

Neuroimaging studies have suggested possible structural and functional brain abnormalities in insomnia [43]. A positron-emission tomography (PET) study showed increased cerebral glucose metabolic rates during wakefulness and NREM sleep in insomniacs compared to healthy controls [44]. Insomnia patients also exhibited smaller declines in glucose metabolism from wakefulness to sleep in wake-promoting brain areas such as the ascending reticular activating system. Another small magnetic resonance imaging (MRI) study has shown reduced hippocampal volumes in primary insomniacs relative to health controls [45], although this was not replicated in other studies [43]. Others have reported correlations between loss of orbitofrontal gray matter and early morning awakening [46], and loss of prefrontal cortex gray matter and insomnia severity and wakefulness after sleep onset as well as pericentral cortex gray matter loss and sleep latency [47]. On the other hand, another study of insomnia subjects did not find any significant abnormalities in gray or white matter volumes in comparison with normal subjects [48]. Functional MRI studies during waking have suggested hypoactivation of cortical areas in response to tasks, and some spectroscopy studies have demonstrated reduced GABA levels in cortical areas [43]. Further studies will be needed to clarify whether specific structural or functional brain abnormalities are associated with insomnia.

Psychological basis. Psychological and behavioral factors also play an important role in the development and maintenance of insomnia as evidenced by higher levels of presleep cognitive arousal (e.g., intrusive thoughts and worries) and general psychological reactivity among individuals with insomnia relative to good sleepers. Chronic exposure to stress may also contribute to trigger or exacerbate insomnia, although some findings also suggest that sleep disturbance is more the result of reduced ability to cope with daily stressors, combined with increased cognitive arousal at bedtime, rather than from stress alone [49].

Learning and conditioning are also involved in the maintenance or exacerbation of sleep disturbances. The discomfort associated with insomnia can lead to a negative association between temporal (bedtime) and environmental (bed/bedroom) stimuli previously associated with sleep and, over time, the combination of maladaptive sleep habits (e.g., excessive amounts of time spent in bed) and sleep-related cognitive factors (e.g., worry about the consequences of insomnia and excessive self-monitoring) may exacerbate or perpetuate what might otherwise have been a transient sleep problem [50, 51].

Although it remains unclear whether hyperarousal is a direct cause, a by-product, or a consequence of insomnia, it is a central feature in the pathophysiology of insomnia [36, 37]. Along with a reduced homeostatic sleep drive, it is likely to arise from the interaction of biologically based predisposing factors and psychologically based exacerbating factors.

Evaluation of Insomnia

Clinical and Laboratory Evaluations

The diagnosis of insomnia is derived primarily from a detailed clinical evaluation of the patient's subjective complaint (see Table 37.2). The sleep history should cover the type of complaint (initial, middle, late insomnia), its duration (acute vs. chronic), and course (recurrent, persistent); typical sleep schedule; functional analysis of precipitating, perpetuating, and alleviating factors; perceived consequences and functional impairments; and the presence of medical, psychiatric, or environmental contributing factors. A complete history of alcohol and drug use and prescribed and over-the-counter medications is also essential [52–54].

The use of a sleep diary is essential in the evaluation of insomnia (see Table 37.3). A daily sleep diary is very helpful to document the nature and severity of insomnia, identify behavioral and scheduling factors that may perpetuate insomnia, and monitor treatment compliance and progress [55]. The *Insomnia Severity Index* [56] is a brief questionnaire that provides a global measure of the patient's perception of insomnia severity and its impact on daytime functioning (see Table 37.4). Several additional measures of insomnia symptoms, fatigue, anxiety, and depressive symptomatology may also provide useful complementary information in the evaluation of insomnia [53]. A more comprehensive psychological evaluation may be necessary for patients with suspected psychiatric disorders.

Although polysomnography is not indicated for the routine evaluation of insomnia, it is often necessary to rule out other sleep disorders that might contribute to the insomnia complaint (e.g., periodic movements during sleep and sleep apnea) [57]. PSG can also be particularly useful in suspected case of paradoxical insomnia or when a patient is unresponsive to treatment. The role of actigraphy in insomnia

Table 37.2 Evaluation of insomnia

- Nature of the complaint—difficulties falling or staying asleep, early morning awakening
- Daytime symptoms—fatigue, mood disturbances, attention/concentration problems
- Clinical significance—frequency, severity, duration of sleep difficulties
- Onset and course of insomnia
- Typical sleep-wake schedule (weekdays, weekends)
- Sleeping environment (noise, light, temperature)
- Functional analysis—evening activities, prebedtime rituals, triggers of nocturnal and morning awakenings (pain, noise); behavioral responses to insomnia
- Perpetuating/exacerbating (worries about sleep loss, daytime napping, excessive amounts of time in bed)
- Beliefs about sleep requirement expectations and consequences of poor sleep
- Use of sleeping aids/substances (caffeine, alcohol, drugs)
- Other medical problems
- Recent life events contributing to insomnia
- Symptoms of other psychiatric disorders (anxiety, depression)
- Symptoms of other sleep disorders (restless legs syndrome, sleep apnea)
- Previous treatment for insomnia and outcome

Table 37.3 Sleep diary

Name: _____

Week: _____ to _____

	Example	Mon	Tue	Wed	Thu	Fri	Sat	Sun
1. Yesterday, I napped from ___ to ___ (note the times of all naps)	1:50 to 2:30							
2. Yesterday, I took ___ mg of medication and/or ___ oz ___ of alcohol as sleep aid								
3. Last night, I went to bed and turned the lights off at ___ o'clock	11:15							
4. After turning the lights off, I fell asleep in ___ min	40 min							
5. My sleep was interrupted ___ times (specify number of nighttime awakenings)	2							
6. My sleep was interrupted for ___ minutes (specify duration of each awakening)	10 45							
7. This morning, I woke up at ___ o'clock (note time of last awakening)	6:15							
8. This morning, I got out of bed at ___ o'clock (specify the time)	6:40							
9. When I got up this morning I felt ___ (1 = exhausted 2 = fair 3 = refreshed)	2							
10. Overall, my sleep last night was ___ (1 = restless 2 = fair 3 = very sound)	3							

From [185]

evaluation and treatment monitoring is not well established. Although it may represent a useful adjunct, actigraphy is not clinically indicated for routine assessment, diagnosis, or management of insomnia. Nonetheless, it is useful for examining night-to-night variability and for identifying individuals with circadian rhythm disorders. It has also been used to document treatment adherence and outcome in clinical trials of behavioral therapies for insomnia [58]. Although a potentially useful complement to self-report and PSG measures, actigraphy devices and algorithms are not all equivalent and there may be significant variability in the reliability and validity of sleep-wake data derived from different devices.

Table 37.4 Insomnia severity index

Insomnia Severity Index (ISI)

For each question below, please circle the number corresponding most accurately to your sleep patterns in the **LAST MONTH.**

For the first three questions, please rate the **SEVERITY** of your sleep difficulties.

1. Difficulty falling asleep:

None	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

2. Difficulty staying asleep:

None	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

3. Problem waking up too early in the morning:

None	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

4. How **SATISFIED**/dissatisfied are you with your current sleep pattern?

Very Satisfied	Satisfied	Neutral	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. To what extent do you consider your sleep problem to **INTERFERE** with your daily functioning (e.g., daytime fatigue, ability to function at work/daily chores, concentration, memory, mood).

Not at all Interfering	A Little Interfering	Somewhat Interfering	Much Interfering	Very Much Interfering
0	1	2	3	4

6. How **NOTICEABLE** to others do you think your sleeping problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little Noticeable	Somewhat Noticeable	Much Noticeable	Very Much Noticeable
0	1	2	3	4

7. How **WORRIED**/distressed are you about your current sleep problem?

Not at all	A Little	Somewhat	Much	Very Much
0	1	2	3	4

Guidelines for scoring/interpretation:

Add scores for all seven items = _____
Total score ranges from 0 to 28
0–7 = No clinically significant insomnia
8–14 = Subthreshold insomnia
15–21 = Clinical insomnia (moderate severity)
22–28 = Clinical insomnia (severe)
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Treatment

The first step in treating insomnia is to identify and remove the contributing factors. General sleep hygiene recommendations are also useful as preventative strategies. Then, insomnia-specific therapies include psychological and behavioral interventions, medications, and a variety of complementary and alternative therapies (e.g., acupuncture, yoga, and herbal therapies). The rest of this chapter focuses on psychological/behavioral and pharmacological therapies; most of the alternative therapies have not been evaluated adequately with regard to their efficacy and safety in the management of insomnia.

Psychological and Behavioral Therapies

Treatment goals and indications. Psychological and behavioral therapies for insomnia include sleep restriction, stimulus control therapy, relaxation-based interventions, cognitive strategies, sleep hygiene education, and combined cognitive behavioral therapy. A summary of those interventions is provided below and in Table 37.5; more extensive descriptions are available in other sources [52, 59]. The main objectives of psychological and behavioral approaches are to alter factors that perpetuate or exacerbate sleep disturbances. Such features may include hyperarousal, sleep scheduling factors, poor sleep habits, and misconceptions about sleep and the consequences of insomnia. Although numerous factors can precipitate insomnia, when it becomes a persistent problem, psychological and behavioral factors are almost always involved in perpetuating it over time, hence the need to target those factors directly in treatment. The primary indication for behavioral treatment is in the management of persistent insomnia, with evidence available for both primary and comorbid insomnia.

Sleep restriction. Poor sleepers often increase their time in bed in a misguided effort to provide more opportunity for sleep, a strategy that is more likely to result in fragmented and poor quality sleep. Sleep restriction consists of curtailing the amount of time spent in bed to the actual amount of sleep [60]. For example, if a person reports sleeping an average of 6 h per night out of 8 h spent in bed, the initial sleep window (i.e., from initial bedtime to final arising time) would be set at 6 h. Subsequent adjustments to this "sleep window" are based on sleep efficiency (SE) for a given period of time (usually the preceding week); time in bed is increased by about 20 min for a given week when SE exceeds 85 %, decreased by the same amount of time when SE is lower than 80 %, and kept stable when SE falls between 80 and 85 %. Periodic (weekly) adjustments are made until optimal sleep duration is achieved. Changes to the prescribed sleep window can be made at the beginning of the night (i.e., postponing bedtime), at the end of the sleep period (i.e., advancing arising time), or at both ends. To prevent excessive daytime sleepiness, time in bed should not be reduced to less than 5 h per night in bed. This procedure leads to improvements of sleep continuity through a mild sleep deprivation and reduction of sleep anticipatory anxiety. Due to potential residual daytime sedation, sleep restriction should be used with caution with patients operating heavy equipment or required to drive long distances [61]. Sleep restriction is contraindicated in patients with a bipolar disorder, with seizures, or with some parasomnias (sleep walking, night terrors).

Stimulus control therapy. Individuals with insomnia may develop apprehension around bedtime and come to associate the bedroom with frustration and arousal rather than with sleep. Stimulus control therapy [62] consists of a set of instructions designed to strengthen the association between temporal (bedtime) and environmental (bed and bedroom)

Table 37.5 Psychological and behavioral treatments for insomnia disorder

Therapy	Description
Stimulus control therapy	A set of instructions designed to strengthen the association between the bed/bedroom with sleep and to re-establish a consistent sleep-wake schedule: (1) Go to bed only when sleepy; (2) get out of bed when unable to sleep; (3) use the bed/bedroom for sleep only (no reading, watching TV, etc.); (4) arise at the same time every morning; and (5) no napping
Sleep restriction therapy	A method designed to restrict time spent in bed as close as possible to the actual sleep time, thereby producing mild sleep deprivation. Time in bed is then gradually increased over a period of few days/weeks until optimal sleep duration is achieved
Relaxation training	Clinical procedures aimed at reducing somatic tension (e.g., progressive muscle relaxation and autogenic training) or intrusive thoughts (e.g., imagery training and meditation) interfering with sleep. Most relaxation requires some professional guidance initially and daily practice over a period of a few weeks
Cognitive therapy	Psychotherapeutic method aimed at reducing worry and changing faulty beliefs and misconceptions about sleep, insomnia, and daytime consequences. Other cognitive strategies can also be used to control intrusive thoughts at bedtime and reduce excessive monitoring of the daytime consequences of insomnia
Sleep hygiene education	General guidelines about health practices (e.g., diet, exercise, and substance use) and environmental factors (e.g., light, noise, and temperature) that may promote or interfere with sleep. This may also include some basic information about normal sleep and changes in sleep patterns with aging
Cognitive behavioral therapy (CBT)	A combination of any of the above behavioral (e.g., stimulus control, sleep restriction, and relaxation) and cognitive procedures

stimuli and rapid sleep onset and to establish a regular circadian sleep-wake rhythm. These instructions are as follows: (a) going to bed only when sleepy, (b) getting out of bed when unable to sleep (e.g., after 20 min), going to another room, and returning to bed only when sleep is imminent; (c) curtailing all sleep-incompatible activities (i.e., no TV watching and problem solving in bed); (d) arising at a regular time every morning regardless of the amount of sleep the night before; and (e) avoiding daytime napping. Despite the straightforward nature of these recommendations, the main challenge for most patients is to comply with all of them, which is essential to reverse the conditioning processes perpetuating insomnia. Caution is advised in using some of these procedures (e.g., getting out of bed when unable to sleep) with the frail elderly who may be at risk for falls.

Relaxation-based interventions. Relaxation is probably the most commonly used nondrug therapy for insomnia. Some relaxation methods (e.g., progressive muscle relaxation) focus primarily on reducing somatic arousal (e.g., muscle tension), whereas attention-focusing procedures (e.g., imagery training and meditation) target mental arousal in the forms of worries or intrusive thoughts. Mindfulness-based stress reduction [63] is another relaxation variant, and all these methods are fairly equivalent in terms of efficacy for insomnia. The most critical issue is to practice diligently and daily the selected method for at least two to four weeks. Professional guidance is often necessary in the initial phase of training.

Cognitive therapy. This psychotherapeutic method seeks to alter dysfunctional sleep cognitions (e.g., beliefs and expectations) and maladaptive cognitive processes (e.g., excessive self-monitoring) through Socratic questioning and behavioral experiments. The basic premise of this approach is that appraisal of a given situation (sleeplessness) and excessive monitoring of sleep-related cues (e.g., fatigue and time left for sleep) can trigger an emotional response (fear, anxiety) that is incompatible with sleep. For example, when a person is unable to sleep at night and worries about the possible consequences of sleep loss on the next day's performance, this can set off a spiral reaction and feed into the vicious cycle of insomnia, emotional distress, and more sleep disturbances. Cognitive therapy is designed to identify dysfunctional cognitions and reframe them into more adaptive substitutes in order to short-circuit the self-fulfilling nature of this vicious cycle. Treatment targets may include unrealistic expectations ("I must get my 8 h of sleep every night") and amplification of the consequences of insomnia ("Insomnia may have serious consequences on my health") [52]. Cognitive therapy is particularly useful to modify these maladaptive cognitions and to teach patients more adaptive skills to cope with insomnia [64].

Sleep hygiene education. Sleep hygiene education is intended to provide information about lifestyle (diet, exercise, substance use) and environmental factors (light, noise, temperature) that may either interfere with or promote better sleep. Sleep hygiene guidelines include (a) avoiding stimulants (e.g., caffeine), several hours before bedtime; (b) avoiding alcohol around bedtime as it fragments sleep; (c) exercising regularly (especially in late afternoon or early evening) as it may deepen sleep; (d) allowing at least a 1-h period to unwind before bedtime; and (e) keeping the bedroom environment quiet, dark, and comfortable. In addition to these guidelines, it is useful to provide basic information about normal sleep, individual differences in sleep needs, and changes in sleep physiology over the course of the life span. This information is particularly useful to help some patients distinguish clinical insomnia from short sleep or from normal (age-related) sleep disturbances. Although inadequate sleep hygiene is rarely the primary cause of insomnia, it may potentiate sleep difficulties caused by other factors or interfere with treatment progress. Addressing these factors should be an integral part of insomnia management, even though it is rarely sufficient for more severe insomnia, which often requires more directive and potent behavioral interventions.

Multicomponent therapies. Despite some unique features, the interventions described above can be effectively combined together. There is a general preference among investigators and clinicians for combining multiple interventions, with cognitive behavioral therapy (CBT) becoming the standard approach in the field [58]. The most common combination involves a behavioral (stimulus control, sleep restriction, and, sometimes, relaxation), a cognitive, and an educational (sleep hygiene) component, usually referred to as CBT. Such combination is often preferred to address the different components presumed to perpetuate insomnia.

Outcome Evidence

Evidence for efficacy. Several meta-analyses [65–67] and systematic reviews commissioned by the American Academy of Sleep Medicine [58, 68] have summarized the findings from clinical trials evaluating the efficacy of psychological and behavioral therapies for persistent insomnia. Evidence from these sources shows that treatment produces reliable changes in several sleep parameters, including sleep-onset latency (effect sizes ranging from 0.41 to 1.05), number of awakenings (0.25–0.83), duration of awakenings (0.61–1.03), total sleep time (0.15–0.49), and sleep quality ratings (0.94–1.14). Based on Cohen's criteria, the magnitude of those therapeutic effects is large (i.e., $d > 0.8$) for sleep latency and sleep quality and moderate (i.e., $d > 0.5$) for other sleep parameters. When transformed into a

percentile rank, these data indicate that approximately 70–80 % of patients with insomnia achieve a therapeutic response with psychological and behavioral therapies.

In terms of absolute changes, treatment reduces subjective sleep-onset latency and time awake after sleep onset from averages of 60–70 min at baseline to about 35 min at post-treatment, and total sleep time is increased by 30 min, from 6 to 6.5 h after treatment. Thus, for the average insomnia patient, treatment effects may be expected to reduce sleep latency and time awake after sleep onset by about 50 % and to bring the absolute values of those sleep parameters below or near the 30-min cutoff criterion initially used to define insomnia. Treatment effects are similar for sleep-onset and sleep-maintenance problems, although fewer studies have targeted early morning awakening problems. Overall, findings from meta-analyses represent fairly conservative estimates of treatment effects as they are based on averages computed across all nonpharmacological interventions and insomnia diagnoses (i.e., primary and comorbid). On the other hand, although the majority of patients benefit from treatment, only about 40 % achieves clinical remission [58].

Treatment outcome has been documented primarily with prospective daily sleep diaries, although several studies have also complemented those findings with data from polysomnography [69–71] and with wrist actigraphy [72, 73]. In general, the magnitude of improvements is smaller on PSG measures, but those changes tend to parallel sleep improvements reported on daily sleep diaries. PSG findings indicate that treatment does not only alter sleep perception, as measured by patient-reported outcomes, but also produce objective changes on EEG sleep continuity measures. Except for a modest increase in stages 3–4 following sleep restriction, there is little evidence of changes in sleep architecture with psychological and behavioral treatment. In addition to improving sleep continuity parameters, there is also some evidence showing improvements on several secondary endpoints including measures of daytime fatigue, quality of life, and psychological symptoms [58, 73].

Long-term outcomes. A fairly robust finding across behavioral treatment studies is that sleep improvements are well maintained over time, with data available up to 24 and even 36 months after treatment completion. Although interventions that restrict the amount of time spent in bed may yield only modest increases (and even a reduction) of sleep time during the initial treatment period, this parameter is usually improved at follow-ups, with total sleep time often exceeding 6.5 h. Long-term outcome must be interpreted cautiously, however, as few studies report long-term follow-ups and, among those that do, attrition rates increase over time. In addition, a substantial proportion of those patients with chronic insomnia who benefit from short-term therapy may remain vulnerable to recurrent episodes of insomnia in the long term. As such, there is a need to develop and evaluate the effects of long-term maintenance therapies to prevent or minimize the occurrence of those episodes.

Treatment of Comorbid Insomnia. Insomnia is often a pervasive problem among patients suffering from other medical and psychiatric conditions [74]. Although sleep may improve with appropriate treatment of the comorbid condition, sleep disturbances are also likely to persist. Thus, the presence of a comorbid medical or psychiatric disorder should not preclude using a behavioral intervention concomitantly as behavioral factors are often involved in perpetuating or even exacerbating the sleep problem. Evidence from small clinical trials [75, 76] suggests that patients with medical and psychiatric conditions can also benefit from insomnia-specific treatment [77]. Controlled studies have also shown that behavioral treatment is effective for insomnia associated with chronic pain [78], fibromyalgia [79], cancer [80, 81], and various medical conditions in older adults [82, 83]. In general, insomnia symptoms are more severe among patients with comorbid disorders, but the absolute changes on those outcomes during treatment are comparable to those obtained with primary insomnia.

Insomnia in older adults is more likely to be comorbid with another medical or another sleep disorder than to be primary in nature. Recent studies have shown that older adults respond to insomnia treatment, particularly when they are screened for other sleep disorders that increase in incidence in older age (e.g., restless legs syndrome and sleep apnea). A meta-analysis [84] suggested that effect sizes were comparable (moderate to large) for middle-aged and older adults on subjective measures of sleep latency, wake after sleep onset, and sleep quality. Older adults with either comorbid medical or psychological conditions can benefit from sleep-specific treatment [82, 83, 85, 86]. Three clinical trials have shown that a supervised and time-limited withdrawal program, with or without behavioral treatment for insomnia, can facilitate discontinuation of hypnotics among older adults with insomnia who are prolonged users [87–89].

Which insomnia therapies work best? Although there has been no complete dismantling of cognitive behavioral therapies to isolate the relative efficacy of each component, direct comparisons of some of those components indicate that sleep restriction, alone or combined with stimulus control therapy, is more effective than relaxation which, in turn, is more effective than sleep hygiene education alone [58]. Sleep restriction tends to produce better outcome than stimulus control for improving sleep efficiency and sleep continuity, but it also decreases total sleep time during the initial intervention. Although some basic education about sleep hygiene is incorporated to most insomnia treatments, sleep hygiene education produces little impact on sleep when used as the only intervention. A recent study has

shown that cognitive therapy alone can be effective in the management of insomnia [64].

There is no strong evidence that a multicomponent approach is more effective than any of its single component. However, the appeal for this multimodal approach may come from the fact that it addresses different facets presumed to perpetuate sleep disturbances. While little information is available about the active treatment mechanisms of cognitive behavioral therapy, some evidence suggests that stimulus control and sleep restriction are particularly effective for improving sleep continuity, whereas changes in sleep-related cognitions are associated with better maintenance of sleep changes over time [90]. With increasing evidence that hyperarousal is implicated in primary insomnia, there is a need for greater attention to identify the biologic as well as psychological mechanisms responsible for sleep changes.

Combined Behavioral and Pharmacological Approaches

Behavioral and pharmacological therapies can play a complementary role in the management of insomnia. No single treatment is effective with all forms of insomnia or acceptable to all patients. Even among treatment responders, few patients reach complete remission and some residual sleep disturbances often persist even after treatment. Thus, combined approaches should theoretically optimize outcome by capitalizing on the more immediate and potent effects of hypnotics and the more sustained effects of behavioral interventions.

Only a few studies have directly compared the effects of behavioral and pharmacological therapies for insomnia. Three studies compared triazolam to relaxation [91, 92] or sleep hygiene [93], and five investigations compared CBT to temazepam [68], zolpidem [71, 94], or zopiclone [95, 96]. Collectively, findings from these studies indicate that both therapies are effective in the short term, with medication producing faster results in the acute phase (first week) of treatment, whereas both treatments are equally effective in the short-term interval (4–8 weeks). Combined interventions appear to have a slight advantage over single-treatment modality during the initial course of treatment, but it is unclear whether this advantage persists over time. Long-term effects are consistent for the single-treatment modalities; patients treated with CBT maintain their improvements, whereas therapeutic effects are typically lost after discontinuation of medication. Long-term effects of combined interventions are more equivocal. Some studies indicate that a combined intervention (i.e., triazolam plus relaxation) produces more sustained benefits than medication alone [91, 92], whereas others report more variable long-term outcomes [69, 93]. Some patients retain their initial sleep improvements, but others return to their baseline values. As behavioral and attitudinal changes are often essential to sustain sleep improvements, patients' attributions of the initial benefits may be critical in determining long-term outcomes. Attribution of therapeutic benefits to the hypnotic alone, without integration of self-management skills, may place a patient at greater risk for recurrence of insomnia once medication is discontinued. Thus, despite the intuitive appeal of combining behavioral and medication therapies, it is not entirely clear when, how, and for whom it is indicated to combine these treatment modalities for insomnia. Additional research is needed to evaluate the effects of combined treatments and to examine optimal methods for integrating these therapies.

Comparisons of effect sizes from meta-analyses [65, 67, 97] on different sleep variables indicate that behavioral therapy may have a slight advantage on measures of sleep-onset latency and sleep quality and pharmacotherapy (benzodiazepine receptor agonists), a more favorable outcome on total sleep time. One study examined different sequences of CBT and medication therapies [96]. The best results were obtained when CBT was introduced first in the sequence, but medication was found helpful to improve total sleep time, which may be an important advantage given that one component of CBT (i.e., sleep restriction) reduces total sleep time during the initial course of therapy and could lead some patients to premature therapy discontinuation.

Until more evidence-based treatment guidelines become available, several strategies can be considered for selecting the most appropriate treatment in the clinical management of insomnia. The use of hypnotic medication may be particularly indicated in the initial stage of therapy to break the vicious cycle of insomnia and to provide some rapid relief. On the other hand, CBT is essential to alter perpetuating factors and to teach coping skills. As such, it is an essential treatment component to maximize durability of sleep improvements. Ideally, medications should be discontinued, under supervision, after an initial treatment course of a few weeks. However, given that insomnia may be a recurrent problem, even among those who benefit from treatment initially, it may be necessary to use medications intermittently after the initial acute treatment.

Pharmacotherapy (See also Chap. 55 [Monti])

Several different classes of medications are used for insomnia (Table 37.6), including both over-the-counter (OTC) and prescription agents; however, many of these are not approved by the US Food and Drug Administration (FDA) for the treatment of insomnia. Current FDA-approved insomnia medications include a group of benzodiazepine receptor agonists (BZRAs), one melatonin receptor agonist (ramelteon), and one tricyclic antidepressant (doxepin). Although not FDA-approved for the treatment of insomnia,

Table 37.6 Drugs used to promote sleep

Benzodiazepine receptor agonists					
Drug	Dose range	Dose in the elderly	Half-life (h)	Effects on sleep	Side effects
Benzodiazepines					
Estazolam	1–2 mg	0.5 mg	10–24	Total sleep time: ↑ Sleep latency: ↓ WASO: ↓ Stage 1 %: ↓ Stage 2 %: ↑ Slow-wave sleep %: ↓ REM %: ↓ REM latency: ↑	Dizziness, drowsiness, hypokinesia, abnormal coordination, amnesia, GI symptoms
Flurazepam	15–30 mg	15 mg	47–100		Dizziness, drowsiness, light-headedness, staggering, ataxia, amnesia, increased risk of falling, GI symptoms
Quazepam	7.5–15 mg	7.5 mg	For quazepam and 2-oxoquazepam, 25–41; *N*-desakyl-1-oxoquazepam, 70–75		Dizziness, drowsiness, dyskinesia, slurred speech, amnesia, GI symptoms
Temazepam	7.5-30 mg	7.5 mg	6–16 (2)		Drowsiness, dizziness, light-headedness, difficulty with coordination, amnesia, GI symptoms
Triazolam	0.25–0.5 mg	0.125–0.25 mg	1.5–5.5		Drowsiness, dizziness, light-headedness, coordination disorders/ataxia, amnesia
Nonbenzodiazepines					
Eszopiclone	2–3 mg	1–2 mg	5–5.8	Sleep latency: ↓ WASO: ↓	Unpleasant taste, dry mouth, dizziness, drowsiness, amnesia, GI symptoms
Zaleplon	10–20 mg	5–10 mg	1	Sleep latency: ↓	Dizziness, headache, GI symptoms, myalgia, drowsiness, amnesia Drowsiness, dizziness, amnesia, GI symptoms
Zolpidem	5[a]–10 mg	5 mg	1.4–4.5	Sleep latency: ↓ WASO during first 6 h: ↓	
Zolpidem CR	6.25[a]–12.5 mg	6.25 mg	1.6–3.6	Sleep latency: ↓	
Zolpidem SL	1.75[a]–3.5 mg	1.75 mg	1.4–3.6	Sleep latency: ↓	
Indiplon	5–10 mg		1.25	Sleep latency: ↓	
Indiplon NR	15 mg			Sleep latency: ↓ WASO: ↓ Total sleep time: ↑	Drowsiness, dizziness

Melatonin receptor agonist					
Drug	Dose range	Dose in the elderly	Half-life (hours)	Effects on sleep	Side effects
Ramelteon	8 mg	8 mg	2.6	Sleep latency: ↓	Drowsiness, dizziness, fatigue
Antidepressants					
Doxepin	3–6 mg	3 mg	10–30	WASO: ↓ Total sleep time: ↑	Drowsiness At higher doses, drowsiness, dizziness, confusion, blurred vision, dry mouth, constipation, urinary retention, arrhythmias, orthostatic hypotension, and weight gain Exacerbation of restless legs, periodic limb movements, or REM sleep behavior disorder

Other Agents					
Antidepressants					
Drug	Dose range[a]	Dose in the elderly (1)	Half-life (hours)	Effects on sleep	Side effects
Amitriptyline	50–100 mg	20 mg	10–28, including the metabolite nortriptyline	Total sleep time: ↑ Sleep latency: ↓ Stage 2 %: ↑	REM %: ↓ REM latency: ↑ Drowsiness, dizziness, confusion, blurred vision, dry mouth, constipation, urinary

(continued)

Table 37.6 (continued)

Melatonin receptor agonist					
Drug	Dose range	Dose in the elderly	Half-life (hours)	Effects on sleep	Side effects
					retention, arrhythmias, orthostatic hypotension, weight gain. Exacerbation of restless legs, periodic limb movements or REM sleep behavior disorder
Mirtazapine	15–45 mg	7.5–15 mg	20–40	Total sleep time: ↑ Sleep latency: ↓ WASO: ↓	Drowsiness, dizziness, increased appetite, constipation, weight gain
Trazodone	150–400 mg	150 mg	7	Sleep latency: ↓ WASO: ↓ Slow-wave sleep %: ↑	Drowsiness, dizziness, headache, blurred vision, dry mouth, arrhythmias, orthostatic hypotension, priapism
Anticonvulsants					
Gabapentin	300–600 mg	300 mg	5–7	WASO: ↔ to ↓ Slow-wave sleep %: ↑	Drowsiness, dizziness, emotional lability, ataxia, tremor, blurred vision, diplopia, nystagmus, myalgia, peripheral edema
Tiagabine	4–8 mg	4 mg	7–9	WASO: ↓ Slow-wave sleep %: ↑	Drowsiness, dizziness, ataxia, tremor, new-onset seizures in patients without epilepsy, difficulty with concentration or attention, nervousness, asthenia, abdominal pain, diarrhea, nausea
Pregabalin	50–100 mg	25–50 mg	6	Sleep latency: ↓ Slow-wave sleep %: ↑	Drowsiness, dizziness, ataxia, confusion, peripheral edema
Antipsychotics					
Olanzapine	5–10 mg	5 mg	21–54	Sleep latency: ↔ to ↓ WASO: ↓ Slow-wave sleep %: ↑ REM %: ↔ to ↓	Drowsiness, dizziness, tremor, agitation, asthenia, extrapyramidal symptoms, dry mouth, dyspepsia, constipation, orthostatic hypotension, weight gain, new-onset diabetes mellitus
Quetiapine	25–200 mg	25 mg	6	Insufficient data	Drowsiness, dizziness, asthenia, dry mouth, dyspepsia, constipation, orthostatic hypotension, weight gain, new-onset diabetes mellitus
Over-the-counter agents					
Drug	Dose range[a]	Dose in the elderly	Half-life (h)	Effects on sleep	Side effects
Diphenhydramine	50 mg diphenhydramine chloride 76 mg diphenhydramine citrate	25 mg	2.4–9.3	Sleep latency: ↓ WASO: ↔ to ↓ Slow-wave sleep %: ↔ to ↑ REM %: ↓	Drowsiness, dizziness, dyskinesia, dry mouth, epigastric distress, constipation, tachycardia
Melatonin	Dosages not empirically determined	Dosages not empirically determined	0.5	Sleep latency: ↓	Concentration difficulty, dizziness, fatigue, headache, irritability

FDA-approved hypnotics
Listed are recommended maximum amounts for a single dose
[a]Recommended starting dose in women
GABA: gamma aminobutyric acid
WASO: wake after sleep onset
↔: no change
↑: increase
↓: decrease

sedating antidepressants have been prescribed widely; other classes of prescription medications used with increasing frequency for their potential sleep-inducing side effects include anticonvulsants and atypical antipsychotics.

There are a number of reasons for the widespread use of nonapproved medications for insomnia. Until the introduction of eszopiclone in 2005, FDA labeling for all BZRA hypnotics stated that they were indicated for the short-term treatment of insomnia, preferably not for more than a few weeks, and it was recommended that patients be re-evaluated if drugs were to be used longer. Since chronic insomnia typically lasts for years, this meant that those with chronic insomnia could only receive short-term treatment. In addition, concerns about tolerance, dependence, and abuse made physicians as well as patients reluctant to use these agents long term. Until the introduction of ramelteon in 2005, no FDA-approved hypnotics were nonscheduled. Antidepressants, anticonvulsants, and antipsychotics, in contrast, are nonscheduled substances and can be used long term. Furthermore, with the recognition that many insomnia patients have comorbid depression and/or anxiety, the use of an antidepressant might be appealing to treat the mood problem as well as the insomnia; the doses of antidepressants that are prescribed for insomnia, however, are almost always subtherapeutic for the treatment of depression. There is a relative lack of data showing that treatment of insomnia reduces any of its comorbidities, which is another possible barrier to the prescription of hypnotics; physicians may be discouraged from prescribing drugs that are perceived to have potential adverse effects.

More individuals with insomnia self-medicate than take prescription medications, and the fact that many individuals self-medicate for insomnia suggests that the disorder may be undertreated. Population-based studies have found that over 12- to 18-month periods, 10–13 % of people have used only alcohol to help them fall asleep and 10 % have used OTC agents alone, whereas only 5–8 % have used prescription medications [98, 99]. Polls by the National Sleep Foundation have found that 16–28 % of adults have used alcohol and 22–29 % have used OTC agents for sleep at some point during their lives [100, 101]. In general, patients who self-medicate with alcohol or OTC agents tend to do so for shorter periods of time and have less severe insomnia than those who take prescription medications [98].

Benzodiazepine Receptor Agonists

The current FDA-approved BZRAs for insomnia include the older benzodiazepines (estazolam, flurazepam, quazepam, temazepam, triazolam) and the newer nonbenzodiazepines (eszopiclone, zaleplon, zolpidem) (see Table 37.6). These medications all bind to the γ-aminobutyric acid (GABA) type A receptor complex. $GABA_A$ receptors are the predominant inhibitory receptors in the brain, and the binding of a BZRA leads to increased flow of negatively charged chloride ions into a neuron, making it less likely to fire an action potential. Benzodiazepines bind to all subtypes of $GABA_A$ receptors, whereas some of the newer nonbenzodiazepines, particularly zaleplon and zolpidem, bind preferentially to the type I $GABA_A$ receptor. This different pattern of receptor binding affinity may be associated with slight differences in clinical effects. The type I receptor is thought to mediate both the hypnotic and the amnestic effects of BZRAs, but drugs acting selectively on this receptor may be less effective as muscle relaxants or anxiolytics. Clinically, it is important to remember that all BZRAs have the potential to produce amnesia.

Benzodiazepines

Benzodiazepine hypnotics, with the exception of triazolam, have relatively long half-lives. Estazolam, flurazepam, quazepam, and temazepam all reduce latency to sleep onset and tend to improve sleep maintenance, as indicated by decreased waking time after sleep onset, reduced number of awakenings, and/or increased total sleep time [102–108]. Triazolam also promotes sleep onset, but, because of its short half-life, does not appear to be helpful for sleep maintenance [109–111]. Benzodiazepines decrease time spent in stage 1 sleep and increase stage 2 sleep, but they also tend to suppress slow-wave sleep and, possibly, REM sleep. Adverse effects of benzodiazepine hypnotics include daytime sedation, cognitive and psychomotor impairment, and memory impairment [105, 110]; such effects are more common with higher doses and longer-acting agents. Abrupt withdrawal may be associated with rebound insomnia with triazolam as well as the longer-acting agents [109, 112].

As noted earlier, benzodiazepine hypnotics are indicated for the short-term treatment of insomnia. None has been studied in a randomized clinical trial for more than 12 weeks [113], so that long-term efficacy data are not available.

Nonbenzodiazepines

The nonbenzodiazepine BZRAs include those with short half-lives (zaleplon and zolpidem) that are indicated primarily for promoting sleep onset and those with either a longer half-life (eszopiclone) or a controlled-release formulation (zolpidem MR) that reduce sleep latency and improve sleep maintenance. Zaleplon, with the shortest half-life of currently available agents at about 1 h, may be dosed as long as the patient has at least 4 h remaining in bed; 4–6 h after ingestion of 10 or 20 mg of zaleplon, healthy volunteers did not demonstrate next-day impairment in driving ability, memory, or psychomotor function [114]. Although 5 to 10 mg doses of zaleplon primarily promote sleep onset, a dose of 20 mg increases subjective total sleep time [115, 116].

Zolpidem is currently the most commonly prescribed sleep agent. It is effective in promoting sleep onset and also increases total sleep time at doses of 10 mg or greater in both subjective and sleep laboratory studies [117]. The increase in sleep efficiency and/or total sleep is likely due to reduced sleep latency, since consistent effects on waking time after sleep onset have not been observed. A 12-week, placebo-controlled study demonstrated that intermittent use (three to five times per week) of zolpidem was associated with continued benefit on the nights the drug was taken, and no obvious evidence of rebound insomnia on the nights it was not taken [118]. Zolpidem has also been shown to be effective in subjects with depression treated with selective serotonin reuptake inhibitors (SSRIs), resulting in subjective increased total sleep and improved sleep quality and daytime function [119]. Doses of 10 mg of zolpidem administered during the night did not lead to clinically significant effects on driving or psychomotor skills the next day, at least 4–6 h after ingestion, in healthy subjects or insomnia patients [114, 120], but higher doses produced significant impairment [114]. Zolpidem MR consists of a dual-layer tablet: a shell containing 7.5 mg of immediate-release zolpidem and a core containing 5 mg of zolpidem that is released in a delayed fashion for a total of 12.5 mg. There is also a 6.25-mg tablet containing 3.75 mg of immediate-release/2.5 mg of delayed-release zolpidem. The half-life of zolpidem MR remains short, but the duration of action is longer than that with zolpidem, as evidenced by decreased waking time during 3–6 h postingestion, presumably related to the higher blood levels. A double-blind, placebo-controlled multicenter study showed clinical efficacy with zolpidem MR at a dose of 12.5 mg for up to 6 months when taken for 3–7 nights per week, without significant rebound insomnia upon discontinuation [121]. Subjects who took medication reported shorter sleep-onset latencies, improved sleep maintenance, and evidence of better next-day function as indicated by subjective reports of improved concentration and decreased morning sleepiness. More recently, a sublingual formulation of zolpidem has been approved for use in the USA in 1.75 and 3.5 mg doses for the treatment of insomnia due to middle-of-the-night awakening; it may be taken when there is at least 4 h of time in bed remaining. In comparison with 10 mg of immediate-release zolpidem, ingestion of 3.5 mg of the sublingual preparation led to higher zolpidem plasma concentrations at 15 min and greater area under the curve (AUC) from 0 to 15 min [122]. A study comparing sublingual zolpidem with placebo for middle-of-the-night awakening in primary insomnia patients showed significant self-reported reductions in sleep latency, improvements in sleep quality, and improvements in morning alertness [123]. In January 2013, the US Food and Drug Administration issued a requirement that the recommended dosages for all forms of zolpidem be lowered because morning blood levels, particularly in women, could otherwise be high enough to cause impairment in activities that require alertness, such as driving.

Eszopiclone was the first hypnotic to be indicated for the treatment of insomnia without recommendations for restricted duration of use. It has a longer half-life than any of the other nonbenzodiazepines, which accounts for its effects on improving sleep maintenance. In a 6-month placebo-controlled clinical trial, it showed persistent efficacy in reducing latency to sleep onset, decreasing wakefulness during sleep, and increasing total sleep time, as subjectively reported [124]. In another 6-month double-blind study, eszopiclone was shown not only to reduce insomnia, but also to enhance quality-of-life measures and reduce reported work limitations [125]. It is also one of the first agents for which data suggest improved daytime function and/or decreased comorbidity from other disorders. Elderly insomnia patients taking 2 mg of eszopiclone reported reduced daytime napping [126], and depressed patients given a combination of fluoxetine plus eszopiclone had better sleep and higher rates of response and remission 8 weeks later in comparison with depressed patients given fluoxetine plus placebo [127].

Outcome Evidence

Efficacy of BZRAs

Several meta-analyses have assessed the efficacy of BZRA hypnotics in comparison with placebo in the treatment of chronic insomnia. In a review of studies done on adults less than 65 years of age, benzodiazepines and zolpidem were shown to produce significant subjective improvement in sleep latency, total sleep, number of awakenings, and sleep quality, with moderate effect sizes ranging from 0.56 to 0.71 [97]. A meta-analysis of studies performed on adults and elderly adults showed that benzodiazepines produced significant improvements in both subjective and objective sleep parameters; sleep latency was reduced by 4.2 min objectively and 14.3 min subjectively, and total sleep amount was increased by 61.8 min objectively and 48.4 min subjectively [105, 128]. Another analysis of drug effects in elderly insomnia patients showed significant improvement in sleep quality (effect size 0.14), increased total sleep (25.2 min), and decreased awakenings (effect size 0.63) with sedative use as compared with placebo [129]. A comparison of benzodiazepine hypnotics with nonbenzodiazepines concluded that zolpidem may show benefits over temazepam in terms of reducing sleep latency and improving sleep quality and over zaleplon in terms of increasing sleep duration and improving sleep quality [130]. Zaleplon, however, may produce less rebound insomnia than zolpidem. This analysis was limited, however, by the lack of comparative studies and short durations of the studies, which makes it difficult to

assess longer term effects. A more recent meta-analysis of data submitted to the US FDA showed that the BZRA hypnotics led to small but statistically significant reductions in both objective (polysomnographically measured) and subjective sleep latencies [131]. Sleep latency reductions were more likely to be found in studies that were published earlier, in studies with larger drug doses, in studies with younger patients and in female patients, and in studies using zolpidem.

BZRA Side Effects

A number of adverse outcomes have been associated with drugs in this class, whether benzodiazepines or nonbenzodiazepines. Sedation/daytime sleep "hangover" and impaired cognitive and psychomotor performance can be seen at peak blood levels and may occur the following day with longer-acting agents [132]. Anterograde amnesia, or loss of memory for events that occur after taking a hypnotic, is more common with higher doses and with drugs with rapidly increasing plasma levels (e.g., triazolam and the nonbenzodiazepines) or when BZRAs are used in combination with alcohol; confusional arousals or sleepwalking episodes may be a related phenomenon. BZRAs should therefore always be taken immediately prior to bedtime to minimize the risk of amnesia or parasomnias and discontinued in patients who report these side effects.

All medications used for sleep, including BZRAs but also antidepressants and anticonvulsants, can increase the risk of nighttime falls in elderly patients [133–135]. However, insomnia is an independent predictor of falls in the elderly [136], and a study has suggested that insomnia, but not hypnotic use, was associated with a greater risk of falls [137]. A recent Korean study assessing the risk of fractures in elderly insomnia patients found an increased risk of fracture associated with the use of zolpidem (adjusted odds ratio 1.72), but no statistically significant association between the use of benzodiazepine hypnotics and fracture [138]. Other side effects associated with BZRAs include tolerance, rebound insomnia, abuse, and withdrawal. Although concerns about tolerance are likely a factor for physicians and patients in avoiding or limiting the use of these agents, in fact the few longer term studies that have been performed with eszopiclone, zolpidem, and zaleplon have not shown evidence of obvious tolerance [118, 119, 125, 139]. Rebound insomnia, or the worsening of insomnia to a degree greater than baseline, is generally seen for not more than 1–2 days and not in all studies. Abuse of and dependence on BZRAs may occur in patients with histories of substance abuse, but the risk is generally overestimated for those without such histories; insomnia patients tend to show therapy-seeking, not drug-seeking, behavior [140]. Nevertheless, BZRAs should be avoided in those with tendencies to abuse substances.

An attempt to assess risks and benefits for BZRAs in the treatment of insomnia concluded that although these agents improved sleep, they also led to adverse effects in comparison with placebo [105, 128]; daytime drowsiness was increased by a 2.4 odds ratio and dizziness or light-headedness was increased by a 2.6 odds ratio. However, the increase in adverse events did not lead to increased rates of discontinuation of hypnotics. A study regarding the use of BZRAs in elderly insomnia patients, however, raised concerns that there were significant risks with both benzodiazepines and nonbenzodiazepines, including adverse cognitive events (4.78 times more common), adverse psychomotor events (2.61 times more common), and daytime fatigue (3.82 times more common) [129]. The authors concluded that in elderly patients, the risks of BZRAs might outweigh the benefits in some cases.

Indications and Limitations

The benzodiazepines zolpidem and zaleplon are indicated for "the short-term treatment of insomnia," whereas eszopiclone and zolpidem MR are indicated for "the treatment of insomnia," without language limiting duration of use. BzRAs should not be used during pregnancy (all are in FDA Pregnancy Category C) or in patients with histories of substance abuse. They should be used with caution in patients who have pulmonary or liver disease and in the elderly; dosage reductions at least are recommended in these populations. No hypnotics are approved for use in children under 18 years of age.

Melatonin and Melatonin Receptor Agonist

Melatonin, a hormone produced by the pineal gland, is available as an OTC preparation and has been widely used for insomnia and related sleep problems. Currently, ramelteon is the only melatonin receptor agonist approved by the FDA for the treatment of insomnia and is available by prescription. These agents presumably act through their effects on melatonin receptors in the suprachiasmatic nucleus in the brain, although their exact mechanism has not been determined.

Melatonin

Over-the-counter melatonin preparations are rapidly absorbed and have a short half-life (up to 1 h). They are not regulated by the FDA and are thus not approved for the treatment of insomnia. The hypnotic effects of melatonin appear to be relatively smaller in comparison with BZRAs; a meta-analysis concluded that the average decrease in sleep

latency was 4 min, total sleep time was increased by 12.8 min, and sleep efficiency increased by 2.2 % [141]. One study of melatonin for secondary insomnia and circadian rhythm disorders (i.e., jet lag and shift work) failed to find any significant differences in comparison with placebo, except for a slight increase (1.9 %) in sleep efficiency. Several studies, however, have demonstrated that low doses of melatonin (300–500 μg) were effective in producing phase shifts in normal subjects and entraining circadian rhythms in blind individuals [142–144]. A more recent meta-analysis of the efficacy of melatonin in primary sleep disorders, however, concluded that it reduced sleep latency (weighted mean difference (WMD) 7.06 min), increased total sleep time (WMD 8.25 min), and improved sleep quality; although these effects were statistically significant, they were generally smaller in magnitude than effects of prescription hypnotics [145]. Melatonin does not appear to have side effects other than sedation.

Ramelteon

Ramelteon is an agonist of melatonin type 1 (MT_1) and type 2 (MT_2) receptors and is structurally unrelated to melatonin; it does not show affinity for the GABA receptor complex or other receptors thought to be involved in sleep or wakefulness. It has a relatively short half-life (2.6 h), and its metabolite also acts as an MT_1/MT_2 agonist. The most robust effects of ramelteon on sleep are the reduction of latency to sleep onset, but it has also been reported to increase the total sleep time in some studies [146]; it does not appear to decrease wakefulness after sleep onset. Ramelteon is indicated for the treatment of insomnia characterized by difficulty with sleep onset. Its main side effects are somnolence, dizziness, and fatigue. Important distinctions from the BZRA class include no evidence of tolerance, withdrawal, rebound insomnia, cognitive or psychomotor impairment, or daytime sedation, and it is therefore not classified as a controlled substance by the FDA [147]. There are no data at present regarding its efficacy in treating circadian rhythm disorders.

A meta-analysis of ramelteon in chronic insomnia reported that it significantly reduced subjective and PSG-measured sleep latency and increased total sleep as measured by PSG, with no evidence of next-day residual effects [148]. Ramelteon may not be as efficacious for insomnia as some of the BZRAs in terms of the magnitude of sleep improvement, but other factors make it an attractive alternative for many patients: its low toxicity and wide safety margin; lack of many of the adverse effects associated with BZRAs; and its ability to be used in patients with substance abuse histories and a variety of medical disorders, including mild-to-moderate pulmonary disease. It should not be used in combination with fluvoxamine or other potent inhibitors of cytochrome P450 isozyme 1A2, since this leads to dramatically increased levels of ramelteon. It is not recommended for use in pregnant women (FDA Pregnancy Category C).

Warnings for Hypnotics

In 2007, the FDA introduced a change in labeling for hypnotics, including BZRAs and ramelteon, based on the reports of rare but potentially serious adverse events following ingestion of hypnotics (www.fda.gov/bbs/topics/NEWS/2007/NEW01587.html) [149]. These included severe allergic reactions and complex sleep-related behaviors, such as sleep driving, sleep eating, and sleep sex, in which individuals are engaged in these activities without fully awakening. Such reactions are more likely to occur when hypnotics are combined with other sedatives, including alcohol, or taken at higher-than-recommended doses.

Sedating Antidepressants

Despite a relative lack of data and no FDA indication for insomnia with the exception of low-dose doxepin, sedating antidepressants, such as the tricyclic antidepressants (TCAs), trazodone, and mirtazapine, are some of the most commonly used agents for treating chronic insomnia. In general, there are relatively few efficacy data regarding the use of these agents in primary insomnia.

Tricyclic Antidepressants

Amitriptyline and doxepin are some of the more commonly used TCAs in the treatment of insomnia [150]. Their therapeutic effects on depression are related to inhibition of serotonin (5-hydroxytryptamine [5-HT]) and norepinephrine reuptake, whereas their effects on sleep are probably mediated by their antagonistic effects on histamine type 1 (H_1), serotonin type 2 ($5HT_2$), and α-adrenergic type 1 receptors. Doxepin has the most potent antihistamine effects in this class and is approved for the treatment of insomnia in doses of 3 and 6 mg. In studies of adults and elderly subjects with insomnia, doxepin increased total sleep time and sleep efficiency, primarily by improving sleep maintenance later in the night [151, 152]. TCAs tend to have long half-lives, which often leads to daytime sedation and other adverse effects. In general, when used to promote sleep, they are prescribed at doses lower than those recommended for treating depression.

The effects of TCAs on sleep have been studied more frequently in patients with major depressive disorder, in whom they have been shown to reduce latency to sleep onset and increase sleep efficiency [153, 154]. A PSG study in subjects with primary insomnia showed that low doses of

doxepin (1, 3, or 6 mg) led to improvements in objective sleep and subjective sleep maintenance and duration in comparison with placebo, without evidence of side effects such as anticholinergic effects, hangover, or memory impairment [155]. TCAs at higher doses have profound effects on sleep architecture, most notably suppression of REM sleep [156, 157]. REM sleep rebound and sleep disturbance may thus occur following abrupt discontinuation of TCAs, making them less attractive for intermittent dosing.

TCAs can also have adverse effects on sleep, including the exacerbation of restless legs syndrome or periodic limb movement disorder, or precipitation of REM sleep behavior disorder [158]. They can also induce hypomania or mania in patients with underlying bipolar disorder, which is generally associated with severe insomnia.

All tricyclics have significant anticholinergic effects, which lead to many of their side effects, including dry mouth, constipation, urinary retention, and sweating; amitriptyline has such strongest effects. Orthostatic hypotension can result from α_1-adrenergic receptor antagonism, increasing the risk for falls. The TCAs also have quinidine-like effects on cardiac conduction, which can result in the prolongation of the QT interval; cardiotoxicity is a major concern, and these drugs have a high degree of lethality in overdosage.

Trazodone

Trazodone has been one of the most frequently prescribed drugs for insomnia over at least the past decade and is probably used almost exclusively for this purpose at present, usually in doses of up to 100 mg at bedtime. Its popularity is probably due to its low cost, low abuse potential, and lack of restrictions on long-term use. Its effects on sleep are probably due to its antihistaminergic effects at the H_1 receptor, α_1-adrenergic receptor antagonism, and $5HT_2$ receptor antagonism. Given its widespread use, there are surprisingly few studies documenting its effects on sleep. Most of the studies showing positive effects on sleep were performed in depressed subjects, although most of these were limited by problems such as small sample sizes and lack of placebo controls; trazodone resulted in reduced sleep latency, increased sleep efficiency, and total sleep in several studies in depressives [159]. Only one double-blind, placebo-controlled study has been performed in primary insomnia; in this study, trazodone 50 mg and zolpidem 10 mg were compared with placebo over a 2-week period [160]. During the first week, trazodone and zolpidem led to subjective reductions in sleep latency, increases in total sleep and sleep quality, and decreased wakefulness after sleep onset, but zolpidem produced a greater reduction in sleep latency than trazodone. During the second week, trazodone did not differ from placebo, whereas zolpidem still produced a significantly shorter sleep latency and more total sleep. In terms of trazodone's objective effects on sleep architecture, the most consistent finding has been an increase in slow-wave sleep. There are insufficient data to conclude that trazodone does not lead to tolerance or rebound insomnia. Some recent studies have suggested that trazodone may improve both subjective sleep and mood in patients with insomnia and depression [161].

Trazodone is associated with a number of frequent adverse effects, including daytime sedation/drowsiness, dizziness, dry mouth, gastrointestinal upset, blurred vision, and headache; these have led to fairly high discontinuation rates in clinical trials [159]. Although less common, trazodone may also have significant cardiovascular effects, such as orthostatic hypotension, prolonged QT interval, and cardiac arrhythmias. Priapism, although quite rare, is a medical emergency and can occur even with low doses. One of the major metabolites of trazodone, *meta*-chlorophenylpiperazine, has serotonergic effects and may contribute to serotonin syndrome (confusion/delirium, hyperreflexia, autonomic instability) when trazodone is used in combination with other serotonergic agents. These potential side effects raise concerns about using trazodone in elderly or medically ill populations.

Mirtazapine

Mirtazapine tends to be used at low doses (7.5–15 mg) as a sleep-inducing agent and probably affects sleep through antagonism of H_1, $5HT_2$, and α_1-adrenergic receptors. As with trazodone, there are relatively few data regarding its efficacy for insomnia. In normal subjects, mirtazapine increased sleep efficiency and slow-wave sleep on the first night of treatment as determined in a sleep laboratory setting [162]. In an uncontrolled PSG study of depressives treated with 30 mg of mirtazapine, slow-wave sleep increased, REM latency was prolonged, wakefulness after sleep onset decreased, and subjective ratings of sleep improved [163]. In comparison with fluoxetine, depressed subjects who received mirtazapine showed significantly improved sleep by PSG criteria [164]. It is generally believed that lower doses of mirtazapine are more sedating than higher doses, but there are few objective clinical data in support of this. Common side effects of mirtazapine include drowsiness, daytime sedation, dry mouth, increased appetite, and weight gain. Its low toxicity is an advantage in comparison with some of the other sedating antidepressants.

Atypical Antipsychotics

Atypical antipsychotics, particularly quetiapine and olanzapine, are also used with increasing frequency for insomnia. In contrast to the older antipsychotics that act primarily through blockade of dopamine type 2 receptors, the newer agents also act on a variety of receptors in addition, including antagonism of $5HT_{2A}$ and $5HT_{2C}$ receptors, antihistaminergic effects, and antagonism of α_1-adrenergic receptors. Although they may have a role in treating comorbid insomnia in patients with primary indications for their use (e.g., psychotic disorders, bipolar disorder, and treatment-refractory depression), their use in primary insomnia should be avoided if possible. One controlled study on the effects of quetiapine at 25 or 100 mg performed in healthy male volunteers [165] resulted in shorter sleep latency, increased total sleep and sleep efficiency, and improved subjective sleep quality. The 100 mg dose, however, caused a significant increase in periodic leg movements. An open-label study in 18 insomnia patients, using doses of 25–75 mg, reported increases in PSG-recorded total sleep time and sleep efficiency and improvements in self-reported sleep quality [166]. In another study, ziprasidone produced effects similar to quetiapine, but also led to increased slow-wave sleep and REM sleep suppression [167]. One night of administration of olanzapine to healthy male volunteers produced effects similar to quetiapine in comparison with placebo [168]. In an open-label study in depressives, olanzapine added to SSRI treatment led to increased sleep efficiency and slow-wave sleep [169].

In addition to the lack of efficacy data for insomnia, atypical antipsychotics are associated with adverse events. They have lower rates of extrapyramidal effects than the older antipsychotics, but these may still occur. Other concerns are risks for weight gain, glucose intolerance, dyslipidemia, daytime sedation, cognitive impairment, restless legs syndrome, and hepatotoxicity. These agents carry a "black box" warning for increased risk of sudden death in elderly patients with dementia.

Anticonvulsants

Several anticonvulsants acting on the GABA system to increase GABA effects in the brain have been used in the treatment of insomnia. There are few, if any, data regarding their use in insomnia, but they appear to have some sedating and/or sleep-promoting effects. Their advantages include low toxicity and that they are not controlled substances. Gabapentin is thought to increase synaptic levels of GABA, but its mechanism of action is not clearly understood [170]. It has been reported to increase slow-wave sleep in patients with epilepsy [171], improve insomnia ratings in an open-label study of alcoholics with insomnia [172], and increase slow-wave sleep in normal adults [173]. A recent open-label clinical trial in primary insomnia subjects who took a mean dose of 540 mg demonstrated increased slow-wave sleep, increased sleep efficiency and decreased arousals, and subjective improvement in sleep quality [174]. Gabapentin is generally well tolerated and has low toxicity, but can cause daytime sedation, dizziness, and leukopenia.

Tiagabine inhibits GABA reuptake through inhibition of the GABA transporter. It is one of the few anticonvulsants with data from placebo-controlled studies in insomnia. In a study of elderly subjects with insomnia, doses of 4–8 mg significantly increased slow-wave sleep, and doses of 6–8 mg led to decreased awakenings [175]. At the 8 mg dose, subjects reported subjective decreases in total sleep, less refreshing sleep, worse daytime functioning, and more adverse events. Similar effects were seen in a study of tiagabine in healthy elderly subjects [176]. A study in nonelderly adults with primary insomnia using tiagabine doses up to 16 mg also showed that the drug produced increased slow-wave sleep and decreased waking after sleep onset (at the 16 mg dose), but there was no significant effect on latency to persistent sleep [177]. Again, higher doses were associated with more adverse effects, including decreased next-day alertness and cognitive performance, dizziness, and nausea. Thus, although potentially helpful for insomnia, the side effects of tiagabine may limit its utility.

Pregabalin, like gabapentin, was designed as a GABA analogue; like gabapentin, its mechanism is unclear. A comparison of alprazolam with pregabalin in healthy subjects showed that both drugs reduced sleep latency and decreased REM sleep amount [178]; however, pregabalin led to significant increases in slow-wave sleep, whereas alprazolam decreased it; only alprazolam prolonged REM sleep latency. Studies on the effects of pregabalin on sleep have been performed in subjects with fibromyalgia and insomnia and have demonstrated significant subjective improvement in sleep [161]. The most common side effects of pregabalin are dizziness and somnolence.

Antihistamines

Antihistamines are the active ingredients in most OTC medications and act through antagonism of H1 receptors. Diphenhydramine and doxylamine are found in virtually all OTC sleeping medications, but it is important to note that doxepin (described earlier) is a more potent antihistamine than any of the OTCs. Histamine1 antagonists cause sedation in most individuals, but can lead to paradoxical excitation in some individuals, particularly with higher doses and/or in children and the elderly. Despite the widespread use of these agents, there are almost no data regarding their effects on sleep, and there are no rigorous, placebo-controlled studies in insomnia. A study of the subjective effects of diphenhydramine in psychiatric patients

with insomnia showed that it led to global improvement in sleep in about two-thirds of subjects [179], and another outpatient study found that mild-to-moderate insomnia patients in a family practice setting reported more restful sleep and shorter sleep latency with 50 mg diphenhydramine in comparison with those taking placebo [180]. An assessment of motor activity and subjective sleep parameters in normal adults showed minimal or no effects on sleep parameters and a tendency for increased motor activity [181]. Finally, a study in normal men showed that diphenhydramine led to rapid tolerance of its sedative effects [182], suggesting that these agents may not be useful for long-term treatment. A recent meta-analysis summarizing the results of 4 small trials of diphenhydramine failed to find significant effects on sleep, but only subjective sleep reports were collected in these studies [183].

These agents are associated with significant adverse effects, such as daytime sedation, cognitive impairment, increased risk of accidents, dizziness, tinnitus, gastrointestinal symptoms, weight gain, and increased intraocular pressure in narrow-angle glaucoma; as a result, their use has been strongly discouraged for patients with allergic rhinitis in favor of antihistamines without central nervous system effects [184].

Current Status of Pharmacotherapy for Insomnia

The National Institutes of Health held a State-of-the-Science Conference on Manifestations and Management of Chronic Insomnia in Adults in 2005 (http://consensus.nih.gov/2005/2005InsomniaSOS026html.htm). This nonpartisan review of currently available treatments came to several conclusions regarding pharmacotherapy for insomnia.

Benzodiazepine Receptor Agonists

Benzodiazepine receptor agonists, including benzodiazepines and nonbenzodiazepines, are effective in the short-term treatment of insomnia, and most have not been studied long term using randomized clinical trials; eszopiclone has shown sustained efficacy for 6 months in primary insomnia patients. Adverse effects of BZRAs include residual daytime sedation, motor coordination and cognitive impairment, dependence, and rebound insomnia. Side effects are greater in elderly patients. Side effects related to the newer BZRAs are much lower, probably related to their shorter half-lives. Abuse liability of BZRAs does not appear to be a major problem, but data related to long-term use for insomnia require further study.

Sedating Antidepressants

Trazodone is the most commonly prescribed medication for insomnia in the USA. It is sedating and improves several sleep parameters, but there are no studies of long-term use for chronic insomnia. Doxepin has beneficial effects for insomnia for up to 4 weeks; there are insufficient data for other antidepressants such as amitriptyline and mirtazapine for the treatment of insomnia. All antidepressants have significant adverse effects.

Other Agents

There are no data regarding the use of antipsychotics for the treatment of insomnia; these agents have significant risks, and they are not recommended for use in insomnia. Antihistamines are commonly used, but there are no data regarding their efficacy for insomnia. Furthermore, they have significant adverse effects. Melatonin is not regulated by the FDA, and there is significant variability in preparations. It appears to be effective for circadian rhythm disorders, but there is little evidence for efficacy in the treatment of insomnia. There are no data regarding safety in long-term use [5].

The American Academy of Sleep Medicine published a clinical guideline for chronic insomnia in 2008 [54]. In terms of pharmacotherapy, they recommended that choice of an agent should be determined based on clinical parameters such as characteristics of the insomnia, treatment goals, response to previous medications, other medical and psychiatric conditions, potential side effects/interactions with other medications, contraindications, cost, and patient preference. The recommended pharmacotherapy choice sequence is the following:

1. Short-intermediate-acting benzodiazepine, benzodiazepine receptor agonist, or ramelteon.
2. Alternate choice from group 1 if the first choice is not effective or tolerated.
3. Sedating antidepressant.
4. Combination of choice from group 1 and a sedating antidepressant.
5. Consideration of other agents, such as anticonvulsant or atypical antipsychotic, preferably in patients with insomnia related to comorbid conditions for which these agents may be beneficial.

Summary and Conclusions

Insomnia is a prevalent health complaint that may present as an independent disorder or as a condition comorbid to a medical or psychiatric disorder. Persistent insomnia is associated with significant morbidity and healthcare costs. Progress has been made to standardize research diagnostic criteria, but there is still little information about the psychological and biologic bases of insomnia and about its natural history and long-term prognosis. Significant

advances have also been made in developing and validating therapeutic approaches for the management of both acute and chronic insomnia. Despite these advances, insomnia remains under-recognized and undertreated in clinical practice. Additional research is needed to further document the etiology of insomnia and its natural history and to optimize therapeutic outcomes, not only in terms of reducing insomnia symptoms but also in terms of impact on other indicators of morbidity and cost-effectiveness. A significant challenge for the future will be to optimize treatment algorithms and ensure validated therapies are integrated in clinical practice guidelines.

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Narcolepsy and Idiopathic Hypersomnia

38

Seiji Nishino

Introduction

Recent progress for understanding the pathophysiology of excessive daytime sleepiness (EDS) particularly owes itself to the discovery of narcolepsy genes (i.e., hypocretin receptor and peptide genes) in animals in 1999 and the subsequent discovery in 2000 of hypocretin ligand deficiency (i.e., loss of hypocretin neurons in the brain) in idiopathic cases of human narcolepsy–cataplexy. The hypocretin deficiency can be clinically detected by cerebrospinal fluid (CSF) hypocretin-1 measures; low CSF hypocretin-1 levels are seen in over 90 % of narcolepsy–cataplexy patients. Since the specificity of the CSF finding is also high (no hypocretin deficiency was seen in patients with idiopathic hypersomnia), low CSF hypocretin-1 levels have been included in the 2nd revision of the International Classifications of Sleep Disorder (ICSDII) as a positive diagnosis for narcolepsy–cataplexy [1] only 5 years after the discovery of hypocretin deficiency in human narcolepsy.

Narcolepsy–cataplexy is tightly associated with human leukocyte antigen (HLA) DQB1*0602. Hypocretin deficiency in narcolepsy–cataplexy is also tightly associated with HLA positivity, suggesting an involvement of immune-mediated mechanisms in the loss of hypocretin neurons. However, the specificity of HLA positivity for narcolepsy–cataplexy is much lower than that of low CSF hypocretin-1 levels, as up to 30 % of the general population shares this HLA haplotype. The new ICSD-3, published in 2014, reclassifies "Narcolepsy" as "Type I-Cataplexy/Hypocretin deficient" and "Type 2-Hypocretin non-deficient" narcolepsy by attempting to emphasize the pathophysiological basis [2].

The prevalence of primary hypersomnia, such as narcolepsy and idiopathic hypersomnia, is not high at 0.05 and 0.005 %, respectively, but the prevalence of symptomatic hypersomnia (hypersomnia due to a medical condition) may be much higher. For example, several million subjects in the USA suffer from chronic brain injury, and 75 % of those people have sleep problems and about half of them claim sleepiness [3]. Symptomatic narcolepsy has also been reported, but the prevalence of symptomatic narcolepsy is much smaller, and only about 120 cases have been reported in the literature in the past 30 years [4]. A meta-analysis of these symptomatic cases indicates that hypocretin deficiency may also partially explain the neurobiological mechanisms of EDS associated with symptomatic cases of narcolepsy and hypersomnia [4].

Anatomical and functional studies demonstrate that the hypocretin systems integrate and coordinate the multiple wake-promoting systems, such as monoamine and acetylcholine systems to keep subjects fully alert and prevent abnormal REM sleep manifestations [5], suggesting that understanding of the roles of hypocretin peptidergic systems in sleep regulation in normal and pathological conditions is important, as alterations of these systems may also be responsible not only for narcolepsy but also for other less well-defined hypersomnia.

Since a large majority of patients with EDS are currently treated with pharmacological agents, new knowledge about the neurobiology of EDS will likely lead to the development of new diagnostic tests as well as new treatments and managements of patients with hypersomnia with various etiologies.

This review focuses on pathophysiological mechanisms and nosological aspects of narcolepsy and idiopathic hypersomnia. For the treatments of these conditions, the readers should refer to more specific publications available [6–9].

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Symptoms of Narcolepsy

Excessive Daytime Sleepiness (EDS)

EDS and cataplexy are considered to be the two primary symptoms of narcolepsy, with EDS often being the most disabling symptom [10]. EDS most typically mimics the feeling that people experience when they are severely sleep deprived but may also manifest itself as a chronic tiredness or fatigue. Narcoleptic subjects generally experience a permanent background of baseline sleepiness that easily leads to actual sleep episodes in monotonous sedentary situations. This feeling is most often relieved by short naps (15–30 min), but in most cases the refreshed sensation only lasts a short time after awaking. The refreshing value of short naps is of considerable diagnostic value. Sleepiness also occurs in irresistible waves in these patients, a phenomenon best described as "sleep attacks." Sleep attacks may occur in very unusual circumstances, such as in the middle of a meal, a conversation, or a bicycle ride. These attacks are often accompanied by microsleep episodes [11] where the patient "blanks out." The patient may then continue his or her activity in a semi-conscious manner (writing incoherent phrases in a letter, speaking incoherently on the phone, etc.), a phenomenon called automatic behavior [11–13]. Learning problems and impaired concentration are frequently associated [11–15], but psychophysiological testing is generally normal.

Sleepiness is usually the first symptom to appear, followed by cataplexy, sleep paralysis and hypnagogic hallucinations [16–20]. Cataplexy onset occurs within five years after the occurrence of daytime somnolence in approximately two-thirds of the cases [17, 19]. Less frequently, cataplexy appears many years after the onset of sleepiness. The mean age of onset of sleep paralysis and hypnagogic hallucinations is also two to seven years later than that of sleepiness [16, 21].

In most cases, EDS and irresistible sleep episodes persist throughout the lifetime although they often improve after retirement (possibly due to better management of activities), daytime napping and adjustment of nighttime sleep.

Cataplexy

Cataplexy is distinct from EDS associated with narcolepsy and pathognomonic of the disease [22]. The importance of cataplexy for the diagnosis of narcolepsy has been recognized since its description [23, 24] and in subsequent reviews on narcolepsy [25, 26]. Most authors now recognize patients with recurring sleepiness and cataplectic attacks as a homogeneous clinical entity, and this is now shown to be tightly associated with hypocretin deficiency (see the section on the pathophysiology of the disease). Cataplexy is defined as a sudden episode of muscle weakness triggered by emotional factors, most often in the context of positive emotions (such as laughter, having good cards at card games, the pull of the fishing rod with a baiting fish, the perfect hit at baseball), and less frequently by negative emotions (most typically anger or frustration). All antigravity muscles can be affected leading to a progressive collapse of the subject, but respiratory and eye muscles are not affected. The patient is typically awake at the onset of the attack but may experience blurred vision or ptosis. The attack is almost always bilateral and usually lasts a few seconds. Neurological examination performed at the time of an attack shows a suppression of the patellar reflex and sometimes that of a Babinski's sign.

Cataplexy is an extremely variable clinical symptom [27]. Most often, it is mild and occurs as a simple buckling of the knees, head dropping, facial muscle flickering, sagging of the jaw or weakness in the arms. Slurred speech or mutism is also frequently associated. It is often imperceptible to the observer and may even be only a subjective feeling difficult to describe, such as a feeling of warmth or that somehow time is suspended [26, 27]. In other cases, it escalates to actual episodes of muscle paralysis that may last up to a few minutes. Falls and injury are rare and most often the patient will have time to find support or will sit down while the attack is occurring. Long episodes occasionally blend into sleep and may be associated with hypnagogic hallucinations. Children with narcolepsy often (about 1/3 of patients) present with a previously unrecognized description of cataplexy that we coined "cataplectic facies," consisting of a state of semipermanent eyelid and jaw weakness [28].

Patients may also experience "status cataplecticus." This rare manifestation of narcolepsy is characterized by subintrant cataplexy that lasts several hours per day and confines the subject to bed. It can occur spontaneously or more often upon withdrawal from anticataplectic drugs [18, 29, 30].

Cataplexy often improves with advancing age. In rare cases, it disappears completely but in most patients it is better controlled (probably after the patient has learned to control their emotions) [16, 31].

Sleep Paralysis

Sleep paralysis is present in 20–50 % of all narcoleptic subjects [19, 32–34]. It is often associated with hypnagogic hallucinations. Sleep paralysis is best described as a brief inability to perform voluntary movements at the onset of sleep, upon awakening during the night, or in the morning. Contrary to simple fatigue or locomotion inhibition, the patient is unable to perform even a small movement, such as lifting a finger. Sleep

paralysis may last a few minutes and is often finally interrupted by noise or other external stimuli. The symptom is occasionally bothersome in narcoleptic subjects, especially when associated with frightening hallucinations [35].

Whereas EDS and cataplexy are the cardinal symptoms of narcolepsy, sleep paralysis occurs frequently as an isolated phenomenon, affecting 5–40 % of the general population [36–38]. Occasional episodes of sleep paralysis are often seen in adolescence and after sleep deprivation, thus prevalence is high for single episodes.

Hypnagogic and Hypnopompic Hallucinations

Abnormal visual (most often) or auditory perceptions that occur while falling asleep (hypnagogic) or upon waking up (hypnopompic) are frequently observed in narcoleptic subjects [39]. These hallucinations are often unpleasant and are typically associated with a feeling of fear or threat [32, 35]. Polygraphic studies indicate that these hallucinations occur most often during REM sleep [32, 40]. These episodes are often difficult to distinguish from nightmares or unpleasant dreams, which also occur frequently in narcolepsy.

Hypnagogic hallucinations are most often associated with sleep attacks, and their content is described by the patient. The hallucinations are most often complex, vivid, dream-like experiences ("half sleep" hallucinations) and may follow episodes of cataplexy or sleep paralysis, a feature that is not uncommon in severely affected patients. These hallucinations are usually easy to distinguish from hallucinations observed in schizophrenia or related psychotic conditions.

Compared to cataplexy, hypnagogic and hypnopompic hallucinations themselves do not have specificity for the diagnosis of narcolepsy, as up to 20–30 % of normal people exhibit these symptoms in various situations [37, 41]. The folklore over the world describes similar phenomenon, including "Kanashibari" in Japan, literally meaning "bound or fastened in metal," "Pinyin" in China, literally meaning "ghost pressing on body."

Other Important Symptoms

One of the most frequently associated symptoms is insomnia, best characterized as a difficulty to maintain nighttime sleep. Typically, narcoleptic patients fall asleep easily, only to wake up after a short nap unable to fall asleep again for an hour or so. Narcoleptic patients do not usually sleep more than normal individuals over the 24-h cycle [42–44] but frequently have a very disrupted nighttime sleep [42–44]. This symptom often develops later in life and can be very disabling.

Other frequently associated problems are periodic leg movements [45, 46], REM behavior disorder, parasomnias [47, 48], and obstructive sleep apnea [46, 49, 50].

Narcolepsy was reported to be associated with changes in energy homeostasis several decades ago. Narcolepsy patients are frequently (1) obese [51, 52], (2) more often have insulin-resistant diabetes mellitus [51], (3) exhibit reduced food intake [53], and (4) have lower blood pressure and temperature [54, 55]. These findings, however, had not received much attention since they were believed to be secondary to sleepiness or inactivity during the daytime. More recently, however, it was shown that these metabolic changes may be found more specifically in hypocretin-deficient patients [56–58], suggesting a direct pathophysiological link.

Narcolepsy is a very incapacitating disease. It interferes with every aspect of life. The negative social impact of narcolepsy has been extensively studied. Patients experience impairments in driving, and there is a high prevalence of either car- or machine-related accidents. Narcolepsy also interferes with professional performance, leading to unemployment, frequent changes of employment, working disability, or early retirement [59–61]. Several subjects also develop symptoms of depression, although these symptoms are often masked by anticataplectic medications [12, 59, 62].

Neurobiology of Wakefulness

In order to understand the neurobiology of hypersomnia, we will first discuss current understandings of the neurobiology of wakefulness. Sleep/wake is a complex physiology regulated by brain activity, and multiple neurotransmitter systems such as monoamines, acetylcholine, excitatory and inhibitory amino acids, peptides, purines, and neuronal and non-neuronal humoral modulators (i.e., cytokines and prostaglandins) [8, 63] are likely to be involved. Monoamines are perhaps the first neurotransmitters recognized to be involved in wakefulness [9, 64] and the monoaminergic systems have been the most common pharmacological targets for wake-promoting compounds in the past years. On the other hand, prototypical hypnotics target the gammaaminobutyric acid (GABA)-ergic system, a main inhibitory neurotransmitter system in the brain [10, 65].

Cholinergic neurons also play critical roles in cortical activation during wakefulness (and during REM sleep) [9, 63]. Brainstem cholinergic neurons originating from the laterodorsal and pedunculopontine tegmental nuclei activate thalamocortical signaling, and cerebral cortical activation is further reinforced by direct cholinergic projections from the basal forebrain. However, currently no cholinergic compounds are used in sleep medicine, perhaps due to the complex nature of the systems and prominent peripheral side effects.

Monoaminergic neurons, such as norepinephrine (NE) containing locus coeruleus neurons, serotonin (5-HT) containing raphe neurons, and histamine containing tuberomammillary neurons (TMN) are wake-active and act directly on cortical and subcortical regions to promote wakefulness [8, 63]. In contrast to the focus on these wake-active monoaminergic systems, researchers have often underestimated the importance of dopamine (DA) in promoting wakefulness. Most likely, this is because the firing rates of midbrain DA-producing neurons (ventral tegmental area [VTA] and substantia nigra) do not have an obvious variation according to behavioral states [11, 66]. In addition, DA is produced by many different cell groups [12, 67], and which of these promote wakefulness remains undetermined. Nevertheless, DA release is greatest during wakefulness [68], and DA neurons increase discharge and tend to fire bursts of action potentials in association with significant sensory stimulation, purposive movement, or behavioral arousal [69]. Lesions that include the dopaminergic neurons of the VTA reduce behavioral arousal [70]. Recent work has also identified a small wake-active population of dopamine-producing neurons in the ventral periaqueductal grey that project to other arousal regions [71]. People with DA deficiency from Parkinson's disease are often sleepy [72], and dopamine antagonists are frequently sedating. These physiologic and clinical evidences clearly demonstrate that DA also plays a role in wakefulness.

Wakefulness (and various physiological systems associated with wakefulness) is essential for the survival of creatures and thus is likely to be regulated by multiple systems, each having a distinct role. Some arousal systems may have essential roles for cortical activation, attention, cognition, or neuroplasticity during wakefulness while others may only be active during specific times to promote particular physiology during wakefulness. Some of the examples may be motivated-behavioral wakefulness or wakefulness in emergency states. Wakefulness may thus likely be maintained by many systems with differential roles to be fully alert. Similarly, the wake-promoting mechanism of some drugs may not be able to be explained by a single neurotransmitter system.

Sleep Physiology and Symptoms of Narcolepsy

Since narcolepsy is a prototypical EDS disorder and since the major pathophysiology of narcolepsy (i.e., deficiency in hypocretin neurotransmission) has recently been revealed, the discussion of neurophysiological aspects of narcolepsy will help understand neurobiology of EDS.

Narcolepsy patients manifest symptoms specifically related to dysregulation of REM sleep [10]. In the structured, cyclic process of normal sleep, two distinct states—REM and 3 stages (S1, S2, S3) of non-REM (NREM) sleep—alternate sequentially every 90 min in a cycle repeating 4 to 5 times per night [73]. As EEG signals in humans indicate, NREM sleep, characterized by slow oscillation in thalamocortical neurons (detected as cortical slow waves) and muscle tonus reduction, precedes REM sleep, when complete muscle atonia occurs. Slow-wave NREM predominates during the early phase of normal sleep, followed by a predominance of REM during the later phase [73].

Notably, sleep and wake are highly fragmented in narcolepsy, and affected subjects could not maintain long bouts of wake and sleep. Normal sleep physiology is currently understood as dependent upon coordination of the interactions of facilitating sleep centers and inhibiting arousal centers in the brain, such that stable sleep and wake states are maintained for specific durations [73]. An ascending arousal pathway, running from the rostal pons and through the midbrain reticular formation, promotes wakefulness [73, 74]. As discussed earlier, this arousal pathway may be composed of neurotransmitters (acetylcholine, NE, DA, excitatory amino acids), produced by brainstem and hypothalamic neurons (hypocretin/orexin, and histamine) and may also be linked to muscle tonus control during sleep [73, 74]. Whereas full alertness and cortical activation require coordination of these arousal networks, effective sleep requires suppression of arousal by the hypothalamus [74]. Narcolepsy patients may experience major neurological malfunction of this control system originated in the hypothalamus.

Narcoleptics exhibit a phenomenon termed short REM sleep latency or sleep onset REM period (SOREMP), in which they enter REM sleep more immediately upon falling asleep than normal [10]. In some cases, NREM sleep is completely bypassed, and the transition to REM sleep occurs instantly [10]. SOREMS are not observed in idiopathic hypersomnia, suggesting a distinct etiology from narcolepsy.

Moreover, intrusion of REM sleep into wakefulness may explain cataplexy, sleep paralysis, and hypnogogic hallucinations, which are symptoms of narcolepsy. Although sleep paralysis and hallucinations manifest in other sleep disorders (sleep apnea syndromes and disturbed sleep patterns in the normal population) [75] (see also "sleep paralysis and hallucinations" section) [75], cataplexy is pathognomic for narcolepsy [10]. As such, identifying cataplexy's unique pathophysiological mechanism emerged to be potentially crucial in understanding overall pathophysiology of narcolepsy.

Discovery of Hypocretin Deficiency in Human Narcolepsy

The significant roles, first, of hypocretin deficiency and, subsequently, of postnatal cell death of hypocretin neurons as the major pathophysiological process underlying narcolepsy with cataplexy, were established from a decade of investigation in employing both animal and human models. In 1998, the simultaneous discovery of a novel hypothalamic peptide neurotransmitter by two independent research groups proved pivotal [76, 77]. One group called the peptides "hypocretin" because of their primary hypothalamic localization and similarities with the hormone "secretin" [77]. The other group called the molecule "orexin" (after the meaning of appetite in Greek) after observing that central administration of these peptides increased appetite in rats [76]. These neurotransmitters are produced exclusively by thousands of neurons, which are localized in the lateral hypothalamus, and project broadly to specific cerebral regions and more densely to others [78].

Within a year, Stanford researchers, using positional cloning of a naturally occurring familial canine narcolepsy model, identified an autosomal recessive mutation of hypocretin receptor 2 (Hcrtr 2) responsible for canine narcolepsy, characterized by cataplexy, reduced sleep latency, and SOREMPs [79]. This finding coincided with the simultaneous observation of the narcolepsy phenotype, characterized by cataplectic behavior and sleep fragmentation, in hypocretin ligand-deficient mice (prepro-orexin gene knockout mice) [80]. Together, these findings confirmed hypocretins as principal sleep/wake-modulating neurotransmitters and prompted investigation of the hypocretin system's involvement in human narcolepsy.

Although screening of high-risk patients with cataplexy (i.e., familial, early onset, and/or HLA negative cases) did not reveal hypocretin-related gene mutation as a major cause of human narcolepsy, narcoleptic patients did exhibit low CSF hypocretin-1 levels [81] (Fig. 38.1). Post-mortem brain tissue of narcoleptic patients, assessed with immunochemistry, radioimmunological peptide assays, and in situ hybridization, revealed hypocretin peptide loss and undetectable levels of hypocretin peptides or prepro-hypocretin RNA (Fig. 38.1). Further, melanin-concentrating hormone neurons, which are normally located in the same brain region [82], were observed intact, thus indicating that damage to hypocretin neurons and its production is selective in narcolepsy, rather than due to generalized neuronal degeneration.

As a result of these findings, a diagnostic test for narcolepsy based on clinical measurement of CSF hypocretin-1 levels for detecting hypocretin ligand deficiency, became available [1]. Whereas CSF hypocretin-1 concentrations above 200 pg/ml almost always occur in controls and patients with other sleep and neurological disorders, concentrations below 110 pg/ml are 94 % predictive of narcolepsy with cataplexy [83] (Fig. 38.2). As this represents a more specific assessment than the multiple sleep latency test (MSLT), CSF hypocretin-1 levels below 110 pg/ml are indicated in the ICSD-2 as diagnostic of narcolepsy with cataplexy [1].

Moreover, separate coding of "narcolepsy with cataplexy" and "narcolepsy without cataplexy" in the ICSD-2 underscores how discovery of specific diagnostic criteria now informs our understanding of narcolepsy's nosology; narcolepsy with cataplexy, as indicated by low CSF hypocretin-1, appears etiologically homogeneous and distinct from most narcolepsy without cataplexy cases, exhibiting normal hypocretin-1 levels [83]. In the 3rd revision, narcolepsy was reclassified as hypocretin-deficient/Type I and hypocretin non-deficient/Type II narcolepsy, and this classification is solely based on the pathophysiological findings. The potential of hypocretin receptor agonists (or cell transplantation) in narcolepsy treatment is currently being explored, and identifying hypocretin deficiency status may be useful in identifying appropriate patients as candidates for a novel therapeutic option, namely hypocretin replacement therapy.

Soon after the discovery of human hypocretin deficiency, researchers identified specific substances and genes, such as dynorphin and neuronal activity-regulated pentraxin (NARP) [84] and most recently, insulin-like growth factor binding protein 3 (IGF BP3) [85], which colocalize in neurons containing hypocretin. These findings underscored selective hypocretin cell death as the cause of hypocretin deficiency (as opposed to transcription/biosynthesis or hypocretin peptide processing problems) because these substances are also deficient in postmortem brain in the lateral hypothalamic area (LHA) of hypocretin-deficient narcoleptic patients [84, 85]. Furthermore, these findings, in view of the generally late onsets of sporadic narcolepsy compared with those of familial cases, suggest that postnatal cell death of hypocretin neurons constitutes the major pathophysiological process in human narcolepsy with cataplexy.

A large kindred of familial narcolepsy (12 affected members) has been reported in Spain [86]. Affected members do not exhibit any symptoms suggesting symptomatic cases of narcolepsy and were diagnosed as familial idiopathic narcolepsy–cataplexy. The family includes a pair of dizygotic twins concordant for narcolepsy–cataplexy in the third generation; the distribution of the disorder indicates an autosomal-dominant transmission of the disease-causing gene. Hor et al. recently performed linkage analysis and sequenced coding regions of the genome (exome sequencing) of three affected members with narcolepsy and cataplexy, and identified a missense mutation in the second exon of the myelin oligodendrocyte glycoprotein (MOG) [86]. A c.398C > G mutation was present in all affected family members but absent in unaffected members and 775 unrelated control subjects [86]. Affected members were hypocretin-deficient, but association with HLA

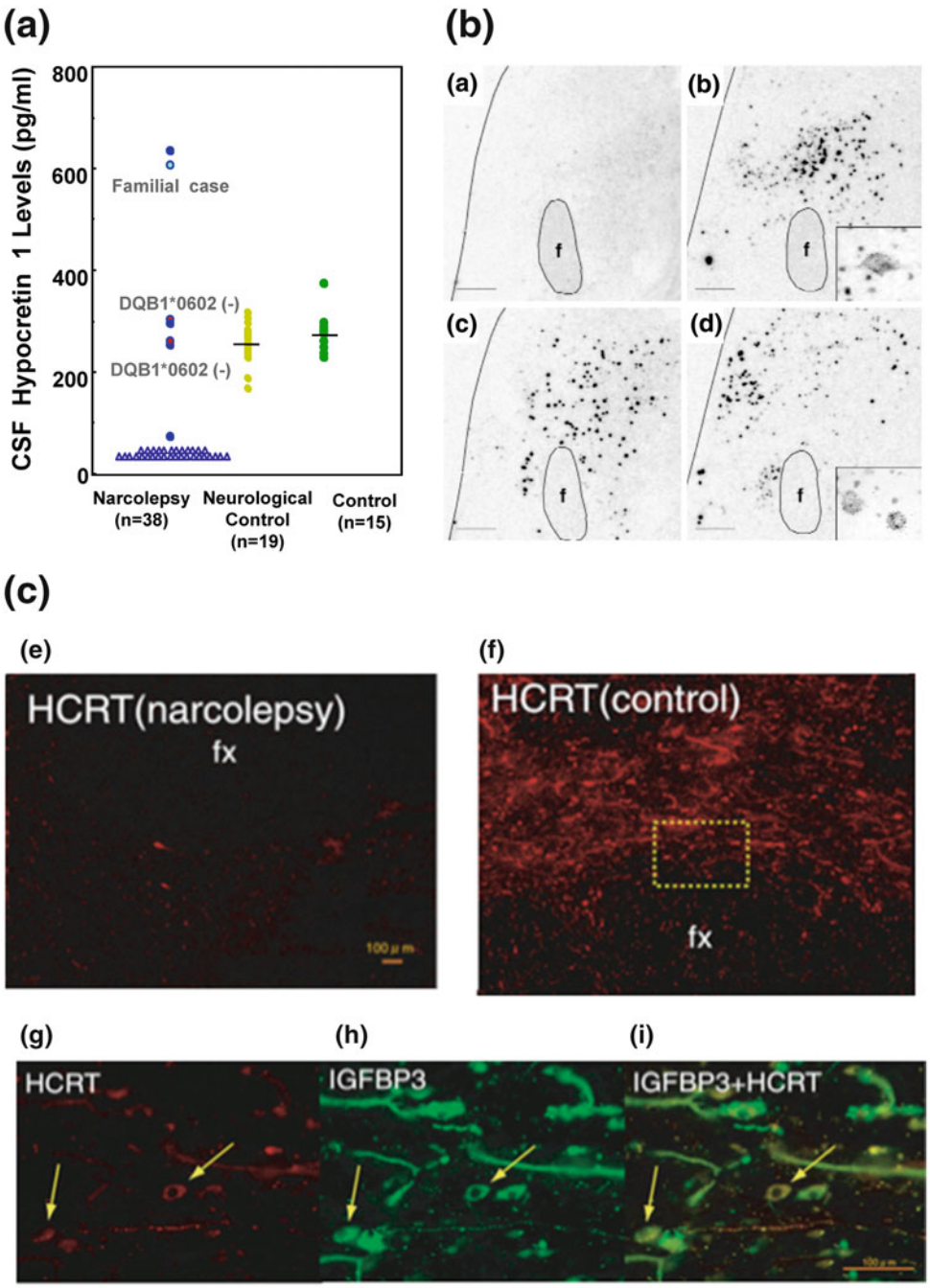

Fig. 38.1 Hypocretin deficiency in narcoleptic subjects. **a** CSF hypocretin-1 levels are undetectably low in most narcoleptic subjects (84.2 %). Note that two HLA DqB1*0602-negative and one familial case have normal or high CSF hypocretin levels. **b** Preprohypocretin transcripts are detected in the hypothalamus of control (*b*) but not in narcoleptic subjects (*a*). Melanin-concentrating hormone (MCH) transcripts are detected in the same region in both control (*d*) and narcoleptic (*c*) sections. **c** Colocalization of IGFBP3 in HCRT cells in control and narcolepsy human brain. *Upper panel* (*e*) Distribution of hypocretin cells and fibers in the perifornical area of human hypothalamus. (*e*, *f*) In control brains, HCRT cells and fibers were densely stained by an anti-HCRT monoclonal antibody (*red fluorescence* VectorRed), while in narcolepsy brains, staining was markedly reduced (*f*). *Lower panel* HCRT immunoreactivity (*g red fluorescence*) and IGFBP3 immunoreactivity (*h green fluorescence*; Q-dot525) and a composite picture (i) arrows indicate HCRT cells colocalized with IGFBP3). Note non-neuronal autofluorescent elements. f and fx, fornix. Scale bar represents 10 mm (*a–d*), 500 mm in *e* and *f*, 100 mm in *g*, *h* and *i* (from [81, 82, 84, 85])

DQB1*0602 was not observed [86]. The mutation may induce secondary hypocretin deficiency with or without immune-mediated mechanisms. MOG has been linked to various neuropsychiatric disorders and is considered a key autoantigen in multiple sclerosis and in its animal model experimental autoimmune encephalitis [87] (Fig. 38.1), and thus autoimmune mechanisms may also be involved in these cases. However, even if autoimmune mechanisms are involved in

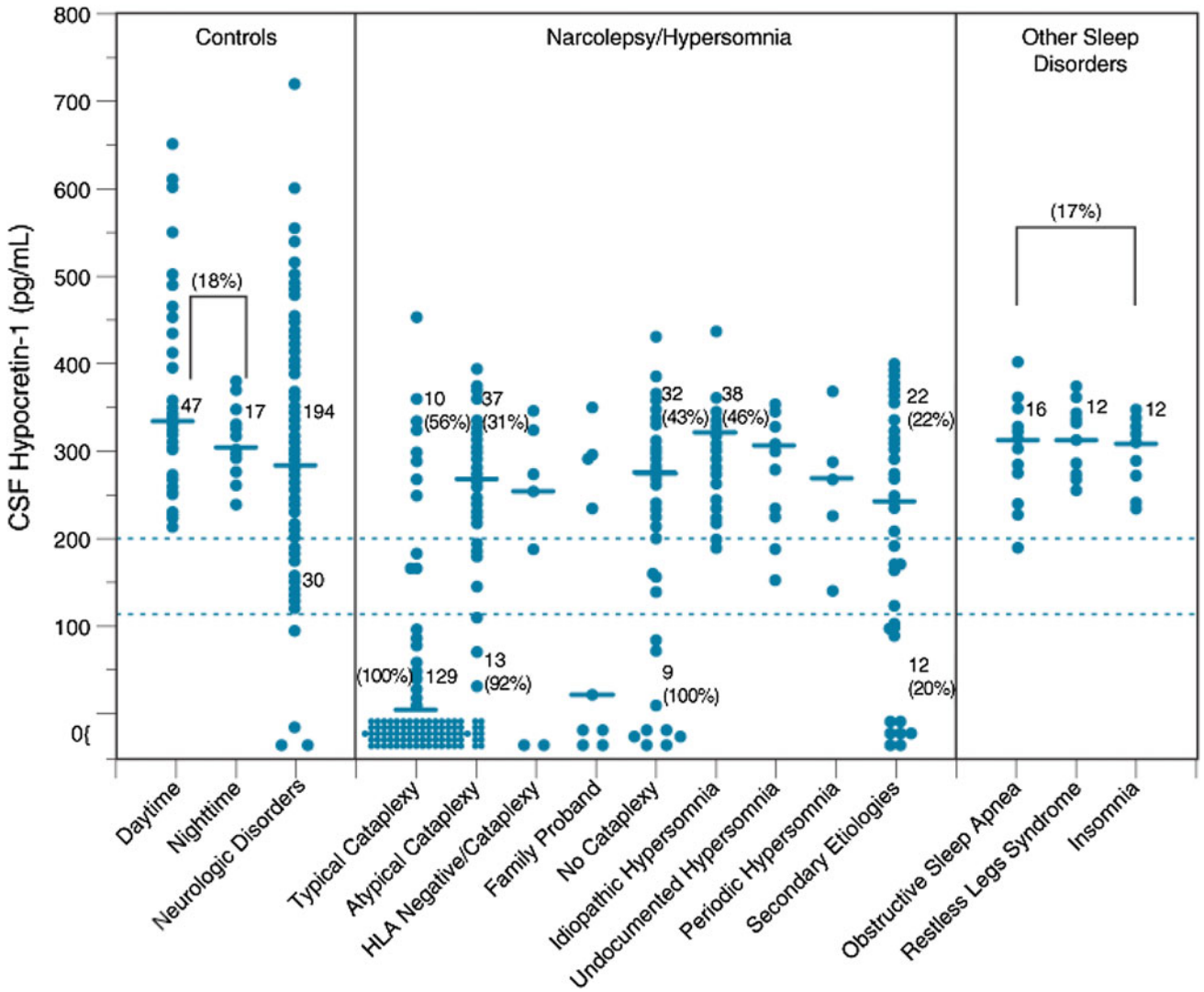

Fig. 38.2 CSF hypocretin-1 levels in individuals across various control and sleep disorders. Each point represents the crude concentration of Hypocretin-1 in a single person. The cutoffs for normal (>200 pg/ml) and low (<110 pg/ml) Hypocretin-1 concentrations are shown. Also noted is the total number of subjects in each range, and the percentage of human leukocyte antigen (HLA)-DQB1*0602 positivity for a given group in a given range is parenthetically noted for certain disorders. Note that control carrier frequencies for DQB1*0602 are 17–22 % in healthy control subjects and secondary narcolepsy, consistent with control values reported in whites. In other patient groups, values are higher, with almost all hypocretin-deficient narcolepsy being HLA DQB1*0602 positive. The median value in each group is shown as a horizontal bar (Updated from previously published data in [82, 83])

these cases, it is possible that the primary target for the immune attack is not the hypocretin system. These results suggest the heterogeneity of the etiology of idiopathic narcolepsy–cataplexy.

What Causes Loss of Hypocretin Neurons?

Because of its strong association with certain HLA alleles (i.e., HLA DQB1*0602 and DQA1*0102) [88], it has long been speculated that narcolepsy results from an autoimmune -mediated mechanism. Increase in antistreptolysin O [ASO] titer in narcolepsy, especially in the period close to the disease onset, was reported [89]. However, attempts to identify specific autoantibodies have been unsuccessful for decades. Recently, Tribbles homolog 2 (Trib2) was reported as a candidate antigen involved in the destruction of hypocretin neurons in narcolepsy [90]. Trib2 was shown to be abundantly expressed in hypocretin neurons, and levels of Trib2-specific antibodies were much higher in patients with narcolepsy, especially shortly after the disease onset. Thus, Trib2 is the first antibody specifically associated with hypocretin-deficient narcolepsy [90]. However, it is still unknown whether Trib2-specific antibodies are directly involved in cell death, or

whether the antibody production is a consequence of cell damage by other unknown mechanisms [91].

Recent large-scale genome-wide association studies (GWAS) showed that susceptibility to narcolepsy is associated with single-nucleotide polymorphisms (SNPs) in the T-cell receptor alpha gene locus [92]. Other SNPs identified are located between *carnitine palmitoyl-transferase 1B* (*CPT 1B*) and *choline kinase beta* (*CHKB*) [93] and those on *purinergic receptor P2Y11* [94], *Cathepsin H* (*CTSH*), and *Tumor necrosis factor (ligand) superfamily member 4 (TNFSF4*, also called *OX40L*) [94]. These genes may be involved either in degeneration of hypocretin neurons or enhancing narcolepsy symptoms. Note that the association with the T-cell receptor alpha locus may be of importance, as the interactions between HLA molecules on antigen-presenting cells and T cell receptors on T cells play critical roles in self/non-self discrimination by the immune system. Many of these genes, including *P2Y11, CTSH,* and *OX40L*, are involved in T cell activation and/or antibody processing [95].

Recently, incidences of narcolepsy–cataplexy after pH1N1 influenza vaccination were reported in Northern Europe [96, 97]. These narcoleptic cases are typically HLA DQB1*0602 positive and hypocretin ligand deficient [96, 97]. In these countries, AS03-adjuvanted vaccination was used. Since the incidence associated with pH1N1 influenza vaccination was less or unchanged in other countries using other adjuvant (or without adjuvant in Japan), it is likely that the enhancement of immunization may induce narcolepsy. However, it is also reported in China that seasonal variation in the narcolepsy onset (most frequent in April and least frequent in November) and increased incidences of narcolepsy (a 3-fold) following the 2009 H1N1 winter influenza pandemic were observed [98]. A large majority of these subjects did not receive influenza vaccinations suggesting influenza infection itself may enhance the incidence of narcolepsy.

These epidemiological data further suggest the involvement of immunological mechanisms responsible for the loss of hypocretin-producing neurons in narcolepsy.

How Does Hypocretin Ligand Deficiency Cause the Narcolepsy Phenotype?

Since hypocretin deficiency is a major pathophysiological mechanism for narcolepsy–cataplexy, it is important to know how the hypocretin ligand deficiency can cause the narcolepsy phenotype.

Hypocretin/Orexin System and Sleep Regulation

Hypocretins/orexins (hypocretin-1 and hypocretin-2/Orexin A and Orexin B) are cleaved from a precursor prepro-hypocretin (prepro-orexin) peptide [76, 77, 99] (Fig. 38.3a). Hypocretin-1 with 33 residues contains four cysteine residues forming two disulfide bonds. Hypocretin-2 consists of 28 amino acids and shares similar sequence homology especially at the C-terminal side but has no disulfide bonds (a linear peptide) [76]. There are two G-protein-coupled hypocretin receptors, Hcrtr 1 and Hcrtr 2, also called orexin receptor 1 and 2 (OX_1R and OX_2R), and distinct distribution of these receptors in the brain is known. Hcrtr 1 is abundant in the locus coeruleus (LC) while Hcrtr 2 is found in the TMN and basal forebrain (Fig. 38.3b). Both receptor types are found in the midbrain raphe nuclei and mesopontine reticular formation [5].

Hypocretin-1 and hypocretin-2 are produced exclusively by a well-defined group of neurons localized in the lateral hypothalamus. The neurons project to the olfactory bulb, cerebral cortex, thalamus, hypothalamus, and brainstem, particularly the LC, raphe nucleus, and the cholinergic nuclei (the laterodorsal tegmental and pedunculopontine tegmental nuclei), and cholinoceptive sites (such as pontine reticular formation) [78, 99]. All of these projection sites are thought to be important for sleep and wake regulation.

A series of recent studies have now shown that the hypocretin system is a major excitatory system that affects the activity of monoaminergic (DA, NE, 5-HT and histamine) and cholinergic systems with major effects on vigilance states [99, 100] (Fig. 38.3b). It is thus likely that a deficiency in hypocretin neurotransmission induces an imbalance among these classical neurotransmitter systems, with primary effects on sleep-state organization and vigilance.

Many measurable activities (brain and body) and compounds manifest rhythmic fluctuations over a 24-h period. Whether or not hypocretin tone changes with zeitgeber time was assessed by measuring extracellular hypocretin-1 levels in the rat brain CSF across 24-h periods, using in vivo dialysis [101]. The results demonstrate the involvement of a diurnal pattern of hypocretin neurotransmission regulation (as in the homeostatic and/or circadian regulation of sleep). Hypocretin levels increase during the active periods and are highest at the end of the active period, and the levels decline with the onset of sleep. Furthermore, sleep deprivation increases hypocretin levels [101].

Recent electrophysiological studies have shown that hypocretin neurons are active during wakefulness and have reduced activity during slow wave sleep [102]. The neuronal

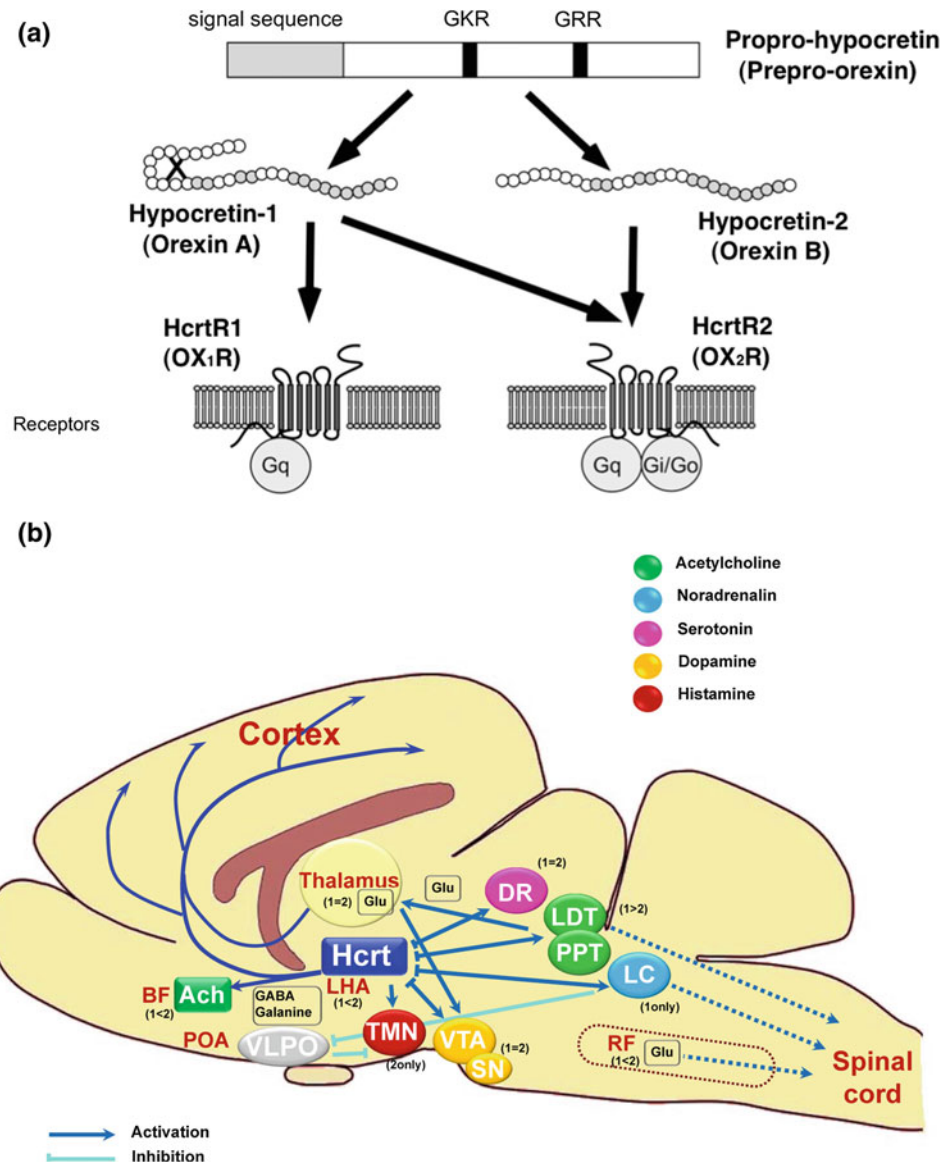

Fig. 38.3 **a** Structures of mature hypocretin-1 (orexin-A) and hypocretin-2 (orexin-B) peptides. **b** Projections of hypocretin neurons in the rat brain and relative abundances of hypocretin receptor 1 and 2. (**a**) The topology of the two intrachain disulfide bonds in orexin-A is indicated in the above sequence. Amino acid identities are indicated by shaded areas. (**b**) The actions of hypocretins are mediated via two G protein-coupled receptors named hypocretin receptor 1 (Hcrtr 1) and hypocretin receptor 2 (Hcrtr 2), also known as orexin-1 (OX_1R) and orexin-2 (OX_2R) receptors, respectively. Hcrtr 1 is selective for hypocretin-1, whereas Hcrtr 2 is nonselective for both hypocretin-1 and hypocretin-2. Hcrtr 1 is coupled exclusively to the G_q subclass of heterotrimeric G proteins, whereas in vitro experiments suggest that Hcrtr 2 couples with $G_{i/o}$, and/or G_q. Adapted from Sakurai [9]. (**c**) Hypocretin-containing neurons project to these previously identified monoaminergic and cholinergic and cholinoceptive regions where hypocretin receptors are enriched. The relative abundance of Hcrtr 1 versus Hcrtr 2 in each brain structure was indicated in parenthesis (data from Marcus et al. [5]). Impairments of hypocretin input may thus result in cholinergic and monoaminergic imbalance and generation of narcoleptic symptoms. Most drugs currently used for the treatment of narcolepsy enhance monoaminergic neurotransmission and adjust these symptoms. *VTA* ventral tegmental area; *SN* substantia nigra; *LC* locus coeruleus; *LDT* laterodorsal tegmental nucleus; *PPT* pedunculopontine tegmental nucleus; *RF* reticular formation; *BF* basal forebrain; *VLPO* ventrolateral preoptic nucleus; *LHA* lateral hypothalamic area; *TMN* tuberomamillary nucleus; *DR* dorsal raphe; *Ach* acetylcholine; *Glu* glutamate; *GABA* gamma-aminobutyric acid; *HI* histamine; *DA* dopamine; *NA* noradrenalin, *5-HT* serotonin

activity during REM sleep is the lowest, but intermittent increases in the activity associated with body movements or phasic REM activity are observed [102]. In addition to this short-term change, the results of microdialysis experiments also suggest that basal levels of hypocretin neurotransmission fluctuate across the 24-hour period and slowly build up toward the end of the active period. Adrenergic LC neurons are typical wake-active neurons involved in vigilance control

and firing rates rapidly change during short sleep/wake cycles, but it has been demonstrated that basic firing activity of wake-active LC neurons also significantly fluctuates across various circadian times [103].

Several acute manipulations such as exercise, low glucose utilization in the brain, and forced wakefulness increase hypocretin levels [100, 101]. It is therefore hypothesized that a build-up/acute increase in hypocretin levels may counteract homeostatic sleep propensity that typically increases during the daytime and during forced wakefulness [104].

Hypocretin/Orexin Deficiency and Narcoleptic Phenotype

Human studies have demonstrated that the occurrence of cataplexy is closely associated with hypocretin deficiency [83]. Furthermore, hypocretin deficiency was already observed at very early stages of the disease (just after the onset of EDS), even before the occurrences of clear cataplexy. Occurrences of cataplexy are rare in acute symptomatic cases of EDS associated with a significant hypocretin deficiency (see [4]); therefore, it appears that a chronic and selective deficit of hypocretin neurotransmission may be required for the occurrence of cataplexy. The possibility of involvement of a secondary neurochemical change for the occurrence of cataplexy still cannot be ruled out. If some of these changes are irreversible, hypocretin supplement therapy may only have limited effects on cataplexy.

Sleepiness in narcolepsy is most likely due to the difficulty in maintaining wakefulness as normal subjects do. The sleep pattern of narcoleptic subjects is also fragmented; they exhibit insomnia (frequent wakening) at night. This fragmentation occurs across 24 h, thus the loss of hypocretin signaling is likely to play a role in this vigilance stage stability (see [105]), but other mechanism may also be involved in EDS in narcoleptic subjects. One of the most important characteristics of EDS in narcolepsy is that sleepiness is reduced and patients feel refreshed after a short nap, but this does not last long as they become sleepy within a short period of time. Hypocretin-1 levels in the extracellular space and in the CSF of rats significantly fluctuate across 24 h and build up toward the end of the active periods [104]. Several manipulations (such as sleep deprivation, exercise, and long-term food deprivation) are also known to increase hypocretin tonus [101, 104]. Thus, the lack of this hypocretin increase caused by circadian time and by various alerting stimulations may also play a role for EDS associated with hypocretin-deficient narcolepsy.

Mechanisms for cataplexy and REM sleep abnormalities associated with impaired hypocretin neurotransmission have been studied. Hypocretin strongly inhibits REM sleep and activate brainstem REM-off LC and raphe neurons and REM-on cholinergic neurons as well as stimulation of local GABAnergic neurons. Therefore, disfacilitation of REM-off monoaminergic neurons together with stimulation of REM-on cholinergic neurons mediated through disfacilitation of inhibitory GABAnergic local interneurons caused by impaired hypocretin neurotransmission are proposed for abnormal manifestations of REM sleep.

Narcolepsy with Normal CSF Hypocretin Levels

There are debates about the pathophysiology of narcolepsy with normal hypocretin levels. Over 90 % patients with narcolepsy without cataplexy show normal CSF hypocretin levels, yet they show apparent REM sleep abnormalities (i.e., SOREMS). Furthermore, even if the strict criteria for narcolepsy–cataplexy are applied, up to 10 % of patients with narcolepsy–cataplexy show normal CSF hypocretin levels. Considering the fact that occurrence of cataplexy is tightly associated with hypocretin deficiency, impaired hypocretin neurotransmission is still likely involved in narcolepsy–cataplexy with normal CSF hypocretin levels. Conceptually, there are two possibilities to explain these mechanisms: (1) specific impairment of hypocretin receptor and their downstream pathway and (2) partial/localized loss of hypocretin ligand (yet exhibit normal CSF levels). A good example for the first hypothesis is Hcrtr 2-mutated narcoleptic dogs; they exhibit normal CSF hypocretin-1 levels [106], while having full blown narcolepsy. Thannickal et al. recently reported one narcolepsy patient without cataplexy (HLA typing was unknown) who had an overall loss of 33 % of hypocretin cells compared to normal, with maximal cell loss in the posterior hypothalamus [107]. This result favors the second hypothesis, but studies with more cases are needed.

Idiopathic Hypersomnia, a Hypocretin Non-deficient Primary Hypersomnia

With the clear definition of narcolepsy (cataplexy and dissociated manifestations of REM sleep), it became apparent that some patients with hypersomnia suffer from a different disorder. Bedrich Roth was the first in the late 1950s and early 1960s to describe a syndrome characterized by EDS, prolonged sleep, and sleep drunkenness, and by the absence of "sleep attacks," cataplexy, sleep paralysis, and hallucinations. The terms "independent sleep drunkenness" and "hypersomnia with sleep drunkenness" were initially suggested. [108], but now this syndrome is categorized as idiopathic hypersomnia with and without long sleep time [1]. Idiopathic hypersomnia should therefore not be considered synonymous with hypersomnia of unknown origin.

In the absence of systematic studies, the prevalence of idiopathic hypersomnia is unknown. Nosologic uncertainty causes difficulty in determining the epidemiology of the disorder. Recent reports from large sleep centers reported the ratio of idiopathic hypersomnia to narcolepsy to be 1:10 [109]. The age of onset of symptoms varies, but it is frequent between 10 and 30 years. The condition usually develops progressively over several weeks or months. Once established, symptoms are generally stable and long lasting, but spontaneous improvement in EDS may be observed in up to one-quarter of patients [109].

The pathogenesis of idiopathic hypersomnia is unknown. Hypersomnia usually starts insidiously. Occasionally, EDS is first experienced after transient insomnia, abrupt changes in sleep–wake habits, overexertion, general anesthesia, viral illness, or mild head trauma [109]. Despite reports of an increase in HLA DQ1,11 DR5 and Cw2, and DQ3, and a decrease in Cw3, no consistent findings have emerged [109].

The most recent attempts to understand the pathophysiology of idiopathic hypersomnia relate to the investigation of potential role of the hypocretins. However, most studies suggest normal CSF levels of hypocretin-1 in idiopathic hypersomnia [83, 110].

Nosological and Diagnostic Considerations of Major Primary Hypersomnias

Narcolepsy–cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia are diagnosed mostly by sleep phenotypes, especially by occurrences of cataplexy and SOREMPS (Fig. 38.4) (ICSD-2). Discovery of hypocretin deficiency in narcolepsy–cataplexy was a breakthrough, but also brought a new nosological and diagnostic uncertainty of the primary hypersomnias. Up to 10 % of patients with narcolepsy–cataplexy show normal CSF hypocretin-1 levels (Fig. 38.4). As discussed above, altered hypocretin neurotransmissions may still be involved in some of these cases. However, up to 10 % of patients with narcolepsy without cataplexy instead show low CSF hypocretin-1 levels, suggesting a substantial pathophysiological overlap between narcolepsy–cataplexy and narcolepsy without cataplexy, and

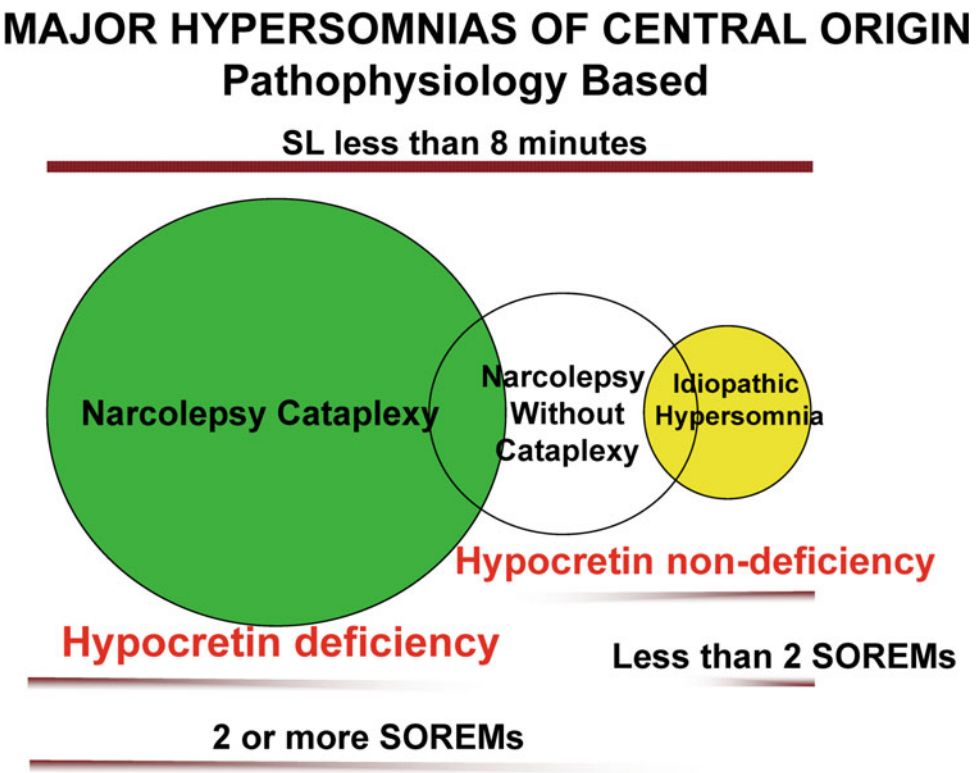

Fig. 38.4 Nosological and diagnostic considerations of major primary hypersomnias. Narcolepsy–cataplexy, narcolepsy without cataplexy and idiopathic hypersomnia are diagnosed by occurrences of cataplexy and SOREMPS. A pathophysiology-based marker, low CSF hypocretin levels are included in the ICSD2 for the positive diagnosis for narcolepsy–cataplexy. However, up to 10 % of patients with narcolepsy–cataplexy show normal CSF hypocretin levels. In contrast, up to 10 % of patients with narcolepsy without cataplexy show low CSF hypocretin-1 levels. These results suggest a substantial pathophysiological overlap between narcolepsy–cataplexy and narcolepsy without cataplexy. Similarly, a substantial overlap likely exists between narcolepsy without cataplexy and idiopathic hypersomnia, as these disorders are diagnosed by the occurrences of SOREMs (2 or more). However, test–retest reliability of detecting number of SOREMs in these conditions has not been systematically evaluated.

the hypocretin-deficient status (measured in CSF) does not completely separate these two disease conditions (Fig. 38.4). The situation is still the same under the ICSD-3 classification.

Similarly, concerns about the nosology of narcolepsy without cataplexy and idiopathic hypersomnia should also be addressed. Since patients with typical cases of idiopathic hypersomnia exhibit unique symptomatology such as long hours of sleep, no feeling of refreshment from naps, and general resistance to stimulant medications, the pathophysiology of idiopathic hypersomnia may be distinct from that of narcolepsy without cataplexy. However, current diagnostic criteria are not specific enough to diagnose these disorders; the test–retest reliability of numbers of SOREMS during MSLT is relatively low (less than 70 %) in narcolepsy and idiopathic hypersomnia [111].

CSF Histamine and GABAA Receptor Modulators in Narcolepsy and Idiopathic Hypersomnia

Although pathophysiology of hypocretin non-deficient hypersomnia is largely unknown, neurochemical changes in these conditions, namely reduced CSF histamine contents and increased activity of GABAA receptor modulators in the CSF, have recently been reported by two groups [112–114].

Histamine is one of these wake-active monoamines [115], and low CSF histamine levels are also found in narcolepsy with hypocretin deficiency [112, 113]. Since hypocretin neurons project and excite histamine neurons in the posterior hypothalamus, it is conceivable that impaired histamine neurotransmission may mediate sleep abnormalities in hypocretin-deficient narcolepsy. However, low CSF histamine levels were also observed in narcolepsy with normal hypocretin levels and in idiopathic hypersomnia, and decreased histamine neurotransmission may be involved in a broader category of EDS than in hypocretin-deficient narcolepsy [113]. Since CSF histamine levels are normalized in EDS patients treated with wake-promoting compounds, low CSF histamine levels may be a new state marker for hypersomnia of central origin [113]. The low CSF histamine levels in EDS were confirmed in a smaller sample of patients [116], but in a much larger sample size, the results were not replicated [117]. The reason for these discrepancies was not known, but an animal study indicated that CSF histamine levels are under the influence of the vigilance state/diurnal changes [118], and histamine in the CSF is very unstable, and thus a highly controlled study design is crucial for drawing definitive conclusion. The methodological differences in histamine measures (HPLC/post-column derivatization vs liquid chromatography-tandem mass spectrometry assay) may also be another factor to be considered for the discrepancy.

Rye et al. [119] recently reported that activities of substance in CSF that augments inhibitory GABA signaling are enhanced in hypersomnia. The authors demonstrated that in the presence of GABA (10 μM), CSF can stimulate GABAA receptor function in vitro (measures of GABAAR-mediated chloride currents in recombinant pentameric human GABAAR-expressed cultured cells). Interestingly, stimulations of GABAA receptor function by CSF of hypersomnolent patients (idiopathic hypersomnia with and without long sleep, long sleepers and narcolepsy without cataplexy) are significantly enhanced compared to those by CSF of control subjects (84.0 % vs. 35.8 %) [119]. This bioactive CSF component had a mass of 500–3000 daltons and was neutralized by trypsin. Flumazenil, a benzodiazepine receptor antagonist, reversed enhancement of GABAA signaling by hypersomnolent CSF in vitro, and flumazenil normalized vigilance in all seven hypersomnolent patients who underwent the drug challenge [119]. The authors conclude that a naturally occurring substances in CSF augment inhibitory GABA signaling, revealing a new pathophysiology associated with EDS. These results are especially interesting, as GABAAR has never been targeted for the treatment of hypersomnia. It is still unknown whether these changes are primary or secondary to the changes in other neurotransmitter systems. In this regard, it is critical to test whether the same change is observed in hypocretin-deficient narcolepsy–cataplexy.

These new findings are interesting as they are some of the first biomarkers for idiopathic hypersomnia, and these finding may lead to the development of new treatments for somewhat treatment-resistant hypersomnia. However, these markers do not discriminate the types of hypersomnia, and similar changes were observed in various types of hypersomnia.

Conclusion

Idiopathic narcolepsy–cataplexy is likely to be a clinical entity and be caused by postnatal selective cell death of hypocretin neurons. This is likely to be mediated by the autoimmune process (i.e., autoantibody presentation by specific human leukocyte antigen subtypes and T cell receptors), but the exact mechanism of the disease is not yet revealed.

Symptomatic narcolepsy has also been reported, but the prevalence of symptomatic narcolepsy is much smaller than the idiopathic type. The meta-analysis of these symptomatic cases indicates that hypocretin deficiency may also partially explain the neurobiological mechanisms of EDS associated with symptomatic cases of narcolepsy.

The pathophysiology of hypocretin non-deficient narcolepsy is debated, and the pathophysiology of idiopathic hypersomnia is largely unknown, but hypocretin deficiency is not likely to be involved in this condition. Decreased histaminergic neurotransmission is observed in narcolepsy and idiopathic hypersomnia, regardless of hypocretin status. Another study reported that activities of substance in CSF that augments inhibitory GABA signaling are enhanced in hypersomnia with various etiologies. Functional significances of these new findings (if these mediate sleepiness or passively reflect sleepiness) need further evaluation.

Although much progress has been made regarding the pathophysiology of EDS, this new knowledge has yet to be incorporated into the development of new treatments, and further research is critical.

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Motor Control and Dyscontrol in Sleep

39

Sudhansu Chokroverty, Sushanth Bhat, and Richard P. Allen

Introduction

Motor control in humans is the end result of a complex, intricate interplay between several central and peripheral loci, including the cerebral cortex, basal ganglia, brain stem motor centers, cerebellum, spinal cord, and the peripheral neuromuscular system [1–3]. The delicate balance of excitatory and inhibitory influences, created through the coordination of these systems, determines the occurrence of volitional movements and the suppression of unwanted ones. As an individual progresses from drowsiness to light sleep, slow-wave sleep (SWS), and rapid eye movement (REM) sleep, several additional factors come into play to further modulate motor activity. In recent years, there has been growing interest and a lot of research into normal and abnormal motor control in sleep. Disorders of motor control that occur in sleep may be those that are present during the day (diurnal movement disorders) but that impact sleep, either directly through their motor effects or indirectly through a variety of other mechanisms. Alternately, some motor disturbances are exclusive to sleep or the sleep–wake transition period. Motor disturbances in this latter group are generally classified as *sleep disorders*; the third edition of the International Classification of Sleep Disorders (ICSD-3) includes them in a specific category of sleep disorders called *Sleep-Related Movement Disorders* [4], and the American Academy of Sleep Medicine has elaborated on rules for recognizing them during polysomnography (PSG) [5].

This chapter discusses how motor control in sleep differs from that in wakefulness, classifies and describes disorders of motor control that intrude into sleep, including recommended treatment options, and discusses the investigative techniques employed in the evaluation of motor disorders in sleep. Non-motor symptoms in hypokinetic and hyperkinetic movement disorders that impact sleep are also briefly discussed. The main purpose of this chapter is to provide an overview of the various motor disturbances that impact sleep and to demonstrate a usable approach to the diagnosis and management of these disorders. This chapter should be useful to sleep medicine practitioners who deal with patients presenting with abnormal movements in sleep; however, readers are referred to several excellent volumes that discuss movement disorders in greater depth [6, 7].

Motor Control in Wakefulness and Sleep

The motor system is organized in a functional hierarchy at three levels: the forebrain, brain stem, and spinal cord (Fig. 39.1a, b). These three levels are under the control of two subcortical systems, the cerebellum and basal ganglia, and receive sensory inputs. The spinal cord is the lowest level in the scheme of the motor organization and contains neuronal circuits mediating reflexes and rhythmic movements. The motor neurons and interneurons of these circuits receive inputs both segmentally and supraspinally from higher centers. All motor commands ultimately converge either directly or indirectly (through the descending brain stem pathways) on the motor neurons in the anterior horn cells of the spinal cord, which Sherrington called

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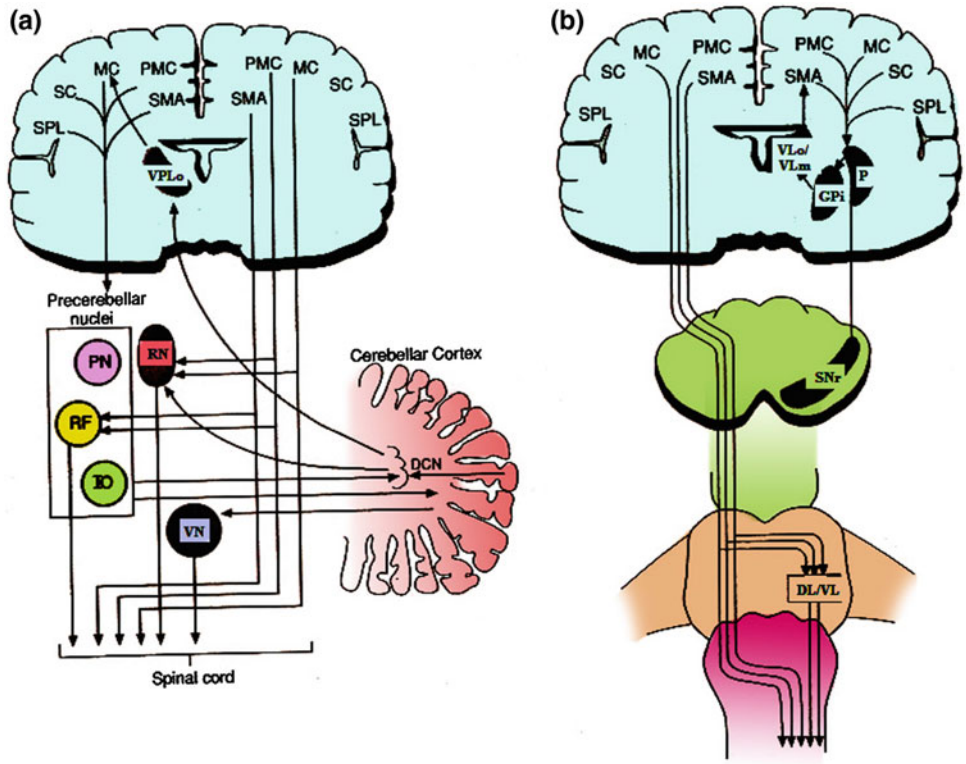

Fig. 39.1 **a** Showing schematically the principal relationships between cerebellum and other components of the motor system. *PMC* Premotor cortex, *SMA* Supplementary motor area, *MC* Motor cortex, *SC* Somesthetic cortex, *SPL* Superior Parietal Lobule, *DCN* Deep Cerebellar Nuclei, *VN* Vestibular Nucleus, *RN* Red Nucleaus Magnocellular portion, *PN* Ponitine Nuclei, *IO* Inferior Olive, *RF* Reticular formation, *VPLo* The oral portion of the ventral posterolateral nucleus of the ventrolateral thalamus. **b** Schematic diagram to show the basal ganglia-thalamocortical motor circuit. PMC, SMA, MC, SC, SPL: As in figure **a** *GPi* Globus Pallidus, internal segment, *SNr* Substantia Nigra pars reticulata. *VM* Ventromedial group of brain stem descending pathways (see text). *DL* Dorsolateral group of brain stem descending pathways (see text). *VLo/VLm* The nucleus ventralis lateralis pars oralis and ventralis lateralis pars medialis of the thalamus

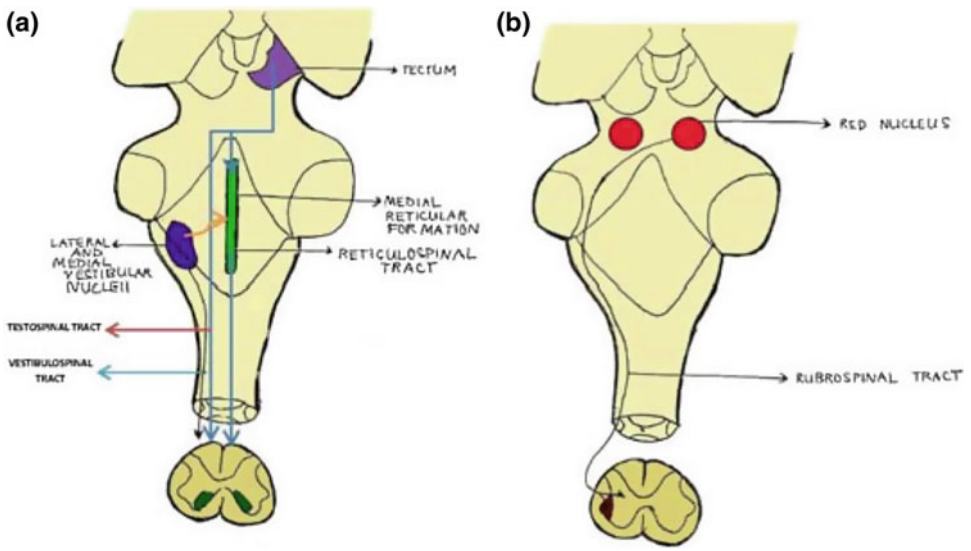

Fig. 39.2 Schematic diagram showing brain stem motor control. **a** Medial motor control pathway in the brain stem. **b** Lateral motor control pathway in the brain stem. (Modified from Ref. [8])

the "final common pathway" for motor actions [1]. In the next higher level at the brain stem, there are two descending systems: the medial descending systems consisting of the reticulospinal, vestibulospinal, and tectospinal tracts controlling posture and the lateral descending system consisting mainly of the rubrospinal system, controlling more distal limb muscles (Fig. 39.2a, b). The highest level, located in the cerebral cortex, controls spinal motor neurons directly through the corticospinal tracts and the brain stem motor neurons through the corticobulbar pathways. The cerebral cortex also controls spinal motor neurons indirectly through its influence on the descending brain stem systems. The major subcortical inputs to the motor cortex originate from the cerebellum and basal ganglia controlling the cerebral cortex through their projections to the thalamic nuclei.

The prefrontal cortex is responsible for the planning and initiation of voluntary movement. The premotor cortex and the supplementary motor cortex are involved in the programming of voluntary movement. Other parts of the cerebral cortex (e.g., somatosensory and association cortices including those responsible for tactile sensations, vision, and hearing) send their projections to the motor cortex for the coordination of skilled movements. Two subcortical circuits, the thalamocorticostriate and dentatorubrothalamocortical circuits, play a significant role in controlling coordination, posture, and muscle tone.

Muscle Tone, Posture, and Reflexes

In addition to voluntary targeted activity, motor control includes the control of muscle tone and posture directed by central generators and spinal stretch reflexes [1]. Phasic muscle contractions producing movements occur on a background of constant muscle tone, which can be defined as a state of mild contraction due to the firing of a few motor units of the muscle (i.e., due to asynchronous sustained firing of motor neurons). Clinically, muscle tone is perceived as the resistance offered by the muscle to stretch as a result of passive movement (flexion or extension) of a joint. The resting muscle tone is produced by viscosity and elastic properties of the muscle. Muscle tone is related to posture, state of alertness, and the degree of muscle stretch. Reticulospinal and vestibulospinal tracts influence the alpha and, to an extent, also the gamma motor neurons to maintain muscle tone.

Movements can be divided into three categories: voluntary, rhythmic, and reflexive. Reflexes are involuntary movements elicited by peripheral stimuli. Voluntary movements are goal-directed. The circuits for rhythmic movements lie in the spinal cord and brain stem. Alterations of muscle tone and movements may be *negative* (atonia and paralysis) or *positive* (hypertonia and abnormal movements). Central pattern generators responsible for locomotion are located in the mesencephalic and spinal locomotor centers. Central pattern generators in the midbrain and pons drive spinal locomotor generators. The mesencephalic locomotor region is under the control of the cerebral and limbic cortex (Fig. 39.3). The nature, however, of pattern generators is uncertain because the exact connection of interneurons is not known.

Motor Control in Wakefulness

In wakefulness, several circuits are involved in the generation and modulation of voluntary movement. These include the cortico-basal ganglionic-thalamo-cortical circuit, cortico-ponto-cerebello-thalamo-cortical circuit, descending brain stem motor pathways, brain stem, and spinal segmental

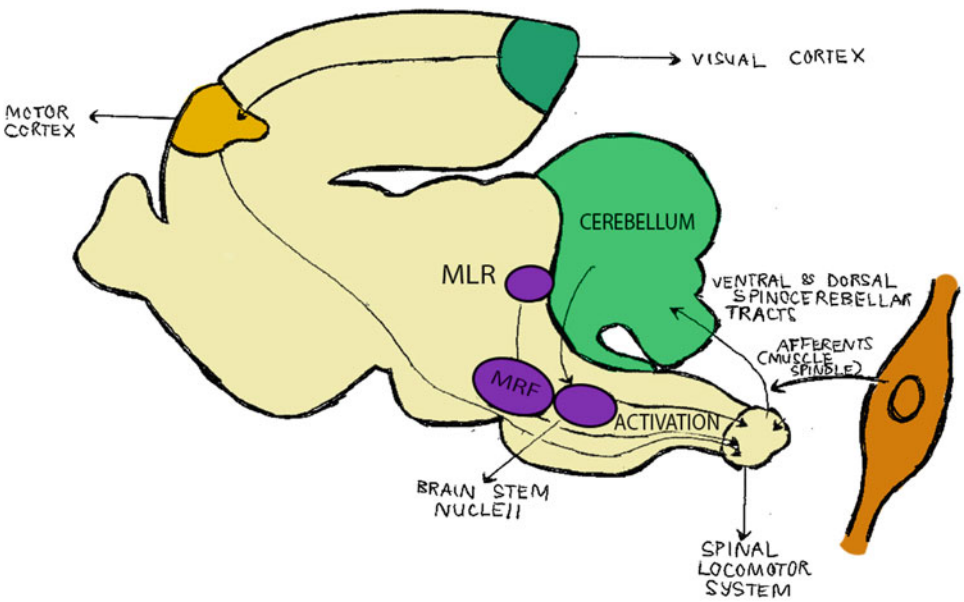

Fig. 39.3 Schematic diagram showing brain stem motor control: Mesencephalc locomotor ergion (MLR) and medial reticular formation (MRF) activating spinal locomotor region after receiving inputs from cerebellum, visual and motor cortices. (Modifed from Fig. 36.10 in "Locomotion." Ref. [8])

circuits. All these circuits are influenced by peripheral afferent inputs. To summarize, the cerebellum participates in the initiation, timing, and coordination of the movements; the basal ganglia help in influencing the direction, force, and amplitude of the movements, as well as the internal generation and assembly of movements; and the cerebral cortex selects, plans, programs, and commands the movement. The corticospinal system then distributes the commands, and the segmental spinal motor apparatus drives the muscles to execute the movements.

Changes in Motor Control in Sleep

In the simplest sense, it can be said that sleep causes a progressive decrease in muscle tone and inhibits gross movements. However, motor control in sleep is far more complex than this simple statement suggests. As in wakefulness, organized movements during sleep are the result of intricate checks and balances at multiple levels of the central nervous system—cerebral cortex, basal ganglia, thalamus, brain stem, cerebellum, and spinal cord. Sleep in general is dominated by central inhibitory drive, but the excitatory mechanism intermittently breaks through the inhibitory phase in normal individuals giving rise to physiologic motor activities during sleep (e.g., gross body shifts and hypnic jerks). It is the breakdown of this delicate mechanism of organized movements during non-rapid eye movement (NREM) sleep and REM sleep, due to a number of inciting factors and diseases, that causes abnormal motor events in sleep. In particular, lower centers (e.g., mesencephalic locomotor region and spinal locomotor generators) are released from controls by forebrain mechanisms as a result of a variety of conditions causing abnormal jerks, shakes, and screams during sleep. It is notable that Pakhomov in 1947 first observed a reduction in muscle tone in finger flexors during sleep [1]. The discovery of REM sleep associated with phasic eye movements and desynchronized EEG in 1953 by Aserinsky and Kleitman [9] paved the way to intense research into motor control during sleep. In 1959 Jouvet and Michel [10] observed muscle atonia in cats during REM sleep. This was followed by Berger's [11] observations of similar atonia in laryngeal muscles during human REM sleep, thus completing the description of REM sleep phenomena. Fundamental contributions to understanding motor control and muscle tone during sleep were subsequently made by Pompeiano [12], Chase and Morales [13], and Morrison [14] and Siegel [15]. To paraphrase Chase and Morales, "motor control landscape" in sleep is characterized by "storms of inhibition" coupled with brief "whirlwinds of excitation" directed toward the "final common pathway" [16, 17].

Modulation of Neuronal Firing

During wakefulness, most central neurons fire irregularly, at different frequencies in different brain regions. In NREM sleep, and especially during SWS, they fire more slowly compared to wakefulness (lower frequency) but tend to fire in bursts. During SWS, for example, thalamic cells fire slowly and are less responsive to afferent activity. These changes are related to the greater synchronization of surface electrical activity as measured by electroencephalography (EEG) during sleep. In REM sleep, by contrast, cellular activity is increased in many motor regions of the brain such as the primary motor cortex [18], thalamus, red nucleus, and cerebellum [19]. This increased firing in the motor centers of the brain is presumably balanced by the increased descending drive that occurs during REM sleep.

Motor Neuronal Modulation

More focused studies have examined motor neurons in the brain stem and spinal cord and traced backward some of the descending influences which modulate them depending on state. Recent studies have begun to establish the brain stem centers whose altered activity is related to the various stages of sleep and wake causing alterations in motor activity [20]. Particular information has been obtained about the control of REM sleep [21]. Neurons located near the border between the pons and midbrain such as the pedunculopontine nucleus (PPN) and laterodorsal tegmental (LDT) nuclei [22] appear to release acetylcholine into the more central reticular formation of the pons and medulla. These neurons can be divided into two classes: REM-on cells are selectively active during REM, while wake/some REM-on cells are also activated during wake. The REM-on cells are selectively inhibited by serotonin [23]. Various, as yet poorly defined, centers or cell groups in the reticular formation are then stimulated [24] to exert descending influences that act upon motor neurons. One current model suggests that cholinoceptive cells in a pontine inhibitory area project to the medulla where they release glutamate to stimulate inhibitory neurons in the medullary reticular formation [25]. Some of this modulation may also occur through suppression of the orexinergic system, which appears to cause arousal and increased motor activity in wake [26].

Reflex Modulation

Since much of motor behavior is generated, at least in part, by reflexes, studying reflexes can be quite relevant to examining changes of the motor system with state. The most commonly studied reflex has been the Achilles tendon reflex or its electrical counterpart, the H reflex. This reflex is diminished in NREM sleep, especially SWS, and then almost completely abolished in REM sleep, especially during rapid eye movements (REMs) [27]. Polysynaptic

spinal reflexes are similarly depressed in NREM and REM sleep [28]. A somewhat related bulbar reflex, the response of the genioglossus muscle to negative pressure in the airway, is decreased in NREM sleep [29] and may be further reduced in REM sleep [30, 31]. This reduced response has significant consequences, because reduced reflex gain may contribute to airway collapse and respiratory difficulties in sleep, especially obstructive sleep apnea (OSA). It has been noted that some brain stem reflexes, such as vestibular reflexes and the blink reflex, show decreased gain in NREM sleep but may then recover partially in REM sleep [32–34]. This recovery of some brain stem reflexes during REM sleep parallels the relatively greater activity of the eye muscles, compared to trunk and limb muscles at that time, and reinforces the mixed picture of excitation and inhibition characteristic of REM. Even drowsiness, short of actual sleep, can attenuate some reflexes, such as the vestibulo-ocular reflex, which has two outputs: quick restorative jerks to head rotation and slower smooth compensatory eye deviations [35]. The more polysynaptic quick jerks are more easily suppressed by even modest drowsiness. While all these various changes in reflex gain indicate altered excitability, they do not indicate where in the reflex arc the changes occur.

The basis for much of the reduced reflex gain during sleep is most likely inhibition of motor output, rather than decrease of sensory response. In one supportive study, Morrison et al. [36] created pontine tegmental lesions in cats that caused REM sleep without atonia. They found that both orienting to tone stimuli and acoustic startle responses were evident in REM sleep in the lesioned cats, but rare or absent throughout sleep in intact cats. Since the same tones elicited brain stem generated ponto-geniculo-occipital (PGO) waves in both normal and lesioned cats, it seems likely that the block to the further responses of orienting and startle reflexes is on the motor side of the reflex arc. PGO waves were also identified in the human pons, recorded during placement of a pedunculopontine nucleus stimulator [37]. On the other hand, sensory transmission may itself be altered by sleep. Studies have indicated that in primary afferent neurons located both in the spinal cord [38] and in the brain stem [39] there is a significant, presynaptically mediated decrease in responsiveness during REM sleep but not NREM sleep.

Reflexes can also change their characteristic motor output in sleep [40] indicating that sleep is not merely a general change in activity levels but a rearranged organization of responsiveness. Sensory stimulation, which would cause motor neuron excitation in waking, can cause additional inhibitory potentials in sleep [41]. In addition, certain reflexes which would be abnormal during waking, such as the Babinski sign, may be elicited in sleep [42, 43].

Effect of NREM Sleep on Motor Control

Progressive muscle hypotonia is a cardinal feature of sleep. In NREM sleep, motor activity is less than in the waking or resting state. At the onset of NREM sleep, intracellular microelectrode recording of motor neurons by Chase et al. [44] clearly showed either no change in membrane potential or a slight hyperpolarization. This, as well as disfacilitation of brain stem motor neurons controlling muscle tone, likely explains the mild muscle hypotonia seen in NREM sleep. Postural shifts, which may signal stage changes (into or out of wake or REM), occur. There are also small flickering movements, called sleep myoclonus, which may cause no apparent movement and are associated with very brief, highly localized electromyography (EMG) potentials seen on PSG [45, 46]. In some cases, these movements may have a greater amplitude and be of increased frequency, at which point they are called excessive fragmentary myoclonus, (EFM, discussed later in this chapter) but the significance of these movements, if any, is unknown [47]. The frequency of all movements decreases with depth of sleep, being least in SWS [48–50]. Postural shifts rarely occur before entrance into SWS. A number of abnormal motor activities such as somnambulism or periodic limb movements of sleep (PLMS) occur predominantly during NREM sleep. In infants, who move more in sleep, most NREM movements are generalized, full body movements or jerks, while REM movements tend to be more focal and uncoordinated [51].

Effect of REM Sleep on Motor Control

REM sleep is dramatically different from NREM. During REM sleep there is tonic reduction in muscle tone, even below that of SWS, in the presence of a highly active forebrain (paralyzed body with activated brain) with inhibition of the mesencephalic locomotor region. This is a protective mechanism to prevent abnormal movements during REM sleep in the presence of highly active cerebral cortex and forebrain regions. However, bursts of small movements ("phasic twitching"), similar to those seen in NREM sleep but more clustered, occur in REM sleep in association with bursts of REMs. During REM there is a close balance between strong upper motor center excitation and inhibition at the level of the motor effecter. When the inhibitory influences break down, significant motor activity may be released. Infants lack this inhibition and have more movement during REM. Inhibition can also be disrupted by lesions in the brain stem of animals which destroy the

inhibitory centers [52, 53] or, it is believed, in human sleep disorders such as REM Sleep Behavior disorder (RBD). The resulting movements may represent an "acting out" of dreams, which characteristically have a motoric component [54, 55].

The mechanism of muscle atonia during REM sleep includes an activation of a polysynaptic descending pathway from the perilocus coeruleus alpha region in the pons to the lateral tegmentoreticular tract, nucleus gigantocellularis, and magnocellularis in the medial medulla (the inhibitory area of Magoun and Rhines), ventral tegmentoreticular, and reticulospinal tracts to the alpha motor neurons, causing hyperpolarization and thus giving rise to muscle atonia (see Fig. 41.5) (see also Chap. 41). Immunocytochemical techniques detected an increased number of C-Fos (a nuclear protein synthesized during neuronal activation) labeled cells in the inhibitory region of Magoun and Rhines [56] during REM sleep. A key element in the REM sleep-generating mechanism in the pons is the activation of GABAergic neurons located in a subgroup of pontine reticular formation, as well as GABAergic neurons in the ventrolateral periaqueductal gray. An activation of GABAergic neurons causes an activation or disinhibition of cholinergic neurons and inhibition of noradrenergic and serotonergic neurons in the pons. The cholinergic neurons, in turn, excite pontine glutamatergic neurons projecting to the glycernergic pre-motor neurons in the medullary reticular neurons, causing hyperpolarization of the motor neurons and motor paralysis during REM sleep. Disfacilitation of motor neurons as a result of a reduction of the release of serotonin and norepinephrine partially contribute to muscle atonia. While many interneuronal regions of the brain stem show increased activity in REM sleep, motor nuclei (masseter, facial, and hypoglossal nuclei) show depressed activity. This is consistent with studies that have shown glycinergic inhibition of hypoglossal neurons in REM [57], perhaps contributing to the difficulties with airway patency in this sleep stage.

Motor neuron control at the cellular level results from synaptic transmission as manifested by the presence of excitatory post-synaptic potentials (EPSPs) or inhibitory post-synaptic potentials (IPSPs). During REM sleep, motor neurons are hyperpolarized by 2–10 mv (Fig. 39.4). There is post-synaptic inhibition causing a decrease in 1a monosynaptic EPSPs resulting in motor neuron hyperpolarization. During wakefulness and NREM sleep, there are a few spontaneously occurring low amplitude IPSPs, but during REM sleep, in addition to an increase of these low amplitude ISPSs, there are additional high amplitude sleep-specific IPSPs noted. These are generated by sleep-specific inhibitory interneurons located mainly in the brain stem (immunocytochemical techniques are used to prove this observation), which send long projecting axons to the spinal and short axons to the brain stem motor neurons. Glycine, the major inhibitory neurotransmitter, is the driving force for these IPSPs. The REM-specific IPSPs are abolished after strychnine (a glycine antagonist) administration [58] by microiontophoretic application into the ventral spinal cord but not after application of bicuculline or picrotoxin (GABA antagonists), thus proving that it is glycine and not GABA which is responsible for these IPSPs. Intermittently during REM sleep

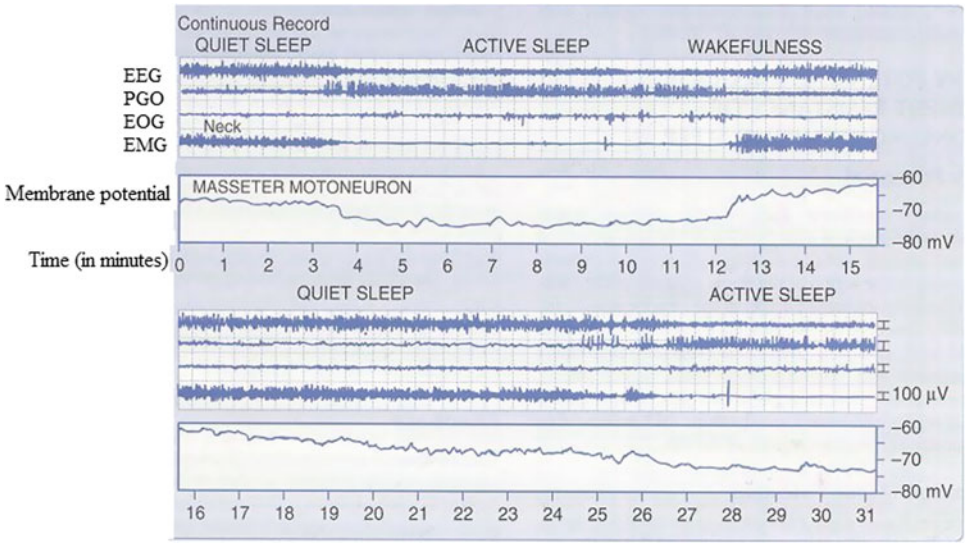

Fig. 39.4 Intracellular recording from a masseter motoneuron of a cat showing membrane potential and state changes during wakefulness, active (REM), and quiet (NREM) sleep. Note abrupt membrain hyperpolarization during active sleep accompanied by neck muscle hypotonia in the eletromyagram (EMG) and depolarization during wakefulness. In quiet sleep, membrane potential resembles that in wakefulness. Electroencephalogram (EEG); EOG, electro-otulogram: PG0, ponto-geniculo.occipital potential. (From Ref. [59])

there are excitatory drives causing motor neuron depolarization shifts as a result of EPSPs [28]. Glutamate is the excitatory amino acid for the REM EPSPs as these EPSPs are abolished by kynurenic acid (a glutamate antagonist) application near the ventral horn cells but not by NMDA antagonists. Muscle movements caused by these excitatory drives during REM sleep are somewhat different from the movements occurring during wakefulness. These are abrupt, jerky, and purposeless. EPSPs during REM sleep reflect increased rates of firing in the motor facilitatory pathways during REM sleep and enhanced IPSPs during REM sleep check these facilitatory discharges thus balancing the motor system during this activated state; otherwise the blind, unconscious subject will jump out of bed, as may happen in RBD (see below) [14]. Facilitatory reticulospinal fibers are responsible for transient EPSPs (phasic discharges) causing muscle twitches in REM sleep. Corticospinal or rubrospinal tracts are not responsible for these twitches because destruction of these fibers in cats [12] does not affect these twitches.

There are several additional factors that dictate the nature of motor control during sleep.

Circadian Activity Cycles

In humans, as in most animal species, the motor system's level of activity is dependent on an underlying circadian rhythm, even in the absence of a day–night light cycle (i.e., under constant conditions). As discussed in Chap. 6, circadian regulation of sleep, like many other important physiologic variables such as temperature, also shows circadian periodicity. While there may be a number of supplementary oscillators which control these rhythms [60–62], the suprachiasmatic nucleus (SCN) is thought to contain the most important oscillator [63] and to be the center which is responsible for the circadian variation of motor activity. The basic mechanism is a transcription–translation feedback loop [64, 65], elements of which are widely distributed in peripheral tissues [66]. Another mediator may be an expression of clock genes, such as the period gene, rPer2, which are widely distributed in different tissues and controlled by the SCN, and a large amount of SCN output is channeled through the subparaventricular zone of the hypothalamus (SPZ), which contains a specific region specialized in modulating motor activity [67, 68]. The SPZ also acts as an integrating center for various environmental influences that can impact on circadian rhythm, such as food availability, ambient temperature, and social interactions. Some of the hypothalamic regulation of motor activity is via the hypocretin system, which stimulates activity at the end of the activity period (the evening for humans) [69, 70]. In humans, activity is concentrated during the daytime hours and sleep at night; decreased movements in sleep may in fact be a marker of better quality sleep [71]. Movements in sleep are associated with autonomic surges, which may have long-term cardiovascular implications [72]. Therefore, this circadian periodicity of movement may be a protective factor. The clear separation of these periods begins to break down in normal aging and in cases of poor sleep or sleep-related disorders as well as in many movement disorders and degenerative conditions.

Development and Aging

The nature and occurrence of movements in sleep are affected by age. Movement frequency during sleep is greatest in infants, then decreases with age, even within the first few months of life [73, 74]. This is most likely due to the immaturity of regulatory mechanisms that maintain motor control in sleep. For instance, in one study, Kohyama [75] found that younger infants appear to lack the profound motor inhibition during phasic REM that is seen in older children and adults. Perhaps as a result of such immaturity, parasomnias such as somnambulism, or soliloquy are present with a greater prevalence during childhood, tending to decrease with age from early childhood on [76, 77]. Rhythmic movement disorder (RMD, see below) is also primarily a disorder of early childhood but may persist into adolescence or even adulthood in patients with significant cerebral injury or with autism [78]. With age, movements in sleep decrease; one study showed that position shifts during sleep decreased from 4.7 per hour in 8–12 year old subjects to 2.1 per hour in those 65–80 years old [79]. With aging, excessive motor activity may emerge again [80], including PLMS, RBD, and increased instability in NREM sleep manifesting as an increase in cyclic alternating pattern (CAP) [81]. In fact, these changes in CAP (see below) at various ages are increasingly being seen as a factor in age-related variation in the frequency and nature of motor dysfunction in sleep.

Drowsiness and the Sleep–Wake Transition Period

Even before sleep onset, the motor system reduces its level of activity. The sleep–wake transition period, a period of relative repose, has been called the *predormitum* by Critchley [82]. The subsequent transition to sleep is signaled by a variety of behavioral and EEG features [83]. The transition to sleep is a frequent inciting factor for a variety of jerks, jumps, and starts that may be a cause of concern to patients and their bedpartners. The most common of this is the "sleep start" or hypnic jerk. Another movement disorder activated in the transition to sleep is a form of propriospinal myoclonus [84]. These conditions are discussed in greater detail below. It is also during the sleep–wake transition period that the symptoms of restless legs syndrome (RLS) become prominent (see Chap. 40). RLS is relatively distinctive in that, unlike almost all other movement disorders, it is activated by rest.

Arousals, brief periods of interrupted, lighter sleep that may or may not lead to full awakening, are often associated

with movements. Arousals may both follow and lead movements such as body shifts. Abnormal movements, such as parkinsonian tremor [85] may recur during arousals. Sleep-related movements, such as PLMS, may provoke frequent arousals or even awakenings and may also continue during periods of arousal from sleep.

Metabolically, physiologically and behaviorally the period just after awakening, or "*postdormitum,*" is distinctly different from the predormitum [86–88]. Sleep offset occurs with abrupt changes in the EEG activity, unblocking of the afferent stimuli and restoration of postural muscle tone accompanied by a reduction of cerebral blood flow with concomitant decrement of cerebral metabolism as compared with that in presleep wakefulness [89]. This is in contrast to sleep onset with gradual changes in the EEG, blockade of the afferent stimuli at the thalamic level (essentially converting an "open" brain into a "close" one) and a reduction of postural muscle tone [90]. Because of these differences between the two states certain motor or other disorders preferentially occur in either predormitum (e.g., propriospinal myoclonus at sleep onset, hypnic jerks, RMD, hypnagogic imagery, and exploding head syndrome) or postdormitum (e.g., sleep inertia, awakening epilepsy of Jang, and sleep benefit in some Parkinson's disease patients). Sleep paralysis and hallucinations may occur in both states (hypnagogic and hypnopompic). Many of these conditions are discussed in greater detail below.

Effects of Sleep Stage on Motor Control

Changes in motor activity are dependent on the sleep state (i.e., wake, NREM sleep, and REM sleep). As discussed above, there is an orderly progression of loss of muscle tone as an individual proceeds through these stages, with muscle hypotonia being most pronounced in REM sleep, where only the diaphragm and extraocular muscles (as well as the middle ear muscles) are spared from almost complete paralysis. This is the underlying principle in measuring chin EMG during PSG. During wake, chin muscle tone is high and a tonically active chin EMG is interrupted by phasic contractions (facial expressions, tension, chewing, etc.). With relaxation and drowsiness, the level of EMG activity decreases. It further decreases as NREM sleep is achieved and deepens to SWS levels. Then, during REM sleep, EMG activity becomes minimal or even inapparent, although it may be occasionally interrupted with brief, irregular bursts of activity in phasic REM sleep, including the tongue [91]. These changes mirror, to a fair degree, the changes undergone by much of the motor system during sleep.

Any discussion on the effects of sleep stages, as determined by PSG, on motor control needs to be tempered by the fact that sleep staging in 30-second epochs, as is standard [5] (see Chap. 24) is based on rules that are arbitrary and are subject to a great degree of interscrorer variation. Physiologic processes are unlikely to adhere to these convenient timescales. For example, Mahowald and Schenck [92] reported on six patients with marked admixture of features from the different sleep–wake states (i.e., wake, NREM sleep, and REM sleep). These patients showed abnormal distribution of motor activity with relation to sleep features. Motor events, although typical of one sleep stage or state, may less commonly occur in other stages. For example, although PLMS are primarily a sleep phenomenon, these movements may also occur during arousals or periods of wakefulness after sleep onset (periodic limb movement in wake, PLMW), often as part of a periodic sequence of movements that span the sleep–wake divide [93]. PLMS occur primarily in NREM sleep but may also occur in REM sleep [94], especially in disorders of disturbed REM sleep such as narcolepsy and RBD [95, 96]. Patients with somnambulism, which typically occurs in NREM sleep, may show REM sleep motor abnormalities suggestive of RBD [97], and confusional arousals have been reported in REM sleep [98]. Even dream-enacting behavior, traditionally thought of as a REM parasomnia seen in RBD, has been reported in NREM sleep [99].

Table 39.1 summarizes the frequency of normal and abnormal motor activities that occur during the various phases of sleep and waking.

Cyclical Alternating Pattern and Movements in Sleep

The evaluation of periodic alternations in EEG activity represents an important additional means of scoring that may be more meaningful than the traditional, AASM mandated epoch-by-epoch scoring of sleep stages from a physiological perspective [5]. In NREM sleep, especially stage N2, this periodicity is common and designated the cyclical alternating pattern (CAP) [100]. First described by Terzano et al. [101], this pattern shows an alternation between bursts of both slow and fast activity (A phase) alternating with a medium frequency, lower amplitude activity (B phase). The burst-like activity (A phase) is associated with autonomic activation (Fig. 39.5). The A phases can include greater or lesser amounts faster frequencies: A1 has the least and A3 the most fast frequencies. A2 and A3 phases are often associated with arousals that can disrupt sleep [102, 103]. A number of different abnormal sleep-related movements are found to be associated with specific phases of the CAP cycle, especially the A phase. These include: PLMS [104] parasomnias or other sleep-related abnormal movements, such as bruxism [105], somnambulism [106, 107], or alternating leg movement activity during sleep (ALMA) [108], and nocturnal paroxysmal dystonia (NPD) [109]. CAP, especially phases A1 and A2, occurs more in early childhood [110], decreases during school age [111], may transiently increase during the adolescent period [112],

Table 39.1 Persistence of various movements in sleep

Motor activity	Awake/active	Drowsiness/sleep onset	Arousal/awakening	Stage 1 NREM	Stage 2 NREM	Stage 3 NREM	REM sleep
Normal motor activity							
Postural shifts	Very frequent	Frequent	Frequent	Common	Occasional	Rare	Occasional
Sleep myoclonus	Unreported	Rare	Rare	Common	Occasional	Rare	Frequent
Hypnic jerk	Unreported	Frequent	Occasional	Occasional	Rare	Rare	Unreported
Sleep paralysis [1]	N.A.	Common	Common	Rare	Unreported	Unreported	Frequent
Movement disorders							
Bobble headed doll syndrome	Frequent	Diminished	Diminished	None?	None?	None?	None?
Chorea	Very frequent	Frequent	Common	Occasional	Rare	Very rare	Rare
Dystonia	Very frequent	Common	Common	Occasional	Rare	Very rare	Rare
Fasciculations	Present	Present	Present	Present	Present	Present	Present
Hemiballismus	Very frequent	Common	Common	Occasional?	Occasional?	Very rare	Occasional?
Hemifacial spasm	Very frequent	Frequent	Frequent	Common	Common	Occasional?	Common
Hiccups—chronic	Frequent	Frequent	Frequent	Common	Common	Common	Common
Myoclonus: cortical/subcortical	Very frequent	Common?	Occasional?	Occasional?	Occasional?	Rare	Rare
Myoclonus: spinal	Very frequent	Frequent	Common	Common?	Common?	Occasional	Common?
Palatal tremor	Constant	Frequent	Frequent	Frequent	Frequent	Common?	Common?
Parkinsonian tremor	Very frequent	Common	Common	Occasional	Rare	Very rare	Occasional
Tics	Very frequent	Common	Common	Occasional	Occasional	Rare	Common
Sleep disorders							
Benign infantile myoclonus	N.A.	Unreported	Unreported	Common	Common	Common	Common
Bruxism	Common	Occasional?	Occasional?	Frequent	Frequent	Occasional	Frequent
Fragmentary myoclonus	Unreported	Unreported	Unreported	Frequent	Frequent	Common	Occasional
Mandibular myoclonus	Unreported	Unreported	Occasional?	Frequent	Frequent	Uncommon	Common
Npd	N.A.	Unreported	Common?	Frequent	Frequent	Occasional	Rare
PLMS: isolated or with RLS	N.A	Occasional	Occasional	Frequent	Common	Rare	Occasional
PLMS: narcolepsy, RBD	N.A.	Occasional?	Occasional?	Frequent	Common	Rare	Common
Propriospinal myoclonus at rest	N.A.	Frequent	Occasional	Rare	None	None	None
REM behavior disorder	N.A.	Unreported	Occasional?	Rare	Rare	Rare	Frequent
Rhythmic movement disorder	Common	Very frequent	Common?	Common	Common	Rare	Occasional?
RLS: restlessness	Rare	Very frequent	Frequent	Occasional	N.A.	N.A.	N.A.
Sleep terrors	N.A.	Unreported	Common? [2]	Rare	Uncommon	Usual	Occasional?
Somnambulism	N.A.	Unreported	Common?	Occasional	Common	Frequent	Occasional
Somniloquy	N.A.	Occasional	Common	Common	Usual	Uncommon	Occasional?

N.A. = Not Applicable
? = Limited Information
(1) In narcolepsy, presents as cataplexy in wake state
(2) Occurs together with incomplete, confusional arousal
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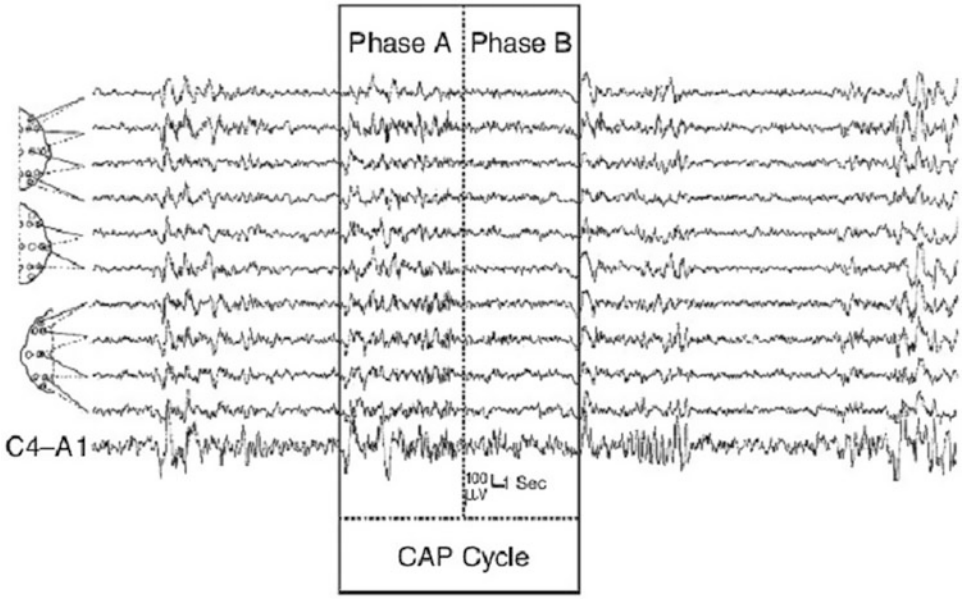

Fig. 39.5 Shows a cyclic alternating pattern (CAP) as part of a CAP sequence in Stage N2 sleep. The CAP cycle (highlighted) is defined by a Phase A (classified into threee subtypes A1, A2, A3 [subtype A2 is shown here] depending on the amount of high amplitude slow waves and low amplitude fast rhythms) followed by a phase B (relatively inactive) [each phase is 2–60 s in duration]. Bipolar EEG derivation (international electrode placement). Channels 1-6 from top: FP2-F4; F4-C4; C4-P4; P4-O2; F8-T4; T4-T6. Channels 7-11 from top: FP1-F3; F3-C3; P3-O1;C4-A1. (Reproduced with permission from Ref. [114])

decreases again in young adulthood, and then finally increases again in older ages [104]. CAP is a normal pattern, but deviations from normal amounts, especially excessive CAP can be abnormal [113].

Classification of Motor Disorders in Sleep

Motor disorders of sleep can broadly be classified into (1) diurnal movement disorders persisting into sleep and (2) primary sleep motor disorders (exclusive to sleep). The latter category can be further subclassified into disorders of motor control as the subject lays in bed trying to get to sleep, immediately before and at sleep onset, during NREM sleep, during REM sleep, during both NREM and REM sleep, and at sleep offset. These are listed in Box 39.1, and the individual motor disorders are discussed in detail in the following sections.

Box 39.1: Disorders due to Failure of Motor Control in Sleep

I. Diurnal Movement Disorders Persisting in Sleep

- Usually persisting in sleep
  - Symptomatic palatal tremor
- Frequently persisting in sleep
  - Spinal and propriospinal Myoclonus
  - Tics in Tourette's syndrome
  - Hemifacial spasm
  - Hyperekplexia
- Sometimes persisting in sleep
  - Tremor
  - Chorea
  - Dystonia
  - Hemiballismus

II. Disorders of Motor Control Unique to Sleep

A. Failure of motor contol while resting in bed trying to get to sleep

- Restless legs syndrome (myoclonic-dystonic movement in quiescence)

B. Failure of motor control at NREM sleep onset (including predormitum, an ill-defined stage between sleeping and waking)

- *Physiological*
  - Physiological body movements and postural shifts
  - Physiological hypnic Myoclonus

  - Hypnic jerks
  - Hypnagogic foot tremor
  - Alternating leg muscle activity
  - Rhythmic limb movements
- *Pathological*
  - Intensified hypnic jerks
  - Rhythmic movement disorder
  - Propriospinal Myoclonus at sleep onset

C. Failure of motor control during NREM sleep

- Partial Arousal Disorders
  - Confusional arousals
  - Sleepwalking
  - Sleep terrors
  - Sleep-related eating disorder (SRED)
- Others
  - Periodic Limb Movements in Sleep

D. Failure of motor control during REM sleep

- *Physiological*
  - Phasic muscle bursts (Myoclonus) including fragmentary hypnic myoclonus
  - Phasic tongue movements
  - Phasic rapid eye movements
  - Periorbital integrated potentials (PIPs)
  - Sleep paralysis
- Pathological
  - REM Behavior Disorder (RBD)
  - Sleep paralysis with narcolepsy
  - Familial sleep paralysis

E. Failure of Motor Control in both NREM and REM sleep

- Rhythmic movement disorder
- Catathrenia
- Excessive fragmentary Myoclonus
- Sleep bruxism
- Upper airway obstructive sleep apnea

F. failure of Motor Control during Sleep offset

- Sleep paralysis
- Hypnopompic hallucinations
- Sleep inertia ("sleep drunkenness")

Description of Individual Motor Disorders of Sleep

A. Diurnal Motor Disorders Persisting into Sleep

As a general rule, most abnormal movements seen during the daytime show a markedly decreased frequency, amplitude, and duration in sleep and tend to be limited to light NREM sleep (stages N1 and N2) [115]. Much less commonly, they will be reactivated during REM sleep as well. Only tardive dyskinesias and primary palatal tremor may show complete cessation of movements during sleep.

The degree of persistence of various abnormal daytime movements into sleep varies greatly (Table 39.1). In one of the most informative studies on the topic, performed using EMG, accelerometry, and split screen video recording. Fish et al. [85] examined the relationship of motor activity not only to conventional sleep staging, but also to epochs with transitions (to lighter or deeper sleep stages or to wakefulness). They also monitored the 2-second periods before onset of dyskinesias in patients with Parkinson's disease, Huntington's disease, Tourette syndrome, and torsion dystonia (both primary generalized and secondary) and scored them for presence of arousals, REMs, sleep spindles, and slow waves. They compared these dyskinesias to normal movements both in patients and in normal subjects. Forty-one of 43 patients had characteristic movements that persisted in sleep. In every disorder, both normal movements and dyskinesias followed the same general plan: most common in wakeful epochs followed by lightening, in stage N1 sleep, REM sleep, then stage N2 sleep, with no movements in SWS. Only Tourette patients had dyskinesias during transition from wake to sleep. The 2-second period before both normal and abnormal movements showed arousals most commonly, followed by REMs, with spindles and slow waves rarely. These results support prior speculation [116] that both dyskinesias and normal movements are likely to be modulated by sleep in a similar fashion. This may be due either to the general suppression of centers for both normal and dyskinetic movements or suppression of some common descending path, such as the pyramidal tract.

It should be noted that all of the abnormal motor activities described in the experiment above, which tended to become attenuated and repressed by sleep, are thought to be generated in higher motor centers, most of them located above the brain stem. On the other hand, movement disorders associated with

abnormalities of the lower motor centers, specifically the brain stem and spinal cord, have a greater tendency to persist during sleep [117]. Perhaps the best example is acquired (rather than primary) palatal myoclonus or palatal tremor (see below), which persists in sleep, although the frequency or persistence of these movements may vary with sleep stages [118]. In addition, spinal myoclonus will often persist during sleep [119]. Similar persistence may be seen in hemifacial spasm [120, 121], which is thought to involve damage either in the brain stem facial nucleus or in the peripheral nerve (cross talk due to ephaptic transmission) or both. Also, fasciculations due to damage to the lower motor neuron, whose generator lies at the spinal cord level, may persist in sleep [122].

In addition to the impact of the movements in sleep themselves, many disorders in which abnormal movements are a prominent feature impact sleep in other ways, including by causing changes in sleep architecture, mood, and level of daytime alertness, and medications treating the primary condition may equally affect the above domains, decreasing the patient's quality of life. These aspects are discussed below.

i. Sleep-Associated Problems of the Hypokinetic Disorders

Parkinson's Disease

Sleep impairment is a cardinal feature of Parkinson's disease. The original quotes from James Parkinson are worthy of note [123].

> But as the Malady proceeds …. (P.6)
>
> In this stage (stooped posture with "unwillingly a running pace"… most likely stage 3), the sleep becomes much disturbed. The tremulus motion of the limbs occur during sleep and augment until they awaken the patient, and frequently with much agitation and alarm. (P.7)
>
> …. and at the last (advanced bedridden stage), constant sleepiness, with slight delirium, and other marks of extreme exhaustion, announce the wished-for release. (P.9)

A spectrum of sleep dysfunction occurs in Parkinson's disease (see Fig. 39.6). Many studies have confirmed the fact that sleep is a major issue for patients with Parkinson's disease and their quality of life [124, 125]. Sleep disturbances also appear to impact cognition in Parkinson's disease, although the mechanisms and exact relationships remain unclear [126]. Many studies have shown sleep architectural disturbances in Parkinson's disease, including shorter total sleep time, lower sleep efficiency, and increased REM latency [127]. There have been conflicting reports on whether dopaminergic therapy improves sleep architectural changes [128, 129]. Early reports do seem to suggest that deep brain stimulation in Parkinson's disease appears to improve NREM sleep, abnormalities of REM sleep, and improve daytime sleepiness [130]. Compared with controls, there appears to be disruption of a number of circadian processes in parkinson's disease; including a sustained elevation of serum cortisol levels, reduced circulating melatonin levels, and altered peripheral clock gene expressions, and sleep disturbances, at least in part, may be related to this mechanism [131]; however, recently published data also suggest that dopaminergic therapy, while increasing melatonin levels (thus theoretically promoting sleep), may also show a delayed sleep onset relative to dim light melatonin onset (DLMO), suggesting that it may uncouple circadian

Fig. 39.6 Schematic diagram showing the spectrum of sleep dysfunction in Parkinson's Disease

and sleep regulation [132]. In recent years, several questionnaires have been developed and validated that can be used to assess sleep-related problems in Parkinson's disease, and liberal use of these instruments helps detect sleep issues [133–137]. Poor sleep in patients with Parkinsons's disease is multifactorial but can broadly be divided into being due to motor and non-motor symptoms.

Motor Symptoms Impacting Sleep

The persistence of the parkinonian tremor into sleep, and its reoccurrence during periods of sleep–wake transition, is a major cause of sleep fragmentation. Parkinsonian tremor decreases in amplitude and duration in early NREM sleep and may lose its alternating aspects and is rarely seen in Stage N3 and often disappears in REM sleep [138]. Bradykinesia often causes trouble turning in bed, which is an additional source of discomfort and may contribute to poor sleep quality.

On the other hand, sleep can also influence these motor symptoms in a positive way; in some patients, sleep can reduce Parkinsonian disability and alleviate symptoms [139–141], perhaps due to the circadian peak of dopamine in the morning [142]. Sleep benefit may last from 30 min to three hours. This may be particularly true of patients suffering from early onset Parkinsonism such as that due to the most common recessive Parkin (PARK2) mutation. Sleep benefit is less consistent in those with the recessive Pink1 (PARK6) mutation [143, 144]. Sleep benefit in this group of early onset patients is often associated with some degree of dystonia.

A major parasomnia that causes motor dysfunction occurring in patients with Parkinson's disease is RBD, which can disrupt sleep and be potentially injurious to the patient and the bedpartner. RBD may precede the diagnosis of Parkinson's disease or other extrapyramidal disorders by several decades. This association may be due to the Parkinsonian degeneration affecting brain areas and systems responsible for sleep–wake regulation [145]. A recent scheme postulates that the synuclein pathology of Parkinson's disease (Lewy Body pathology) ascends from the brain stem to the basal ganglia and finally to the cortex [146, 147], with early involvement of sleep regulatory nuclei before development of motor symptoms [148]. The combination of RBD with olfactory dysfunction may be a strong predictor for later development of Parkinson's disease [149]. In general, RBD patients show subtle motor, cognitive, autonomic, olfactory, and visual changes that are associated with Parkinsons's disease [150, 151], as well as brain perfusion changes determined by single photon emission computerized tomography (SPECT) imaging [152]. A recent finding is that of markedly reduced cardiac I-metaiodobenzylguanidine (MiBG) uptake, consistent with the loss of sympathetic terminals, in idiopathic RBD similar to the deficit seen in Parkinson's disease [153]. One recent study suggests that RBD occurs primarily in Parkinson's disease patients who have the non-tremor form [154]. The authors also suggest that RBD will not precede early onset Parkinson's disease, an observation supported in cases of PARK6 (PINK1) early-onset familial PD [155]. RBD later in the course of Parkinson's disease may be associated with additional complications such as hallucinations [156, 157], which may represent REM intrusions and cognitive decline [158]. A detailed analysis of movements in five patients with Parkinson's disease and RBD found that they had many more movements in sleep than controls, but that most movements were brief and restricted in scope [159]; 3.6 % of all movements were violent while 10.5 % involved vocalizations. It has also been proposed that RBD-related movements may show "normalization" of motor control in Parkinson's disease, with reduction in bradykinesia and vocal hypomimia [160]. Diagnosis and management of RBD is discussed in detail in Chap. 49 and 50.

There has been much research into the association between Parkinsons's disease on the one hand, and RLS and PLMS on the other. Recent studies have suggested that the prevelance of RLS is increased in patients with Parkinson's disease [161–163], including association in one family with a parkin mutation [164]. But this association is only poorly understood [165–167]. Some studies report that most RLS symptoms develop after onset of Parkinson's disease and initiation of dopaminergic treatment. This suggests that RLS may be provoked by such treatment rather than the disease itself; indeed, such treatment has been shown to induce RLS through a process of "augmentation," even in those who do not have RLS [168]. In one communication, subthalamic deep brain stimulation was reported to have induced RLS [169], but this may have been due to decreased medication doses. Similarly, some studies have found increased PLMS in patients with Parkinson's disease [170, 171], but one small study of de novo patients found no such elevation [172]. Thus, while it remains unclear if RLS and PLMS truly occur more frequently in patients with Parkinson's disease outside of dopaminergic treatment, when they do occur, they represent another factor that fragments sleep. Both RLS and PLMS are discussed in greater detail in Chap. 40.

Nonmotor Symptoms Impacting Sleep

Excessive Daytime Sleepiness and Irresistable Sleep Attacks

Excessive daytime sleepiness (EDS) is a common symptoms in Parkinson's disease and has been found to be more frequent in patients than in controls (15.5 % vs. 1 %) [173]. More advanced disease, higher frequency of cognitive decline and co-occurrence of depressive symptoms, more hallucinations,

and longer time on levodopa are predictive factors [174]. This daytime somnolence can exist even without evidence for or complaints of severely disrupted sleep [175, 176]. A related condition is the occurrence of Parkinson's disease-related "irresistable sleep attacks," sudden episodes of sleep that appear without warning on a background of normal alertness [177]. These attacks are much rarer than pervasive daytime sleepiness that the patient is aware of [178, 179]. Genetic variants of the preprohypocretin [180] and dopamine D2-receptor genes [181] have been associated with predisposition to sleep attacks. Some patients with Parkinson's disease have a narcoleptic phenotype, including a finding of sleep onset REM periods (SOREMPs) [182, 183]. This can be seen as 2 or more SOREMPs on multiple sleep latency test (MSLT; 4 or 5 naps scheduled during the day at 2 h intervals). Consistent with narcolepsy, hypocretin neurons are progressively lost with more severe Parkinson's disease [184], most likely due to Lewy Body degeneration. The picture in Parkinson's disease, however, is often more complex, while cataplexy, a key finding in narcolepsy, is generally absent [185]. Additionally, both EDS and irresistable sleep attacks can be caused by dopaminergic medication, especially at higher doses; non-ergot agonists specifically, may be more likely to cause somnolence. Treatment of daytime sleepiness may include the use of stimulants. Some recent studies have supported the use of modafinil as a relatively well tolerated stimulant [186–188], but one double-blind placebo-controlled study failed to support efficacy [189].

Sleep-Disordered Breathing

Respiratory disturbances are common in Parkinson's disease and other related neurodegenerative disorders due to changes in upper airway function or disturbed central regulation of breathing. This may be due to Lewy Body deposition leading to cell loss. Altered upper airway function may be based on weakness of respiratory and upper airway muscles or on altered muscle tone and coordination. The prevelance of SDB in Parkinson's disease has been demonstrated to be indepenedent of the degree of severity of motor and non-motor symptoms [190], but male gender and greater duration of illness are predictors [128]. Patients with Parkinson's disease may have stridor or laryngeal spasm associated with off-states or dystonic episodes [191], although this is more common in multiple system atrophy (MSA, see below). Abnormal vocal cord function with regular rhythmic movements or irregular jerky movements in the glottic area may also produce changes of airflow and contribute to intermittent airway closure [192]. Similar activity persisting during sleep can lead to OSA or upper airway resistance syndrome [193]. Snoring has occurred in the majority of subjects in some series [194]. It has not been definitely established that the prevalance of respiratory dysfunction during sleep in patients with Parkinson's disease as a whole is any higher than in healthy elderly persons [195, 196]. However, in some studies sleep-disordered breathing was more frequent and occurred in up to 50 % of patients with Parkinson's disease [197]. Trouble turning in bed may be a contributory factor in those patients with positional OSA [198]. Patients with parkinsonism and autonomic impairment more often develop sleep apnea and related respiratory abnormalities, including central and obstructive apneas and nocturnal hypoventilation. In the presence of sleep apnea, patients with autonomic impairment are probably more likely than other patients to have nocturnal cardiac arrhythmias. An interesting recent report suggested that treatment with dopaminergic agonists predisposed patients with Parkinson's disease to central sleep apnea [199] but more research on the subject is clearly needed.

Insomnia Insomnia, both sleep initiation and sleep maintenance, is a common complaint among patients with Parkinson's disease and is likely multifactorial [200]. Intrusion of motor symptoms into sleep (see above), depression and anxiety, concomitant sleep-disordered breathing and RLS, and in many cases dopaminergic treatment itself may contribute to insomnia in this population [201]. Other side-effects of medication include nightmares that may worsen underlying anxiety. Nevertheless, where motor symptoms seem to be the biggest impediment to quality sleep, appropriate therapy, including long-acting forms of dopaminergic medications to cover the night [202, 203], and, in some cases, deep brain stimulation [204, 205] may be helpful. Treatment of mood disorders with cognitive behavioral therapy and suitable antidepressants and anxiolytics is also recommended. SDB must be identified and adequately treated with continuous upper airway pressurization (CPAP) therapy.

Other Extrapyramidal Neurodegenerative Conditions

Alpha-synuceinopathies other than Parkinson's disease (the "*Parkinson's plus*" *syndromes*) have sleep disurbances as severe as those seen in Parkinson's disease itself, most likely due to the same pathology of Lewy Body-related neurodegeneration. RBD occurs in most of them and is in fact more common in MSA than in Parkinson's disease. Disturbances of sleep architecture, SDB, EDS, and insomnia are also frequent.

Progressive Supranuclear Palsy (PSP) Patients with this condition have been reported to have severe sleep disruption with reduced total sleep, marked diminution in sleep spindles, reduced REM sleep time with abnormal REMs, disordered sleep architecture, and frequent awakenings [206–212]. RBD is frequent [213, 214], although possibly less common than with Parkinson's disease [215]. As with

Parkinson's disease, sleep disruption increases with severity of the motor abnormalities [208–210]. The greater sleep abnormalities of PSP compared to Parkinson's disease may be due to the greater brain stem pathology, especially that in the pedunculopontine tegmentum, a region linked to control of REM sleep; one report also found that cerebrospinal fluid (CSF) hypocretin levels were lower in patient with PSP than in those with Parkinson's disease [216].

Multiple System Atrophy (see also Chap. 41)

Among the extrapyramidal disorders, sleep disruption appears to be worst in MSA [217–221], and these patients may be especially sensitive to the hypersomnolence induced by dopaminergic therapy [222]. Patients with severe MSA may even lack normal circadian regulation of sleep [223]. As mentioned above, RBD is very common [224], although RBD is unlikely to be seen in pure autonomic failure and provides one means of differentiating the two conditions [225]. PLMS is prevalent as well [221]. A somewhat characteristic feature of MSA is the occurrence of atrophic paralysis of the laryngeal abductor [226], or sleep-related hyperactivity of the adductors, which has been described as dystonic [227], leading to a coarse, snoring-like sound, and laryngeal stridor [228]. In fact, stridor, a potentially life-threatening condition that may cause sudden death from respiratory arrest [229, 230], has been reported as the first or even only apparent sign of MSA [231, 232]. Milder cases may be managed with CPAP [233]; more severe cases require tracheostomy. In some cases, patients with MSA may have predominantly central sleep apnea [234].

ii. Sleep-Associated Problems of the Hyperkinetic Disorders

The hyperkinetic disorders are a diverse group characterized by excessive involuntary movement, often coupled with a deficiency of voluntary movement such as bradykinesia.

Chorea

Chorea consists of movements that occur in a flowing or irregular pattern and appear to migrate from one part of the body to another. They may be increased with action and typically are seen in the face and distal limbs [6].

The best-known cause of chorea is *Huntington's disease*, an autosomal dominant disease with a known mutation of the *IT15* gene located on the short arm of chromosome 4. The mutation in Huntington's disease is the expansion of a CAG repeat in the DNA that leads to increased length of a polyglutamine tract in the protein product, now called *huntingtin*. Currently, research is directed at finding the function of huntingtin in the normal brain and the elucidation of the toxic effect of the mutated protein. Although huntingtin is widely distributed in the brain, the pathology of Huntington's disease is more restricted. Patients also have prominent psychological symptoms, including depression, psychosis, and behavioral disorders. Onset is typically between the ages of 25 and 50, although it may occur even in the first decade or in late adult life. Progression is slow but relentless, with eventual debility, dementia, and inanition occurring in those with onset before old age.

Sleep disturbances in Huntington's disease have been the focus of considerable research. Recently, investigators found that sleep disturbances may be the earliest manifestation of Huntington's disease [235]. There appears to be no correlation between CAG repeat length and sleep disturbances [236]. Investigators have shown a variable persistence of chorea during sleep, with most chorea present in awakening, and in the lighter stages of NREM sleep (stages N1 and N2), similar to other dyskinesias [85]. One study reported an increase in overall sleep movements in Huntington's disease [237]. There has also been some research into sleep architecture in Huntington's disease, but the results have been inconclusive. Some reported deficits include prolonged sleep latency, excessive waking, decreased SWS and REM sleep, and decreased sleep efficiency, possibly correlating to caudate atrophy [238–240]. Reports of alterations in sleep spindles in Huntington's disease have been inconsistent [241, 242]. It has been suggested that nocturnal agitation and sleep disruption in Huntington's disease patients is secondary to anosognostic voluntary movements on arousals, rather than to RBD [236]. A recent study of 30 patients with Huntington's disease showed that they, compared to controls, had shorter sleep duration, reduced sleep efficiency, increased arousals and awakenings, and higher PLMS index in both NREM and REM sleep, but were not at increased risk for RBD or SDB. Greater clinical disease severity predicted decreased REM sleep percentage and greater daytime sleepiness [243]. Other studies have confirmed that unlike patients with parkinsonism, patients with Huntington's disease have not been found to have a significant number of sleep apneas contributing to impaired sleep [244].

Sleep has not been well-studied in other conditions with predominant chorea. Broughton et al. [245] reported that four patients with *Sydenham's chorea*, which follows a streptococcal infection, had reactivation of their movements during REM sleep. Neuroacanthocytosis or chorea-acanthocytosis, is an often inherited movement disorder with chorea, tics, vocalizations, and self-mutilation together with frequent seizures, associated with elevated acanthocytes (spiked red cells) in blood smears [246–248]. Silvestri et al. [249, 250] reported that in this condition, abnormal movements persisted during sleep, but with decreased amplitude, duration, and frequency. Patients frequently vocalized during REM sleep. Sleep was

fragmented and of poor quality. Two siblings with neuroacanthocytosis showed EEG slowing (predominantly delta) both while awake and during REM sleep [251], indicating abnormal cerebral function. RLS has been reported to occur in this condition [252].

Dystonia

Dystonia is a condition characterized by sustained distorted or twisting postures and contorting movements, often mixed with a variety of jerk-like or oscillatory movements [253]. Dystonia can be primary or secondary and can be of variable extent, focal, segmental, or generalized, depending on the area of involvement. Dystonia includes a number of different conditions, some of which, such as early onset torsion dystonia, have a single-gene basis. The protein for early-onset torsion dystonia, torsin A, has been found to bind adenosine triphosphate, but how it causes dystonia itself remains unresolved [254–258]. Not all idiopathic dystonia patients have been shown to have a genetic mutation, however, and there are many cases of secondary dystonia that do not appear to depend on common dystonia genes [259]. One problem in evaluating sleep complaints in dystonia is that the studies so far have often examined a fairly heterogeneous collection of patients with different distributions of dystonia and different etiologies.

Although they usually subside significantly, dystonic movements may persist during sleep at a reduced frequency and amplitude. They are maximally reduced during SWS and may be partially reactivated during REM sleep episodes [260]. In the study by Fish et al. [85] of dyskinetic movements, both primary and secondary dystonic patients followed the general pattern of more frequent dyskinetic movements during wakefulness, fewer movements in stage N1 sleep, only infrequent movements in stage N2, REM, and SWS, and no movements during epochs of deepening sleep. In a study including focal and segmental dystonias, Silvestri et al. [249] found that Meige's syndrome (oromandibular dystonia), blepharospasm, and tonic foot syndrome all showed persistent abnormal activity during sleep, with reduced amplitude, duration, and frequency of EMG bursts. The greatest suppression was in SWS and REM sleep.

Inhibitory mechanisms are postulated to be defective in dystonia. This prompted Fish et al. [261] to study both primary and secondary dystonics to determine whether REM inhibition is intact. They found that all dystonics had normal chin EMG atonia. No patients had complex abnormal activity during REM sleep. In an attempt to analyze motor excitability, the authors successfully stimulated three normals and seven primary dystonics with a magnetic coil over the vertex to evoke a motor response in the fifth finger abductor, the abductor digiti minimi. Whereas response amplitudes were highly variable, dystonics, like controls, showed a decrease in the mean response during REM sleep relative to responses obtained before and after the sleep study in relaxed wakefulness. Latencies were prolonged on average in all groups. The findings of decreased amplitude and prolonged latency were consistent with REM motor inhibition. Occasional high-amplitude responses may have corresponded to periods of phasic excitation. These results indicate that, whatever may be the decreased inhibitory processes in dystonia, they do not involve the descending inhibitory pathways of REM sleep.

Studies of sleep in dystonia have not been systematic; studies have involved small numbers of patients on diverse medications, some of whom had prior thalamic surgery [262]. In these studies, sleep has been found to be inconsistently disrupted, with more severe fragmentation seen in more advanced cases [263]. A number of studies have reported the presence of exaggerated sleep spindles in dystonia [264, 265]. The major therapeutic effort in these patients is the attempt to reduce the dystonic movements. Successful therapy of the movements should also improve sleep.

It is not known that to what degree different forms of dystonia—early- versus late-onset, focal versus generalized—differ in their relationships to sleep, although one striking form of dystonia, variably called *hereditary progressive dystonia with marked diurnal fluctuations* (HPD), *dopa-responsive dystonia* (DRD), and the *Segawa variant*, often shows distinct circadian variability [266–268]. These patients typically present at a young age, often in the middle of the first decade, with postural dystonia, usually affecting one leg and sparing the trunk and neck. Thereafter, the dystonia spreads and parkinsonian signs, which are present at onset in a minority of patients, become more prominent. The condition is usually inherited in an autosomal dominant mode with a mutation in GTP cyclohydrolase I (GCHI) [269, 270]. A number of different mutations in GCHI have been described, but, less commonly, it seems that the condition can be inherited recessively with a mutation in tyrosine hydroxylase [271]. Some studies have found that even patients thought to have more typical idiopathic torsion dystonia may harbor a mutation in the *GCHI* gene [272]. A number of these patients may obtain significant symptomatic relief from sleep, similar to the sleep benefit seen in Parkinson's disease, and therefore are minimally impaired early in the day, and even some dystonic patients unresponsive to L-dopa may have similar benefit from sleep. These patients do show abnormal movements in sleep. Segawa et al. [273] obtained movement counts from PSG with multiple EMG channels (8–12 surface recordings on trunk and limbs) and found that in DRD, there is a decrease in gross body movements in stage I sleep, an increase in stage II sleep, and a decrease in REM sleep. In

contrast, localized twitch movements were depressed in all sleep stages, but followed the normal relative distribution between stages.

Patients with diurnal dystonia or the nocturnal sleep abnormalities of DRD are responsive to low doses of L-dopa, often as little as 50–200 mg per day with decarboxylase inhibitor [274]. Some patients can maintain a stable therapeutic effect with doses every other day. Patients with long-standing disease (24–45 years before treatment) may benefit as well as those with recent onset. DRD patients can use L-dopa without the development of the dyskinetic side effects that are so prominent in juvenile parkinsonism. A few patients may develop "wearing off" phenomena, the re-emergence of symptoms several hours after an oral dose of L-dopa. Older family members may present with a "parkinsonian picture," but still show the same persistent, positive response to L-dopa. This finding is consistent with the idea that a single underlying disease has different manifestations that vary with age, dystonia being prominent in early and late parkinsonism [275–278].

With fluorodopa positron emission technology (PET) scanning, it has been shown in a number of families that patients with DRD have normal to modestly reduced striatal uptake of fluorodopa, including those who present with parkinsonian features later in life [276]. Because of this finding, it can be concluded that these patients have relatively intact dopamine uptake, decarboxylation, and storage systems in the striatum. The genetic abnormalities so far uncovered are involved with the dopamine synthetic system. It has also been speculated that the diurnal fluctuations that characterize DRD may be due to the circadian variation in dopamine production, with greater synthetic activity possible at night. One study found that acute dystonia secondary to neuroleptic medication also shows a circadian pattern [279], with maximal dystonia present between 12:00 noon and 11:00 PM. This could not be accounted for by sleep, fatigue, or time since the last dose of medication (in this case, injections twice daily). Some of this circadian variability may be accounted for by circadian variations in the dopamine system, which seem to show the least activity in the evening hours with maximal activity in the morning [280].

Nocturnal Paroxysmal Dystonia

Nocturnal Paroxysmal Dystonia (NPD) was first described by Lugaresi's group as a condition which might be considered analogous to diurnal paroxysmal movement disorders [281]. Although it is now established that this and related conditions are variants of frontal lobe epilepsy, their atypical presentation often makes the diagnosis quite challenging. The characteristically short lasting attacks of NPD begin with arousal, including an abrupt autonomic activation that can include substantial tachycardia, followed by dystonic choreo-athetoid or ballismic movements and large-scale semi-purposive movements of all limbs. Vocalizations are common. The attacks are quite diverse if considered between patients but appear to be stereotyped in a single patient. Attacks are brief, last about a minute (range 15 s to 2 min for typical attacks) and may be vaguely remembered. Neither tongue biting nor urinary incontinence is common and tend to resolve without a significant period of post-ictal confusion, which is one of the reasons that it was not appreciated early on that at least the brief attacks are a form of epilepsy. In some patients, the attacks are decidedly unilateral The epileptiform nature of these attacks, together with two other conditions, paroxysmal arousals (in which patients awake abruptly from NREM sleep, perhaps with a start or cry, and have fleeting dyskinetic movements, then fall back to sleep) [282] and episodic nocturnal wanderings (attacks of sudden motor activity, including violent ambulation, loud vocalizations, and a variety of forceful gestures commonly occuring in stage 2 NREM sleep [283–285] is now clearly established [286, 287]. Therefore, the diagnosis and treatment of these disorders is discussed in detail in Chap. 44.

However, it is worth mentioning that there have been reports in the literature of attacks similar to NPD that did not respond to antiepileptic treatment. In the original description, two cases had longer duration (2–50 min) attacks, with no epileptic associations [281]. In one case, a patient afflicted with such attacks for 20 years developed Huntington's disease. There are a number of more recently described disorders of at least uncertain etiology. Lugaresi's et al. [288] described a periodic form of NPD which recurs every 30 s to 2 min with usually quite brief attacks (2–13 s in duration) and associated arousals which they called atypical periodic movements in sleep. While showing overlap with the short-lasting NPD, this condition was unresponsive to seizure medications, even though one patient in the original series had a vascular orbital frontal tumor on computerized tomography (CT) scanning and spikes on depth recording. Other such disorders include dystonic attacks provoked both by sleep and exercise [289], apnea-associated paroxysmal dyskinetic movements [290, 291], and post-traumatic nocturnal hemidystonia [292]. Thus, when the diagnosis is in doubt, it is prudent to order a PSG with an extended seizure montage as well as extra EMG channels to distinguish between a motor disorder and an epileptic phenomenon; in our laboratory, we employ a hybrid montage for this purpose (Table 5 from Chap. 18).

Myoclonus

The myoclonias [293] are a diverse group of conditions with abnormal movements generated at various levels of the neuraxis, from cortex (cortical reflex or epileptic myoclonus) to spinal cord (spinal or segmental myoclonus). The basic abnormal movement is a single, repeated, or periodic jerk,

most typically abrupt and "lightning-like." Most of the studies of myoclonus and sleep have focused on the persistence of myoclonic movements during sleep. Whether myoclonus persists in sleep or not appears to be related to the source of the discharge; elegant experiments have shown that myoclonus with a cortical source shows suppressed movements during sleep while (as in epilepsy) cortical discharges persisted, myoclonus of presumed subcortical origin is rapidly suppressed during sleep, and myoclonus of lower-level origins (spinal cord or secondary to peripheral damage) persists during sleep [294]. Thus, cortical and subcortical myoclonus tends to be attenuated by sleep, whereas myoclonus of peripheral origin, such as spinal myoclonus, and propriospinal myoclonus, shows persistence into sleep in varying degrees [295, 296]. Myoclonic jerks associated with startle disease also persist during sleep, although with diminished intensity [297].

Palatal Myoclonus (Palatal Tremor) Palatal myoclonus (more accurately described as palatal tremor) is characterized by rhythmic movements of the soft palate and pharynx at a rate of 1–3 Hz. It is sometime associated with rhythmic ocular, buccal, lingual, laryngeal and diaphragmatic movements, and occasionally also movements of the upper limbs [298]. Two types have been described as follows: a primary or essential type (idiopathic) due to contraction of the tensor veli palatini muscle presenting with a clicking noise in one or both ears, and an acquired or secondary due to contraction of the levator veli palatini muscle [299]. When acquired, it is usually secondary to brain stem damage within Mollaret's triangle (dentatorubroolivary pathways, with damage most common in the central tegmental tract which runs from the region of the red nucleus to the ipsilateral olive). While primary palatal tremor may be completely abolished by sleep, electrophysiologic studies in a small number of patients demonstrated that palatal contractions persist during sleep, albeit with shifts in amplitude and frequency or even altered rhythmicity [300–302]. The range of such cyclic motor dyskinesias may be broader than currently known: a similar tongue movement was reported to persist largely unchanged in sleep [303]. The finding of persistent rhythmicity suggests a relatively autonomous oscillator consistent with the idea that these segmental myoclonias may represent release of a primitive rhythmic center. In contrast to other forms of myoclonus, these dyskinesias appear to arise at a segmental level and to be associated with decreased motor control from higher centers. This dissociation may explain their resistance to modulation by descending inhibitory influences during sleep. The dyskinesias are not completely removed from higher motor centers or the periphery, however, because they may disappear in sleep, change with state, and be influenced by attention [304–306]. In one interesting case, palatal tremor was associated with time-locked respiration, suggesting a coupling of these two rhythms [307].

Palatal tremor is generally refractory to treatment. There are reports of occasional response to anticholinergics, botulinum toxin injections, baclofen, valproic acid, lamotrigine, tetrabenazine, and carbamazepine [308].

Tics

Tics are typically brisk, stereotyped, complex, often repetitive movements [309]. Usually, any given patient has a somewhat limited repertoire of movements that may change over a period of months to years. The prototypical tic disorder is Gilles de la Tourette's syndrome, a condition involving multiple motor tics with vocalizations that usually begins in childhood or adolescence but may subside in later adult life [310]. Tics may be associated with a sensory penumbra and an urge to move. Tourette's patients also have a number of commonly-associated behavioral abnormalities, especially obsessive-compulsive disorder [311, 312]. Of all tic disorders, sleep disorders have been best studied in patients with Tourette's syndrome.

Tics in Tourette's syndrome have been found to persist during sleep in most cases, mostly in stages I and II of NREM sleep, with fewer during SWS or REM sleep [313, 314]. Also observed is increased frequency of disorders of arousal (e.g., somnambulism and pavor nocturnus) and parasomnias in general, as well as poor quality and fragmented sleep [315, 316] in children with Torette's syndrome. Bodily movements in general are increased in Tourette's syndrome; Hashimoto et al. [317] found that both twitch-like and gross body movements were increased over controls during all stages of sleep, with total movements in tic patients markedly increased during REM sleep. Those authors did not attempt to analyze such movements in detail, so it is not clear what fraction of them were actual tics. In one study, patients were monitored after successful treatment of their movements with tetrabenazine, and it was found that sleep also improved [318].

Hemifacial Spasm

Hemifacial spasm consists of intermittent contraction of one side of the face that can be repetitive and jerk-like or sustained. It is believed to arise from irritation of facial nerve or nucleus. Both central and peripheral (ephaptic transmission between adjacent nerve fibers without synapses) factors are responsible for the spasms. EMG recording shows highly synchronous discharges in upper and lower facial muscles. Montagna et al. [319] studied 16 patients, recording from upper and lower facial muscles during sleep studies. In most patients, the dyskinesias decreased during sleep, being approximately 80 % less frequent in SWS and REM

sleep. One patient showed almost no change in the prevalence of spasms. Current therapy for hemifacial spasm includes medications such as carbamazepine, botulinum toxin injection into the affected muscles, or varied surgical treatments, such as vascular decompression of the facial nerve. Combined treatment with pregabalin and botulinum toxin injections has been reported [308].

Other Hyperkinetic Disorders

In *hemiballismus*, there are proximal flinging movements of one side of the body, which may be of a violent nature, associated with damage to the contralateral subthalamic nucleus [320]. In most cases, hemiballismus is a transient phenomenon after local injury to the subthalamus, usually ischemic, although it may be transformed into a chronic choreiform disorder. It was initially thought that the movements totally subsided in sleep. Askenasy [321], however, reported a patient whose movements persisted in sleep, and Silvestri et al. [115] found that the movements were present during stages N1 and N2, as well as during REM sleep, although diminished in intensity and frequency. Puca et al. [322] reported one case in which spindle density and amplitude were greater ipsilateral to the damaged subthalamic nucleus. There was also disrupted sleep, with prolonged latency and an absence of both SWS and REM sleep. Successful treatment with haloperidol improved the sleep and decreased the spindling.

In *athetoid cerebral palsy*, abnormalities of REM sleep have been noted. Hayashi et al. [323] reported on a group of severe adolescent and young adult patients. The significant motor abnormalities were associated with REM sleep: three patients had decreased numbers of REM, two had increased chin muscle tone, and seven had reduced numbers of muscular twitches. The authors suggest this may be related to brain stem pathology in these birth-injured patients. One family with five generations affected by *paroxysmal dystonic choreoathetosis* with dominant transmission was found to show substantial benefit from even brief periods of sleep [324]. In a Serbian family with mutations in the Myofibrillogenesis regulator 1 gene, sleep was reported to be the most effective means of terminating attacks [325].

Sleep-Associated Problems of the Ataxic Disorders

Relatively little research has been done on sleep disturbances in the ataxic disorders. Today, a large number of different genetically based variants of spinocerebellar ataxia have been described and some of these have been examined with respect to sleep. Patients with Machado–Joseph disease (Spinocerebellar atrophy type 3, SCA3) may have both RLS and RBD as common sleep-related problems. Patients with SCA2 can have reduced REM-sleep atonia. One report suggests increased PLMS and RLS in SCA6. SCA6 patients also have impaired subjective sleep quality and tend to have greater daytime sleepiness. It seems likely that the paucity of associations reported to date is more due to the lack of studies than the absence of sleep problems in these disorders [326–331].

B. Motor Disorders Exclusive to Sleep

i. Failure of motor control while resting in bed trying to get to sleep.

This category includes RLS and PLMW, which are discussed in Chap. 40.

ii. Failure of motor control immediately before and at sleep onset

Since normal individuals enter the sleep cycle through NREM sleep, these disorders can also be considered failures of motor control in NREM sleep. Many of these are of unclear clinical significance and require no treatment.

Physiological Hypnic Myoclonus

The term physiological hypnic myoclonus (PHM) was first coined by De Lisi [332] to describe brief asynchronous, asymmetric, and aperiodic muscle twitches during sleep in all body muscles of man and domestic animals resembling fasciculations seen prominently in face and distal body parts (e.g., face, lips, fingers and toes). PHM is also known as physiological fragmentary hypnic myoclonus and is seen prominently in babies and infants. Quantitative study by Dagnino et al. [333] and Montagna et al. [334] in 1988 showed the maximum occurrence of these twitches in stage N1 and REM sleep, decreasing progressively in stages N2 and N3. Presence of PHM also during relaxed wakefulness challenges the term hypnic Myoclonus [335, 336]; however, it should be noted that propriospinal myoclonus at sleep onset and intensified hypnic jerks in many patients [336] are present in relaxed wakefulness before sleep onset. The origin of PHM remains controversial. Facilitatory reticulospinal tract, pontine tegmentum, and corticospinal tract [337, 338] have all been suggested as the generator of PHM. These movements are physiologic without disrupting sleep architecture and require no treatment.

Hypnic jerks including intensified hypnic jerks

Hypnic jerks or "sleep starts" are sudden, brief contractions of the body that occur at sleep onset and are due to excitation of motor centers. They are physiological and occur in up to 70 % of the population at some point in their adult lives. They are often accompanied by a sensation of falling [339]. The movement itself is an abrupt, myoclonic flexion movement, generalized or partial, often asymmetric, which may be accompanied by a sensation or an illusion of falling. Unless very frequent (which does occur rarely) [336, 340] this is a benign movement which has little effect on sleep and carries no negative prognosis. When it occurs, it is

usually a single event, which causes a brief arousal. EMG records show relatively brief EMG complexes (<250 ms in duration) that may be simultaneous or sequential in various muscles. The earliest mention of this phenomenon is credited to Mitchell [341], who described insomnia occurring as a result of hypnic jerks in 1890. Oswald [339] first described the EEG correlates of hypnic jerks. In 1965, Gastaut and Broughton [342, 343] performed the first polygraphic study of hypnic jerks. It was not until 1988 that Broughton [340] coined the term "intensified hypnic jerks" to describe the clinical phenomenon of sleep onset insomnia caused by accentuated and disruptive hypnic jerks occurring at sleep onset. More recently, Chokroverty et al. [336] performed a polysomnographic and polymyographic analysis of ten patients with intensified hypnic jerks and identified four patterns of propagation: synchronous and symmetrical patterned muscle bursts between the two sides and agonist–antagonist muscles similar to those noted in audiogenic startle reflex; reticular reflex myoclonus; dystonic myoclonus; and pyramidal myoclonus with rostrocaudal propagation of muscle bursts.

Hypnagogic Foot Tremor and Alternating Leg Muscle Activation

Hypnagogic foot tremor (HFT) (Fig. 39.7) and ALMA (Fig. 39.8) rarely come to clinical attention, being discovered as incidental findings on PSG. Both occur during lighter sleep and in transitional states into and out of sleep. ALMA has also been documented in wakefulness, all stages of NREM and also, though less frequently, in REM sleep in patients with a variety of sleep disorders [344]. Another feature of ALMA is its occurrence, in addition to the traditional tibialis anterior EMG, in gastrocnemius and sometimes in quadriceps muscles alternating between two sides. Because variant patterns are reported in each, and there is at least some plausible degree of overlap between HFT and

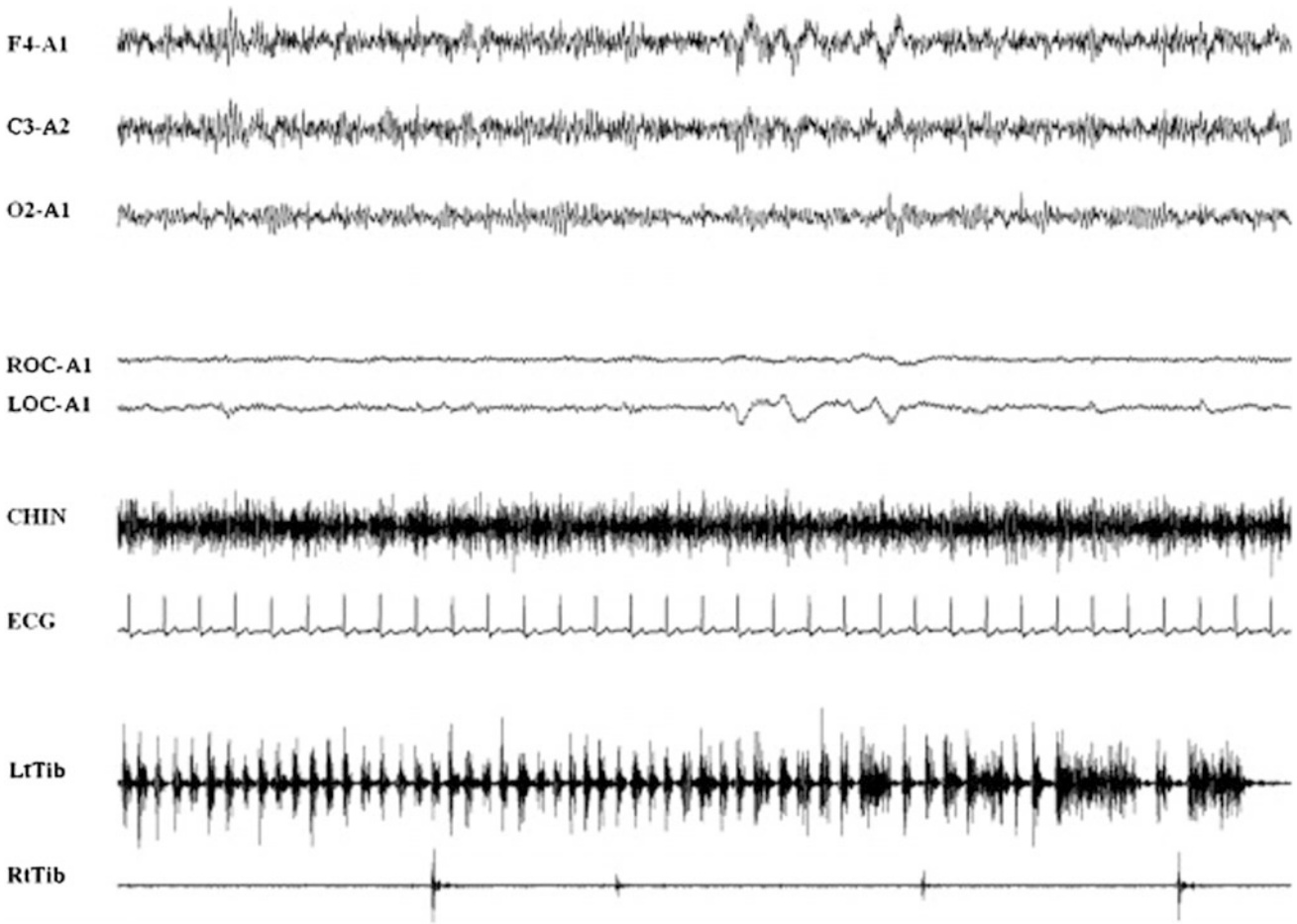

Fig. 39.7 Hypnagogic foot termor. A 30-s epoch of relaxed wakefulness from the polysomnogram of a 69-year-old man affected by snoring and nonrestorative sleep. Note the occurrence of a series of rapid tibialis anterior activations longer than 30 s, with single burst durations of 200–300 ms. Top three channels, electroencephalography. ROC and LOC: electrooculogram channels. ECG, electrocardiogram. LtTib and RtTib, tibialis anterior electromyography channels. (Reproduced with permission from Ref. [114])

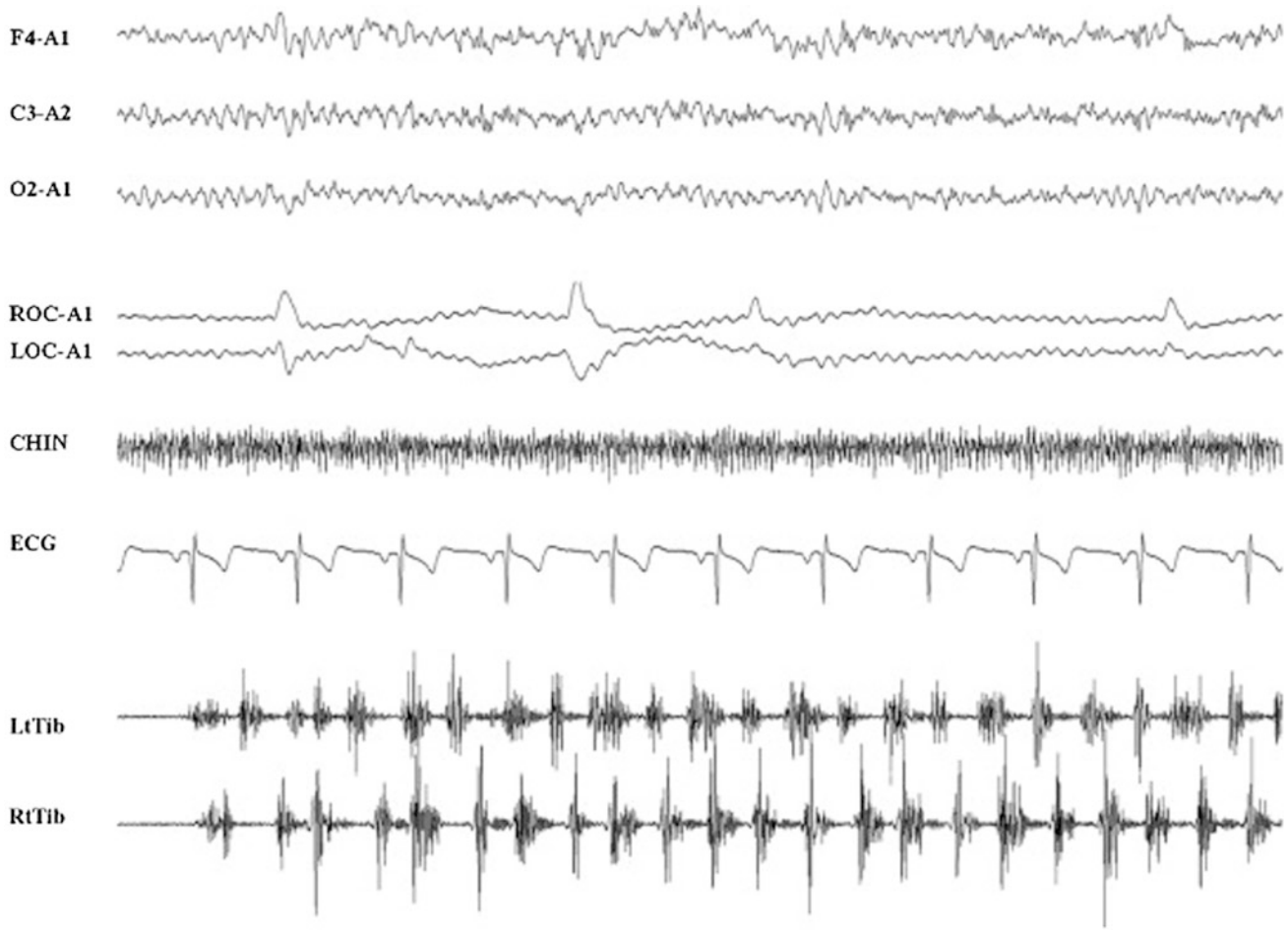

Fig. 39.8 Alternating leg muscle activation. A 10-s epoch of relaxed wakefulness transitioning to N1 sleep from the polysomnogram of a 32-year-old man with chronic insomnia and no comorbid history of restless legs syndrome, affected by snoring and nonrestorative sleep. Note the occurrence of a series of alternating tibialis anterior activations longer than 10 s, with single burst durations of 200–300 ms. Top three channels, electroencephalography. ROC and LOC: electrooculogram channels. ECG, electrocardiogram. LtTib and RtTib, tibialis anterior electromyography channels. (Reproduced with permission from Ref. [114])

ALMA (and also PLMS) further investigation may be required to ascertain whether they are distinct or merely variant conditions. It has also been suggested that both may be variants of RMD (see below). HFT is defined by the AASM Manual for the Scoring of Sleep and Associated Events as rhythmic contractions of foot and leg occurring during sleep onset generally bilaterally but asynchronously at a frequency of 0.5–4 Hz [5] and was first described by Broughton [340]. Wichniak et al. [345] later performed polysomnography on 375 consecutive subjects and found HFT (which they called "rhythmic feet movements while falling asleep" and described as rhythmic, oscillating movements of the whole foot or toes) in 7.5 %. Per the AASM Manual for the Scoring of Sleep and Associated Events, ALMA consists of EMG bursts that occur alternately in each leg in a rhythmic pattern of 0.5–3 Hz and was first described by Chervin's et al. [346], who found it in just over 1 % of reviewed PSGs; most of those showing the phenomena were taking anti-depressants. The duration of an individual movement varies between 100 and 1000 ms. For both HFA and ALMA, at least 4 movements must be present in a row to make the diagnosis [5]. ALMA requires the presence of alternating activity and has been suggested to be an equivalent of a locomotor rhythm [347]. Diagnosis of either requires a PSG recording. Convincing evidence of any definite clinical consequence of these movements is yet to be presented. In one patient, pramipexole-reduced ALMA and improved sleep [347], together with a reduction of associated CAP. The clinical significance of both HFT and ALMA remains undetermined requiring no treatment.

Rhythmic Movement Disorder

RMD (Fig. 39.9) is characterized by repetitive, stereotyped, rhythmic movements involving large muscle groups,

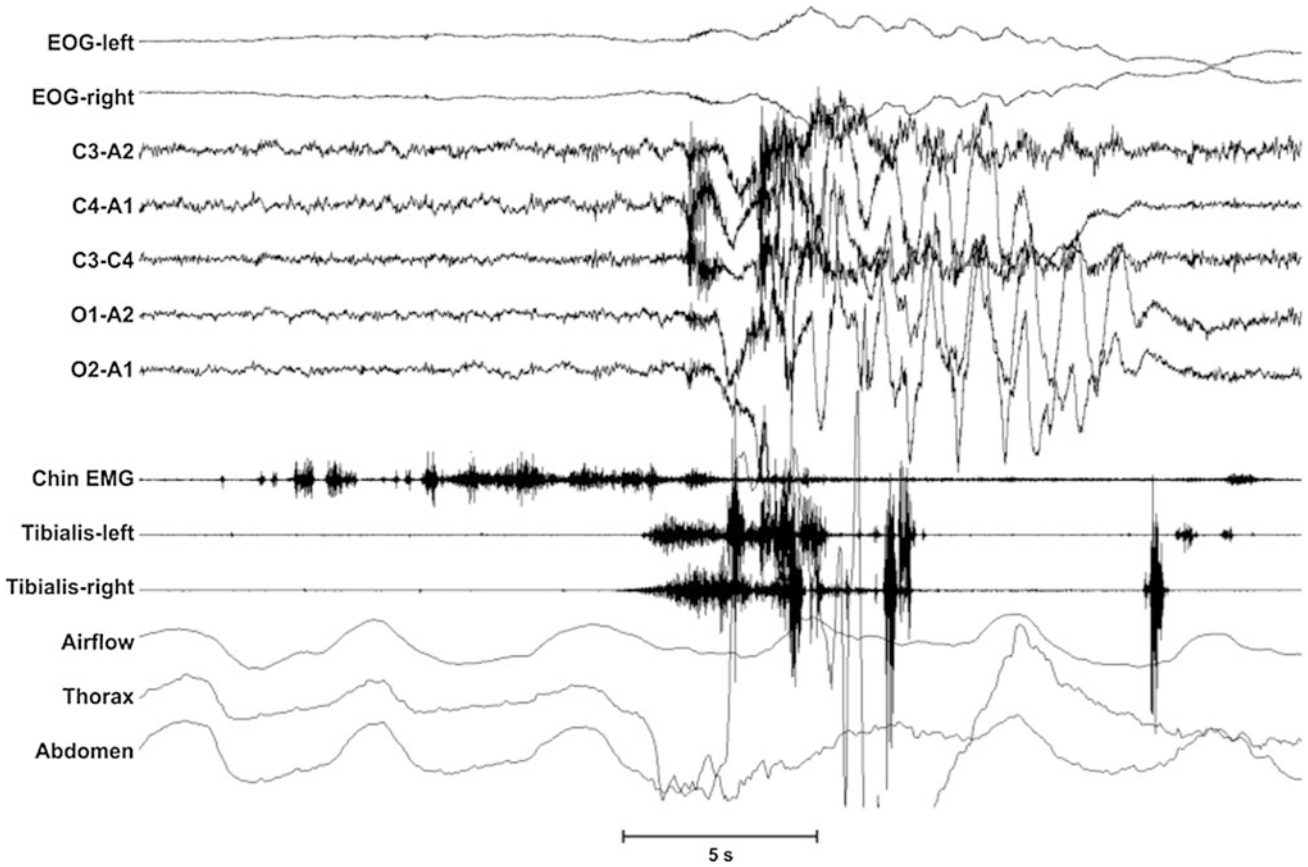

Fig. 39.9 Rhythmic movement disorder. Polysomnographic recording of a rhythmic movement disorder (RMD) episode. RMD typically consists of repetitive stereotyped and rhythmic motor behaviors, such as head banging, body rolling, and body rocking. These movements generally occur at sleep–wake transitions and after arousals from sleep but may also occur in wakefulness, and rarely during REM sleep. These episodes may also occur at the termination of a respiratory event in obstructive sleep apnea syndrome. (Reproduced with permission from Ref. [114])

occurring predominantly during sleep onset or during sleep–wake transitions, at a frequency of 0.5–2 Hz. It can take many forms, including head banging ("jactatio capitis nocturna"), body rocking, body rolling, and leg rolling. Reports of events matching the current description of RMD have been abundant in the literature [348, 349] and even reported as early as in 1880 [350] although the term *jactatio capitis nocturna* was first used by Zapert [351]. According to the AASM Manual for the Scoring of Sleep and Associated Events, in addition to the above frequency criterion, the minimum number of individual movements to make a cluster of rhythmic movements is 4 movements and the minimum amplitude of an individual rhythmic burst must be at least 2 times the background EMG activity [5].

RMD generally presents before 18 months of age and tends to occur immediately before sleep during relaxed wakefulness continuing into stage N1 and sometimes into stage N2. Rare case may show a REM predominance [352, 353]. Bouts of movements may be related to CAP [354]. While RMD is most common in pre-pubertal children, there are older children [355] and also adults [356–361] who will show persistent or emergent rhythmic movement. Most older children with persistent disorder are usually suffering from organic brain dysfunction (cerebral palsy, autism or attention deficit disorder). In developmentally normal children, however, RMD is generally benign and the child usually outgrows the movements by the second or third year of life.

Because RMD is a benign phenomenon in itself, treatment is not always necessary. However, it may cause significant injury. In addition, RMD may be secondary to frequent arousals from another condition, commonly OSA [362]. RMD may present in a rather dramatic fashion, and so may need to be distinguished from tremor or segmental myoclonias, as well as RBD or nocturnal seizures. Given this, evaluation of a patient with suspected RMD requires careful clinical history and physical examination, viewing of a video recording of the events if possible, and occasionally PSG. PSG is always recommended for most cases of RMD in patients in whom a primary sleep disorder is being

considered and should be performed with an extended seizure montage if nocturnal epilepsy is suspected. In case of primary RMD, behavioral therapy and in severe cases with potential for inflicting injury clonazepam (0.5–1 mg nightly), imipramine (10 mg at night) or melatonin [363] maybe helpful [308]. Protective measures should be used in cases with violent movements.

Propriospinal Myoclonus at Sleep Onset

Propriospinal myoclonus is a form of spinal myoclonus in which the excitatory impulses are believed to travel through relatively slow-conducting intersegmental propriospinal pathways [364–366]. However, *propriospinal myoclonus at sleep onset* was described fairly recently by Montagna et al. [367, 368] who performed polygraphic studies that showed that the myoclonic activity began in spinally innervated muscles, propagating at low speed to rostral and caudal muscular segments, and hypothesized that a spinal generator may be facilitated by changes in supraspinal control related to vigilance levels. They identified it as a potential cause of severe anxiety and insomnia. The myoclonic movements typically involve the trunk with possible extension into the limbs. In a recently described form of this myoclonus, the myoclonic jerks are only evident during relaxation or recumbency [369], especially when the patient is drowsy. Unlike PLMS, the movements are relatively easily abolished by even light sleep. They may, however, produce a substantial difficulty with sleep induction and can therefore be a cause of significant insomnia. Cases have been described that are associated with RLS [370] and an important consideration in the differential diagnosis of propriospinal myoclonus at sleep onset is the myoclonic form of PLMW seen while sitting or lying in patients with RLS [371]. One case of propriospinal myoclonus that occurred during sleep was reported after a thoracic spine fracture that progressed to "myoclonic status" and respiratory failure [372]. The treatment of this condition is challenging and some cases respond to clonazepam, zonisamide and other antiepileptic drugs used in the classic propriospinal myoclonus [308].

iii. Failure of Motor Control During NREM Sleep

This includes PLMS (discussed in Chap. 40) and the disorders of partial arousal, such as sleep terrors, confusional arousals and sleepwalking/Parasomnias (discussed in Chap. 50).

iv. Failure of Motor Control During REM Sleep

This includes RBD (discussed in Chaps. 49 and 50). The scoring criteria for REM without atonia, an essential neurophysiological component in the diagnosis of RBD, is provided in Table 39.3.

v. Failure of Motor Control in both NREM and REM Sleep

Benign Sleep Myoclonus of Infancy

This is a transient, sometimes familial condition that begins soon after birth and resolves within months [373–377]. It may, however, persist for up to a year after birth, hence the recent change in nomenclature from "benign neonatal sleep myoclonus" to "benign sleep myoclonus of infancy." The myoclonic jerks are brief, asynchronous, and repetitive, involving primarily the distal limbs, especially the arms, but also the trunk; the jerks are often generalized. The jerks occur during all stages of sleep, with most occurring in NREM sleep, and typically do not arouse or wake the infant [378]; waking the child will cause them to cease promptly. The movements do not occur continually in sleep and, when not present in sleep, they may be precipitated by rocking the infant or by gentle restraint during sleep [379]. The exact pathophysiology is unknown, but these movements most likely represent an exaggeration of the normally greater sleep-related movements in infants [380]. Although completely benign, self-limiting and with no long-term sequelae, the clinician is often called upon to reassure frantic parents that their baby is not having seizures, which it may superficially resemble [381–383]. When in doubt, EEG or PSG may help alleviate some of the concern.

Sleep Bruxism

While bruxism or teeth grinding can occur during the day, *nocturnal bruxism* (Fig. 39.10) is to be clearly differentiated from daytime bruxism. Nocturnal, or sleep bruxism, when frequent and intense enough, can interrupt sleep and cause significant dental wear [384]. It is associated with arousals and autonomic activation during sleep [385, 386]. SPECT studies show an asymmetry in D2 dopamine receptor binding in bruxism patients at the level of the basal ganglia compared to controls suggesting that dopaminergic cell dysfunction may play a role in the pathogenesis of bruxism [387]. Bruxism tends to decrease with age, although bruxers may also have increased movements during sleep in general, and may be more common in the supine position [388]. Bruxism may also be a sign of recurrent OSA-related arousals, and thus any patient with bruxism should be screened for possible sleep-disordered breathing.

Bruxism may need to be distinguished from other dyskinetic movements which involve the jaws, including oromandibular dystonia and idiopathic myoclonus in the oromandibular region during sleep. Idiopathic myoclonus in the oromandibular region (e.g., faciomandibular myoclonus) during sleep is an apparently isolated, non-epileptic condition that occurs predominantly in stages 1 and 2 NREM sleep [389–391]. It consists of isolated or short runs of shock-like jaw movements with brief EMG bursts.

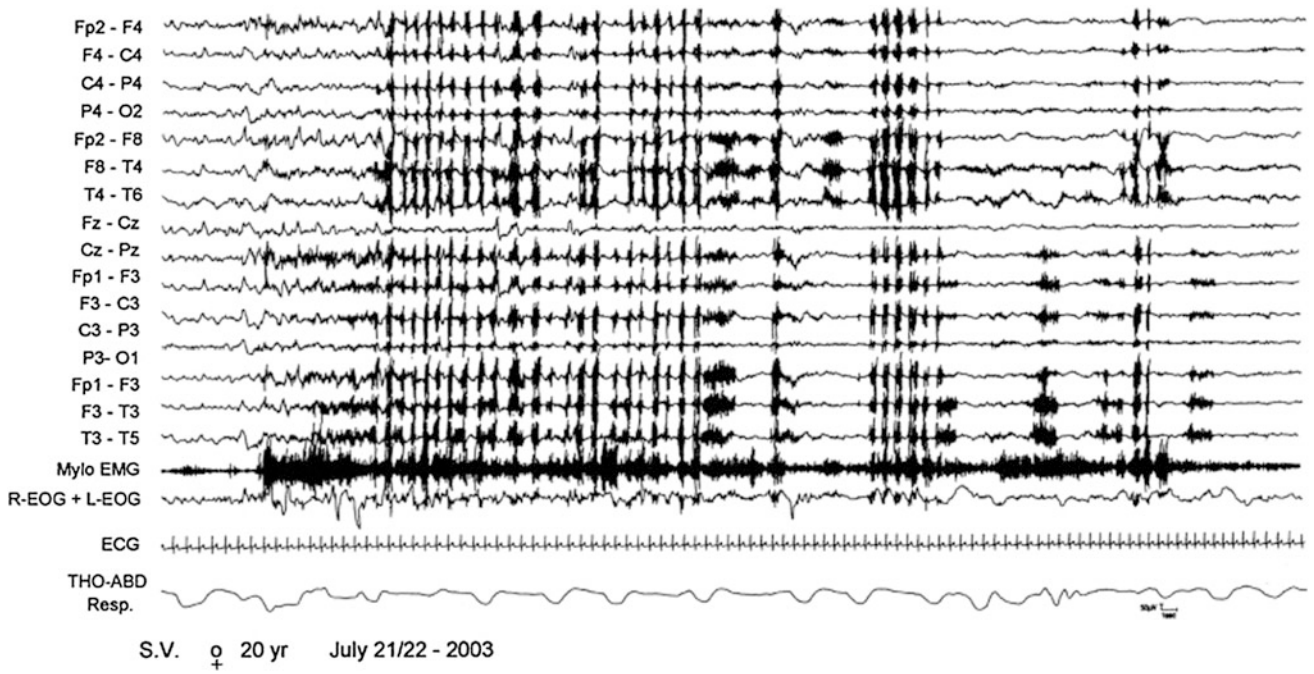

Fig. 39.10 Sleep bruxism. A 20-year-old woman referred for nocturnal awakeings with vocalization and sleepwalking. Polysomnogram shows arousal from slow-wave sleep with subsequent rhythmic masticatory muscle activation and teeth grinding (note electromyographic [EMG] artifacts on electroencephalogram [EEG] channels) typical of sleep bruxism. Top 15 channels, EEG. Mylo EMG, mylohyoid EMG activity. R-EOG + L-EOG, right and left electrooculogram; ECG, electrocardiogram; THO-ABD, thoracoabdominal respiration. (Reproduced with permission from Ref. [114])

Sleep-related bruxism has been described in every stage of sleep. While highest level of activity occurs during stage N3 and wakefulness, no difference has been described with regard to percentages of the sleep stages [392]. A close association between sleep bruxism and REM sleep has also been described [393, 394]. In 2008, Manconi et al. [395] published an interesting case report of a patient with sleep bruxism and catathrenia (see below) occurring in a synchronized fashion. They hypothesized about the presence of a common trigger mechanism for both phenomena.

According to guidelines put forth by the new AASM Manual for the Scoring of Sleep and Associated Events [5], bruxism can be identified by either brief (phasic) EMG elevations of 0.25–2 s and sustained (tonic) EMG elevations of >2 s. These EMG elevations must be at least twice the amplitude of the background EMG. Phasic bruxism events must occur in a sequence of 3 or more and this sequence can be said to comprise a bruxism episode. At least 3 s of stable EMG must be present before a new episode of bruxism can be scored. Bruxism can be reliably scored by audio in combination with polysomnography by a minimum of 2 audible tooth grinding episodes/night of polysomnography in the absence of epilepsy. In addition to chin EMG, additional masseter electrodes may be placed at the discretion of the investigator or clinician for optimal detection of bruxism. An alternate term for the phasic type of bruxism is *Rhythmic Masticatory Muscle Activity*.

The treatment for bruxism has yet to be standardized; various modalities have been employed, including dopaminergic agents [396], anticonvulsants [397], or with botulinum toxin injections [398]; dental devices may also help [399, 400] but some studies suggest caution in their use [401].

Catathrenia (see also Chap. 41)

Catathrenia, or nocturnal groaning, is a relatively newly described entity characterized by loud expiratory vocalization, whose exact pitch and timber may vary from individual to individual but is fairly stereotyped in a given patient (see Fig. 41.12). Not strictly a disorder of motor control, it may rather represent a disorder of breathing in sleep and is classifies as such according to the ICSD-3, although this is disputed by some [402]. While far more frequent in REM sleep, it may also occur in NREM sleep and alternates with normal breathing. It was actually first described by Pevernagie et al. [403] but was first named by Vetrugno et al. [404]. The same group subsequently reported in 2007 [405] that the groaning was accompanied by disproportionately prolonged expiration causing reduced tidal volume and bradypnea without oxygen desaturation, and that patients experienced no additional symptoms after a mean follow up

of 4.9 years. They speculated that catathrenia was due to persistence of a vestigial type of breathing pattern. In 2011, Ott et al. [406] performed laryngoscopy under deep sedation in a patient with catathrenia and found that while the glottis was open at inspiration, there was subtotal closure of the glottis at expiration, resulting in the characteristic groaning. The following year, Koo et al. [407] performed acoustic analysis of catathrenia and found that it had morphologic regularity, with two types of sound pitches (either a monotonous sinusoidal pattern or a sawtooth-shaped signal with higher fundamental frequency), as opposed to snoring which was distinct from catarthrenia and had an irregular signal. Several authors have reported the efficacy of CPAP in treating this benign but socially awkward condition [408–410]. The anatomical factors that predispose to catathrenia, namely broad upper airway, yet protrusive upper incisors and flat mandibular angles, have recently been described [411].

Excessive Fragmentary Myoclonus

Excessive Fragmentary Myoclonus (EFM) is essentially a variant PSG finding (Fig. 39.11), often found incidentally, that has yet to be demonstrated to be of clinical relevance. This condition may be another in which inadequate inhibitory drive fails to block descending activation from higher centers or it may represent a condition of excessive activation of higher centers during sleep. A neurophysiologic analysis by Vetrugno et al. [412] failed to disclose any cortical prepotential on EEG–EMG backaveraging suggesting a subcortical origin. The condition has been found in degenerative developmental disease (Niemann-Pick) [413] and as a consequence of brain stem lesions [414] but usually occurs in isolation [415]. Generally, EFM is not accompanied by gross visible movements; if movements are present at all they are small movements involving the corner of the mouth or small movements of the fingers or toes. In most cases no movement across a joint space occurs and the movements may resemble fasciculations, mere dimplings seen over the muscle associated with very brief EMG potentials (<50 ms). According to the AASM Manual for the Scoring of Sleep and Associated Events [5], EFM is present when at least 20 min of NREM sleep is recorded on PSG with the characteristic EMG pattern present (bursts typically <150 ms and of variable ampltude) and at least 5 EMG potentials per minute. Although classically described in the lighter stages of NREM sleep, they may occur in REM sleep, where the pattern resembles the normal phasic twitches seen in REM sleep, except they are more evenly spread throughout an individual epoch and not clustered as are phasic REM twitches. Some, [416] but not all [417] reports suggest that they are least common in slow-wave sleep. Given the lack of known clinical consequences, treatment is not required.

vi. Failure of motor control at sleep offset

Sleep paralysis

Transitions out of sleep may also be associated with *sleep paralysis,* a condition in which an individual is paralyzed while awakening from sleep. Weir Mitchell [341] is given credit for an early description of the condition in 1876 and he termed it "night palsy". Adie [418], in the 1920s observed occurrence of sleep paralysis in narcolepsy patients and Wilson in 1928 [419] introduced the actual term. There are earlier descriptions in the Chinese, Indian, Persian and Greek cultures and mythologies, as well as in famous novels such as Herman Melville's *Moby-Dick* (1851).

During episodes of sleep paralysis, breathing and eye movements are usually preserved. This condition is thought to represent a variety of REM sleep tonic motor inhibition [420]; recordings of the state can show REMs together with an electrophysiological pattern consistent with REM sleep [421]. Sleep paralysis is generally associated with arousal from a REM period (hypnopompic) or, less commonly progress into REM sleep from wake (hypnagogic) [422]. The latter would be very unusual in the normal course of events and more likely to occur with narcolepsy, though it may occur in many non-narcoleptic individuals, sometimes with a familial pattern. There are three forms of sleep paralysis, isolated or recurrent isolated sleep paralysis (physiological occurring mostly in adults up to 30–50 % of the population), familial sleep paralysis and sleep paralysis as part of narcolepsy. Several studies suggest that, at least in some populations, sleep paralysis may be quite common [423–425]. When it does occur in normal individuals, it is generally infrequent, but may cause significant anxiety, especially the first time that it occurs. A similar condition, *nocturnal alternating hemiplegia of childhood*, involves paralysis limited to one side while awakening from sleep [426]. This may be a variant of hemiplegic migraine, a complicated headache disorder with paralysis due to suppressed activity in certain brain regions.

Physiological sleep paralysis is generally brief, lasting for seconds to a few minutes, but sometimes may last longer, particularly *recurrent isolated sleep paralysis*. On occasions the episodes are accompanied by hypnagogic or hypnopompic hallucinations. The episodes may be triggered by sleep deprivation, stress, physical exertion or supine position. Isolated or recurrent sleep paralysis does not require any specific treatment other than reassurance, life-style changes, regularizing sleep–wake schedule but in severe cases causing anxiety and panic short-term treatment with

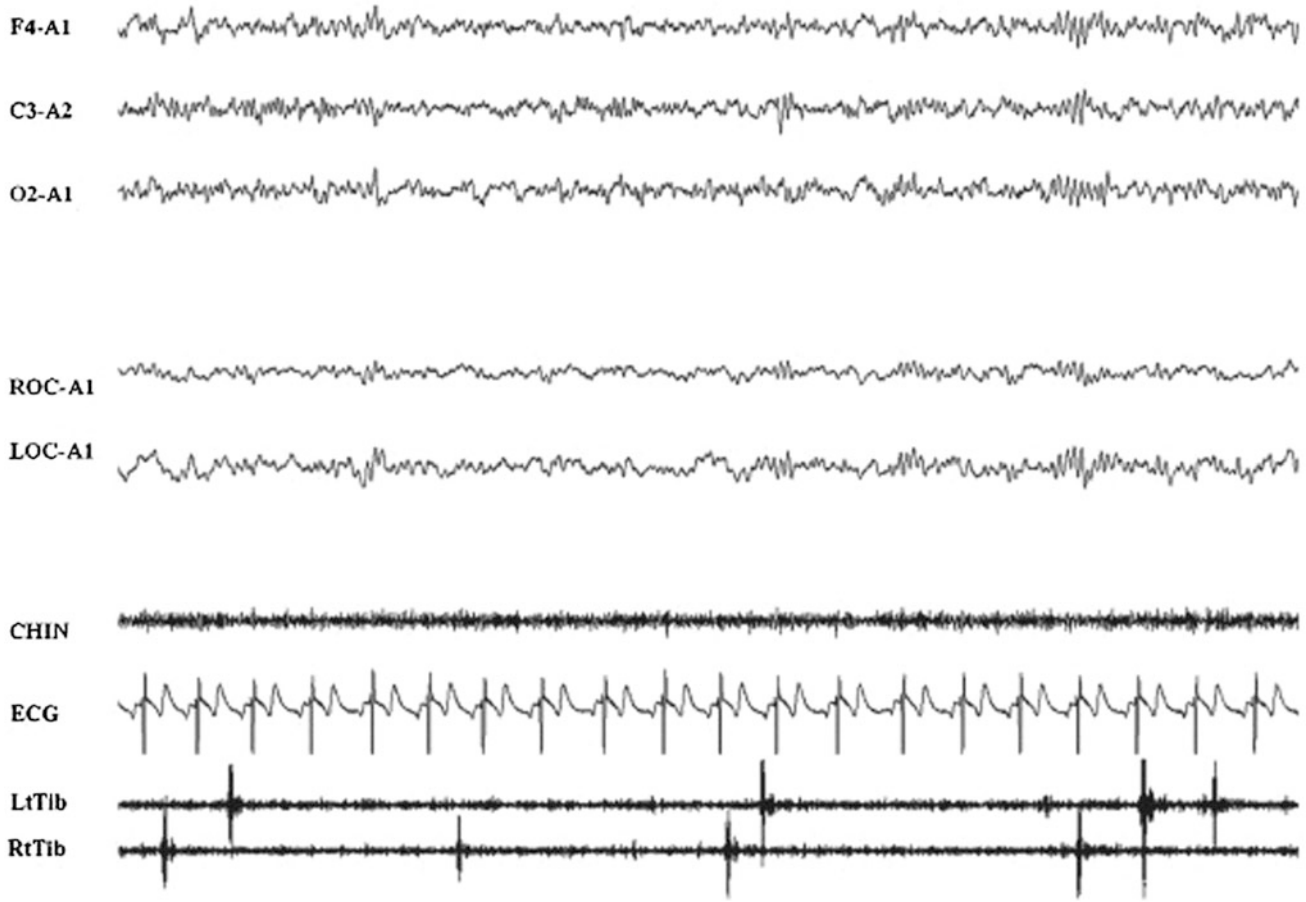

Fig. 39.11 Excessive fragmentary myoclonus. Poysomnogram epoch from the study of a 71-year-old man who presented a 2-year-history of continuous twitch-like movements of the arms and legs throughout the night, which did not wake him from sleep. Note the brief, asynchronous, asymmetric potentials in the limb electromyography (EMG) channels (RtTib and LtTib). Visually, they presented as brief twitch-like movements not causing movement of major joints. Excessive fragmenrtary myoclonus is considered a benign phenomenon with no clinical consequence. Top three channels, EEG. ROC-A1, LOC-A2, electrooculography channels. CHIN, chin EMG. ECG, electrocardiography. (Reproduced with permission from Ref. [114])

selective serotonin reuptake inhibitors (SSRIs) or tricylic antidepressants may be beneficial.

Sleep Inertia

This is most likely not a disorder of motor control in sleep in the strictest sense, but is discussed here for conveneience. Sleep inertia, also known as *sleep drunkenness* is a transient physiologic state of hypovigilance, confusion, impaired cognitive and behavioral performance, and grogginess that immediately follows awakening from sleep [427]. Put simply, the subject is physiologically awake (body awake) but cognitively asleep (brain asleep). EEG of sleep inertia is characterized by a generalized decrease of high frequency beta-1 and beta-2 EEG power but an increase of delta power in the posterior scalp region concomitant with decreased frontal delta power [428]. This state can last from minutes up to four hours, most commonly about five minutes and rarely may exceed 30 min. Prior sleep deprivation, awakening from SWS and short naps may aggravate sleep inertia. It is also more intense when awakening from near the trough rather than the peak of the circadian core body temperature rhythm. Sleep disorders, particularly idiopathic hypersomnia, as well as narcolepsy-cataplexy syndrome and obstructive sleep apnea syndrome may be associated with prolonged sleep inertia. Bedrich Roth and collaborators were probably the first to describe idiopathic hypersomnia with sleep drunkenness in the 1950s [429]. One suggestion for the pathogenesis of sleep inertia is build-up of adenosine and this state can be reversed by caffeine acting through adenosine A2a receptors, thus explaining the well-known reinvigorating effects of an early morning cup of coffee.

Table 39.2 American Academy of Sleep Medicine (AASM) polysomnography scoring criteria for sleep-related movements [5]

Movement	Criteria
Hypnagogic foot tremor	• Frequency of EMG bursts 0.5–4 Hz • Duration of each burst: 250–1000 ms • Minimum number of bursts needed to score: 4 • Occurs at sleep–wake transition, stage N1 and stage N2 sleep • Burst series duration: 10–15 s
Alternating leg muscle activation	• Frequency of EMG bursts 0.5–3 Hz • Duration of each burst: 100–500 ms • Minimum number needed to score: four • Occurs at sleep–wake transition, arousals, NREM and REM sleep • Burst series duration: 20–30 s
Rhythmic movement disorder	• Frequency of EMG bursts: 0.5–2 Hz • Episode duration variable: seconds or minutes • Series of RMD: at least 4 rhythmic movements • Occurrence mainly during drowsiness or sleep, or after sleep onset (mostly during stage N1 or N2) • Amplitude of EMG burst at least twice the EMG background
Excessive fragmentary myoclonus	• At least 5 bursts per minute during NREM sleep • Burst duration: 75–150 ms • Myoclonus index: number of 3-s mini-epochs containing at least one fragmentary myoclonus potential, included within each 30 s epoch
Periodic limb movements	• PLM sequences are identified by at least four LM • Interval between two consecutive PLM (onset-to-onset) is 5–90 s • PLMS index: number of PLMS divided by the number of hours of sleep • PLMS with arousal index: number of PLMS associated with arousal divided by the number of hours of sleep • Periodicity index: ratio of consecutive intermovement intervals, all separated by 10–90 s (at least 3 intervals) divided by the total number of movements
Sleep bruxism	Phasic or tonic increase of chin EMG signal, at least twice the amplitude of the background EMG activity (A) Tonic increase of the chin EMG signal lasting more than 2 s (B) Phasic increase of the chin EMG signal, rhythmic masticatory muscle activity (RMMA); at least 3 consecutive contractions, with a frequency of 1 Hz • Burst duration: 0.25–2 s • Interval between each episode of sleep bruxism: 3 s of stable background chin EMG signal • At least 4 episodes of sleep bruxism/hour of sleep, or at least 25 individual masticatory muscle bursts per hour of sleep associated with at least two audible episodes of tooth-grinding

Scoring Criteria for Sleep-Related Movements

These are summarized in Tables 39.2 and 39.3.

Methods for Studying Sleep-Related Movements

As with any branch of clinical medicine, there is no substitute to a well-taken history and thoroughly-conducted physical examination. Not only is this good clinical practice that ensures that the appropriate test is ordered, but in many cases where the underlying disorder is clearly benign, and reassurance and observation is desirable (such as hypnic jerks), may obviate the need for testing at all.

A. Accelerometry Based Testing

i. Actigraphy

Actigraphy is a validated, relatively cost-effective and convenient alternative to expensive, cumbersome in-laboratory procedures in the assessment of sleep–wake cycles and movements in sleep, in both clinical practice and research. Depending on the equipment and technique used, recordings can be made for many days or even months. In assessing sleep disorders, this extended recording can allow for the capture of rare events, overcoming the problem of variability which can limit the accuracy of more abbreviated studies, and repeated measurement of sleep in different conditions (evaluation of sleep patterns, disease progression or remission, therapeutic responses). In addition to the cost consideration, the small size, light weight and ease of use of most of these devices allows for its application in multiple settings; the activity monitors can be taken out of the laboratory, self-applied, and even transmitted by mail. They may be particularly useful in uncooperative patient groups with degenerative disease who would not tolerate a laboratory sleep study.

The limitations on activity monitoring result from the relatively non-specific results and the limited information monitored. All movement, even transmitted movement, is recorded. There is generally no information about cerebral

Table 39.3 Scoring criteria for REM without atonia

Criteria	Lapierre and montplaisir [95]	SINBAR	REM sleep atonia index
Muscle	Submental	Mental, FDS	Chin
EMG activity	Tonic: 50 % tonic >2 × background amplitude (or >10 μV) Phasic: >4 × background amplitude 0.1–10 s	Tonic: 50 % tonic >2 × background amplitude (or >10 μV) Phasic: >2 × background amplitude 0.1–5 s Any: >2 × background amplitude 0.1 s	Tonic: ≥1 μV
Epoch duration	20/2 s mini-epochs	30/3 s mini-epochs	1 s
Cut-off and combination	Tonic: >30 % Phasic: >15 %	Phasic chin: 16.3 % Any chin EMG (3 s): 18 % Any chin EMG + phasic FDS EMG (3 s): 32 % Any chin EMG + phasic FDS EMG (30 s): 27 %	AI <0.8

SINBAR Sleep innsbruck barcelona group; *FDS* Flexor digitorum superficialis; *EMG* Electromyography; *AI* Atonia index
Reproduced with permission from Ref. [430]

state (EEG), eye movements (too small to be reflected in a limb monitor), or breathing. Therefore, they do not provide much useful information about physiological state and crucial information about exact sleep stages.

Typically, activity monitoring devices use accelerometry to quantify movement. Several small self-contained devices currently available on the market provide a direct assessment of the amount of activity or body movement at the point of the body where they are attached. These are all derived from the work of Colburn and Smith who produced the first of these meters and documented the methods for others to use [431]. Virtually all of these use a piezoelectric sensor (usually a ceramic bender unit). The ceramic bender generates its own electric current that is directly proportional to the amount of acceleration. The activity devices usually include a volatile memory chip and a small computer or micro-controller chip. They are programmed to determine the amount of activity in a unit time and record that amount at a determined storage rate. The activity accepted by these devices is usually filtered so that they cover the dominant frequency ranges for human movement of about 0.5 to 10–15 Hz [432]. Later the data are downloaded to a computer, typically a desktop or laptop PC, usually through a special interface device. Various manipulations can then be performed on the downloaded data for further quantification or illustration. The activity data are maintained with a time-date code so that the activity can be analyzed by the time of each day recorded. The self-contained units are battery powered; current models provide batteries capable of actively recording for from 14 days to 4 years. Although shorter battery life does limit the maximum duration of the recording, battery life may increase as this technology develops. Another limitation on the duration of monitoring is the amount of computer memory available to retain the stored values. Currently, the memory size available for these monitors is 4 MB–1 GB. Duration of monitoring is inversely proportional to the rate at which values are stored. For low storage frequencies (e.g., once every minute), these capacities translate into a total monitoring period of 3–720 days. However, at high storage rates useful for examining individual movements (e.g., 10 per second), total monitoring would only be from about 7 min up to 29 h. These devices all use internal circuitry to sample the output voltage at a certain frequency (sample frequency or rate). The amount of activity can be determined by checking the number of times the voltage reaches or exceeds a minimum criteria (threshold crossing) or by some integration or summation of the total voltage from the individual samples. Integration provides the more sensitive approach, especially for examining individual movements as opposed to total activity. After a certain number of samples, the result either in total threshold crosses or integrated voltage is stored. The storage frequency or rate limits the time resolution of this technique. For assessing total activity occurring in spans of a few seconds to minutes, the digital sampling can be at relatively low rates (e.g., 4–8 Hz) and still provide an adequate measurement. But for higher storage frequencies designed to examine individual movements, a sampling frequency of 10–40 Hz is probably necessary. Storage rates of 10 Hz or more would be ideal although slower movements can be analysed with storage rates perhaps as low as 1 Hz.

In sleep–wake detection for the evaluation of various circadian rhythm disorders and in insomnia, the patient wears the device on the non-diominant wrist, and simultaneously keeps a sleep log for comparison. There have been several validation studies published, in both children and adults as well as in special populations, under a variety of conditions, evaluating a large number of wrist actigraphs from various manufacturers. Most devices show good sensitivity and specificity (of the order of 86–96 %), but low specificity (30–40 %); detection of wake is usually unsatisfactory [433–437]. These caveats should be borne in mind when interpreting data from actigraphy.

For movement disorders, the activity monitor is placed at the site of the abnormal movement. In general, the goal of such recording is to count and quantify such movements, not merely to indicate when movement occurs. Various earlier studies showed that abnormal movements associated with hyperkinetic disorders could be quantified using actigraphy [438, 439], if appropriate filtering was used to select for frequencies associated with the movements. Early studies attempted such a quantitation in PLMS. The total movement activity during sleep for patients was determined from activity monitors worn on the ankle of the affected leg, but the correlations between overall activity and the number of PLM were not high (values of about 0.6) [440]. More recently, sophisticated systems for counting movements have been developed and validated [441–443], making these systems useful for therapeutic monitoring or assistance in diagnosis of PLMD and RLS [444–446]. A much better correlation between total activity and specific abnormal movements may be obtained with a finer-grain analyses [447]. Recognizing the distinctive profile of individual movements requires matching the descriptive powers of an EMG record. To detect the onset and end of a specific movement requires sensitivity to higher-frequency components of the movement, necessitating sampling rates in the range of 10–40 Hz. Moreover, there are major data-storage problems for this condition. PLM are, by definition, greater than 0.5 s in duration (see Chap. 40). Activity measurements to detect PLM should have storage frequencies of at least 4 Hz and preferably 8–10 Hz to enhance measurement accuracy. A fine-grain analysis with 40 Hz sampling and storage at 10 Hz available from one of these monitors (PAM-RL, Respironics, Pittsburg, PA) provides a description closely matching the EMG recordings for these movements (Fig. 39.12). The recording at 10 Hz can then be saved for up to 7 days depending on the memory size in the units. In the more advanced activity meters such as the PAM-RL detections are based on sampling at 40 Hz with data stored for the activity summed over 4 samples (10 Hz data storage). The descriptive information about the movement along with total activity per 0.1 s permits a review of

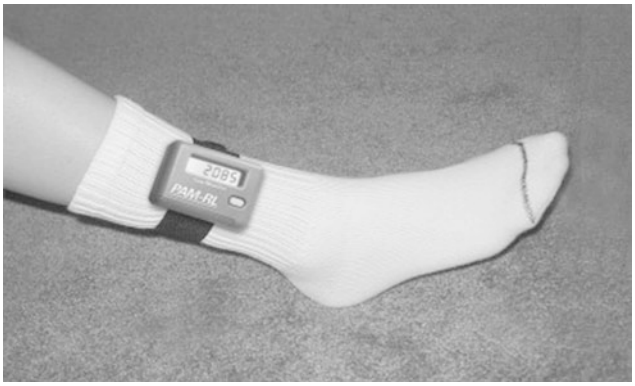

Fig. 39.12 Example of a high-precision activity monitor worn on the ankle to detect leg movements

machine scoring to determine if criteria are met for periodic movements of sleep. The data provides an excellent agreement with the nocturnal PSG for number of leg movements (Fig. 39.13) with a correlation of 0.997 and an average error for rates per hour of less than 1.0. when done in the laboratory setting with calibrated meters [448]. The monitors when used off the shelf in a standard clinical setting also have very good agreement with results from the PSG and are considered validated for this use [443]. The PAM-RL has an advantage for home recordings since it records separately the PLM rates when the legs are stretched out from when they are upright (subject sitting or standing). Thus they give the PLM rates for the sleep position (although not sleep, per se) (Fig. 39.14).

The use of the new ambulatory monitors that provide this fine-grain analyses of movements might be further extended to assess other movement disorders in sleep, such as RBD or rhythmic movement disorder. But even such a development would fail to provide relevant information about the patient's sleep–wake state. This can be approached by adding illumination or position information. To detect body position, a system has been developed [449] which requires wearing small monitors on the trunk and also on the leg just above the knee. Each monitor records position in three-dimensional space for each epoch (30 s to 1 min), and the combination of the two provides a description of the overall body position as standing, sitting, reclining, supine, prone, or lying on the right or left side. These monitors, when compared to direct observation of a subject's body position, show an excellent overall agreement (contingency coefficients C = 0.85–0.91, maximum value of C for these data = 0.913). Activity data collected at the same time as position data permits differentiating abnormal movements that occur while the patient is lying down from those while standing or sitting. It also permits the detection of events during the sleep time when the patient sits or stands up, such as occurs for sleepwalking.

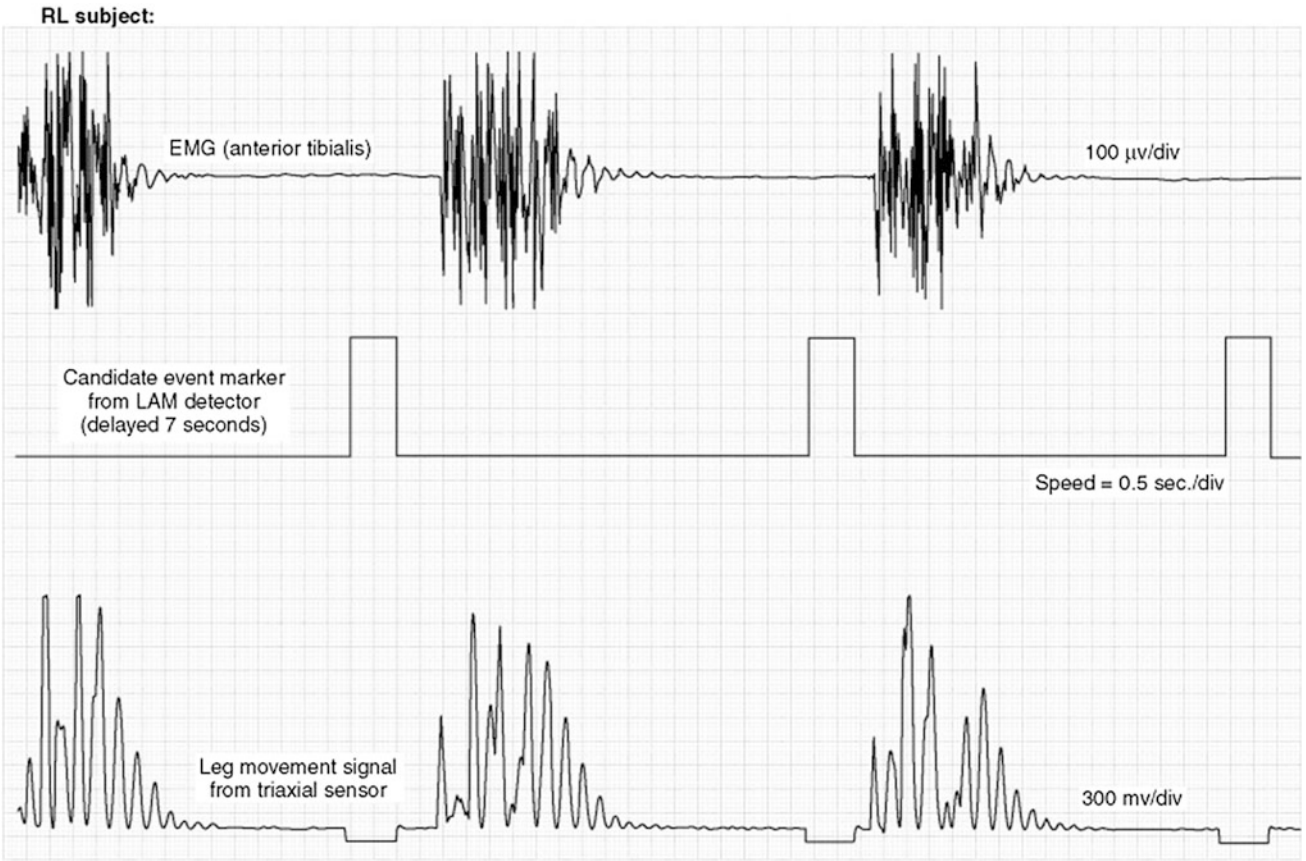

Fig. 39.13 Example of the real-time output of a high-precision activity monitor worn on the ankle (*bottom line*) compared to anterior tibilais EMG activity (*top line*). The *middle line* shows the real-time automatic detection of a significant leg movement made by the activity meter. The decision rules for the real-time leg movement detector create a 7-s delay in the detection

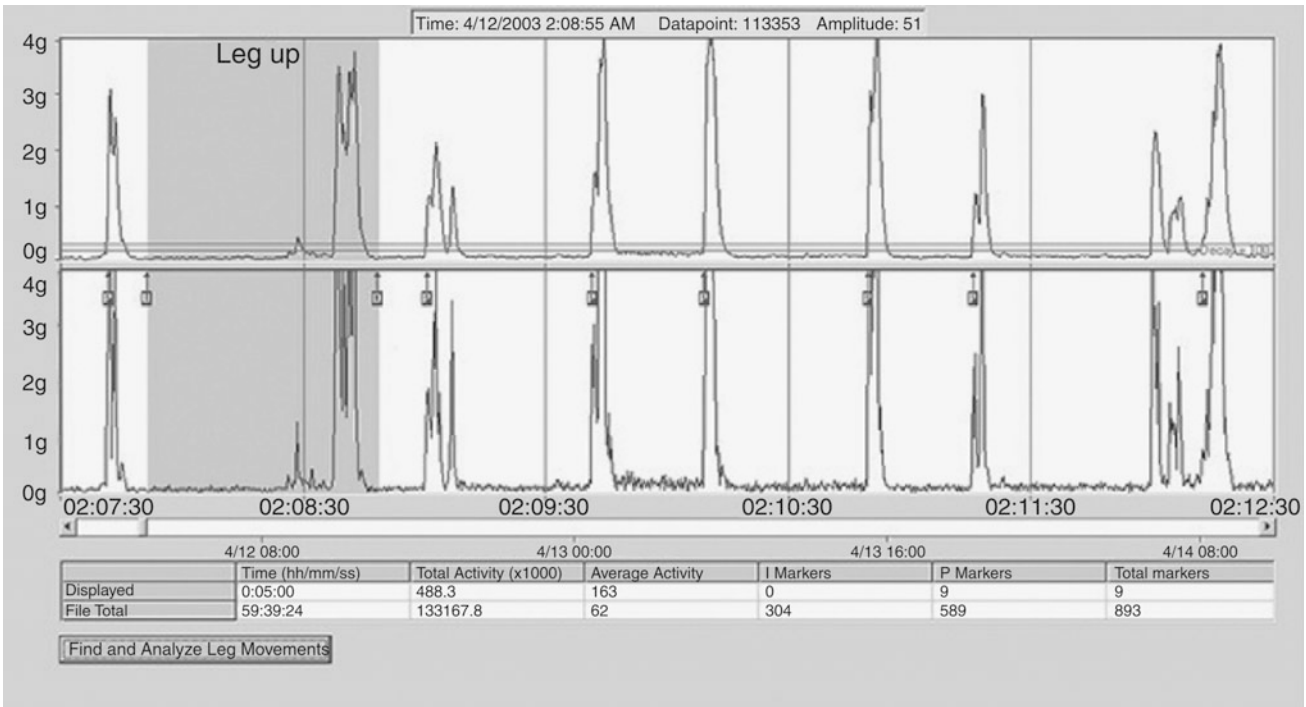

Fig. 39.14 Example of a computer display of stored leg activity and leg position data from a high-precision activity monitor worn on the ankle. The lighter areas on the graph (*white background*) indicate the leg is in a mostly horizontal position

ii. Consumer-oriented sleep technology

In recent years, there has been an explosion of inexpensive, consumer-oriented, readily available technology that is meant to monitor, among other parameters, sleep quality and duration. Entries into this category include standalone wearable devices (e.g., FitBit, Jawbone) as well as smartphone-based software programs ("apps") [450, 451]. While they all essentially use accelerometry-based techniques, as does actigraphy, to score sleep or wake (and in some cases distinguish between "light" and "deep" sleep) based on body movement, in most cases, the exact technology is proprietary, which limits detailed evaluation. "No-contact" bedside devices that detect sleep through radiowaves have also recently become available [452]. While such consumer-oriented sleep technology is very popular, mainly due to its convenience and easy accessibility, there is very little data validating it against established means of evaluating sleep [453]. Therefore, the sleep community remains uncertain as to how to approach this technology and how to interpret the information obtained from such devices and apps that patients bring with them to their clinic evaluations [454]. Recently published studies do suggest that this technology, while showing variable correlation with PSG-based scoring, has a sensitivity and specificity for sleep–wake detection that may be comparable to actigraphy [452, 455–458]. However the data are preliminary as of now. Thus, although the use of consumer-oriented sleep technology is likely to increase in the coming years, until larger studies that evaluate this technology are available, its exact role in clinical sleep medicine and research, if any, remains unclear.

B. Neurophysiological Studies

Polysomnography

Video PSG is the gold standard in diagnosing a variety of sleep disorders, specifically sleep-disordered breathing, abnormal movements in sleep, and nocturnal seizures. PSG techniques are discussed in detail in Chap. 17, and the scoring of sleep stages and respiratory events in sleep is discussed in Chaps. 24 and 25 respectively. Many abnormal movements in sleep as well as parasomnias are induced by arousals, which can be due to factors not obviously associated with the movements themselves, most commonly OSA. Treating OSA will decrease arousals, in turn decreasing the abnormal movements and parasomnias. Thus, even patients with what appear to be typical abnormal movements in sleep (HFT, ALMA, RMD, etc.) should be screened for possible OSA and undergo a PSG if they present with risk factors for sleep-disordered breathing.

When dealing with patients with abnormal movements in sleep, certain modifications to the PSG montage are helpful (see Chap. 18). While the standard PSG with a single EMG lead for the legs does provides a certain degree of information about certain motor disturbances, specifically PLMS, they may not be helpful when dealing with abnormal movements involving the upper extremities, the cranially innervated muscles, or even more proximal or more distal lower extremity muscles. For this reason, a multiple muscle montage that includes extra EMG channels recording from additional cranially innervated muscles (such as the sternocleidomastoideus, masseter and other muscles), upper limb (e.g., biceps, triceps, extensor digitorum communis, flexor digitorum subliminis), and lower limb muscles (e.g., quadriceps, hamstrings, gastrocnemius, and extensor digitorum brevis) and axial muscles (e.g., cervical, thoracic and lumbar paraspinals, rectus abdominis, intercostal muscles) (see Table 18.4) is recommended in those patients who have more complex movements by history. Similarly, an extended seizure montage with extra EEG channels (see Table 18.2), or a hybrid montage using select additional EEG and EMG channels (see Table 18.5) may be of benefit in patients in whom abnormal movements in sleep are suspected to be secondary to nocturnal seizures. Technician observations are invaluable in the documentation and description of events, and where the question is one of RBD, in eliciting dream recall. The sleep specialist can ask for no stronger ally than a vigilant technician who is aware of the clinical question being asked and is able to focus the camera on the area and movement of interest when abnormal movements occur.

Where patients complain of daytime sleepiness or abnormal movements during daytime naps, multiple sleep latency testing (MSLT), with multiple muscle montage if indicated, may be considered (see Chap. 22).

While ambulatory sleep studies (or home sleep tests [HST]) are gaining increasing acceptability and use in the evaluation of OSA, they suffer from significant limitations in the evaluation of abnormal movements in sleep, including a limited number or most often no EEG or EMG channels, no corresponding video recording, and no observer to document unusual behavior. Therefore, at the present time, HST is not recommended in the evaluation of patients with abnormal movements in sleep, such patients need to be evaluated by in-laboratory PSG.

Motor Evoked Responses

To more directly examine the impact of sleep on the motor system itself, motor evoked potentials (MEPs) can be studied. In one study of MEPs evoked by stimulating the motor cortex with a strong magnetic stimulus during sleep, it was noted that the MEPs decreased during NREM sleep [459]. Results during REM sleep have shown a much greater degree of variability in amplitude of evoked responses. Hess et al. [459] found that responses were of normal or increased amplitude, suggesting enhanced cortical excitability during REM sleep. In contrast, Fish et al. [261] found that average amplitude was decreased in 3 normal subjects with prolonged latencies in REM sleep compared to wakefulness

despite variability of response amplitudes indicating maintenance of motor inhibition during REM sleep. In a group of narcoleptic patients, stimulation during cataplexy resulted in apparently normal MEPs [460]. While these results remain to be harmonized, the variability is consistent with the fluctuating balance between inhibitory and excitatory processes in REM. A finding of decreased mean amplitude, however, is more consistent with the general inhibitory balance of REM sleep in normals. When sleep apneas are superimposed on sleep, MEP amplitude may decrease further [461]. The use of MEPs in the evaluation of abnormal movements in sleep is mainly in the realm of research at this point and not of much value in everyday clinical practice.

Other methods used in Special Circumstances

In selected cases, a number of specialized techniques to evaluate for abnormal movements occurring in sleep can be performed. These include EEG–EMG studies with back averaging, reciprocal inhibition, long loop reflex (the "C" reflex), startle reflex, and somatosensory evoked potentials (SEP, e.g., giant SEP in cortical myoclonus). A detailed description of these techniques is beyond the scope of this chapter, but the reader is referred to other sources for further information [462].

C. Neuroimaging Studies

The development of new imaging techniques that permit assessment of activity in the waking brain provides an additional method of studying regional contributions to state-dependent motor activity. Studies of cerebral blood flow and metabolism have largely paralleled those of cellular activity. Techniques, including functional magnetic resonance imaging (fMRI), SPECT, and PET scans including ligand studies, MR spectroscopy, functional or resting connectivity, diffusion tensor imaging (DTI) and tractography (for white matter imaging), voxel-based morphometry (for gray matter imaging), and transcranial sonography have all been employed in research and are discussed in greater detail in Chap. 21.

Blood flow and metabolism may be greater during REM sleep than in waking but are widely depressed during NREM sleep, especially SWS [463, 464]. Examining differential regional activities in relation to sleep states or features can provide insights into sleep mechanisms. In one study, Hofle et al. [465] correlated activity in different brain regions with power in different EEG frequency domains (e.g., delta, here 1.5–4.0 Hz). The greatest decrement associated with increased delta power (characteristic of SWS) was in the thalamus, consistent with the depressed thalamic activity of sleep. The presence of sleep spindles, most common in stage N2 sleep, is associated with activation of the thalamus, paralimbic areas, and the superior temporal gyrus [466]. Slow (11–13 Hz) and fast (13–15 Hz) spindles show this common activation, plus distinctive activations of the superior frontal gyrus (slow spindles) compared to sensorimotor cortical areas (fast spindles), medial frontal areas, and hippocampus. During REM sleep, in contrast to NREM sleep, there is activation of the brain stem core and thalamus as well as limbic areas of the brain and primary and secondary sensory areas [467–469], including visual cortices [470]. Hong et al. [471] examined the association between REMs and blood flow and found associations both with the midline attentional system active in REM sleep and areas involved in generating waking saccadic eye movements and subserving visual attention. Higher cortical areas, including prefrontal cortex and multimodal sensory and associative cortex, remain suppressed during all sleep stages [472]. REM sleep can be divided into those baseline periods without REMs and the periods with REMs, during which sensory receptivity is decreased [473]. During actual rapid eye movements, fMRI studies have shown additional activation in posterior thalamus and occipital visual cortex [474] or within a thalamocortical network including limbic and parahippocampal areas. Additional studies have shown that the basal ganglia are suppressed in SWS, but very strongly activated in REM sleep [463]. The significance of these basal ganglia changes for the motor system and for movement disorders in sleep remains unclear but is of great potential interest. These results in imaging studies suggest an evolving of sleep states in terms of the involved brain structures, including the motor system.

Imaging studies can also begin to assess potential deficits due to altered sleep conditions, such as sleep deprivation [475], which can cause depression of frontal lobe activity that is only partially restored after a compensatory sleep.

Principles of Treatment of Sleep Disorders Related to Abnormal Movements

The first and foremost step is to determine if sleep dysfunction is related to these abnormal movements at night, or if these are due to an associated common primary sleep disorder (e.g., OSA which has a prevalence in the population of about 14 % in men and 6 % in women between 30 and 70 years old; or a persistent insomnia disorder which may affect the quality of life in about 10 % of the population), or a comorbid psychiatric illness (e.g., anxiety, depression).

The basic treatment can be divided into two categories:

1. Treatment of the abnormal movements at night possibly responsible for sleep dysfunction using standard treatment for these movements. If these movement disorders are causing sleep dysfunction, optimal treatment of these involuntary movements should improve patient's sleep dysfunction. Pharmacologic treatment of these jerks and shakes has been addressed briefly in the text (see above).

Most of these abnormal movements do not require a specific treatment as these are mostly benign and will disappear in time but sometimes may persist into adulthood. However, treatment may be required if the movements are violent, injurious, or potentially violent. Pharmacotherapy usually includes benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), or other antidepressants or anxiolytics for short-term relief. Non-pharmacological treatment may consist of psychotherapy, reassurance, and education of the patient and the family, progressive relaxation, and good sleep hygiene (sleep health) practice (e.g., regularize sleep–wake schedule, avoid alcohol, coffee consumption, and smoking near bed-time.). Also, attention should be paid to environmental safety measures, such as removing harmful sharp objects from bedroom, placing a mattress or other soft surface next to the bed, locking doors, and windows to prevent the patient from injuring himself/herself.

2. If sleep dysfunction is due to a primary sleep disorder, this should be treated using the standard method (e.g., CPAP for OSA and cognitive behavioral therapy (CBT) for insomnia with or without hypnotics used intermittently). Any comorbid psychiatric illness should be treated using generally accepted measures (e.g., SSRIs or other antidepressants and anxiolytics for depression and anxiety). Patients should always follow some common sense sleep hygiene measures. In a subset of patients with sleep onset or maintenance insomnia and circadian disruption associated with abnormal movements, especially when caused by neurodegenerative disease (e.g., Alzheimer's disease and Parkinson's disease) appropriately timed bright light therapy has been found to be useful. A word of caution is in order. Pharmacotherapy should be initiated at low doses, particularly in the elderly and those with neurodegenerative diseases, to minimize side effects. Finally, patients should be advised to avoid prolonged use of sedative-hypnotics and reduce or eliminate medications that may contribute to sleep dysfunction or OSA.

Box 39.2 lists these general principles of treatment.

Box 39.2: Principles of Treatment of Sleep Dysfunction Related to Abnormal Nocturnal Movements

- First determine if sleep dysfunction is related to abnormal nocturnal movements or a primary sleep disorder or a comorbid psychiatric-illness
- Treat primary movement disorder if it is causing sleep dysfunction
- Treat associated primary sleep disorder
- Treat comorbid psychiatric illness
- Initiate good sleep hygiene measures including regular sleep–wake dysfunction
- For pharmacotherapy try a non-benzodiazepine receptor agonist or a melatonin receptor agonist for short-term hypnotic use
- Start with a small dose and gradually increase the dose to minimize side effects in the elderly or those with neurodegerative disease
- Reduce or eliminate medications that may contribute to sleep disturbance or sleep apnea
- Attend to environmental safety precautions to avoid injury to patients
- Use appropriately timed bright light exposure in a subset of patients with insomnia and circadian rhythm disruption.

Summary and Conclusion

This chapter discussed an important aspect of human motor control (and dyscontrol) that has been largely neglected for a long time because it sits in the borderland of two important disciplines in medicine—those specializing in movement disorders and those specializing in sleep medicine. An understanding of motor control mechanisms is important for both fields. A breakdown in the delicate balance of motor control due to an affection of the afferent, central, or efferent structures can cause a dysfunction of voluntary movements or appearance of abnormal movements causing both positive and negative symptoms. Sleep modulates motor phenomena with progressive decline of motor activity due to increasing dominance of central inhibitory drive; concomitantly, the excitatory mechanism breaks through the inhibitory phase causing the appearance of motor events (some are physiological, but others are clearly pathological) Movement disorder specialists deal with diurnal involuntary movements, whereas sleep specialists encounter abnormal motor activities during sleep that may disturb sleep and result in impaired daytime functioning. The question often arises as to whether these are diurnal movements persisting during sleep, or abnormal movements triggered by sleep or intruding into sleep. This dilemma is highlighted by the fact that there are considerable similarities and overlaps between nocturnal and diurnal movements, and sleep may be disturbed by both diurnal and nocturnal motor events. There is a growing realization that both diurnal and nocturnal motor events may result from a common neurobiological alteration in the molecular mechanisms of motor control and sleep wakefulness. In this chapter, we briefly outlined motor control of human voluntary movements in wakefulness and sleep as well as suggested some pathophysiological mechanisms for abnormal jerks and shakes at night. We also provided a brief description of these conditions based on a method of

classification for easy comprehension. Finally, we summarized principles of treatment of sleep dysfunction associated with these abnormal nocturnal motor events.

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Evaluation and Management of RLS and PLMD

40

Richard P. Allen

Periodic Leg Movements of Sleep (PLMS)

Periodic Leg Movements of Sleep have been well defined as stereotyped involuntary movements occurring during sleep periods in a series of movements that for a given individual have a remarkably stable period, typically about 15–30 s. The naming and very loose criteria defining these have unfortunately created considerable confusion. The periodicity requirement became extended to include movements occurring with intermovement intervals (IMI) of 5–90 s ignoring movements with an IMI <5 s [1]. This has led to the identification of movements as periodic that are actually somewhat random without a well-defined mode describing their period. For example, some reports describe these as occurring for arms [2], leading to the unfortunate use of the term periodic limb movements. More careful analyses revealed that arm movements rarely show the well-defined modal period required for periodic phenomena [3]. They reflect somewhat randomly occurring frequent arm activity that is considered periodic because of an overly inclusive period requirements that have been used to define PLM.

Leg movements meeting the broad criteria for PLMS have also been found to occur in resting waking either during the night sleep period or for RLS patients when lying down attempting to rest without movement during the day in what has been called the suggested immobilization test [4]. These periodic leg movements in waking have been termed PLMW, but it should be again noted that the periodicity is not well established for these events during waking [5] except possibly when they occur in transitions into or out of sleep during the night's sleep period [6].

There is an extensive literature on PLMS that is exclusively based on EMG recordings of the anterior tibialis muscle. Thus, the considerable knowledge we have about PLM applies to activation of the anterior tibialis muscle that produces only a dorsiflexion and small inversion of the foot. This may occur with leg movements, but the PLM we measure is not a leg movement, nor does it involve any other part of the body. The foot dorsiflexion of PLM often occurs with activation of other muscles producing leg movements, but in one study about 39 % of the PLM occurred without any significant leg movement [7]. The appropriate terminology therefore is periodic foot dorsiflexions, but given the terminology history, the term periodic leg movements is acceptable with the caveat that the legs are often not moving.

The dorsiflexion of PLMS has been described as part of a larger envelope of episodic muscle activation, but the few studies attempting to document a more extended muscle pattern of periodic leg muscle activations during sleep have not provided a coherent picture except for the consistently primary role of the anterior tibialis muscle. Thus, when other leg muscles are recorded for observed periodic EMG events, the anterior tibialis is essentially always involved and usually is the first muscle to contract [8]. In about 13–39 % of the cases, it is the only muscle or movement involved [7, 9, 10]. Sometimes the anterior tibialis muscle activation of PLMS also occurs with activation of the extensor hallucis longus producing an extension of the big toe with some ankle dorsiflexion partially mimicking the Babinski's reflex [11]. PLMS occasionally occur with a triple flexion reflex at the ankle, knee and hip [10]. PLMS are too slow to be called myoclonus. PLMS typically last a few seconds (see Fig. 40.1). However, the movements may begin with one or more brief, myoclonic jerks that then blend into a more tonic phase; alternatively, a more sustained movement may terminate in a jerk [12, 13]. Movements are often bilateral, involving both feet, but may be predominant in one foot or alternate between feet. This may depend on sleeping position as well as biological factors. The most striking characteristic feature of PLMS is their repetitive, very periodic nature

This chapter is a revision of a portion of a chapter from the third edition written by our dear departed and esteemed colleague Wayne Hening, MD, PhD, as the lead author.

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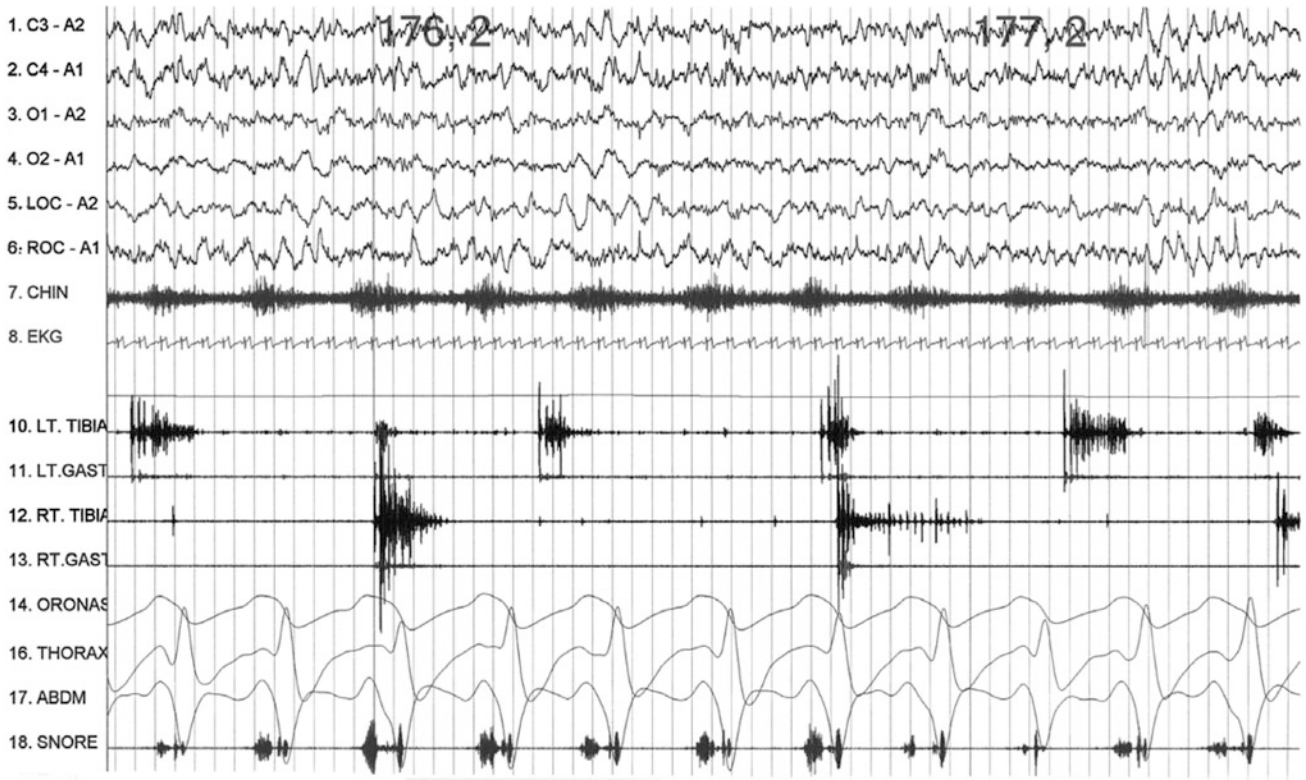

Fig. 40.1 Polysomnographic (PSG) recording showing periodic limb movements in sleep (PLMS) characterized by dystonic and dystonic–myoclonic electromyographic (EMG) bursts in left (LT) and right (RT) tibialis (TIBIA) and gastrocnemius (GAST) muscles during stage 2 (N2) non-rapid eye movement (NREM) sleep in an adult patient with restless legs syndrome (RLS). Top 4 channels show electroencephalograms (EEG) using international nomenclature (*A1* left ear; *A2* right ear; *ABDM* abdominal respiratory effort; *CHIN* submental EMG; *EKG* electrocardiogram; *LOC* left electro-oculogram; *ORONAS* oronasal airflow; *ROC* right electro-oculogram; *THORAX* chest respiratory effort)

providing a well-defined mode for the period or inter-movement interval (IMI). The variation in the inter-movement interval (IMI) between onsets of PLM approximates a lognormal distribution for the classically defined IMI ranging from 5 to 90 s. The average and standard deviation of the log IMI provides a measure of the periodicity and its spread which are both more stable over nights than is the measure of actual number of PLMS [14]. These measures with number of PLMS describe the periodic nature of the movements and the density with which they occur. There are also leg movements in sleep with IMI <5 that appear to be somewhat random in log space. An IMI of 10 s provides the best discrimination between these different distributions for short and long IMI. Thus, PLMS events are better described as occurring with IMI >10 s [15]. PLMS in moderate-to-severe RLS patients often occur in bouts of dozens to a hundred or more movements that last for many minutes. While most PLMS occur in stage 2 sleep, they also occur in all of the other stages of sleep including some in REM sleep and in waking during the sleep period [6].

Periodic Leg Movements of Sleep are defined by PSG recording. The current American Academy of Sleep Medicine (AASM) manual [16] and the World Association of Sleep Medicine (WASM) [1] criteria count movements if they occur in sleep as part of a series of four or more movements during any sleep stage including wake with IMI intervals of 5–90 s (in some older publications, intervals as short as 4 s or as long as 120 s have been accepted). Recent data have indicated the IMI interval for PLMS should be adjusted to be 10–90 s [15]. EMG activation must last 0.5–10 s. The number of movements associated with arousals may also be counted [1]. Box 40.1 lists the WASM criteria defining PLMS. Although patients may also have foot movement meeting the PLM criteria during wakefulness, only movements that occur during sleep are typically counted. A new measure, the periodicity index, is a ratio of all PLMS (with IMI range of 10–90 s) to all leg movements in sleep [17].

Box 40.1: Definition of Periodic Leg Movements in Sleep or Resting Wake (PLM)

Candidate leg movement (CLM) is defined by the following characteristics of a surface EMG recording of the anterior tibialis muscle

CLM onset occurs with EMG ≥ 8 μV above resting EMG.
CLM ends at the onset of the first 0.5 s with EMG always <2μV above resting EMG
CLM must be ≥ 0.5 and ≤ 10 s duration

Periodic leg movement (PLM) is a CLM that

has an intermovement interval (IMI) defined by onset from preceding CLM to onset of this CLM that is ≥ 5 and ≤ 90 s.

Is one of the 4 consecutive CLM that meet the IMI criterion above (giving 3 consecutive IMIs of 5–90 s).

Combining movements from two legs into one PLM event.

The movements from either leg should be counted.

Movement in one leg separated by less than 0.5 s from a movement in the other leg should be counted as a single leg movement.

From Zucconi et al. [1].

The biological basis for PLMS is particularly complicated by interaction with sleep state and the expression of these with spinal cord transactions. It is unclear how much the periodicity of PLMS stems from spinal versus brain activity, but certainly brain activity at least modulates PLMS expression and periodicity if not driving these. For example, neurotoxic lesions at the ventral mesopontine junction in cats produce increased leg movements in sleep that to some degree imitate PLMS [18]. The genetics of PLMS appear to match at least in part that for RLS with shared association for allelic variations in BTBD9, MEIS1, MAP2k4/SKOR1, TOX3, and PTPRD [19–21]. The possible genetic relation of RLS to PLMS is further supported by family history data indicating that increased PLMS occur with older adults without RLS who have an RLS relative but do not occur for those with a family member who has neither RLS nor significant number of PLMS [22]. PLMS also like RLS occur more with low serum ferritin, indicating a shared relation to impaired iron status [23]. Thus, occurrence of PLMS not attributed to medical conditions or medications may represent significant increased risk of RLS and accordingly may carry some of the health risks associated with RLS.

Individuals with elevated frequency of PLMS are often asymptomatic, but may have unrecognized sleep problems, particularly for those with higher rates of PLMS and/or more pronounced general leg movements occurring with the PLMS. Unfortunately studies do not provide information of the extent of general leg movement with the PLMS, so the potential for PLMS impact on sleep is not adequately described. Some small studies have indicated that the number of PLMS, disregarding any amplitude considerations, have little impact on sleep [24–26]. A larger population study, however, documented that PLMS with rates >15/h relate to poor sleep [27]. Amount of PLMS may relate to sleep disturbance more when the PLMS involve a greater spread of muscle activation not limited to the foot movement of the anterior tibialis, as is often clinically reported in RLS patients, but aside from limited data reported in one abstract [28], this has not been adequately documented. Bed partners sometimes complain more about the movements than the patients and are often an excellent source of information about the condition and its severity.

Periodic Leg Movements of Sleep may begin at any age, but prevalence increases markedly in healthy elderly people, with as many as 58 % having a PLMS index greater than 5 [29, 30]. Some studies have found no association between number of PLMS and either objective measures of sleep or symptomatic reports in the elderly, or only very weak associations [31]. Because of these findings, elderly patients with PLMS should only be treated when the PLMS can be linked to their sleep complaints, which usually means excluding other sources of sleep dysfunction.

Periodic Leg Movements of Sleep may occur as an isolated condition or may be associated with a large number of sleep, neurologic, or other medical disorders, and with medications such as neuroleptics and antidepressants. Among sleep disorders, the more striking associations are with narcolepsy [32–36] and RLS [37], because PLMS are common in these patients even at a relatively young age. PLMS are also common in patients with OSA [38] and RBD [39]. Patients with OSA may have a significant degree of PLMS, sometimes associated with significant sleep fragmentation even after successful treatment of their apnea [38]. The presence of PLMS in disorders involving the basal ganglia including Parkinson's Disease (PD) [40, 41], Lewy-Body Dementia [42], and MSA [43–45] is also noteworthy and may contribute to sleep problems in these disorders. Among medical conditions, the association of PLMS with uremia and end-stage renal disease is likely to be an important one related to mortality [46, 47] and to risks of stroke, cardiovascular disease, and cardiac structural abnormalities [48, 49]. PLMS have also been associated with increased risk of mortality for patients with systolic heart failure [50]. It has been reported that intrinsic and extrinsic lesions of the spinal cord may be associated with PLMS. This has been noted for multiple sclerosis [51, 52], radiculopathy [53], and transection [54]. It should be noted that the degree that these conditions produce leg movements with well-defined periodicity has not been well evaluated.

A number of studies have examined the relationship between PLM and other measures of central nervous system (CNS)/autonomic activity such as EEG, heart rate, and blood pressure. A general summary is that PLM are linked to periodic changes in activity level in different neural and neuro-responsive systems; furthermore, these modulations

do not appear to be caused by the PLM themselves, but are likely to be parallel phenomena produced by some common or associated biology [55–57]. Reducing the PLMS for RLS patients using dopamine agonists, however, appears to involve a biology that also reduces the associated cardiovascular changes. One suggestion is that the sympathetic nervous system may actually have a role in generating PLMS [58].

A specific feature of NREM sleep, the cyclic alternating pattern (CAP) is a recurrent alternation between "baseline" and more activated EEG patterns [59, 60]. PLM almost always occur during the activated ('A') phase of CAP [61]. The 'A phase' can be further subcategorized depending on the EEG frequencies most common: A1 activations consist primarily of slow waves while A3 activations are dominated by faster rhythms. The A3 phases are very strongly related to AASM-defined arousals. It has been proposed that a hierarchy of activations may be correlated with PLMS, with milder activations consisting solely of autonomic changes, slow waves, or K complexes while more intense ones are associated with EEG desynchronization and arousals [56, 57].

Periodic Limb Movement Disorder (PLMD)

Periodic Limb Movement Disorder is a condition diagnosed by excessive PLMS (>15/h for adults and >5/h for children) related to either significantly disturbed sleep at night or significant problems with functioning during the day that cannot be better explained by another disorder [62]. The prevalence and overall significance of PLMD is somewhat controversial. Individuals with elevated frequency of PLMS are often asymptomatic, but may have unrecognized sleep problems, particularly for those with higher rates of PLMS and/or more pronounced general leg movements occurring with the foot dorsiflexion of the PLMS. Unfortunately prior studies do not provide information of the extent of any general leg movement with the PLMS foot dorsiflexion, so the potential for PLMS impact on sleep is not adequately described. Small foot dorsiflexion no matter how many may not produce significant sleep or wake problems. Some small studies have found that the number of PLMS, disregarding any amplitude considerations, have little impact on sleep [24–26]. A large population study, however, documented that PLMS with rates >15/h relate to poor sleep [27]. Bed partners sometimes complain more about the movements than the patients and are often an excellent source of information about possible PLMD and its severity.

Restless Legs Syndrome

RLS is a neurological disorder of sensorimotor functioning predominantly characterized by an urge to move or restlessness focused on the legs that is provoked by rest, relieved by movement or CNS arousal, and increased with a circadian pattern during the evening and night [37]. RLS is a common disorder in the North American and European populations [63]. Associations with 16 specific allelic variants have been found by genome-wide association studies [21, 64–66]. However, while the degree of heritability determined by twin studies is relatively high (69 %) [67], the degree of familiarity is modest [68], and the 16 known RLS allelic variations account for a very small part (<15 %) of the familial pattern. The relative risk (Risch's lambda [69]) in first-degree relatives is in the range of 3–5 [68]. This suggests that RLS like other common diseases has a complex genetic diathesis that interacts with strong environmental factors. RLS, however, unlike other common diseases has one major well-defined commonly occurring environmental factor of iron deficiency [70]. Thus, all conditions compromising iron status produce increased risk of RLS. Conversely effectively all of the conditions that are associated with increased risk of RLS also have decreased iron status, e.g., pregnancy [71, 72], rheumatoid arthritis [73], and uremia [74, 75]. A unifying theme may be deficiency of iron in critical brain regions, particularly well documented for the substantia nigra and thalamus [76–83]. Box 40.2 lists major risk factors for RLS.

Box 40.2: Restless Legs Syndrome Risk Factors

Demographic and Lifestyle Factors

Increasing age
Female sex
Family history (early onset)
Living at high altitude
Smoking
Sedentary lifestyle
Caffeine
Alcohol consumption.

Medical, Surgical, and Neurological Conditions

Renal failure
Diabetes mellitus
Iron deficiency and anemia
Rheumatoid arthritis
Magnesium or vitamin B_{12} deficiency

Hypothyroidism
Heart failure
Surgical Gastric resection
Lung transplantation
Neurologic Polyneuropathies and radiculopathies
Parkinson's disease
Multiple sclerosis
Spinocerebellar ataxia (SCA3 or Machado–Joseph disease).

Other Factors
Pregnancy
Blood donations.

Medications (These may increase PLMS and also RLS)
Anti-histamines (only CNS-active)
Dopamine antagonists, e.g., antiemetics, antipsychotics (only CNS-active)
Serotonin and Norepinephrine reuptake inhibitors (SSRI, SNRI)
(Serotonin- and norepinephrine-releasing agents are also expected to increase PLMS and possibly RLS, but this has not been evaluated).

RLS significantly impacts patient's health and quality of life. Cross-sectional surveys have found RLS occurrence to be associated with general poor health, both physical and mental [63, 84–86], as well as specific disorders such as diabetes [87] and heart disease [88–90]. RLS may occur secondary to these disease states, particularly for cardiac diseases, rather than causing them [91]. RLS, in turn, relates to a diminished quality of life [63, 85, 92] and may be responsible for varied forms of psychological distress, particularly anxiety and depression [93, 94], impaired daily functioning [95], and loss of work productivity [96]. In vulnerable populations, such as dialysis patients, RLS occurs with increased mortality [96, 97]. Thus, there is evidence that RLS is provoked by a number of different disorders and also contributes to both morbidity and mortality. Much of this effect may occur through the impairment of sleep (Fig. 40.2) caused by RLS [98, 99]. Almost all studies have found RLS to be a chronic disease with both increasing prevalence (Fig. 40.3) and generally increasing severity with age [63]. Thus, RLS presents a cumulative burden substantially contributing to loss of quality of life and decreased health status in old age. Subjects with RLS report the same very poor health-related quality of life on the Medical Outcomes Short Form-36 as do those with other chronic diseases such as hypertension, congestive heart failure, and angina [85].

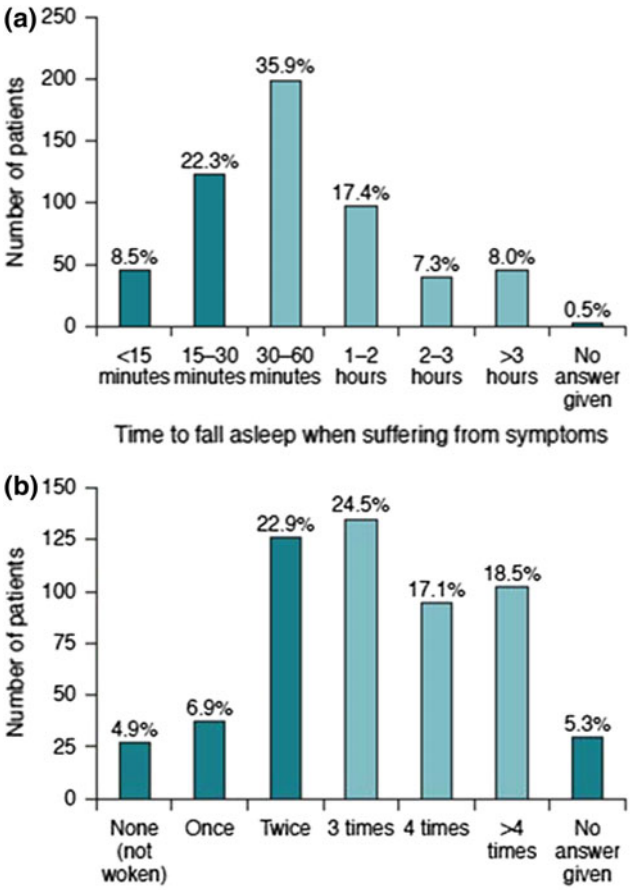

Fig. 40.2 Sleep impairment with RLS Fig. 40.1. Time to fall asleep (**a**) and number of reported awakenings (**b**) for RLS patients on nights when bothered by symptoms. *Unshaded bars* indicate those in the range considered abnormal and consistent with insomnia. Data are derived from RLS, Epidemiology, Symptoms, and Treatment (REST) general population study in the USA, France, Germany, Italy, Spain, and the United Kingdom. Reproduced with permission from Hening et al. [99]

Clinical Features and Diagnosis of RLS

restless legs syndrome was first extensively described by Karl Ekbom, a Swedish neurologist who named the condition and elucidated its clinical features [100–102]. Over the last decade, the key clinical features required for diagnosis have been determined through a consensus process [37, 103, 104] and include the 5 essential diagnostic features presented in Box 40.3. In addition, there are two significant specifiers that should be considered with the diagnosis: Clinical Course and Clinical Significance (see Box 40.3).

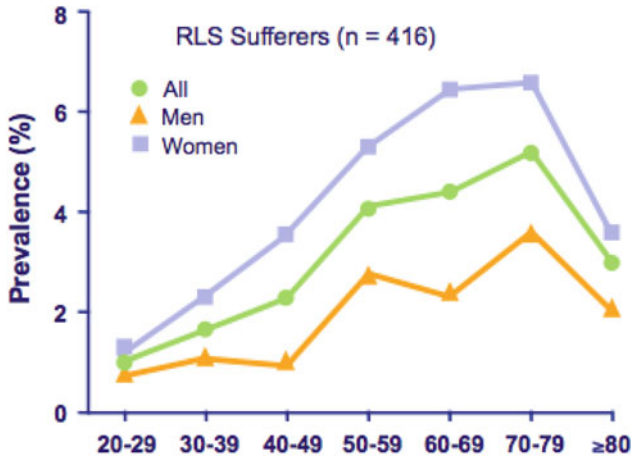

Fig. 40.3 RLS prevalence by age and gender. Population based sample of 15,391 adults ≥age 18 in Western Europe and the USA. RLS sufferer defined as those with RLS symptoms ≥2/week with moderate or severe distress when present. Note that there is little gender difference in the youngest group. Graph slightly modified from Allen et al. [63]

Box 40.3: Restless Legs Syndrome (Willis Ekbom Disease): Clinical Diagnostic Criteria

Adapted from Allen et al. [37].

Essential Diagnostic Criteria for RLS/WED

1. An urge to move the legs usually but not always accompanied by uncomfortable and unpleasant sensations in the legs.
2. The urge to move and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.
3. The urge to move and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move and any accompanying unpleasant sensations during rest or inactivity are worse in the evening or night than during the day or only occur in the evening or night (when symptoms are very severe, the worsening at night may not be noticeable but must have been previously present).
5. The occurrence of the above features is not solely accounted for by symptoms primary to another disorder or behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).

Specifiers for Clinical Course of RLS/WED

(a) Chronic-Persistent RLS/WED: untreated symptoms on average occurred ≥2/week for past year
(b) Intermittent RLS/WED: untreated symptoms occur on average <2/week for past year but with more than 5 lifetime events.

Specifiers for Clinical Significance

RLS/WED symptoms significantly impair social, occupational, educational, or other important areas of functioning

Special notes

1. Sometimes the urge to move occurs with discomfort involving arms as well as legs.
2. For very severe symptoms or in an advanced stage or in intractable cases relief with activity and/or the worsening in the evening may not be present, but then must have been previously present earlier in the course of the disease.
3. The specifiers for clinical course may not apply to children nor to special cases of provoked RLS/WED where frequency may be high but duration short, e.g., pregnancy.

Other body parts, especially the arms can be involved in RLS [105], especially during sever exacerbation of symptoms as occurs with RLS dopaminergic augmentation [106]. The legs, however, are almost always involved first and more prominently. RLS without leg symptoms at onset is at least rare [107], and the diagnosis requires involvement of the legs.

Clinical features supporting but not required for diagnosis [37] include familial aggregation [68, 108], significant numbers of PLM [4, 109] with established periodicity [110], prominent response to dopaminergic treatment [111], and daytime alertness despite significant sleep loss (Table 40.4). These supportive clinical features can be used to support diagnosis in uncertain cases, but the diagnosis must be based on evaluation of clinical history. The current diagnostic criteria apply to all conditions. Special problems with eliciting the sensory symptoms from children [112] and cognitively impaired elderly may require diagnosis guided by evaluating other conditions supporting the diagnosis (see Box 40.4).

Because frequent PLM are associated with RLS, the measurement of PLM has been proposed as a diagnostic test. The Montreal group has taken the lead in validating such a

test. They reported finding that the best discrimination for RLS from matched healthy controls was the PLMW per hour wake during sleep time but not dramatically better than the accuracy for PLMS per hour of sleep (92 % vs. 84 %). In contrast, somewhat unexpectedly the number of PLMW with arousal per hour of sleep had much lower accuracy (74 %) [109]. That study also included evaluation of the diagnostic accuracy of the Suggested Immobilization Test (SIT), a test designed to provoke RLS symptoms by having the subject remain sitting reclined in a bed without activity for a sustained period (usually an hour). The subject's rating of sensory discomfort provided about the same accuracy as the PLMS and PLMW, but there is an obvious problem of expectation for this sensory report from healthy versus diagnosed RLS patients. The PLMW from the SIT had poor accuracy (75 %). Work on evaluating the periodic nature of the PLM may provide better diagnosis, but this is only recently being considered [17].

To study responsiveness to dopaminergics, a test dose of levodopa was used. A greater than 50 % improvement of symptoms was strongly associated with a true RLS diagnosis, and a positive response to this test was a reliable indicator that a patient would subsequently benefit from dopaminergic treatment [113]. This has to be balanced against two larger clinical trials, where about 40 % of patients did not respond to the dopamine agonist ropinirole despite using a dose escalation to maximize treatment benefit [114, 115]. Thus, a failure to respond to dopamine treatment cannot be considered 100 % accurate for a negative diagnosis of RLS, and clearly there are always placebo responders in any clinical treatment.

Because there is, as of yet, no accepted laboratory marker for RLS, the standard for diagnosis remains a clinical one and is derived from the patient's history [116]. Laboratory evaluation is useful mainly to support the diagnosis of RLS and to identify any possible underlying medical condition (e.g., uremia) [116]. To determine RLS, in the clinic or the community, it is necessary to first establish the presence of the five diagnostic features noted previously. While earlier epidemiologic studies used ad hoc questions to ascertain the presence of RLS [117, 118], more recent ones have generated probes based on the first four diagnostic features [63, 119] [88, 95, 120–123]. A study at Johns Hopkins University, however, has demonstrated that up to 16 % of individuals without RLS may meet the original four diagnostic criteria [124]. Definitive diagnosis, therefore, requires discriminating RLS from its mimics as required by the 5th diagnostic criterion in the current diagnostic standard for RLS [37].

Several multi-question diagnostic instruments have been developed for epidemiologic studies. Two have been validated. One three-question instrument developed by Klaus Berger and endorsed at the National Institutes of Health (NIH) diagnostic consensus conference [104] had an inter-rater kappa of 0.67 between two experts who, however, had access to the questionnaire results [125]. This questionnaire, however, does not exclude mimics as required by the current diagnostic criteria. Another questionnaire developed at Johns Hopkins University was validated by independent clinician interview. It dealt somewhat with excluding mimics [126] and had a sensitivity of 89 % and specificity of 80 % in an American primary care practice. A much revised version of the questionnaire that specifically included items to exclude common mimics (Cambridge Hopkins RLS diagnostic questionnaire—CHRLSQ) was validated by the previously validated telephone diagnostic interview [127], had a sensitivity of 87 % and a specificity of 94 % in a population of blood donors [128]. The 13 items that are the validated diagnostic part of this questionnaire, the CHRLSQ-13, is available from the authors and has been used in clinical studies [70].

Two different approaches have been taken to make more definitive interview-based diagnoses for clinical or research purposes. First is a telephone interview, the Hopkins Telephone Diagnostic Interview for RLS (HTDI) [127]. This includes questions that address the diagnostic features, but also questions to assist with differential diagnosis and uncover mimics. Finally, there are questions concerning the key aspects of the disorder. Agreement with expert interviews was found to be 92 %, approaching the inter-rater reliability of two-expert face-to-face interviews of 96 % [127]. A second approach is a protocol that begins with questions about diagnostic features but then includes tests related to features supporting the diagnosis (see Box 40.4). This diagnostic interview includes questions on family history, a sleep study to look for PLM, a physical examination to exclude other causes for symptoms, and a dopaminergic challenge test [129]. It gives higher scores to patients with more frequent symptoms and therefore may not correctly identify those with sporadic symptoms. Its diagnosis is basically one of clinically significant RLS and is mainly useful in a sleep clinic or sleep laboratory setting.

Box 40.4: Conditions Supporting the RLS Diagnosis

- **Family History**: The prevalence of RLS among first-degree relatives of people with RLS is 3–5 times greater than in people without RLS.
- **Response to Dopaminergic Therapy**: Nearly all people with RLS show at least an initial positive therapeutic response to either L-dopa or a dopamine receptor agonist at doses considered to be very low in relation to the traditional doses of these medications used for the treatment of Parkinson's disease. This initial response is not, however, universally maintained.
- **Periodic Limb Movements** (during wakefulness or sleep): Periodic limb movements in sleep (PLMS) occur in at least 85 % of people with RLS; however, PLMS

also commonly occur in other disorders and in the elderly, but are uncommon in children.

- **Sleep Disturbance**: Disturbed sleep is a common major morbidity for RLS and deserves special consideration in planning treatment. This morbidity is often the primary reason the patient seeks medical attention.
- **Lack of profound daytime sleepiness**: The significant sleep disruption with moderate-to-severe RLS often fails to produce the expected profound daytime sleepiness (this may also occur for other hyperarousal conditions including some insomnias).

Overall either the CHRLSQ-13 or the HTDI (also appropriate for a clinical interview) provide the best general methods for diagnosis of RLS in studies.

Epidemiology, Biology, and Genetics of RLS

Prevalence of RLS in Different Ethnic Groups

It is not clear whether substantial and true differences exist between different ethnic groups in the prevalence of RLS. RLS must be defined clinically from history. Different groups with different languages unfortunately may respond differently when asked apparently equivalent questions about their medical history. Population-based studies, even when using several questions to diagnose RLS, vary in how many individuals detected have true RLS and how many of those with RLS are missed [125, 130]. A rough guide from one study with validation using trained physician diagnosis [131] is that the positive predictive value—how many of those identified with RLS actually have the disorder—is on the order of 40–60 % in studies using well-established diagnostic criteria based on the first 4 consensus diagnostic criteria without some screening required by the 5th diagnostic criterion. This means that less than half may actually have RLS. It is generally considered that false positives in such studies are more likely than false negatives, but this has not been tested.

Despite these methodological limitations, repeated studies have shown that there is a high prevalence of RLS in Western (European and European-derived) populations [63, 88, 95, 119–123]. It seems reasonable that the true rate in Western adults is on the order of 4–10 % for RLS at any frequency. One large-scale study, the REST population study conducted in the USA and Europe, found an overall prevalence of 7.2 % in adults [63]. That study used a questionnaire later found to have a positive predictive value of 59 % [131]. The study also looked at a measure of clinically significant RLS, a frequency of twice a week or more and moderate or greater distress when symptoms occurred and found a frequency of 2.7 %. A later study based on trained physician diagnosis found an overall frequency of approximately 4.4 % and confirmed the prior study showing clinically significant RLS frequency was 2.7 %; the prevalence of RLS with high impact of symptoms on patients life was 0.8 % [131]. These trained physician diagnosed rates are considered the most reliable estimates of RLS prevalence in the European and presumably white North American populations.

While several studies have suggested a lower prevalence in some non-Western countries [132–135]. other studies have found approximately the same prevalence as in the European/USA populations [136, 137]. In two methodologically rigorous studies, which used personal interviews to verify diagnosis, the frequency in Japanese elderly was around 1 % [134] and among Korean adults, 7.5 % [138]. The information on African Americans is scant. Very few African Americans seek treatment for RLS in clinics, and the previous published epidemiologic studies have not addressed the prevalence of RLS among African Americans. One preliminary study in Baltimore did not find a lower frequency in African Americans [139]. Given these uncertainties, it is not completely established that RLS is much more common in whites than in other ethnic populations.

Besides ethnicity, age and gender are strongly associated with RLS. Almost all studies [63, 88, 95, 119–123] have reported positive correlations of RLS with age (but see Sevim et al. [132]) that is more pronounced for women. Adults younger than 35 years appear to have no gender differences in prevalence [63], but after that prevalence increases significantly more for women than men. This critical age likely relates to pregnancy occurring since nulliparous women have the same risk of RLS as men [123, 140]. A systematic study of RLS frequency in children [141] found that 1.9 % of those 8–11 years of age and 2.0 % of those 12–17 years of age reported symptoms of RLS; 0.5 % of the younger group and 1 % of the older group had clinically significant RLS (twice a week and bothersome when occurring). There was no gender difference for children.

Incidence and Natural History of RLS

As noted above, RLS onset can occur at any age from childhood to old age for both genders. Incidence has been reported for one sample of American adults $\geq$ 40 years old to be 1.7 % per year [142]. RLS incidence per year in two different German population samples was 1.3 and 4.1 %. Persistence of RLS was low over 2–5 years at about 40–50 %, suggesting marked variability in RLS symptoms [143]. Unfortunately, these studies on incidence and persistence of RLS have been based on diagnostic methods that as noted above have low positive predictive values of about

50 %. The percentage falsely identified as having RLS (40–50 %) approximates the percentage not reporting persistence of RLS symptoms at the 2–5 year follow-up interview. Thus, it is unclear how many reporting on follow-up interview new onset or remission of symptoms were not those previously misclassified as RLS by the survey methods.

It has been assumed that the natural course of RLS is that of slowly progressive worsening, but while this is reported for some it is not always the case. Many cases report spontaneous remissions sometimes lasting years [144]. Although gradual worsening and spontaneous remissions are reported, the degree and rates of occurrence of these are not known. Three placebo studies of augmentation have reported evidence for definite spontaneous worsening of RLS during placebo treatment for 6 months at median 6 month rate of 1.0 % (<0.5, 1.0, and 6.0 %) [145–147]. The blinded comparison of pregabalin and pramipexole treatment [148] found approximately the same rate of RLS worsening on pregabalin (2.1 % for 12 months) consistent with the natural worsening on placebo. These studies would suggest that the natural progressive worsening beyond current moderately severe RLS occurs at a low rate of about 2 % of the patients over one year. But this remains to be better studied. Overall, it appears that the natural course of RLS is highly variable, including natural gradual worsening with changes in medical factors (e.g., iron status), periods of exacerbation, and also spontaneous remissions.

Secondary (Causally Related) and Comorbid Conditions for RLS

Elevated prevalence (>20 %) of RLS has been reported in studies based on clinical samples of persons with a number of medical conditions such as iron deficiency [70, 149], pregnancy [150–152], and uremia [153–155]. Their causative relation to RLS is supported by the reversibility of symptoms of RLS after treatment or resolution of iron deficiency anemia [156], pregnancy [151], and uremia [157]. Considerably higher prevalence of RLS has also been reported among these putatively causal comorbid conditions (iron deficiency [70], pregnancy [158], and uremia [159, 160]) even in Asian countries with low prevalence of RLS in the general population. One constant factor noted in these causally related conditions is that they typically predispose to low iron stores [161]. Decreased iron stores may also explain the finding that RLS may be more common among those who have been regular users of nonsteroidal anti-inflammatory medications that can cause gastrointestinal bleeding [162] and may be aggravated by blood donation [163] and may be more common among frequent blood donors [164] but not among those donating 3 times a year or less [165]. Such conditions may not only provoke RLS, but increase risk of RLS later in life. It has been also hypothesized that pregnancy similarly causes significant iron deficiency and may also cause lasting metabolic changes that predispose to increased RLS in later life [123, 166].

In some co-morbid neurologic conditions, the association with RLS is not so clearly related to iron metabolism, nor do any of these, unlike the iron-related ones noted above, show clear temporal patterns suggesting a causal relation, i.e., RLS resolved with treatment of the associated condition. These appear to be more comorbid rather than causal. It has long been suggested that neuropathy might predispose to RLS. Neuropathic findings have been reported in RLS patients [167, 168]. However, one study did not find an unusual prevalence in a neuropathy clinic [169], while another study reported that 30 % of neuropathy patients had RLS [170]. Radiculopathies [171, 172] and myelopathies may also cause or exacerbate RLS. There has also been an association between RLS and certain neurodegenerative conditions, including Machado–Joseph disease (SCA3) [173, 174], and demyelinating diseases such as multiple sclerosis [175–177]. Treatments of these conditions have not been reported to reduce RLS. In PD, RLS actually generally starts after beginning dopaminergic therapy [178], suggesting some analogs of the augmentation seen with dopaminergic therapy of RLS (see later).

RLS Biology

The cause of RLS remains unknown, though the functional abnormality is almost certainly neural in origin [179, 180]. A striking finding has been the almost universal response of RLS patients to medications that enhance dopamine system function [181]. Measures of dopamine dysfunction, however, have been equivocal or mixed [179, 182], but the larger imaging studies [183, 184], CSF studies [185], and autopsy studies [186] document increased not decreased dopamine in RLS. The reason that levodopa and dopamine agonists relieve the condition remains unclear but may reflect overcorrection of postsynaptic downregulation of response to dopamine [187, 188]. Drugs that antagonize the dopamine system may also unmask RLS symptoms, especially in treated patients [189, 190].

Studies have almost universally supported regional deficiency of brain iron in RLS despite normal peripheral iron (See Fig. 40.4). This most clearly involves the substantia nigra [76, 77, 81, 83, 191, 192] and the thalamus [79, 83]. Nigral iron deficiency has been shown in animals to produce increased striatal dopamine [193] as seen in RLS [184, 188]. Autopsy studies have suggested that the iron deficiency in RLS is associated with abnormal levels of cellular iron regulatory proteins [194, 195]. Brain iron deficiency is expected to cause RLS [188, 196] by producing a

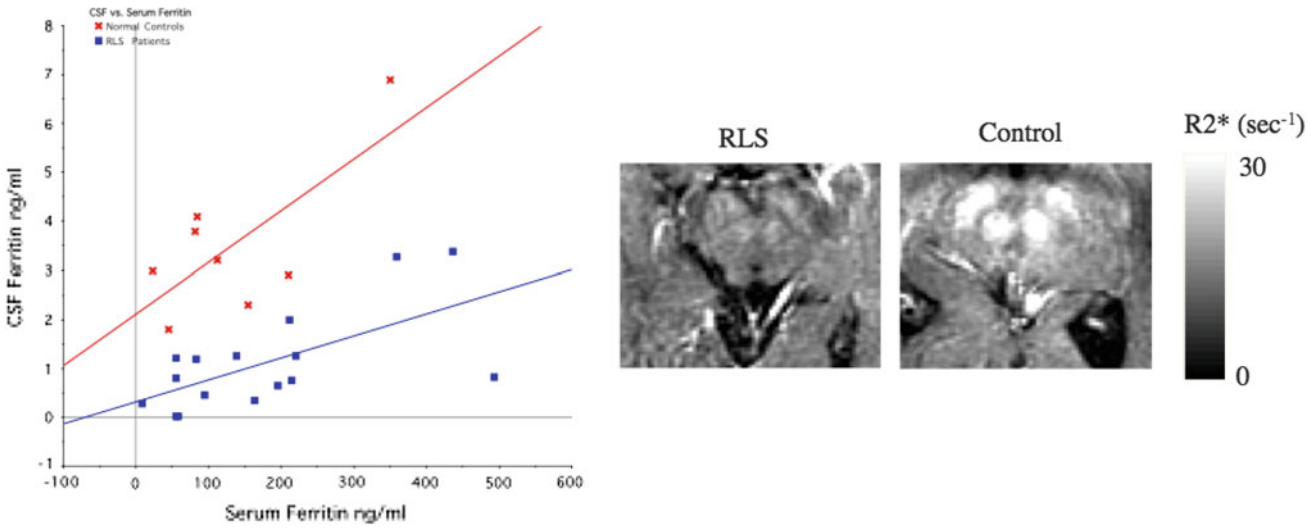

Fig. 40.4 Brain iron deficiency in RLS with normal levels of peripheral iron (serum ferritin *left graph*) but low levels of CSF ferritin (*left panel*) and also low levels of iron on MRI R2* (*right panel*)

dysregulation of brain dopamine function, perhaps related to altered amplitude of circadian dopamine variation. Recent identification of activation of hypoxic pathways in RLS [197, 198] indicates possible synergistic interaction between iron deficiency and hypoxia factors contributing to the dopaminergic dysfunction in RLS. Thus, COPD patients [199, 200] and those traveling or living at high altitudes [201] activating hypoxic pathways show higher rates or exacerbation of RLS.

It has been suggested on theoretical grounds that the A11 dopamine system, which descends to the spinal cord, could be involved in RLS, acting through D_3 dopamine receptors [202]. D_3 knockout mice show increased activity, as do mice with A11 lesions [203, 204]; however, these do not show the appropriate circadian pattern except when combined with iron deficiency [205]. Moreover, as noted above, RLS does not occur with neuronal loss and has increased not decreased dopamine; thus lesion studies reducing dopamine cells have somewhat limited usefulness. An autopsy study also failed to find any abnormalities in the A11 system of RLS patients [206].

The opioid system has also been suggested to be abnormal in RLS based largely on the therapeutic benefits of opioids for RLS [207–209]. A recent autopsy study documented decreased thalamic beta-endorphin cells [210], but an opioid imaging study failed to find significant difference from controls [211].

There is no evidence of neurodegeneration in RLS [212, 213]. Thus, RLS appear to have a pervasive functional abnormality in which brain systems are intact but have multiple abnormal functioning and interactions. Some limited evaluations of the resting state have documented abnormal interactions for RLS involving particularly the thalamus [214, 215]. Transcranial magnetic stimulation has also revealed increased excitability of the motor cortex in RLS [216–220] that is reduced by dopamine agonists [221, 222]. Further documenting the pervasive nature of the RLS brain abnormalities decreased myelination has been found in autopsy studies [223] and correspondingly decreased white matter in specialized MRI studies [223–225].

Overall, a mild brain iron deficiency possibly appears to be the most consistent abnormality reported for RLS and based on animal and clinical studies appears to largely explain the known biological abnormalities in RLS particularly those related to changes in dopamine [188]. Animal models of iron deficiency demonstrate increased activity that can occur in the hours before the primary sleep period, similar to RLS [226]. In this iron model of RLS causation, iron deficiency is expected to act principally through a dysregulation of brain dopamine function, perhaps related to altered amplitude of circadian dopamine variation [188]. The iron deficiency could also cause decreased myelination, white matter, resting state, and cortical excitability changes in RLS. The iron deficiency synergism with hypoxic pathways deserves special attention.

Familial Aggregation and Genetics in RLS

A striking finding in series of RLS cases is that some families have a high proportion of members with RLS [144, 153, 227, 228]. One obvious explanation would be that the disorder is under a large degree of genetic control. Three twin studies have suggested an elevated risk to monozygotic co-twins of affected individuals [67, 229, 230]. The first two studies suffered from major methodological limitations [229,

230]. The first study restricted to monozygotic twins had biased sampling from a clinical setting [231]. The second used general unvalidated questions for identification of RLS that cannot be considered accurate [230]. The third study used a preexisting twin sample with accurate diagnoses and found significantly greater concordance in monozygotic twins providing the heritability factor of 69 % [67].

The search for genetic determinants of RLS has been limited by two factors. First, the risk to first-degree relatives of patients has only been modest, on the order of three- to sevenfold [68]. Second, the frequency of RLS (4–10 % of adults) is quite high for a simple genetic disorder and suggests complex genetics likely involving environmental interaction. An initial approach to finding genetic determinants, searching for candidate genes active in the dopamine and iron pathways presumed to be involved in RLS did not reveal specific mutations contributing to RLS [232, 233]. One exception was the association of a fast metabolizer allele of monoamine oxidase A with RLS in women [234]. Another exception was the finding that variants in the neuronal nitric oxide synthase 1 gene (*NOS1*) are associated with RLS [235]. This gene is active in the nitric oxide/arginine pathway that is involved in sensory processing and affects both dopamine and endogenous opioid transmission. Multiple linkage analyses using large families with high rates of RLS occurrence failed to find any gene significantly related to RLS.

Genome-wide association studies in case-control populations, however, have found multiple specific allelic variations associated with an increased risk of RLS. Two groups initially reported significant associations in three genes [21, 66] *BTBD9* (6p), *MEIS1* (2p), and *MAP2K5/LBXCOR1* (15q). These genes do not have clearly known functions in adults, but are active during development, especially in the formation of the limbs. They are expressed within the nervous system [236]. One group found that *BTBD9* was better linked to the presence of increased PLM than to the purely subjective symptoms of RLS [21], underscoring the important connection between RLS and PLM. The group also found that serum ferritin, the best marker of body iron stores, was decreased in a dose-response fashion in patients with the RLS-PLM predisposing variant. Further association studies have identified RLS risk alleles in 5 other genetic regions. There are now a total of 16 allelic variations identified with increased risk of RLS. These occur on MEIS1, BTBD9, PTPDR, MAP2K5/LBXCOR1, TOX3, and the 2p14 region. The alleles are on intron (noncoding) portions of the genes. The functional relation of these genes to known biology of RLS is being explored. One important study documents the MEIS1 RLS alleles relating to a loss of function [237]. Knockout animal and fly studies have shown that BDBT9 and MEIS1 are both involved in the development of the dopamine system and also have effects on iron metabolism [238, 239]. Overall, these genetic data further support the strong relation between iron metabolism, dopamine, and RLS.

Evaluating the Severity and Impact of RLS

Standard Clinical tools have been developed and validated to evaluate the severity of RLS. The first of these was the Johns Hopkins Restless Legs Severity Scale (JHRLSS) that categorized the patients by time of onset of symptoms: mild for bedtime and evening only, moderate for afternoon before 6PM, and severe formorning before 12 noon [240]. This scale was designed to evaluate severity only for patients who had nearly daily symptoms, and the scale is rarely used today.

The second scale developed by the International Restless Legs Syndrome Study Group to evaluate RLS severity (IRLS) has become accepted as the primary scale for use in evaluating RLS severity (see Box 40.5). It has been well validated [241] and found to be responsive to changes in clinical estimates of RLS severity [242, 243]. This 10-item scale scores each item as 0–4 with 4 indicating greatest severity. Total scores of 0–10 indicate mild, 11–20 moderate, 21–30 severe, and 31–40 very severe RLS [241]. The IRLS has been found to have two factors, one for symptoms of RLS and the other for effects of RLS on life [244]. The IRLS scale has been translated into at least 15 different languages and is available from MAPI Research Trust at http://www.proqolid.org/.

The current diagnostic criteria for RLS also include added specifiers describing the RLS severity based on the clinical course as chronic-persistent (symptoms at least twice weekly for most of the past year) vs. intermittent (symptoms < twice weekly over the past year) [37].

Box 40.5: International Restless Legs Syndrome Study Group Rating Scale (IRLS)

(For permission to use contact: MAPI Research Trust at http://www.proqolid.org/).

The subject is given a copy of the questions. The clinician asks before each question:

"*In the past week…*"

The clinician not the patient records the subject's answers on the data sheet.

Each item is scored for 0—none, 1—mild, 2—moderate, 3—severe, 4—very severe (exceptions to this scoring are noted below)

1. Overall, how would you rate the RLS discomfort in your legs and arms?
2. Overall, how would you rate the need to move around because of your RLS symptoms?
3. Overall, how much relief of your RLS arm or leg discomfort did you get from moving around?
   4—No relief
   3—Mild relief
   2—Moderate relief
   1—Either complete or almost complete relief
   0—No RLS symptoms to be relieved
4. How severe was your sleep disturbance due to your RLS symptoms?
5. How severe was your tiredness or sleepiness during the day due to your RLS symptoms?
6. How severe was your RLS as a whole?
7. How often did you experience RLS symptoms?
   4—Very often (6–7 days in 1 week)
   3—Often (4–5 days in 1 week)
   2—Sometimes (2–3 days in 1 week)
   1—Occasionally (1 day in 1 week)
   0—Never
8. When you had RLS symptoms, how severe were they on average?
   4—Very severe (8 h or more per 24 h)
   3—Severe (3–8 h per 24 h)
   2—Moderate (1–3 h per 24 h)
   1—Mild (less than 1 hour per 24 h)
   0—None
9. Overall, how severe was the impact of your RLS symptoms on your ability to carry out your daily affairs—for example, carrying out a satisfactory family, home, social, school, or work life?
10. How severe was your mood disturbance due to your RLS symptoms—for example, angry, depressed, sad, anxious, or irritable?

The total score ranges from 0 to 40.

As a rough guide, the overall score divides into different levels of severity: 0 No, 1–10 Mild, 11–20 Moderate, 21–30 Severe, 31–40 Very Severe RLS.

(Note, IRLS is copyright protected and not to be used without permission. Fees may apply)

There are two well-validated disease-specific quality of life scales for RLS that have been used in the major clinical trials, i.e., the RLSQoL developed at Johns Hopkins [242, 245, 246] and the RLS-QoL developed in Germany [247]. The Hopkins scale is available from MAPI Research Trust at http://www.proqolid.org/, and it has been translated into several different languages.

Treatment of RLS and PLMD

A spectrum of treatment options, both non-pharmacologic (Box 40.7) and pharmacologic (Box 40.8), is available to address the wide range in severity and frequency of RLS symptoms. Before embarking on a decision to treat RLS or PLMD, some general comments about treatment guidelines are warranted (Box 40.6). For the purpose of treatment guidelines, patients can be classified (Table 40.1) into intermittent (usually mild), chronic, and persistent (usually moderate-to-severe with the added category of refractory or intractable [248] and into degree of clinical significance. These classifications depend on the intensity and frequency of symptoms, impairment of quality of life, and response to treatments. The IRLS, a validated clinical scale assessing RLS severity (Box 40.5), has been used as a primary end point in almost all clinical trials.

Box 40.6: General Treatment Guidelines for Restless Legs Syndrome (RLS)

Does the patient have RLS? (this must be established first).

- Does the patient have primary RLS or comorbid (secondary) RLS?
  (This distinction is important as the comorbid conditions must be identified and treated where possible).
- Always evaluate iron status and also determine if non-pharmacological treatment will suffice.
  (It is important to determine if mild or intermittent symptoms without significant disability can be managed by non-pharmacologic measures).
- Define RLS severity to guide treatment evaluation.
  Use the IRLSSG [see Box 40.5 and Table 40.1] or provide an overall clinical impression.
- Define end points in therapy and evaluate these on follow-up.
  For example, elimination of RLS symptoms or IRLS score <11, reduction or elimination of leg jerks during sleep as obtained by history from bed partner or polysomnography study, a significant reduction in IRLS scale score, quality-of-life improvement.

Box 40.7: Non-pharmacologic Treatment of Restless Legs Syndrome (RLS)

- Follow sleep hygiene measures (see Table 26.17 in Chap. 26).
- Consider discontinuing or reducing medications that can worsen RLS (see Box 40.2).

Table 40.1 Classification of RLS for treatment purpose

Categories	Key features
Mild (Intermittent) RLS	• Intermittent mild symptoms (< 2/week, mild-to-moderate distress when present) • Sometimes bothersome • Maybe predictable and situational
Minimal RLS	• IRLS score of 1–10 (see Box 40.5)
Moderate RLS	• Symptoms (significantly bothersome) occurring at least twice a week interfering with quality of life • IRLS score of 11–20
Moderately severe RLS	• Same as moderate RLS symptoms • IRLS score of 21–30
Severe RLS	• Significant and intense symptoms occurring daily interfering with daytime function and quality of life • IRLS score of 31–40
Refractory or intractable RLS	• Severe daily symptoms despite adequate doses of dopaminergic medication • IRLS score of 40 • Severe sleep disturbance • Impairment of quality of life and severely impaired daytime function

IRLSSG International Restless Legs Syndrome Study Group; RLS, restless legs syndrome
Modified and adapted from Hening et al. [327] and Silber et al. [328]

- Avoid substances that may trigger RLS (e.g., alcohol, smoking, caffeine-containing drinks).
- Exercise regularly at moderate intensity (avoid vigorous exercise, which may exacerbate RLS symptoms).
- Participate in mentally alerting activities (activities promoting alertness benefit RLS symptoms).
- Use counter stimulation measures (e.g., hot or cold showers, massage, getting up, and walking).
- Adjust sleep schedule to be somewhat delayed.
- Participate in patient support groups.

Important pharmacologic treatment options for RLS (see Box 40.8) include the α2δ ligands (particularly gabapentin enacarbil), the dopaminergic agents, the opioids, the sedative-hypnotics, and both oral and intravenous (IV) iron. Box 40.9 lists some general principles of pharmacotherapy for RLS. The first review and standards for RLS treatment were published in 1999 by the AASM [86, 249]. They established that clinicians managing RLS should be able to make an accurate diagnosis, understand primary and secondary RLS and the comorbidities of RLS, and follow patients at appropriate intervals to adjust treatment as needed. The most recent evidentiary reviews include one from the American Academy of Neurology [250]. A management paradigm has been published by the Medical Advisory Board of the RLS Foundation [248]. Two important treatment guidelines have been published by the International Restless Legs Syndrome Study group (ILRSSG): one for long-term treatment [251] and another important one in collaboration with the European RLSSG and the USA RLS foundation on initial treatment and managing augmentation [252].

Box 40.8: Pharmacologic Agents commonly used in Restless Legs Syndrome

Alpha-2-delta ligands:

Gabapentin enacarbil (approved), pregabalin, gabapentin

Dopaminergic medications:

Dopamine agonists: pramipexole (approved), ropinirole (approved), rotigotine patch (approved), cabergoline (not recommended*)
Levodopa combined with a decarboxylase inhibitor

Opioids (mild, moderate, strong):

Oxycodone/naloxone (approved in Europe)
Oxycodone, hydrocodone, methadone, buprenorphine

Benzodiazepines:

Clonazepam

Iron treatments:

Oral iron (in those with low serum iron or ferritin below 75 ng/ml)
IV iron (iron deficiency and non-responders to oral iron)
Ferric Carboxymaltose (FCM)

Low molecular weight dextran
Iron Sucrose (uncertain benefit for adults with RLS)

*concerns about fibrosis require added regular cardiac monitoring.

Box 40.9: Principles of Pharmacotherapy for Restless Legs Syndrome
Individualize the therapy.

- Start with monotherapy rather than polytherapy.
- Begin with a very small dose and gradually increase every 3–5 days to an optimal or maximal tolerable dose.
- Try monotherapy even in an apparently severe case using small-to-medium dose (a surprising number of such patients will respond satisfactorily).
- Try to convert patients on polytherapy (placed on treatment before referral to you) to monotherapy if possible (it is possible to do so in many such patients).
- Try to reduce the dose or eliminate some medications if patients complain of undesirable side effects from multidrug treatment.

Perform regular follow-up to monitor for side effects, progression of the disease, augmentation, tolerance, and rebound.

The treatment guidelines include as-needed medication for infrequent RLS, α2δ agents as preferred, and dopamine agonists as a second choice initial treatment for moderate-to-severe RLS, second-line treatment involves low-dose, very long acting dopamine agonists, moderate strength opioids, and combinations of α2δ agents, low-dose dopamine agonist and moderate strength opioids. An array of strategies (switching agents, combination treatment, strong opioid agents, IV iron) is used for refractory patients who fail other treatments. These reviews, particularly the ones from the IRLSSG, provide an easy route into the RLS therapeutic literature.

Pharmacologic Treatment of RLS (see Boxes 40.8, 40.9, 40.12, and Table 40.1)

Historic Note and RLS Augmentation

Opioids as the first treatment used for RLS [253, 254] were rapidly replaced by levodopa and then dopamine agonists when they became available. The dopaminergic medications showed more consistent and immediately effective treatment than opioids [255, 256] without the dependence and abuse problems. Gabapentin was also used to treat RLS, but the early results were somewhat mixed [257] complicated by its uneven uptake into blood and apparently less effect on PLMS. The dramatic efficacy of the dopaminergic treatment left little room for this alternate treatment except in non-responders. This changed with the awareness that treatment with the dopaminergics over 3–10 years produced a major problem of augmenting the RLS symptoms. RLS augmentation produced symptoms becoming more severe, more extensive, and occurring for more of the day especially in the afternoon and morning where they had not previously occurred [106]. Augmentation on the dopamine agonists did not usually appear until after 6 months to 10 years of treatment [258, 259]. Initially, there was some uncertainty if augmentation was iatrogenic or a natural progression of symptoms. It also was unclear if effective treatment by non-dopaminergic drugs might also produce significant augmentation. This issue was directly addressed in a major large clinical study comparing at therapeutically effective doses the dopamine agonist pramipexole with the α2δ ligand pregabalin over one year of treatment. The results of this study showed that pregabalin compared to pramipexole was equally or more effective and had significantly less augmentation. The one-year augmentation rate for pregabalin (1.7 %) was the same as that seen in other studies on placebo, indicating this reflected possible natural progression in this study without any dose increase and/or noise in the clinical measure of augmentation. In contrast, the 9 % augmentation on 0.5 mg pramipexole for one year demonstrated that augmentation was iatrogenic, not natural progression, and based on other studies probably occurred for all dopaminergic treatment of RLS. The study also demonstrated augmentation occurred mostly after the initial 6 months of treatment and was increased with higher dose (see Fig. 40.5). After this study, the treatment of RLS shifted from using dopamine agonists as the primary first-line treatment to instead using the α2δ agents as first line and dopaminergics only when there was a reason not to use the α2δ agents. Moreover, with increased experience, very severe and intractable cases of RLS have been identified and often require returning to using dopamine agonists, but those with very long half-lives, e.g., rotigotine, and also the initial drug used for RLS, i.e., opioids. Now with the most extreme RLS moderate and high potency opioids are used. The one relatively new treatment for RLS that at this point in 2016 is still being evaluated is intravenous (IV) iron. Given the RLS biology of brain iron deficiency, it is hoped that some treatment, possibly IV iron, could actually reduce this biological abnormality and thereby provide effective treatment. The range of current treatments is presented in brief here as they are currently (2016) recommended by the IRLSSG.

α2δ Ligands

The α2δ ligands have analgesic and anticonvulsant activity. They bind to the α2δ voltage gated calcium channel

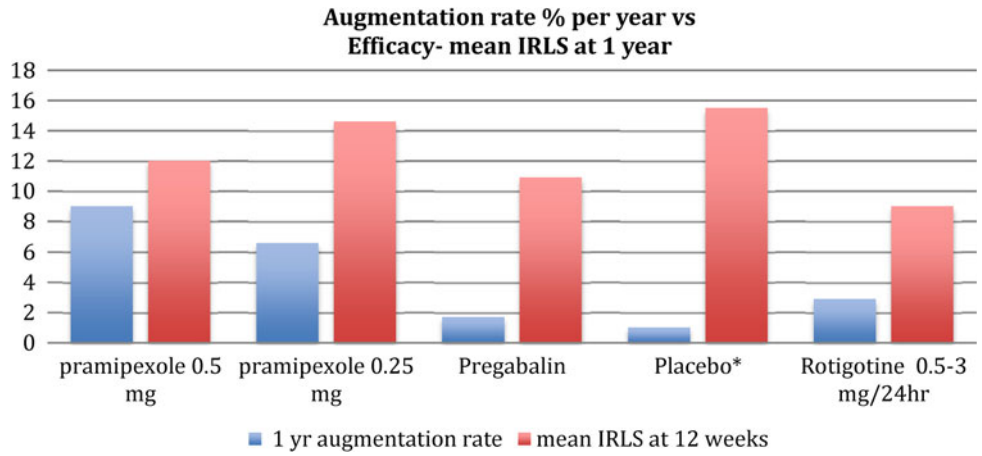

Fig. 40.5 Long-term treatment efficacy versus augmentation. *Red bars* indicate mean clinical severity of RLS on the IRLS scale after 12 weeks of treatment. *Higher values* indicate more severe RLS, with <10 considered minimal RLS, 10–15 mild RLS, >15 moderate RLS symptom severity. *Blue bars* indicate rates of RLS augmentation after 1 year of treatment. Higher values are more augmentation. The 1 % on placebo indicates natural progression without treatment, the values significantly higher than that indicate the percentage with drug induced worsening of RLS (augmentation). Note Pregabalin 300 mg in this study is as effective as pramipexole 0.5 mg with augmentation not significantly greater than for placebo. In contrast, pramipexole shows significant dose-related augmentation. Data sources for pramipexole: Allen et al. [37]; rotigotine: Benes et al. [147]; Placebo: Garcia-Borreguero et al. [145] and Benes et al. [147] pro-rated from 6 months data

reducing neurotransmitter release in pathways involving several neurotransmitters [260], including glutamate [261]. There are three α2δ ligands used for RLS: gabapentin enacarbil, pregabilin, and gabapentin. Gabapentin was initially used for RLS with generally good but mixed results in uncontrolled, open label trials for mild-to-moderate RLS. The studies were small, and results were considered inconclusive for a first-line treatment recommendation [257, 262]. Trials comparing gabapentin to other RLS treatments generally found gabapentin to be almost as effective, although somewhat less effective in reducing the PLMS [263, 264]. In a double-blind, cross-over study, gabapentin in doses of 600–2400 mg was more effective than placebo in treatment of RLS, but 13 % of the RLS patients continued to have abnormally high rates of PLMS [265]. Gabapentin is poorly taken up into the blood with wide variations between individuals and even across days in a given individual. This problem limits reliably delivering effective treatment and leads to needing larger doses. The other two α2δ ligands resolve that problem. One, gabapentin enacarbil is a pro-drug overcoming the gabapentin uptake problem. It reliably delivers gabapentin to the blood and maintains a reasonable blood level for 12–18 h with almost complete clearance in 24 h [266]. Large controlled clinical studies have documented efficacy with mostly mild side effects for gabapentin enacarbil treatment of RLS at single daily doses of 600–1200 mg [267–271]. This drug is now approved by US Food and Drug Administration (FDA) for treatment of moderate-to-severe RLS at a dose of 600 mg per day, although in the clinical studies effective doses range from 300 to 1200 mg. Pregabalin has a different chemical structure, and has none of the uptake problems of gabapentin. In controlled clinical trials compared to placebo, one dose of 100–300 mg pregabalin provided effective treatment for 12–16 h [148, 272–275] with higher doses up to 600 mg used for RLS with neuropathic pain [276].

The α2δ ligands currently recommend (Box 40.8) for initial first-line treatment of RLS based on adequate clinical studies are gabapentin enacarbil (300–600 mg once daily) and pregabalin (100–300 mg usually only once daily). Gabapentin is likely to be effective except for the problem of its variable uptake into blood. It also has not been evaluated in large clinical trials, so there may be other unknown limitations. Gabapentin use is thus complicated by a wide range of doses ranging from 300 to 2400 mg a day and a need to give it 1–3 times a day. Failure with gabapentin given its uptake problems does not mean the other α2δ agents will not be effective.

Cost is a significant issue. Gabapentin but not the other α2δ ligands are available as a generic at a lower price than the other α2δ agents.

Levodopa

Akpinar [277] and Montplaisir et al. [189] first reported a profound response of RLS symptoms to small doses of levodopa. Subsequent studies have consistently found that levodopa reliably ameliorates RLS symptoms, decreases PLM [255, 256], and improves sleep [181, 278], but in the

vast majority of cases daily chronic longer term use produces RLS *augmentation* [106, 146]. It is not recommended for daily use.

Dopamine Agonists

Dosing of dopaminergic agents for RLS differs from the typical dosing schedule in PD. Many RLS patients can be successfully managed with low doses given 2 h before symptom onset. Generally, a single dose taken at night can benefit those with late evening and bedtime symptoms, while more severe patients with significant evening symptoms can take one dose in the early evening and a second before bedtime. For the patient who develops a rapid escalation in RLS severity, with increasing medication requirements in the first 2 years of therapy, augmentation should be carefully considered.

Because of reports of fibrosis and valvulopathy with ergot-derived agonists (pergolide, bromocriptine, cabergoline) [279] non-ergot-derived agonists are preferred treatment. Ropinirole, pramipexole, and rotigotine have been approved for the treatment of RLS after several large multicenter studies [114, 115, 280–284]; they have also been shown to markedly decrease PLMS in RLS [285–287]. Rotigotine is provided as a transdermal patch that, unlike oral agents, provides continuous delivery over 24 h and sustains a near-constant blood level.

RLS Augmentation on Dopaminergic Treatment: Rates and Management

As noted above in the history of RLS treatment, augmentation is an iatrogenic increase in the severity of RLS with long-term dopaminergic treatment (see Fig. 40.5). It also occurs for tramadol [288]. Its primary manifestation is worsening of RLS and the progression of symptoms earlier in the day. This has been defined for clinical studies at the NIH RLS consensus conference [104] (Box 40.10). Based on a study of levodopa patients in which 60 % developed augmentation, a validated severity questionnaire has been developed [289]. A series of questions for early identification of augmentation have been proposed by the IRLSSG as part of their official guidelines for managing augmentation [252] (Box 40.11).

Box 40.10: NIH Workshop Diagnostic Criteria for RLS Augmentation

Adapted from Allen et al. [104].

RLS augmentation can be diagnosed if A and B are met

(a) Either of the following two criteria are met:
   1. Criterion 1: RLS symptoms occur at least 2 hours earlier than was typical during the initial course of beneficial stable treatment.
   2. Criterion 2: Two or more of the following key features of RLS augmentation are present:
      - An increased overall intensity of the urge to move or sensations is temporally related to an increase in the daily medication dosage, or a decreased overall intensity of the urge to move or sensations is temporally related to a decrease in the daily medication dosage.
      - The latency to RLS symptoms at rest is shorter than the latency either during initial therapeutic response or before treatment was instituted.
      - The urge to move or sensations are extended to previously unaffected limbs or body parts.
      - The duration of treatment effect is shorter than the duration during initial therapeutic response.
      - Periodic limb movements while awake occur for the first time or are worse than either during initial therapeutic response or before treatment was instituted. In addition to meeting one of these two criteria, the diagnosis requires both of the following:
      - Augmented symptoms meeting these criteria are present for at least 1 week for a minimum of 5 days.

(b) No other medical, psychiatric, behavioral, or pharmacologic factors explain the exacerbation of the patient's RLS and any symptoms meeting these criteria for augmentation.

Box 40.11: Indications for early identification of RLS augmentation

Adapted from Garcia-Borreguero et al. [252].

1. RLS/WED symptoms appearing earlier than before the drug was started?
2. Higher doses or dosing earlier in the day than after the first 2 months on treatment
3. Intensity of symptoms when present is worse than before starting treatment?
4. Symptoms occur for the first time in new parts of the body (e.g., arms) not affected before starting treatment.

Levodopa augmentation rates have been reported to occur in as many as 80 % of RLS patients, with 50 % of them requiring a change in medication [106, 290]. Dopamine agonists have slower development of augmentation with rates of 20–30 % over 3 years (20–30 %) [291–293] but persisting development at the rate of about 7–8 % new cases each year for over 9 years and presumably indefinitely [259, 294]. Any increasing dose requirement for relief of

increasingly intense symptoms may suggest tolerance. Tolerance does not itself cause augmentation with an earlier onset of symptoms or spread to other parts of the body. Tolerance, however, is often an early observable sign of augmentation [291] and should always be considered a warning sign of augmentation. Iron deficiency may be a predisposing factor for augmentation [295].

The treatment of augmentation involves primarily reducing or discontinuing the use of dopaminergic and switching to or adding a non-dopamine medication. The options are well described in the treatment guidelines provided by the IRLSSG [252]. The critical issue involves appreciating the importance of minimizing the use of dopaminergic medication for patients who develop augmentation. The continuously acting dopaminergic medication, rotigotine, appears to have fewer problems with augmentation and may provide a treatment for augmented RLS although often at higher than regulatory approved doses [296], but in general avoiding any dopaminergic medication is the safest way to minimize augmentation problems.

Anticonvulsants (Other than α2δ Agents)

Carbamezapine had in earlier studies demonstrated successful use in RLS [297–300]. However, clinical experience has not demonstrated as good a response as that seen with dopamine agonists or gabapentin. There are only limited case reports or small series with other anticonvulsants, such as lamotrigine [301, 302] and topiramate [303]; thus, these are usually tried only in patients who are unable to tolerate other agents.

Opioids

Moderate potency opioids (e.g., oxycodone, hydrocodone) are used mostly for second-line treatment, and the moderate-to-high potency opioids (methadone, buprenorphine) are used only for treatment of refractory RLS. Opioids have been documented to be effective in RLS [208, 209, 259, 304]. Because of individual variation in response to the different classes of opioids, it is often worthwhile trying more than one agent. Longer acting medications such as methadone often provide relief for some of the most severely affected patients, including those who have failed dopaminergic therapy [209, 304]. One opioid agent, tramadol, which also has serotoninergic properties, has been reported to cause augmentation [288, 305].

Sedative Hypnotics

Despite the early use of benzodiazepines for treating RLS and PLMD, the sedative-hypnotic agents do not have reliable effectiveness in eliminating RLS sensations or eliminating PLMS [306, 307]. They are best reserved for mild cases with primary sleep disruptions where they may enable the patient to sleep through the symptoms or as adjunctive therapy for persisting insomnia. When used alone, they may increase the risk of falls if during the night the patient awakens and gets out of bed to relieve the RLS symptoms.

Iron Treatment

The biological basis of RLS includes brain iron deficiency. Thus, iron unlike other treatments may correct the biology causing the disease and modify the course of the disease. Barriers to changing brain iron status include limited absorption of iron from the gut, regulation of iron transport across the blood brain barrier, and the biological problems with iron management that may have contributed to the development of the brain iron deficiency in the first place.

Oral iron treatment despite limitation of absorption from the gut is considered a primary treatment for all RLS patients based on the biology of RLS, general clinical experience, and one small placebo-controlled, double-blind clinical trial [308]. Iron transport from the gut to blood is generally extremely limited when serum ferritin values are high. Oral iron is unlikely to be effective for patients with higher values of serum ferritin as shown by failed benefit when given to RLS patients with a mean serum ferritin of 135 mcg/l [309]. In contrast, oral iron was shown to be effective treatment for RLS patients with serum ferritin ≤ 75 mcg/l [308]. Oral iron (usually iron sulfate 325 mg with vitamin C 100 mg taken once or twice a day) is recommended for all RLS patients with fasting morning serum ferritin ≤ 75 mcg/l and transferrin saturation <45 %. These serum values indicate iron levels are likely too low for RLS, and there is no indication for iron overload such as that associated with hemochromatosis. Oral iron treatment is usually continued if tolerated until serum ferritin increases to >100 mcg/l or transferrin saturation increases to >45 %. It can be reinstated as needed to keep serum iron levels high. Recent data on effects of oral iron on hepcidin levels indicate that taking oral iron more than once a day provides little extra benefit, and it may even suffice or be preferable to take it once every other day [310].

IV iron treatment bypasses the gut rapidly increasing iron in the blood available for transport to the brain. IV iron has been found to provide effective treatment in both open-label studies at doses of 500 mg of ferric carboxymaltose (FCM) [311] and 1000 mg iron dextran [312–314], and also two well-controlled clinical trials of 1000 mg of FCM [315, 316]. About half of the cases in these studies reported significant benefit from the iron treatment lasting for at least 2–4 months, and about 20 % of all patients reported essentially complete relief from RLS lasting for more than 6 months. Two controlled studies with 1000 mg IV iron sucrose failed to show significant benefit compared to placebo [317, 318], but the iron sucrose unlike iron dextran and FCM releases its iron rapidly and is thus less likely to provide the longer duration of iron availability needed for transport to the brain. Iron dextran at high molecular weight can produce

anaphylaxis and is therefore not recommended. This problem is much less for iron dextran at low molecular weight and may not be a significant problem at all for the other IV iron formulations. Curiously, IV iron appears to benefit about 40–60 % of RLS patients with long lasting benefit for 20–30 %, but some show no benefit at all even from a second added dose treatment [315]. The role of IV iron in treatment of RLS remains to be better developed, but it holds promise for at least some RLS patients.

Treatment of Refractory and Intractable RLS

Box 40.12 provides reasonable guidelines for treatment of intermittent and chronic persistent RLS. The situation is much more complicated for the severe RLS refractory to most of the treatments for RLS. The general guidelines for these patients is to first ensure adequate iron stores and if serum ferritin is < 100 mcg/l consider a trial on 1000 mg IV iron using one of the formulations that provides relatively slow release of the iron, e.g., ferric carboxymaltose. These infusions can usually be arranged through hematology clinics. The main pharmacological approach in these patients is the use of low doses of long half-life, potent opioids, e.g., methadone [259, 304], buprenorphine, or prolonged release oxycodone–naloxone [209]. The prolonged release oxycodone–naloxone has been approved for treatment of refractory RLS in Europe, but opioids are not approved for any use in RLS. All of these drugs need to be used carefully given the risk of dependence. The dose for these drugs will be below or at the low end of the doses used for treating pain. If higher doses are needed, care should be taken to ensure the drug is not treating some other condition, e.g., pain, or that dependence has not developed.

Box 40.12: Treatment Strategies for Mild, Moderate, Severe, and Refractory or Intractable Restless Legs Syndrome (RLS)

All RLS

Oral iron treatment if serum ferritin $\leq$75 mcg/l and transferrin saturation <45 %.

Mild or Intermittent RLS

Non-pharmacologic measures (NP)

Levodopa PRN (no more than once a week), low-dose α2δ ligand

Sedative-hypnotic PRN for sleep if needed and helpful.

Moderate-to-Moderately Severe RLS

α2δ agent nightly

Very low-dose dopamine agonist (with caution regarding augmentation)

Combination of α2δ agents and very low-dose dopamine agonist

Mild-to-moderate potency opioids.

Severe, Refractory RLS

Combination opioid and α2δ agents and low-dose dopamine agonists

Oxycodone–naloxone (approved for RLS in Europe)

High-potency opioids in very severe cases at very low doses (e.g., Methadone at 5–10 mg/day not to exceed 20 mg/day). Evaluate for possible IV iron treatment.

Pharmacologic Treatment of PLMD and PLMS

The periodic limb movement disorder (PLMD) occurs with high rates of PLMS (>15/h for adults and $\geq$5/h for children) associated with disrupted sleep or waking unrelated to other sleep disorders or to medications. The PLMS of PLMD may mark inflammatory processes and/or iron deficiency. The iron status should be carefully evaluated and oral or IV iron treatment considered even for low normal iron stores, provided transferrin saturation is <45 %. Iron treatment options are the same as that for RLS above, except treatment success can be evaluated by documenting decrease in the PLMS. Possible causes for the inflammation or low iron should also be evaluated and appropriate treatment considered.

Treatment of PLMD other than with iron starts with α2δ agents to reduce the PLMS and also generally improve sleep. Low-dose L-dopa and dopamine agonists are also very effective for reducing PLMS, but the dopamine treatment of PLMS without RLS can lead to the development of RLS [106] and therefore should be used very cautiously and only at very low doses. Opioids are of uncertain benefit. Clonazepam was demonstrated to improve sleep but not the PLMS [306]. In most cases, it is important to look for other causes of the sleep and daytime functioning complaints and determine that the treatment of the PLMS produced significant changes in these to justify continuing the treatment.

Treatment of PLMS without RLS or PLMD is not clearly indicated. Very high rates of PLMS themselves have been related to significant health, particularly cardiovascular health problems. High rates of PLMS may thus deserve some attention. PLMS are associated with the increase in heart rate [319] and rises in blood pressure [320–322]; it has been suggested that, untreated, they may lead to persistent diurnal hypertension, but this connection appears to be very limited [323]. It nonetheless provides a potential rationale for treating PLMS that occur without a related sleep complaint in vulnerable patients [320]. Treating sleep disruption with PLMS in RLS patients might be less effective than in those without RLS, because some arousals may persist in RLS patients even when PLMS are effectively suppressed [324]. In RLS patients, there may be a different relationship between movements and arousals than in those without RLS [325]: in RLS, the PLMS may be more closely connected to an underlying abnormality. Nonetheless, dopaminergic treatment reducing the PLMS for RLS patients has been

shown to significantly reduce the transitory heart rate and blood pressure increases during sleep [326]. Consideration regarding treatments to reduce PLMS needs to be carefully balanced by the adverse effects of treatments and the limited data indicating clear benefit for the treatments especially in otherwise healthy individuals.

Summary

RLS is the 2nd or 3rd most common neurological disorder after essential tremor and headache. It is often misdiagnosed, under-diagnosed, under-recognized, and mistreated or under-treated. RLS should be strongly considered in any subject complaining of leg discomfort or excessive restlessness of the legs while lying in bed in the evening and of having difficulty falling asleep or maintaining sleep or of non-restorative sleep. Most patients get relief from treatment with α2δ ligands or low-dose dopaminergic drugs. Long-term 5- to 10-year treatment benefits from dopaminergics appear to be severely limited by the augmentation problem. It is hoped, but unclear if the long term treatment with α2δ ligands will be better than dopaminergic treatment.

PLMD treatment benefits are somewhat unclear, but iron status should be evaluated and appropriate treatment considered if serum ferritin is low. PLMS without RLS or PLMD has uncertain clinical significance, except to indicate possible iron deficiency. They may, however, occur with significant unrecognized sleep disruption and treatment as PLMD can be considered. PLMS at very high rates may be associated with health and cardiovascular problems, but there are no data at this point to indicate treating the PLMS themselves provides clinical benefits.

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Sleep, Breathing, and Neurologic Disorders

41

Sudhansu Chokroverty and Federica Provini

Introduction

To understand the effects of neurologic lesions on sleep-wake cycles and sleep states, and to understand the normal interactions of sleep and breathing, it is important to have a clear understanding of the functional anatomy of sleep and breathing. In the first section of the chapter, therefore, a brief overview of the anatomy and physiology of sleep is presented. The section on the functional anatomy of sleep is followed by a short discussion of the control of breathing during sleep. For details, readers are referred to some excellent reviews and monographs [1–10] and to Chaps. 5 and 8 in this volume.

Most of the anatomic structures that control sleep and breathing are located in the central nervous systems (CNS). These regions are influenced not only by other CNS structures but also by inputs from the peripheral neuromuscular system and other body systems. It is important to understand not only that the neurologic illnesses may affect sleep and breathing but also that alterations of sleep and breathing may adversely affect the natural history of a neurologic disorder. A number of excellent sources provide systematic descriptions of the effects of neurologic lesions on the pattern and control of breathing [11–21]. The effect of acute and chronic neurologic disorders on the state of sleep and the resulting interaction on breathing has not received wider attention, and understanding of such an interaction is essential for treatment and prognosis in various neurologic disorders. In neurologic illnesses, breathing disorders may manifest as hypopnea, apnea, irregular or periodic breathing, or alveolar hypoventilation. Similarly, sleep disturbances may manifest as hypersomnia, hyposomnia (insomnia), parasomnia, or circadian rhythm sleep disorders. The discussion is grouped into two major sections: (1) sleep and breathing disorders secondary to somatic neurologic illness and (2) sleep and breathing disorders secondary to autonomic failure. The somatic neurologic disorders are subdivided into CNS disorders and peripheral neuromuscular disorders.

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Functional Anatomy of Sleep and Wakefulness

The neuroanatomic substrate of wakefulness, rapid eye movement (REM) sleep, and nonrapid eye movement (NREM) sleep are located in separate parts of the CNS [1, 22, 23]. There are no discreet sleep/wake-promoting centers; rather, these states are produced by changes in the interconnecting neuronal systems modulated by neurotransmitters and neuromodulators.

Neuroanatomic Substrates of Wakefulness

The ascending reticular activating system (ARAS), consisting of neuroanatomic and neurochemical components of the arousal system containing glutamatergic and other neurotransmitters and neuromodulators (Fig. 41.1), determines the state of wakefulness [1]. Cerebral cortical activation during wakefulness is maintained by projections from the ARAS terminating in the thalamus and by thalamocortical projections to widespread areas of the cerebral cortex. In addition, there are extrathalamic projections from the brain stem reticular neurons ending in the posterior hypothalamus and the basal forebrain regions; the latter in turn project to the cerebral cortex to help maintain wakefulness. All these pathways regulating wakefulness utilize hypocretinergic (orexinergic), cholinergic, noradrenergic, dopaminergic, and

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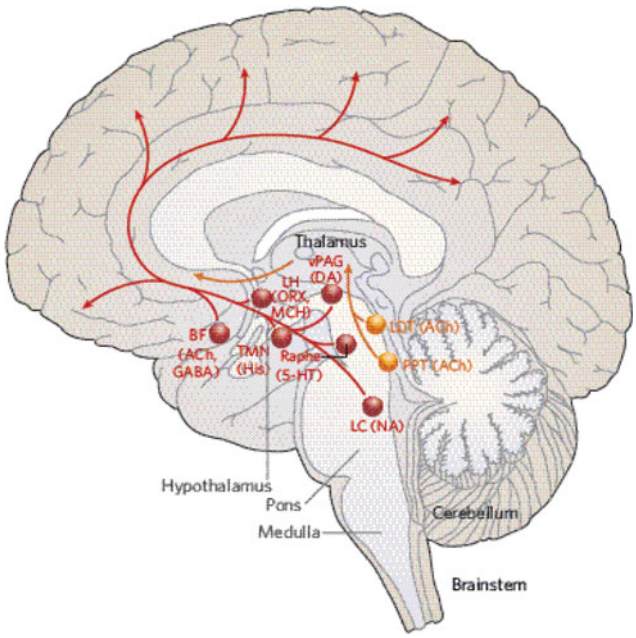

Fig. 41.1 Ascending Reticular Activity system (ARAS): The ascending arousal system. Two major pathways are shown. One (shown in yellow) providing upper brain stem input to the thalamic-relay nuclei and to the reticular nucleus of the thalamus coming from the pedunculopontine and laterodorsal tegmental (PPT/LDT) nuclei, which are acetylcholine (ACh)-producing neuronal groups. The second major group of neurons (shown in *red*) come from the noradrenergic (NA) locus coeruleus (LC), serotoninergic (5-HT) dorsal and median raphe nuclei, dopaminergic (DA) periaquiductal gray matter (vPAG), and histaminergic (His) tuberomamillary neurons (TMN). Additional cortical input merges from the basal forebrain (BF) neurons containing GABA or ACh, and by lateral hypothalamic (LH) peptidergic neurons that contain melanin-concentrating hormone (MCH) or orexin (hypocretin) (ORX). Reproduced from Saper et al. [29], with permission.

histaminergic neurons. The cholinergic neurons fire at the highest rate during wakefulness and REM sleep but decrease their rates of firing at the onset of NREM sleep. The wake-promoting aminergic neurons include noradrenergic neurons in the locus coeruleus (LC), serotoninergic neurons in the dorsal raphe of the brain stem, histaminergic neurons in the tuberomammillary nucleus of the hypothalamus, and also dopaminergic neurons (probably through D1 receptors), particularly in the ventral periaqueductal area. Noradrenergic neurons in the LC show the highest firing rates during wakefulness, the lowest rate during REM sleep, and an intermediate rate during NREM sleep. The excitatory amino acids glutamic and aspartic acids, intermingled within the ARAS and present in many neurons projecting into the cerebral cortex, forebrain, and brain stem, are released maximally during wakefulness. The discovery of hypothalamic hypocretin neurons with their widespread CNS projections (Fig. 41.2) directs our attention to the role of the hypocretinergic system in controlling sleep-wake regulation. De Lecea and coauthors [24] described two neuropeptides in the lateral hypothalamus and perifornical region that were termed hypocretin-1 and hypocretin-2. In the same year, independently, Sakuri et al. [25] described two neuropeptides in the same region that they named orexin A (corresponding to hypocretin-1) and orexin B (corresponding to hypocretin-2). It was shown thereafter that these hypocretin systems have widespread ascending and descending projections to the LC, dorsal raphe nucleus (DRN), ventral tegmental area, tuberomammillary nuclei of the posterior hypothalamus, laterodorsal tegmental (LDT) and pedunculopontine tegmental (PPT) nuclei, ventrolateral preoptic (VLPO) nucleus in the hypothalamus, basal forebrain, limbic system (hippocampus and amygdala), cerebral cortex, thalamus (intralaminar and midline nuclei), and autonomic neurons (nucleus tractus solitarius, dorsal vagal nuclei, and intermediolateral neurons of the spinal cord) (Fig. 41.2) [26–28]. Hypocretin systems promote wakefulness mainly through excitation of tuberomammillary histaminergic, LC noradrenergic, and midline raphe serotoninergic and dopaminergic neurons. Sleepiness may partly be induced by a reduction of activity of the hypocretin systems. These systems also participate in REM sleep regulation indirectly through activation of the aminergic neurons (REM-off), which in turn inhibit REM-generating neurons in the LDT/PPT (REM-on) [22].

Neuroanatomic Substrates of REM Sleep

Transection experiments in cats through different regions of the midbrain, pons, and medulla [22, 30, 31] established the existence of REM sleep-generating neurons in the pons (Fig. 41.3). A transection at the junction of the pons and midbrain (level A) produced all the physiologic findings compatible with REM sleep caudal to this transection, whereas rostral to the section, in the forebrain region, the recording showed no signs of REM sleep. The structures rostral to a section between the pons and medulla (level B) showed signs of REM sleep but structures caudal to the section showed no signs of REM sleep. Following transection at the junction of the spinal cord and medulla (level C), REM sleep signs were noted in the rostral brain areas. Finally, transections at the pontomesencephalic (A) and pontomedullary (B) junctions produced an isolated pons that showed all the signs of REM sleep. The pons is, therefore, sufficient and necessary to generate all the signs of REM sleep.

To explain the mechanism of REM sleep, three animal models are available. The earliest is the McCarley–Hobson reciprocal interaction model (Fig. 41.4) based on reciprocal interaction of REM-on and REM-off neurons [1, 22] (see also Chap. 5). The cholinergic neurons in the PPT and LDT

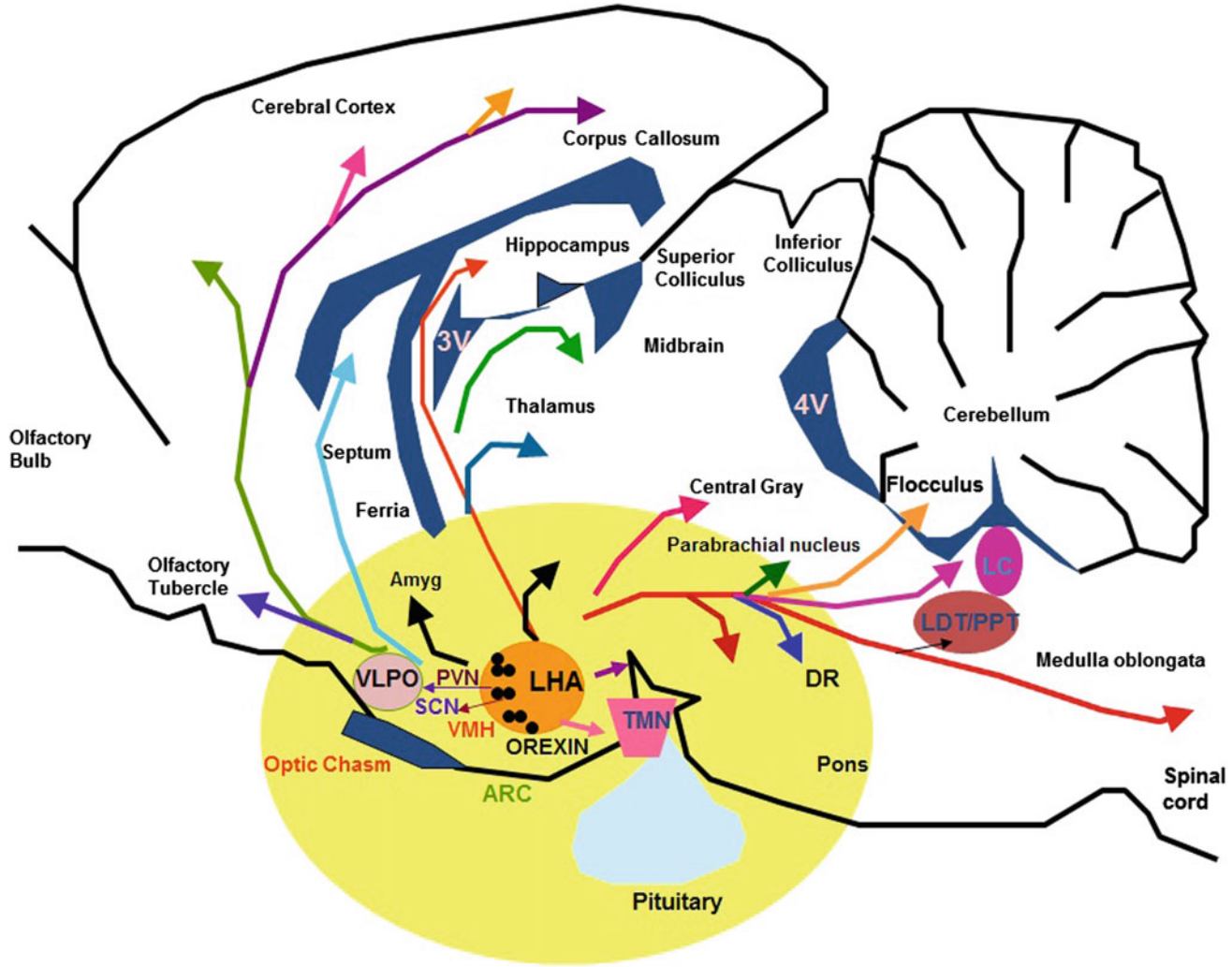

Fig. 41.2 Widespread projection of hypocretin

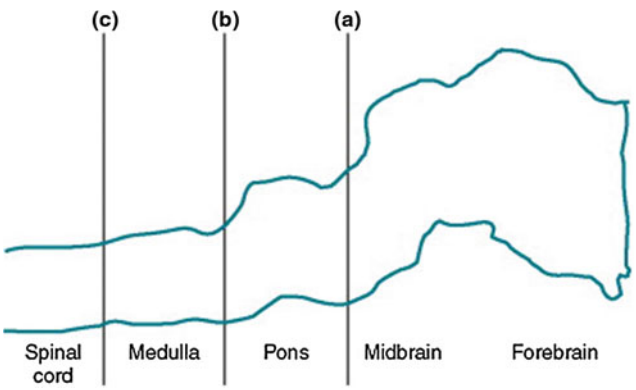

Fig. 41.3 Schematic sagittal section of the brain stem of the cat. **a** Junction of midbrain and pons. **b** Junction of pons and medulla. **c** Junction of medulla and spinal cord. Modified from Jouvet [30] and Siegel [31]

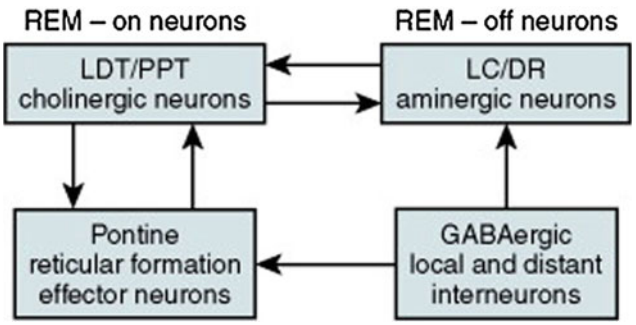

Fig. 41.4 Schematic diagram of McCarley–Hobson model of REM sleep mechanism. *GABA* γ-aminobutyric acid; *LC/DR* locus coeruleus/dorsal raphe; *LDT/PPT* laterodorsal tegmental/pedunculopontine tegmental nuclei. Modified from McCarley [22]

nuclei in the pontomesencephalic region are REM-on cells responsible for REM sleep, showing the highest firing rates at this stage. The aminergic neurons located in the LC and DRN are REM-off cells and are inactive during REM sleep. Histaminergic neurons in the tuberomammillary region of the posterior hypothalamus can also be considered as REM-off cells. Thus, the cholinergic REM-on and aminergic REM-off cells are all located within the transections of the pons as described previously. LDT-PPT cholinergic neurons promote REM sleep through pontine reticular formation (PRF) effector neurons, which in turn send feedback loops to the LDT-PPT. Cholinergic neurons of the PPT and LDT project into the thalamus and basal forebrain regions as well as to the PRF and are responsible for activation and generation of REM sleep. Aminergic cells play a permissive role in maintenance of the REM sleep state. In the latest modification of the reciprocal interaction model, McCarley [22] suggested that γ-aminobutyric acid (GABA) also plays a role in the REM sleep generation. At the onset of REM sleep, there is activation of GABA neurons in the pons that causes inhibition of the LC/DRN (REM-off neurons) as well as activation of (or disinhibition of) cholinergic neurons in the pons [32]. The reason for GABA activation is not known, and the source of GABAergic neurons is probably both local (e.g., a subgroup of PRF GABA neurons) and distant (e.g., GABAergic neurons in the ventrolateral periaqueductal gray). The theory for muscle hypotonia or atonia during REM sleep postulates that inhibitory postsynaptic potentials are generated by dorsal pontine interneurons in the region of the peri-LC alpha ventral to the LC that project to the lateral tegmentoreticular tract and then to the medial medullary region (the inhibitory zone of Magoun and Rhines in and around the nucleus magnocellularis and gigantocellularis in the paramedianus); the reticulospinal tract from this region projects to the anterior horn cells of the spinal cord, causing hyperpolarization and muscle atonia (Fig. 41.5) [1, 2, 33–37]. An experimental lesion in the peri-LC alpha region [38] as well as the medial medullary region [39] produced REM sleep without muscle atonia. In human REM sleep behavior disorder, causing dream-enacting behavior associated with REM sleep without muscle atonia, a structural or functional alteration of the pathway maintaining muscle atonia during REM sleep is most likely responsible [40].

In the model, proposed by Lu et al. [41] (Fig. 41.6), there is a "flip-flop" switch interaction between GABAergic REM-off neurons in the deep mesencephalon, vlPAG, and lateral pontine tegmentum (LPT), and GABAergic REM-on neurons in the sublaterodorsal (SLD) nucleus, with a dorsal extension of the SLD named the precoeruleus. These mutually inhibitory neuronal populations (SLD GABAergic REM-on and GABAergic REM-off neurons in the deep mesencephalon–lateral pontine tegmentum) serve as a flip-flop switch. Ascending glutamatergic projections from precoeruleus neurons to the medial septum are responsible for the hippocampal electroencephalographic (EEG) theta rhythm during REM sleep. Descending glutamatergic projections from the ventral SLD directly to the spinal interneurons, apparently without a relay in the medial medulla, inhibit spinal ventral horn cells by both glycinergic and GABAergic mechanisms. Cholinergic and aminergic neurons play a modulatory role and are not part of the flip-flop switch. McCarley [22] suggested that this model is based on c-fos labeling only without electrophysiologic recordings. Furthermore, this model does not address how REM periodicity occurs in this flip-flop switch utilizing two mutually inhibitory neuronal populations. Finally, this model also does not explain the gradually increasing duration of REM sleep throughout the night and generally absent REM sleep during daytime naps.

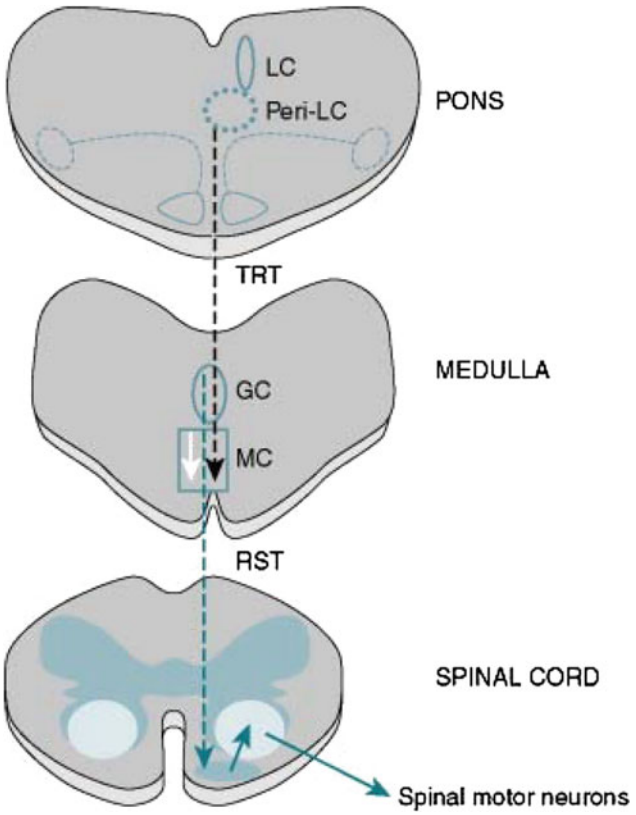

Fig. 41.5 Schematic diagram to explain the mechanism of muscle atonia in REM sleep. *GC* gigantocellularis; *LC* locus coeruleus; *MC* magnocellularis; *Peri-LC* perilocus coeruleus alpha; *RST* reticulospinal tract; *TRT* tegmentoreticular tract

In the model proposed by Luppi's group [42–46] (Figs. 41.7 and 41.8), neurons active during REM sleep are identified in a small area in the dorsolateral pontine tegmentum called the sublaterodorsal (SLD) nucleus in rats (corresponding to the dorsal subcoeruleus nucleus in humans or peri-LC alpha region in cats). At the onset of REM sleep,

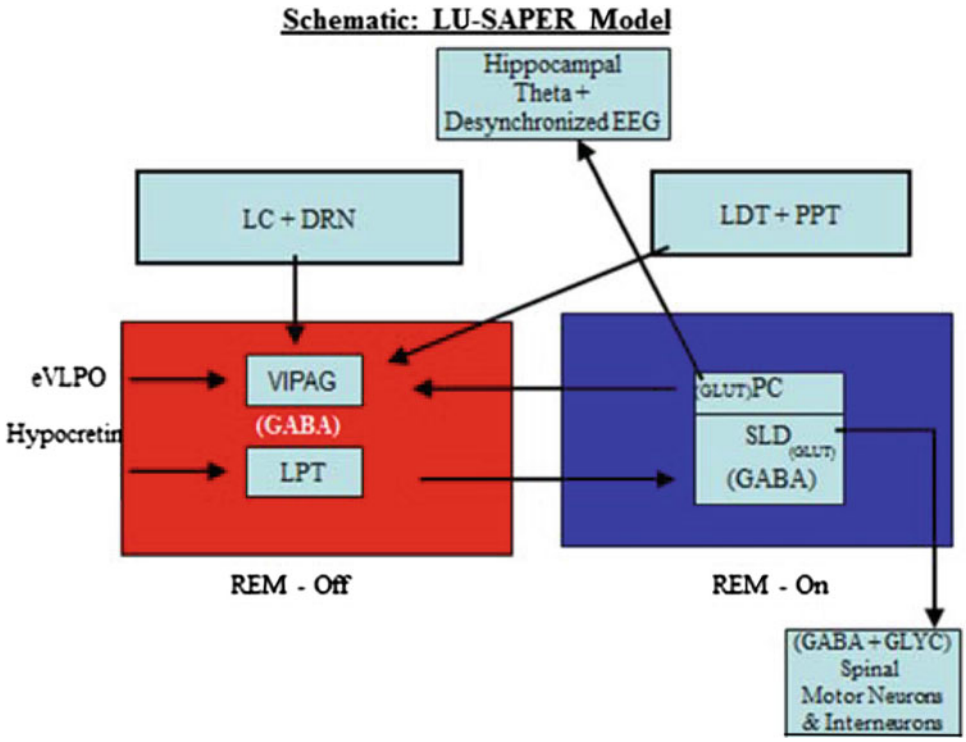

Fig. 41.6 Lu-Saper "flip-flop" model shown schematically to explain REM sleep mechanism. *eVLPO* extended region of ventrolateral preoptic nucleus; *GABA* γ-aminobutyric acid; *GLUT* glutamatergic neurons; *GLYC* glycinergic neurons; *LC + DRN* locus coeruleus + dorsal raphe nuclei; *LDT + PPT* laterodorsal tegmental + pedunculopontine tegmental nuclei; *LPT* lateral pontine tegmentum; *PC* precoeruleus; *SLD* sublaterodorsal nucleus; *VlPAG* ventrolateral periaqueductal gray. Modified from Lu et al. [41]

there is an activation of REM-on glutamatergic neurons from the SLD. During NREM sleep and wakefulness, these neurons in the SLD would be inhibited (hyperpolarized) by tonic GABAergic input from GABAergic REM-off neurons located in the SLD, deep mesencephalic and pontine reticular nuclei, and ventrolateral periaqueductal gray (vlPAG) as well as monoaminergic REM-off neurons. Ascending dorsal SLD REM-on glutamatergic neurons can cause cortical activation through projections to thalamocortical neurons along with REM-on cholinergic and glutamatergic neurons from the LDT/PPT mesencephalic and pontine reticular nuclei and basal forebrain regions. Descending ventral REM-on glutamatergic SLD neurons would cause muscle atonia through excitatory direct and indirect projections to glycinergic and GABAergic premotor neurons in the magnocellularis and parvocellularis reticular nuclei in the medulla, causing hyperpolarization of the motor neurons. In the Luppi model, therefore, the glutamatergic neurons play a crucial role in REM generation. GABAergic neurons are responsible for inactivation of monoaminergic neurons during REM sleep, and cholinergic neurons do not play a crucial role in activating REM executive neurons in this model. In experimental REM deprivation studies in rats, Luppi's group [42] showed that during REM recovery sleep, C-fos-activated SLD neurons were not cholinergic (i.e., there was no increase of choline acetyltransferase and the enzyme synthesizing acetylcholine) nor were they GABAergic (i.e., glutamate decarboxylase, the enzyme synthesizing GABA, did not increase in the majority of the SLD neurons). Most of the C-fos-labeled neurons localized in the SLD after REM recovery expressed vesicular glutamate transporter 2 (vGLUT 2), a specific marker of glutamatergic neurons. Therefore, SLD neurons triggering REM sleep are glutamatergic. The melanin-concentrating hormone (MCH) neurons in the lateral hypothalamus also participate in promoting REM sleep (see further on).

There are thus certain similarities and differences between these two contemporary models (Lu-Saper and Luppi) which can be summarized as follows: In both these models the pontine SLD neurons play a critical role. In the Luppi model the SLD REM-on neurons are glutamatergic, whereas in the Lu-Saper model GABAergic neurons in both REM-off and REM-on (SLD) regions play a crucial role in REM sleep by activating dorsal (for EEG) and ventral (for muscle atonia) glutamatergic pathways in the SLD. Both these models recognize the importance of glutamatergic system for generating EEG desynchronization and REM muscle atonia. In their initial report Luppi's group suggested both a direct and

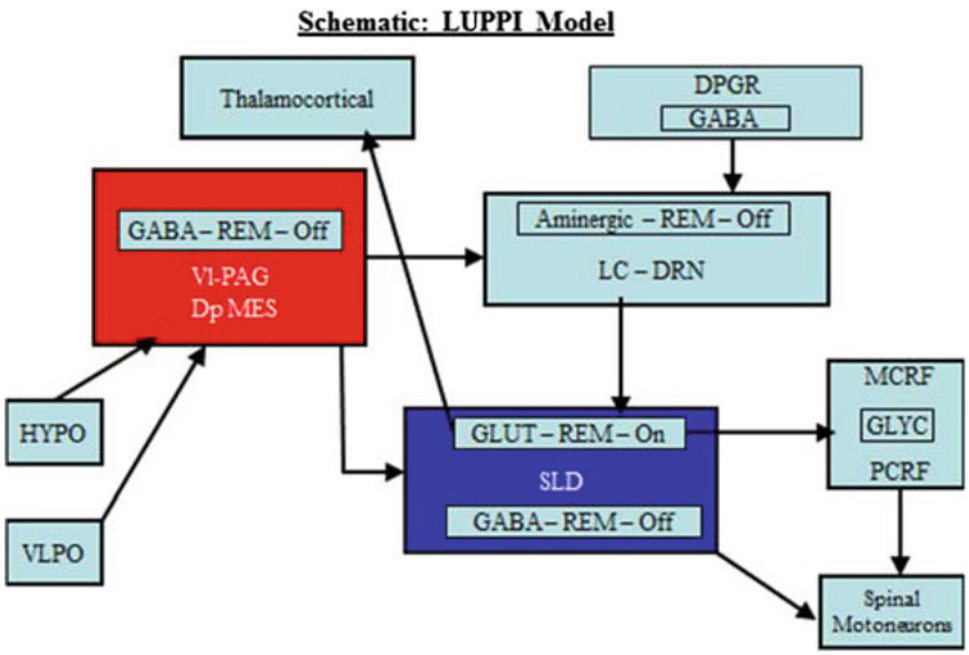

Fig. 41.7 Luppi Model. Schematic diagram of Boissard–Luppi model to explain REM sleep mechanism. *DPGR* dorsal paragigantocellular reticular nucleus; *Dp-MES* deep mesencephalic; *GABA* γ-aminobutyric acid; *GLUT* glutamatergic; *GLYC* glycinergic neurons; *HYPO* hypothalamus [hypocretinergic neurons in lateral hypothalamus]; *LC-DRN* locus coeruleus—dorsal raphe nuclei; *MCRF* magnocellular reticular formation; *PCRF* parvocellular reticular formation; *SLD* sublaterodorsal nucleus; *Vl-PAG* ventrolateral periaqueductal gray; *VLPO* ventrolateral preoptic region. Modified from Luppi and Fort [1] and [42]

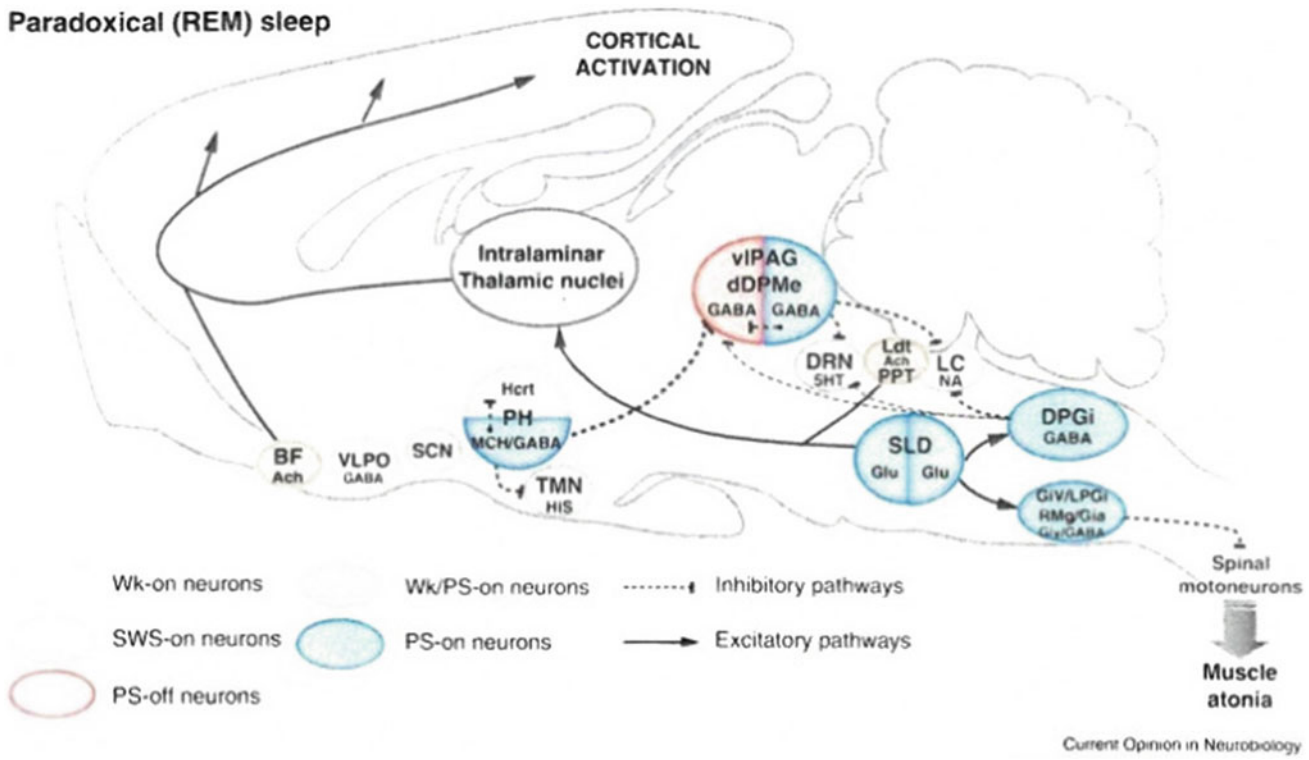

Fig. 41.8 Neuronal network responsible for REM Sleep *PS* paradoxical (REM) sleep; *BF* basal forebrain; *Ach* acetylcholine; *VLPO* ventrolateral preoptic nucleus; *GABA* gamma amino-butyric acid; *SCN* suprachiasmatic nucleus; *Hcrt* hypocretinergic neurons; *PH* posterior hypothalamus; *MCH* melanin concentrating hormone-containing neurons; *TMN* tuberomamillary nucleus; *HIS* histamine; *vlPAG*: ventrolateral periaqueductal gray; *dDPMe* deep mesencephalic reticular nucleus; *DRN* dorsal raphe nucleus; *5HT* 5-hydroxtryptamine; *Ldt* laterodorsal tegmental nucleus; *PPT* peduncutopontine tegmental nucleus; *LC* locus coeruleus; *NA* noradrenaline; *SLD* sublaterodorsal nucleus; *Glu*: glutamic acid; *DPGi* dorsal paragigantocellular reticular nucleus; *Giv* ventral gigantocellular nucleus; *LPGi* lateral paragigantocellular reticular nucleus; *Rmg* nucleus raphe magnus; *Gia* alpha gigantocellular reticular nucleus; *Gly* glycine. Reproduced with permission from reference [22] in the text

an indirect projection from SLD to spinal cord via a relay in the VMM. The latest report [44, 45] from this group, however, suggested that REM muscle atonia is mediated mainly by a relay in the VMM and to a minor extent by a direct projection to spinal cord. Saper's group, on the other hand, initially [41] suggested a direct projection from SLD to spinal cord without a relay in the VMM. In their latest [46] report this group modified their initial suggestion, now saying that REM atonia is mainly due to a direct spinal projection, but VMM may also play a minor role. The two models (Lu-Saper and Luppi) thus seem to be merging in finding a common ground to explain REM muscle atonia.

Luppi's group [44] recently recognized the important role played by the lateral hypothalamus in REM sleep generation (see further on). They hypothesized that the melanin concentrating hormone (MCH)/GABAergic (REM-on) neurons in the lateral hypothalamus constitute a master generator of REM sleep by a direct inhibitory input to vlPAG region and deep mesencephalic (DPMES) reticular nucleus (REM-off GABAergic neurons) controlling onset and maintenance of REM sleep. Earlir Saper's group [47] highlighted also the role played by the diffuse (extended) VLPO neurons of the hypothalamus in REM sleep generation by inhibiting vlPAG regions during REM sleep.

Brooks and Peever [48] initially challenged the glycinergic and GABAergic neurochemical mechanism of REM motor atonia based on microdialysis experimental evidence in rats that REM atonia persists even when glycine and GABA receptors are blocked and after simultaneous application of glutamatergic agonists to the trigeminal motor pool. These authors [49], however, reversed their conclusion and showed that addition of baclofen (a GABA b antagonist) to bicuculline (a GABA a antagonist) and strychnine (a glycine antagonist) during microdialysis restored muscle tone supporting the role of glycinergic and GABAergic neurons in REM motor atonia.

Neuroanatomic Substrates of NREM Sleep

Neurophysiologic studies of sleep really began after astute clinicopathologic observations by von Economo, who examined patients with encephalitis lethargica at the beginning of the twentieth century [50]. It was noted that lesions of encephalitis lethargica, which severely affected the posterior hypothalamic area, were associated with the clinical manifestation of extreme somnolence, whereas morphologic alterations in the anterior hypothalamic region were associated with sleeplessness. These observations led scientists to believe in the existence of the so-called sleep-wake centers [50–53].

Before the middle of the last century, the emphasis of sleep physiologists was on the passive [53–55] theories of sleep. Beginning in the late 1950s, thought shifted toward active sleep theories [3, 5, 56–65]. The passive theory postulates that sleep results from withdrawal of both specific and nonspecific afferent stimuli to the brain stem and the cerebral hemisphere. Proponents of active sleep theories suggest that activity of sleep-promoting neurons or the fibers of these so-called centers determine the onset of sleep. Most likely, proponents of both active and passive theories are partially correct, as far as the physiology and anatomy of sleep are concerned. These conclusions are based on stimulation, ablation, or lesion experiments. Later, these studies were extended to include extracellular and intracellular recordings and pharmacologic injections of chemicals into discrete areas to induce different states of sleep or to inhibit sleep [66].

The passive theory originated with two classic preparations in cats by Bremer [54, 67]: cerveau isolé and encephale isolé. Bremer found that midcollicular transection (cerveau isolé) produced somnolence in the acute stage and that transection at the C1 vertebral level, to disconnect the entire brain from the spinal cord (encephale isolé), caused EEG recordings to fluctuate between wakefulness and sleep. From these experiments, Bremer concluded that in cerveau isolé preparations, all the specific sensory afferent stimuli were withdrawn, and thus, sleep was facilitated, whereas such stimuli maintained the activation of the brain in encephale isolé preparations. These conclusions, however, have been modified since the discovery by Moruzzi and Magoun [55] in 1949 of the existence of nonspecific groups of neurons and fibers in the center of the brain stem called the reticular formation. Moruzzi and Magoun [55] stated that the brain stem ARAS energized the forebrain and that withdrawal of this influence in cerveau isolé preparation resulted in somnolence or coma. The observations of Moruzzi and Magoun [55] that EEG desynchronization results from activation of the midbrain reticular neurons, which directly excite the thalamocortical projections, have been confirmed by more recent intracellular studies [68, 69]. It was thought that wakefulness resulted from activation of the ARAS and diffuses thalamocortical projections [1]. After stimulation of these structures, the EEG shows diffuse desynchronization, whereas lesions in these structures produce EEG synchronization or the EEG NREM sleep pattern. This also supports the suggestion of Steriade et al. [70] that, at the onset of NREM sleep, there is deafferentation of the brain due to blockage of afferent information first at the thalamic level, causing the waking open brain to be converted into a closed brain resulting from thalamocortical inhibition. The reticular nucleus of the thalamus is responsible for the origin of the sleep spindles [1]. Stimulation of this nucleus produces spindle-like activity, whereas destruction of it abolishes the spindles unilaterally and bilateral destruction abolishes the spindles on both sides.

The passive sleep theories were challenged by findings that came in the wake of midpontine pretrigeminal brain stem transection in cats performed by Batini et al. [57, 58]. This preparation is only a few millimeters below the section that produces the cerveau isolé preparation. In contrast to the somnolence produced by the cerveau isolé preparation, the midpontine pretrigeminal section produced persistent EEG and behavioral signs of alertness. These observations imply that structures located in the brain stem regions between these two preparations (cerveau isolé and midpontine pretrigeminal) are responsible for wakefulness. Data demonstrate cholinergic neurons in the PPT nucleus and in the LDT nucleus in the region of the midbrain-pontine junction [1]. These groups of cholinergic neurons have been shown to have thalamic and basal forebrain projections as well as projections toward the medial PRF. These neurons are responsible for activation and for generation of REM sleep in the McCarley–Hobson model [1] (see Chap. 5). The forebrain cholinergic neurons from the basal nucleus of Meynert project to the cerebral hemisphere, particularly to the sensorimotor cortex, and lesions in these neurons disrupt the EEG waves and elicit diffuse slow waves [1]. The finding of cholinergic neurons at the mesopontine junction confirms the conclusions drawn by Batini et al. [57, 58] after midpontine pretrigeminal transections.

The active hypnogenic neurons for NREM sleep are thought to be located in two regions [1]: (1) the region of the nucleus tractus solitarius (NTS) in the medulla and (2) the preoptic area of the hypothalamus and the basal forebrain area (see Chaps. 5 and 8). Recently, another region in the medulla is thought to be promoting slow-wave sleep (SWS) active GABAergic neurons in the medullary parafacial zone (PZ) by releasing synaptic GABA onto parabrachial neurons which then excite basal forebrain by releasing glutamate and modulate cortical EEG [71]. The evidence is based on stimulation, lesion, ablation studies, extracellular and intercellular recordings [1], and expression of c-Fos protein immunoreactivity. The active inhibitory role of the lower brain stem hypnogenic neurons on the upper brain stem ARAS has been clearly demonstrated by Batini et al.'s [57, 58] experiment of midpontine pretrigeminal sectioning. Similarly, electrical [62] stimulation of the preoptic area, which produced EEG synchronization and a behavioral state of sleep, supported the idea of the existence of active hypnogenic neurons in the preoptic area [1]. Nauta's [53] experiments in 1946 that showed insomnia after lesions of the preoptic region also supported the hypothesis of active hypnogenic neurons in the forebrain preoptic area. Experiments by McGinty and Sterman [64] in 1968 confirmed Nauta's observations. More recently, ibotenic lesions in the preoptic region have been found to produce insomnia, and these results support the active hypnogenic role of the preoptic area [1, 72]. In the same experiments, however, injections of muscimol (a GABA agonist) in the posterior hypothalamus transiently recovered sleep, suggesting that the sleep-promoting role of the anterior hypothalamus is dependent on inhibition of posterior hypothalamic histaminergic awakening neurons. It is also notable that in 1934, Dikshit [73] induced sleep by intrahypothalamic injection of acetylcholine, suggesting the presence of a sleep center in the hypothalamus. Contemporary theory suggests that NREM sleep-promoting neurons are found in the VLPO area and the median preoptic nucleus (MnPn) [74] of the anterior hypothalamus as well as in the region of the NTS and the parafacial zone (PZ) in the medulla. VLPO neurons consist of two subgroups—"clustered" and "diffuse" or extended—depending on the distribution pattern [47, 75].

It has recently been shown that MCH neurons (GABAergic) also play an important role in promoting and stabilizing sleep along with VLPO and MnPn of the anterior hypothalamus [47, 74–78]. MCH neurons are intermixed and interconnected with hypocretin (orexin) neurons in lateral hypothalamus and receive inhibitory inputs from arousal neurotransmitter system (e.g., noradrenergic, serotonergic, histaminergic, and cholinergic) [78]. MCH neurons also project widely to other hypothalamic neurons as well as to the limbic system including the amygdala [79]. The hypothalamic preoptic (e.g., VLPO and MnPn) and MCH neurons are sleep-promoting neurons as evidenced by increasing firing of the units on intracellular recordings and increased expression of C-fos immunoreactivity in VLPO and MnPn as well as after optogenetic stimulation of MCH neurons [76, 78]. VLPO neurons are responsible for sleep consolidation and maintenance, whereas MnPn is responsible for sleep onset. Activation of VLPO and MnPn (using GABA and galanine inhibitory neurotransmitters) results in inhibition of the arousal systems in the brain stem (aminergic, serotonergic, and dopaminergic), forebrain (cholinergic), and posterolateral hypothalamus (hypocretinergic and histaminergic). Thus, there is a reciprocal interaction between sleep-promoting and wake-promoting neurons [74, 47]. The beginning and ending of the state may be determined partly by self-inhibition of the respective neurons and dissipation of sleep-promoting factors (e.g., adenosine, the cytokine interleukin-1β or IL-1β and prostaglandin D2 or PGD2). The strong anatomic connection between suprachiasmatic nucleus (SCN) controlling circadian regulation and VLPO-MnPn-MCH neurons responsible for homeostatic regulation suggests an important role for SCN in sleep-wake regulation, but their functional interaction is not clearly determined.

The tightly clustered VLPO neurons project to the tuberomammillary nuclei, inhibiting them and promoting NREM sleep, whereas diffusely distributed (extended) VLPO neurons along with MCH neurons project to and inhibit the aminergic nuclei in the LC and the dorsal raphe

region of the brain stem as well as inhibiting the pontine GABAergic neurons in the ventrolateral periaqueductal gray (VLPaG)/SLD, participating in REM sleep [76, 77, 80]. It is notable that MCH neurons fire maximally during REM sleep and to a lesser extent during NREM sleep [76, 77]. In narcolepsy, loss of hypocretinergic neurons facilitates (disinhibits) MCH neurons, thereby promoting sleepiness and cataplexy.

The contemporary theory for the mechanism of NREM sleep thus suggests a reciprocal interaction between two antagonistic neuron types in the VLPO and MnPn of the anterior hypothalamus and MCH neurons in the lateral hypothalamus and wake-promoting neurons in the tuberomammillary nuclei of the posterior hypothalamus, as well as the LC, dorsal raphe, basal forebrain, and mesopontine tegmentum [1, 22, 47, 74, 75]. Reciprocal interaction between sleep-promoting neurons in the region of the NTS and wake-promoting neurons within the ARAS of the brain stem independent of the reciprocal interaction of the neurons of the forebrain also plays a role in the generation of NREM sleep, as stated earlier. In summary, the active and passive theories of sleep may be viewed as complementary rather than mutually exclusive mechanisms [1]. The role of postulated humoral sleep factors (e.g., prostaglandin D_2, the cytokine interleukin-1β (IL-1β), growth hormone-releasing factor, and muramyl peptides) remains undetermined in the absence of experiments to test their role at the cellular level in critical brain areas. It has been suggested that adenosine, a neuromodulator, may act as a physiologic sleep factor modulating the somnogenic effects of prolonged wakefulness [81]. This has been postulated after experiments in cats have shown that adenosine extracellular concentration in the basal forebrain cholinergic region increased progressively during prolonged spontaneous wakefulness.

Many important unanswered questions remain regarding the mechanism of sleep. Why do VLPO and MnPn neurons fire at sleep onset? What initiates the cascade of disfacilitation in the brain stem wake-promoting neurons? What initiates activation of LDT-PPT neurons during REM? What causes activation of GABAergic pontine SLD neurons at the onset of REM sleep? What activates pontine glutamatergic neurons at REM onset? What causes activation of wake-promoting neurons at sleep offset? And, finally, what maintains NREM-REM cycling? We here provide a speculative summary to answer some of these questions. VLPO, MnPn, and MCH excitation at NREM sleep onset is initiated by progressive accumulation of adenosine (a sleep-promoting factor in the forebrain region accumulated during prolonged wakefulness) and probably also by an excitatory drive from the suprachiasmatic nucleus (SCN) as well as reciprocal inhibition of aminergic and orexin wake-promoting neurons; progressive inhibition of aminergic REM-off and hypocretinergic neurons causes disinhibition of REM-on neurons and initiates REM sleep; a simultaneous cascade of disfacilitation of the brain stem arousal system with decreased environmental afferent stimuli culminates in blockade at thalamic levels. Physiologically, facilitation (or disinhibition) after a certain period (perhaps determined in the case of sleep-wake regulation by the SCN regulatory neurons connected anatomically to sleep-wake neurons) will be followed by inhibition (or disfacilitation), i.e., these sleep-promoting neurons are self-inhibiting, and thus, the cycle will begin again. For additional discussion on the functional anatomy of sleep, the reader is referred to Chaps. 5 and 8.

Marked impairment of the arousal and cognition systems may result in coma or severe sleepiness. The reversibility of this state of awareness differentiates sleep from coma. There are also physiologic and metabolic differences between sleep and coma. Coma is a passive process (loss of function), whereas sleep is an active state resulting from physiologic interactions of various systems in the brain stem and cerebral cortex. Metabolic depression of the cerebral cortex and brain stem characterizes coma and stupor, whereas in sleep oxygen use and metabolic rhythm remain intact. By disrupting the arousal system and stimulating the sleep-promoting neurons, focal neurologic lesions may also cause excessive sleepiness. For example, lesions of the brain stem, thalamus, hypothalamus, and PAG regions may produce excessive sleepiness, stupor, and coma. These lesions may also affect lateral hypothalamic hypocretinergic neurons as well as REM-generating neurons in the pons and cause various REM sleep alterations including symptomatic narcolepsy.

Functional Anatomy of Respiration in Sleep and Wakefulness

The neuroanatomy of respiration, its control, and physiologic changes during sleep in healthy individuals are described in detail in Chap. 11. Briefly, respiration is controlled by the automatic or metabolic and behavioral systems [11–14, 82–86]. The two systems are complemented by a third system known as the *arousal system,* which may also be called the *system for wakefulness stimulus* [86, 87]. These respiratory systems work in concert with the various peripheral and central inputs to maintain acid-base regulation and respiratory homeostasis [9]. The location of the respiratory neurons makes them easily vulnerable to a variety of central and peripheral neurologic disorders, particularly central neurologic disorders involving the brain stem. Many acute and chronic neurologic illnesses may affect central or peripheral respiratory pathways, giving rise to acute respiratory failure in wakefulness and sleep. Some conditions may affect control of breathing only during sleep. Such a condition may cause undesirable, often catastrophic, results, including cardiorespiratory failure and even sudden death.

Sleep-Related Respiratory Dysrhythmia in Neurologic Disorders

Many types of sleep-related respiratory dysrhythmia have been noted in association with neurologic illnesses [87–89] (Fig. 41.9). The most common types are sleep apnea and sleep hypopnea.

Sleep Apnea

Three types of sleep apnea have been noted [87–90]: central, upper airway obstructive, and mixed. Normal individuals may experience a few episodes of sleep apnea, particularly central apnea, at the onset of NREM sleep and during REM sleep. To be of pathologic significance, the sleep apnea

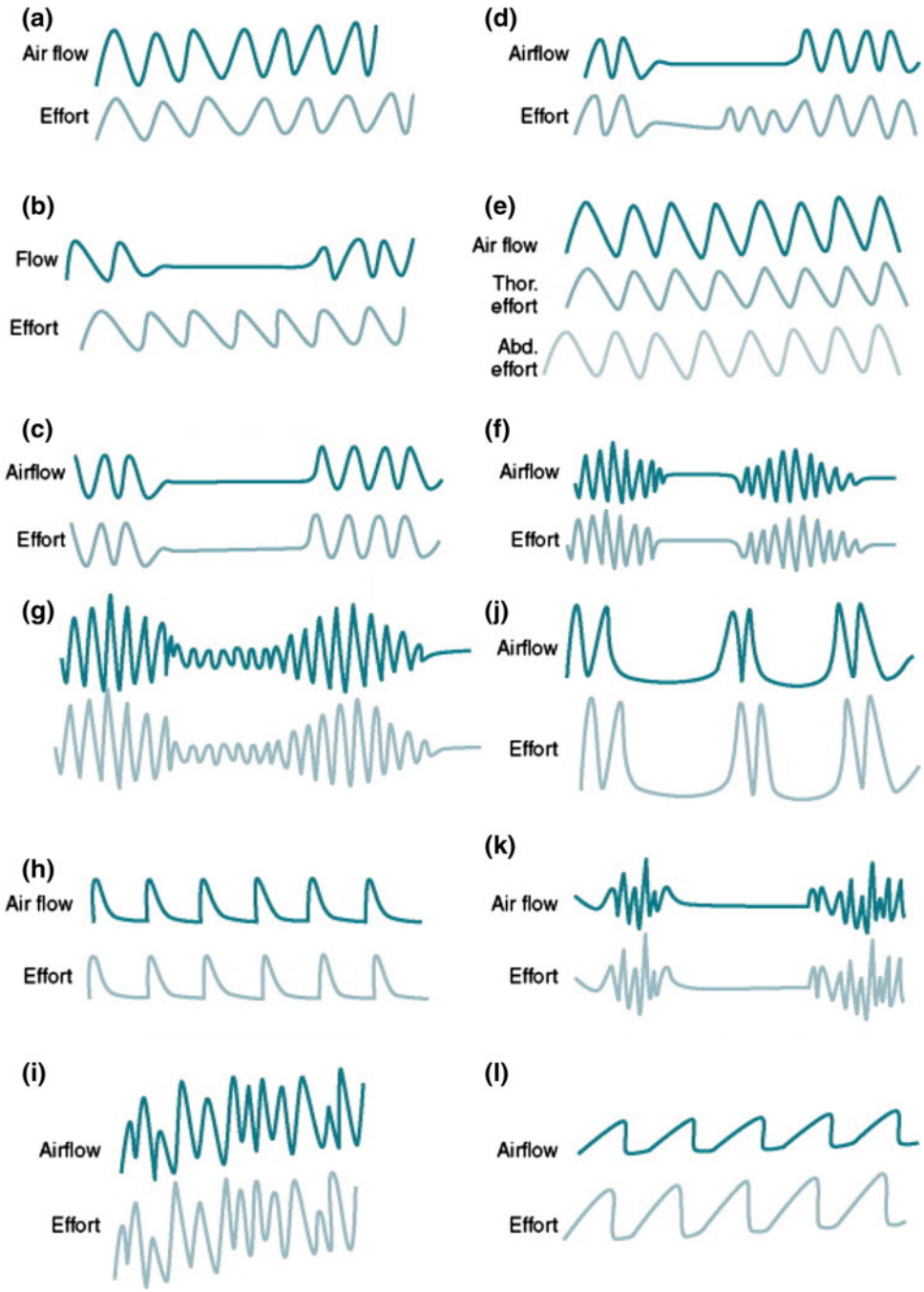

Fig. 41.9 Schematic diagram to show different types of breathing patterns in neurologic illnesses. **a** Normal breathing pattern. **b** Upper airway obstructive apnea. **c** Central apnea. **d** Mixed apnea (initial central followed by obstructive apnea). **e** Paradoxical breathing. **f** Cheyne–Stokes breathing. **g** Cheyne–Stokes variant pattern. **h** Inspiratory gasp. **i** Dysrhythmic breathing. **j** Biot's breathing (a special type of ataxic breathing characterized by 2–3 breaths of nearly equal volume followed by long period of apnea). **k** Ataxic breathing. **l** Apneustic breathing

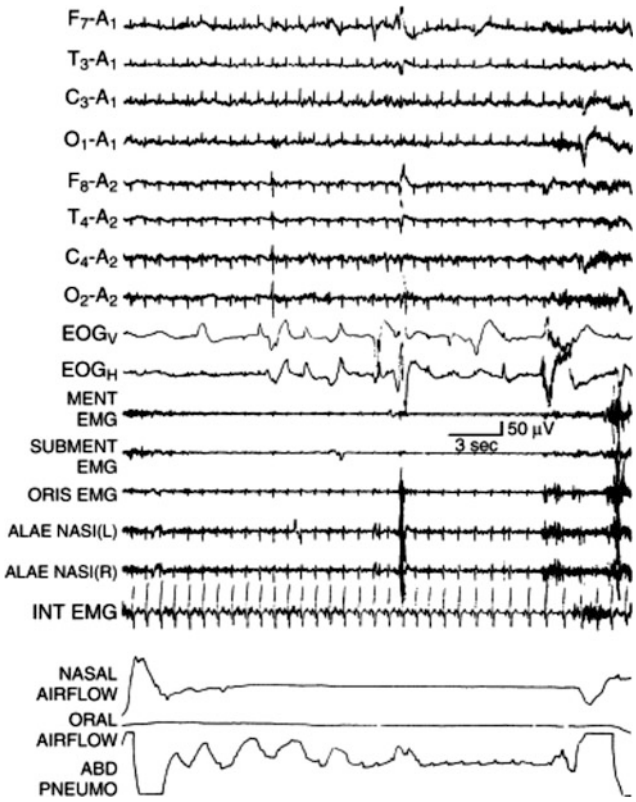

Fig. 41.10 Polysomnographic recording in a patient with narcolepsy and sleep apnea showing the electroencephalogram (EEG; top eight channels); vertical (EOG_V) and horizontal (EOG_H) electrooculograms; mentalis (MENT), submental (SUBMENT), orbicularis oris (ORIS), left (L) and right (R) alae nasi, and intercostal (INT) electromyogram (EMG); nasal and oral airflow; and abdominal pneumogram (ABD PNEUMO). Note unusual type of mixed apnea (initial obstructive apnea for a period of 14 s followed by central apnea for a period of 8 s) during REM sleep

should last at least 10 s and the apnea index (number of apneas per hour of sleep) should be at least 5. In the American Academy of Sleep Medicine (AASM) scoring criteria [89], in addition to duration of 10 s, apnea is scored when the peak amplitude drops by 90 % or more of the baseline, and this amplitude reduction must last for at least 90 % of the event's duration.

Cessation of airflow with no respiratory effort constitutes central apnea. During this period, there is no diaphragmatic and intercostal muscle activity or air exchange through the nose or mouth. Upper airway obstructive sleep apnea (OSA) is manifested by the absence of air exchange through the nose or mouth but persistence of diaphragmatic and intercostal muscle activity.

During mixed apnea, initially airflow ceases, as does respiratory effort (central apnea); this is followed by a period of upper airway OSA. On rare occasions, this pattern may be reversed, resulting in an initial period of OSA followed by central apnea (Fig. 41.10).

Sleep-Related Hypopnea

Sleep-related hypopnea is manifested by decreasing airflow at the mouth and nose and decreased thoracoabdominal movement causing a reduction in tidal volume. Until recently, there was no standard definition of hypopnea; however, in the 2007 AASM scoring criteria [89], the recommended definition for hypopnea is a reduction of nasal pressure signal excursion (or that of the alternative airflow sensor) by 30 % or more of the baseline amplitude lasting for a period of at least 10 s and accompanied by a 3 % or more desaturation from the pre-event baseline or the event is associated with an arousal. Furthermore, at least 90 % of the event's duration must meet the amplitude reduction criteria for hypopnea. An alternative suggestion in the subsequent slight modification (the version 2.1 update) of the same manual is a reduction of the amplitude excursion in the nasal pressure signal (or that of the alternative airflow sensor) by 30 % or more of the baseline lasting for at least 10 s and accompanied by oxygen desaturation of 4 % or more from the pre-event baseline. This amplitude reduction must be present for at least 90 % of the event's duration. An apnea-hypopnea index (AHI; defined as the number of apneas plus hypopneas per hour of sleep) of 5 or less is considered normal. The respiratory disturbance index (RDI), a term often incorrectly used interchangeably with AHI, includes respiratory effort-related arousals in addition to apneas and hypopneas per hour of sleep. Most investigators consider an AHI or RDI of 10 or more to be clinically significant.

Sleep-related apneas and hypopneas in neurologic diseases are secondary sleep apnea syndromes, in contrast to primary OSA syndrome, in which no cause except for some minor deviations of the upper airway anatomic configuration is found to account for the appearance of apnea. The neurologic illness may be aggravated by the secondary sleep apnea because of the adverse effects of sleep-induced hypoxemia and hypercapnia and repeated arousals with sleep fragmentation. In long-standing cases, there may be pulmonary hypertension, congestive cardiac failure, and other manifestations of chronic sleep deprivation.

Paradoxical Breathing

The thorax and abdomen move in opposite directions during paradoxical breathing, indicating increased upper airway resistance. In upper airway resistance syndrome, this may be noted without any change in oronasal airflow; in OSA, however, paradoxical breathing is accompanied by the reduction or absence of oronasal airflow.

Cheyne–Stokes and Cheyne–Stokes Variant Patterns of Breathing

Cheyne–Stokes breathing (CSB) is a special type of central apnea manifested as cyclic changes in breathing with a crescendo-decrescendo sequence separated by central apneas (see Fig. 41.11) [91–94]. The Cheyne–Stokes *variant pattern* of breathing is distinguished by the substitution of hypopneas for apneas [19, 21]. In neurologic disorders, the Cheyne–Stokes type of breathing is mostly noted in bilateral cerebral hemispheric lesions [12, 13] and it worsens during sleep, whereas Cheyne–Stokes variant patterns of breathing may also be noted in brain stem lesions, in addition to bilateral cerebral hemispheric disease. In the AASM scoring manual [89], CSB is scored if there are at least 3 consecutive cycles of cyclical crescendo-decrescendo change in breathing amplitude accompanied by at least one of the following: five or more central apneas and hypopneas per hour of sleep; and a cyclic crescendo-decrescendo change in breathing amplitude and duration of at least 10 consecutive minutes. The cycle length is most commonly in the range of 60 s but must be at least 45 s in duration. The arousals typically occur in the middle of the hyperventilation cycle. This breathing pattern is most prominently seen in NREM sleep, particularly stages 1 and 2 and attenuates or disappears during REM sleep. Besides neurologic lesions, this pattern of periodic breathing is noted in patients with severe congestive cardiac failure and as an adverse effect of opiate intake.

Dysrhythmic Breathing

Dysrhythmic breathing [92, 94] is characterized by nonrhythmic respiration of irregular rate, rhythm, and amplitude during wakefulness with or without O_2 desaturation that becomes worse during sleep. Dysrhythmic breathing may result from an abnormality in the automatic respiratory pattern generator in the brain stem and is commonly seen in multiple system atrophy.

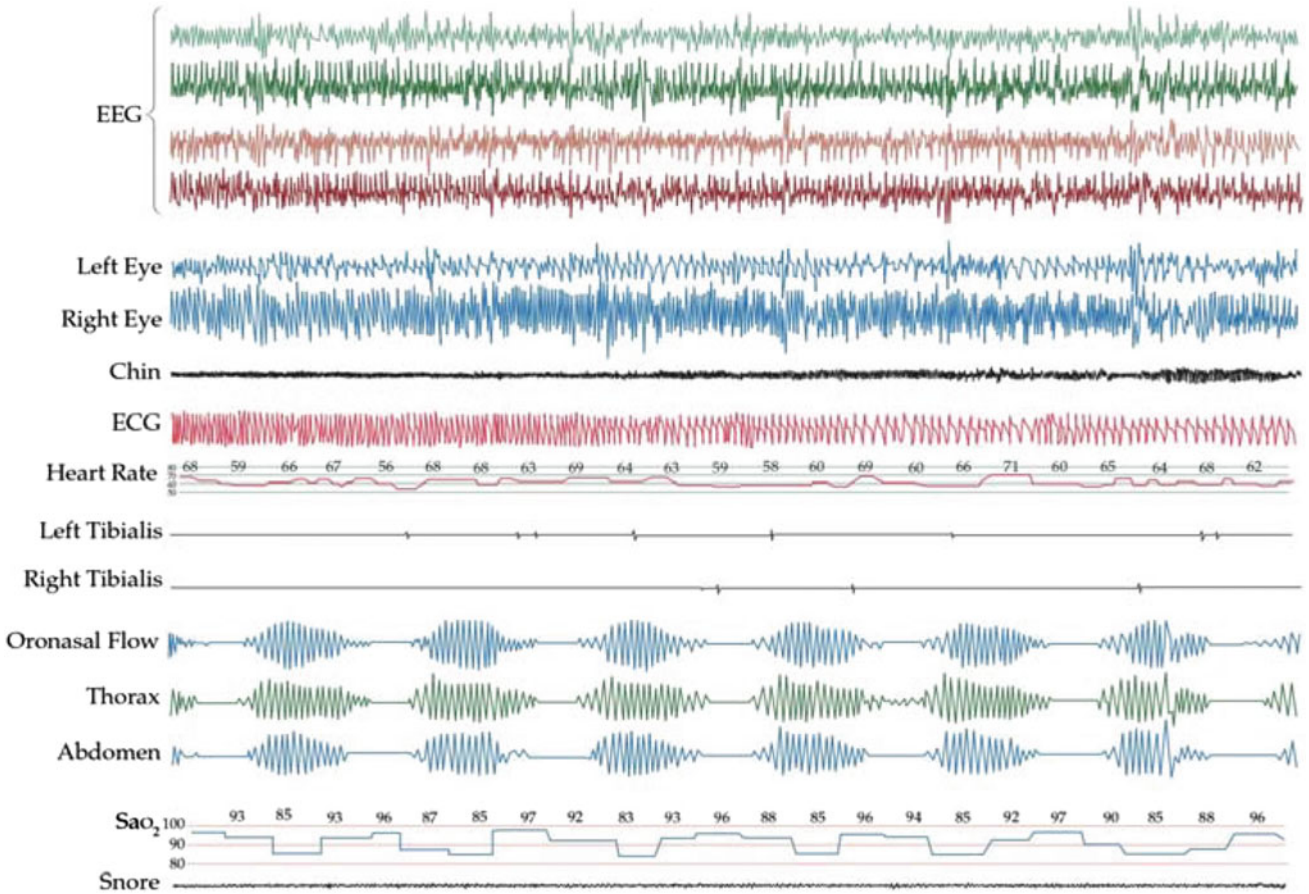

Fig. 41.11 A 500-second excerpt showing the classic Cheyne–Stokes breathing (CSB) crescendo-decrescendo pattern (*arrows*) from an overnight polysomnographic (PSG) recording of a 69-year-old man. The presence of CSB throughout most of the nonrapid eye movement sleep (with marked decrement or absence during rapid eye movement sleep) in this patient with a history of hypertension and excessive daytime sleepiness suggests occult left ventricular failure. ECG electrocardiogram; EEG electroencephalogram; SaO_2 oxygen saturation; Left Eye and Right Eye: Electro-oculograms; Chin: Electromyogram from mental and submental muscles; Left and Right Tibialis: Electromyograms from these muscles; Oronasal Flow: Respiratory flow from thermisters; Thorax and Abdomen: Respiratory effort

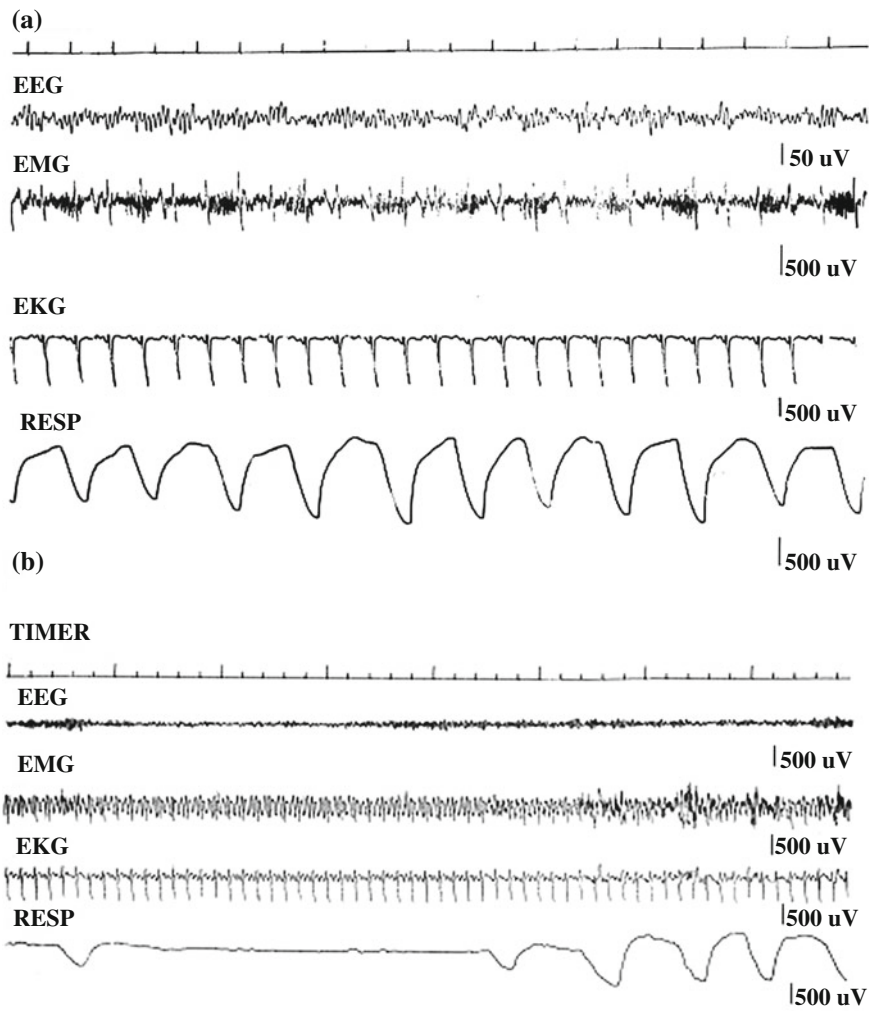

Fig. 41.12 Periodic central apnea in erect posture in a case of Shy–Drager Syndrome. **a** supine posture. **b** erect posture

Apneustic Breathing

Apneustic breathing is characterized by prolonged inspiration with an increase in the ratio of inspiratory to expiratory time [95–97]. This type of breathing may result from a neurologic lesion in the caudal pons that disconnects the so-called apneustic center in the lower pons from the pneumotaxic center (parabrachial and Kölliker–Fuse nuclei) in the upper pons in association with vagotomy [95–97].

Inspiratory Gasp

Inspiratory gasp is characterized by a short inspiration time and a relatively prolonged expiration (reduced inspiratory-expiratory time ratio) [97]. Gasping or irregular breathing has been noted after lesion in the medulla [16, 97].

Ataxic Breathing

This type of breathing is characterized by clusters of cyclic irregular breathing followed by recurrent periods of apnea. The apnea length is greater than the ventilatory phase. Ataxic breathing is often noted in medullary lesions [97] and after opiate ingestion [98].

Biot's Breathing

Biot's breathing is a special type of cluster breathing (ataxic breathing) characterized by two to three breaths of nearly equal volume separated by long periods of apnea [97]. This is really a variant of ataxic or cluster breathing and may be found in patients with medullary lesions.

Other Abnormal Breathing Patterns

The following abnormal breathing patterns have also been noted in neurologic disorders, particularly in patients with Shy–Drager syndrome (multiple system atrophy [MSA]) [87].

- Nocturnal stridor causing severe inspiratory breathing difficulty,

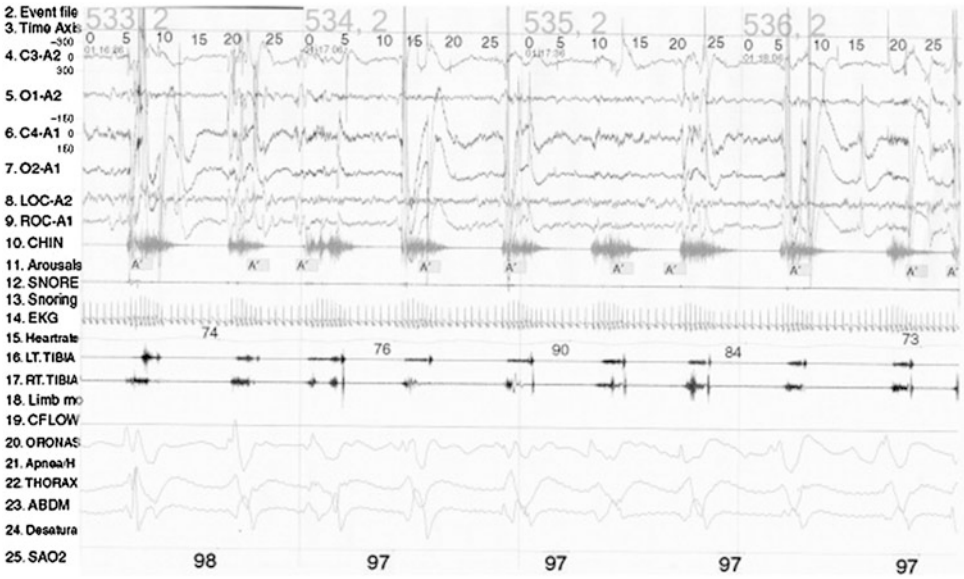

Fig. 41.13 Catathrenia (expiratory groan). A polysomnographic segment of a 120-s epoch showing the electroencephalogram (EEG: C3-A2, O1-A2, C4-A1, O2-A1); left and right eye movements (LOC-A2; ROC-A1); chin, left tibialis (LT.TIBI), and right tibialis (RT. TIBI) electromyograms (EMGs); snoring (SNORE); electrocardiogram (EKG); oronasal airflow (ORONAS); thoracic (THORAX) and abdominal (ABDM) effort channels; and oxygen saturation (SaO_2). Note prolonged expiration in the flow and effort channels followed by arousals without oxygen desaturation in stage 2 NREM sleep. Reproduced with the permission from Siddiqui et al. [100]

- Periodic central apnea in the erect position accompanied by postural fall of blood pressure in Shy–Drager syndrome (Fig. 41.12a and b) [99],
- Prolonged periods of central apnea accompanied by mild O_2 desaturation in relaxed wakefulness, as if the respiratory centers "forgot" to breathe [87, 91, 94],
- Transient occlusion of the upper airway or transient uncoupling of intercostal and diaphragmatic muscle activity [94],
- Transient sudden respiratory arrest,
- Catathrenia (bradypnea and groaning), characterized by prolonged expiration with the characteristic groaning noise. This is seen mostly in REM sleep but has also been noted in NREM sleep. This may be mistaken for a central apnea but is really not an apnea, and there is no oxygen desaturation during the episode [100] (Fig. 41.13). It is included in ICSD-3 under sleep-related breathing disorder section as an isolated symptom and normal variant. The etiology and mechanism are at present unknown.

Sleep-Related Hypoventilation

Finally, sleep-related hypoventilation [101], a type of respiratory dysrhythmia without any apnea or hypopnea, is seen commonly in neuromuscular and intrinsic pulmonary and thoracic restrictive disorders and sometimes in brain stem lesions. Sleep-related hypoventilation is characterized by an increase in the partial pressure of arterial carbon dioxide ($Paco_2$) of 10 mm Hg above the supine awake values during sleep. An abnormal rise in $Paco_2$ immediately on awakening from sleep is suggestive of sleep hypoventilation. Persistent oxygen desaturation is not sufficient to document hypoventilation.

Mechanism of Respiratory Dysrhythmias in Neurologic Disease

Several mechanisms may be responsible for the respiratory abnormalities in sleep associated with neurologic disorders [87, 91].

1 Direct involvement causing structural alterations of the medullary respiratory neurons (automatic or metabolic respiratory controlling system) may result in apnea or hypopnea during NREM and REM sleep. During REM sleep, this problem may be aggravated because of the additional complicating factor of oropharyngeal or other upper airway muscle hypotonia contributing to upper airway OSA.
2 Involvement of the voluntary respiratory control system causes respiratory dysfunction during wakefulness and may give rise to respiratory apraxia.
3 Functional or neurochemical alteration of the respiratory neurons may cause respiratory dysrhythmia.
4 Interference with the afferent inputs to the medullary respiratory neurons (e.g., compromise of the peripheral chemoreceptors located in the vagal and glossopharyngeal nerve endings), supramedullary pathways, and central chemoreceptors in the ventrolateral medulla may cause abnormal breathing.

5 Direct involvement of the efferent mechanism through respiratory muscle weakness may result from either direct involvement of the muscles, as in myopathies, or involvement of the lower motor neurons to the respiratory muscles. In patients with weakness of the principal respiratory and the accessory respiratory muscles, the central respiratory neurons may increase their rate of firing or recruit additional respiratory neurons during wakefulness to maintain ventilation at a level adequate to drive the weak respiratory muscles. Because of the normal vulnerability of the respiratory neurons during sleep, the central respiratory neurons may not be able to participate in such compensatory mechanisms during sleep in patients with respiratory muscle weakness. Ventilatory problems may thus be aggravated, causing more severe hypoventilation and even apnea during sleep. In addition, weakness of the upper airway muscles, which in fact are respiratory muscles and receive phasic inspiratory drive from the respiratory neurons in the brain stem, may cause obstructive apnea.

Sleep and Breathing Disorders Secondary to Somatic Neurologic Illness

Neurologic disorders may affect sleep/wake-generating neurons, causing profound sleep disturbances that may include insomnia, hypersomnia, parasomnia, circadian rhythm disorders, and abnormal movements in sleep at night. An adverse interaction between neurologic illness and sleep dysfunction exists. The sleep disturbances may adversely affect the natural course of the neurologic illness. Sleep dysfunction may result from central or peripheral somatic or autonomic neurologic disorders.

A complaint of insomnia may be related to sleep-onset or maintenance difficulties. Insufficient or fragmented night sleep may result in impaired quality of sleep, fatigue, muscle aches and pains, and poor attention and concentration as well as irritability, anxiety, depression, and impairment of daytime function with daytime somnolence. Most of the neurologic disorders cause hypersomnia, but sometimes insomnia is the predominant complaint [102–109]; an important but rare example, fatal familial insomnia (FFI), is described later in this chapter.

Hypersomnia is generally noted in patients with sleep-related respiratory dysrhythmias. Hypersomnia includes excessive daytime sleepiness (EDS) and irresistible sleep attacks. Associated complaints may include daytime fatigue, lack of concentration, impaired motor skills, morning headaches, and absence of symptom relief from additional sleep. In acute neurologic disorders, the clinical features of neurologic dysfunction may overshadow the sleep and sleep-related respiratory problems [91]. Furthermore, many patients with acute neurologic disorders are actually in stupor or coma. Neurologic lesions may disrupt the sleep architecture, for example, altering the percentage of different sleep stages, increasing awakenings, or causing sleep stage shifts. In addition, sleep apnea (which may occur in various neurologic diseases), intrusion of abnormal movements in sleep, and repeated seizures may disrupt the morphology of sleep and sleep stages. Sleep disturbances may impair memory, cognition, or behavior, or cause cardiopulmonary changes secondary to repeated hypoxemia. These effects, secondary to sleep disturbance, can aggravate the primary neurologic condition. Neurologic causes of hypersomnia have been described in Chap. 3.

The parasomnia (excessive motor activity and abnormal behavior intruding during sleep) most commonly noted in neurologic illnesses is REM sleep behavior disorder (RBD). This is characterized by intense motor activity related to dream-enacting behavior and absence of muscle atonia during REM sleep (see Chaps. 49 and 50). It has been suggested that in the setting of degenerative dementia or parkinsonism, RBD is a manifestation of evolving synucleinopathies (e.g., Parkinson's disease [PD], MSA, and diffuse Lewy body disease [DLBD] with dementia) but is rare in tauopathies (e.g., Alzheimer's disease [AD]) [105, 108]. Patients with RBD generally do not complain of EDS, and the multiple sleep latency test (MSLT) rarely documents increased somnolence. There is potential for injury to self and others in patients with RBD, and therefore, early recognition and treatment are very important. Circadian sleep-wake rhythm disturbances are noted in some neurologic disorders; most prominently, AD may present as a cyclic agitation syndrome [110]. An excessive amount of nocturnal motor activity may be related to the primary neurologic disease (e.g., dystonia in patients with torsion dystonia and nocturnal frontal lobe epilepsy).

Clinical Manifestations

The clinical manifestations of sleep and breathing disorders in chronic neurologic illnesses may be divided into specific and general features [87, 91]. The specific manifestations depend on the nature of the neurologic deficit. The general features that are relevant to the diagnosis of sleep-related hypoventilation and apnea include EDS, fatigue, early morning headache, unexplained pedal edema, disturbed nocturnal sleep, intellectual deterioration, personality changes, and, in men, impotence. Breathlessness is generally not an important feature of CNS disorders except those illnesses that affect the lower motor neurons to the respiratory muscles. The general symptoms of daytime fatigue, somnolence, and morning headache may be related to frequent arousals at night secondary to repeated apnea or hypopnea and carbon dioxide retention [108]. In patients with neurologic disorders, it is very important to recognize alveolar hypoventilation during sleep because assisted ventilation at night improves the symptoms and protects patients from fatal apnea during

sleep. Furthermore, such treatment may prevent the development of serious complications resulting from episodic or prolonged hypoxemia, hypercapnia, and respiratory acidosis in sleep, complications that may include pulmonary hypertension, cor pulmonale, congestive cardiac failure, and occasionally cardiac arrhythmias. Occasionally, neurologic disorders may cause an inversion of the sleep-wake rhythm that is manifested by excessive somnolence during the day and insomnia with agitation during the night [103, 108–110].

To make a clinical diagnosis of sleep disorders or sleep-related breathing disorders (SRBDs), a careful history—from the patient and the caregiver—and a physical examination are essential.

Mechanisms of Sleep Disturbances

Neurologic disorders can be metabolic or structural (e.g., head injury, tumor, infection, toxic-metabolic brain dysfunction, vascular and degenerative CNS disease, headache from any cause, painful peripheral neuropathy, or other neuromuscular disorder). The following are the suggested mechanisms of the sleep disturbances associated with neurologic disorders [87, 91, 105, 108]:

1. Direct involvement of the hypnogenic neurons. Hypofunction of the hypothalamic VLPO neurons or the lower brain stem hypnogenic neurons in the region of the NTS and dysfunction of the thalamus may alter the balance between the waking and the sleeping brain, causing wakefulness or sleeplessness. Similarly, a disorder of the posterior hypothalamic, ARAS, or other brain regions responsible for waking and alertness causes hypersomnolence.
2. Indirect mechanisms associated with the disorder, such as pain, confusional episodes, changes in the sensorimotor system, and movement disorders, can interfere with sleep.
3. Medications used to treat neurologic illnesses (e.g., anticonvulsants, antidepressants, dopamine agonists, anticholinergics, hypnotics, and sedatives) may have a direct effect on sleep and breathing.
4. Neurologic diseases (e.g., hyperkinetic movement disorders and Rett syndrome) may change the neurochemical environment of the sleep-generating and sleep-promoting neurons [107].
5. Comorbid depression or anxiety in neurologic illnesses may disrupt sleep.
6. Certain neurologic disorders may alter circadian rhythm in the suprachiasmatic nuclei (e.g., dementia, PD, and traumatic brain injury), causing insomnia.
7. Finally, neurologic disorders may cause sleep-disordered breathing (e.g., MSA, DLBD, and other neurodegenerative and neuromuscular disorders), resulting in sleep fragmentation and insomnia, and sleep apnea syndrome.

Sleep and Breathing Disturbances in Central Nervous System Disorders

Alzheimer's Disease and Related Dementias

Dementia is characterized by progressive deterioration of memory and cognition (as assessed by mental status and neuropsychologic testing), followed by language dysfunction, hallucinations, other psychotic features, depression, and sleep disturbances. In the advanced stage of the illness, the patient becomes bedridden, mute, and incontinent. Sleep dysfunction with or without abnormal motor activity during sleep is increasingly recognized in patients with irreversible chronic dementing illness. It has been estimated that approximately 10 % of the adult population over the age of 65 years suffer from some kind of dementing illness. The Delphi study in 2005 [111] estimated that there would be 24.3 million people with dementia in the world in 2001, and this was predicted to rise to 81.1 million by 2040. The same panel of experts in a systematic review and metanalysis in 2013 [112] estimated that 35.6 million people lived with dementia worldwide in 2010 with numbers expected to rise to 115.4 million in 2050. However, the Rotterdam study findings published in 2012 [113] provide an optimistic trend that the age-specific dementia incidence has declined between 1990 and 2005 as the population has lived progressively longer, probably as a result of increased use of treatment to minimize vascular risk factors and increased years of education. This observation was reinforced by recent report of robust evidence provided by Satizabal et al. [114] of declining incidence of dementia over three decades in the Framingham Heart Study participants. AD is the most common cause of chronic dementia, accounting for at least 60 % of all cases. Other conditions include DLBD, accounting for at least 15–20 % of the cases; PD with dementia and frontotemporal dementia (FTD) in about 10 %; and corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), multi-infarct or vascular dementia, Huntington's disease (HD), Creutzfeldt–Jakob disease (CJD), and FFI (described later in the chapter), accounting for the rest of the cases.

Dementia can be classified according to location or according to molecular neurobiologic abnormalities (Box 41.1). In terms of location, dementia is classified into cortical dementia, consisting of AD, FTD, and vascular dementia; subcortical dementia, consisting of PD with dementia, PSP, and HD; and mixed cortical-subcortical dementia, including DLBD, CBD, CJD, and FFI. Most of the degenerative dementing illnesses are proteinopathies due to excessive protein misfolding and intracellular protein aggregation [108]. They are mainly classified into tauopathies, synucleinopathies, prion diseases, and polyglutamine disease. Tau proteins belong to the family of microtubule-associated proteins involved in maintaining the cell shape and serve as tracts for axon transport. The main tauopathies include AD, PSP, CBD, argyrophilic grain disease,

Pick's disease, and FTD with parkinsonism associated with chromosome 17. Alpha-synuclein is a presynaptic protein that helps transport dopamine-laden vessels from the cell body to the synaptic cleft. Synucleinopathies are a group of disorders with abnormal deposition of α-synuclein in the cytoplasm of neurons or glial cells and extracellular deposits of amyloid. The main synucleinopathies include PD, DLBD, and MSA, including Shy–Drager syndrome, striatonigral degeneration, and sporadic olivopontocerebellar atrophy.

Box 41.1 Classification of Dementia

According to Location

Cortical dementia

- Alzheimer's disease,
- Frontotemporal dementia,
- Vascular dementia.

Subcortical dementia

- Parkinson's disease,
- Progressive supranuclear palsy,
- Huntington's disease.

Mixed cortical-subcortical dementia

- Diffuse Lewy body disease,
- Corticobasal degeneration,
- Creutzfeldt–Jakob disease,
- Fatal familial insomnia.

According To Molecular Neurobiology

- Tauopathies
- Alzheimer's disease,
- Frontotemporal dementia,
- Progressive supranuclear palsy,
- Corticobasal degeneration.

Synucleinopathies

- Diffuse Lewy body disease,
- Parkinson's disease,
- Multiple system atrophy (Shy–Drager syndrome).

Prion diseases

- Fatal familial insomnia,
- Creutzfeldt–Jakob disease,
- Polyglutamine disorder,
- Huntington's disease.

Types of Sleep Disturbances in Dementia

The major sleep disturbances in dementing illness include insomnia, hypersomnia, circadian sleep-wake rhythm disorders, excessive nocturnal motor activity, "sundowning," and respiratory dysrhythmias. Circadian sleep-wake rhythm disturbances are noted, most prominently in AD, and may present as a cyclic agitation syndrome that is popularly known as sundowning syndrome. Commonly encountered excessive nocturnal motor activity that may occasionally cause sleep disturbance to the patient but very often causes sleep disturbance to the bed partner includes periodic limb movements in sleep (PLMS), which may be noted in many dementing illnesses. Respiratory dysrhythmias and loud snoring (see further on) during sleep occur in some of these conditions, particularly in AD, PD, and DLBD.

Sleep Dysfunction in Alzheimer's Disease

Diagnostic criteria for AD

AD or Alzheimer's dementia is characterized by progressive intellectual deterioration occurring in middle or later life associated with characteristic neuropathologic findings, including cerebral cortical atrophy and neuronal loss in the nucleus basalis of Meynert. There are also alterations in the forebrain cholinergic and noradrenergic systems [109]. Sleep disturbances in AD may be related partly to the severity of the loss of the cholinergic neurons in the basal forebrain regions, as well as to changes in the brain stem aminergic systems. Since the introduction of the criteria for clinical diagnosis of AD developed by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Diseases Association (NINCDS-ADRDA) work group in 1984 [115], there have been significant advances in the development of reliable biomarkers for AD based on structural magnetic resonance imaging (MRI), molecular neuroimaging with positron-emission tomography (PET), and cerebrospinal fluid (CSF) analysis. Based on these advances, in 2011 the National Institute on Aging and the Alzheimer's Association (NIA-AA) revised the criteria for diagnosing AD (Table 41.1) [116–119]. In the revised criteria, the terminology was changed to Alzheimer's dementia rather than Alzheimer's disease. A diagnosis of dementia requires deficits in two of the following five features: episodic memory, executive function, visuospatial performance, language, and personality/behavior including activities of daily living (ADL) [117–119]. The new diagnostic criteria recognize that AD exists along a continuum and include three categories: preclinical (stages 1, 2, 3), mild cognitive impairment (MCI) due to AD, and AD dementia (probable, possible, unlikely). The biomarkers in the revised criteria include markers for amyloid (e.g., cerebrospinal fluid [CSF], low amyloid-β [A β 42], and abnormal amyloid PET imaging) and neuronal injury (e.g., increased levels of CSF tau protein and

Table 41.1 The NIA-AA revised criteria for the clinical diagnosis of Alzheimer's disease (AD) spectrum (modified from Refs. [120–122])

Category	Subcategory	Symptoms/Signs	Biomarkers
Preclinical	Stage 1	Asymptomatic	Amyloid beta (Aβ) (CSF or PET scan)
	Stage 2	Asymptomatic	Aβ + neuronal injury
	Stage 3	Asymptomatic	Aβ + neuronal injury
Mild cognitive impairment	Intermediate likelihood of conversion to AD	Impaired episodic memory	Aβ + neuronal injury
	High likelihood	Other cognitive impairment	Aβ + neuronal injury
	Unlikely	Mild functional impairment	Biomarker negative
AD dementia	Probable	Amnestic; impaired learning	Aβ + neuronal injury
		Nonamnestic executive dysfunction	Aβ + neuronal injury
	Possible	Meets clinical criteria for dementia	Aβ + neuronal injury
	Unlikely due to AD	Meets clinical criteria for typical or atypical AD dementia	Biomarkers negative

hippocampal atrophy on structural magnetic resonance imaging [MRI] or bilateral parietal hypometabolism on PET scan). The NIA-AA criteria incorporated many of the criteria proposed by the International Work Group (IWG) initially devised in 2007 and later revised in 2010 (Box 41.2) [116–119]. The IWG criteria recognize four diagnostic groups [119]: asymptomatic AD at risk stage showing positive biomarkers; preclinical early-onset AD with an autosomal dominant mutation (about 5 % of familial AD cases); prodromal AD with episodic memory loss and presence of a biomarker for AD; and AD dementia with impaired ADL (Table 41.1). In addition, diagnostic criteria have been established for non-AD dementias (e.g., FTD, DLBD with dementia, CBD, and vascular dementia). Many of these entities may fulfill the original NINCDS-ADRDA criteria, but the diagnostic accuracy of the original criteria ranges from 65 % to 96 %, and the specificity ranges from 23 % to 88 %. The new diagnostic criteria, however, need validation studies to optimize their sensitivity and specificity. Furthermore, current biomarkers have limitations (e.g., invasive or expensive). Recently, a group of investigators predicted phenoconversion of some elderly healthy individuals to mild cognitive impairment (MCI) or AD based on lower plasma levels of a set of plasma phospholipids [120]. Confirmation and replication of these findings will simplify preclinical diagnosis of AD and will stimulate research to prevent or halt the progression of the disease.

Box 41.2 International Work Group (IWG) Criteria for the Clinical Diagnosis of Alzheimer's Disease (AD)

Adapted from Dubois et al. [116].

Probable AD Criteria

Category A and one or more supportive features in B, C, D, or E

Core Diagnostic Criteria

(A) Presence of an early and significant episodic memory impairment with gradual and progressive alteration in memory function over the previous 6 months or more associated with the objective evidence of impaired episodic memory.

Supportive Features

(B) Presence of medial temporal lobe atrophy on MRI.
(C) Abnormal cerebrospinal fluid biomarker with low amyloid-β (1-42) concentrations with increased tau concentrations.
(D) Specific pattern on functional neuroimaging with PET showing reduced glucose metabolism in temporal parietal regions bilaterally.
(E) Proven AD autosomal dominant mutation within the immediate family.

Sleep dysfunction in AD

Sleep dysfunction in AD may occur even in the early stage but is more common and severe in advanced stages. In addition to sundowning, these patients often sleep early in the evening, waking up frequently and staying awake most of the night. Their sleep is fragmented and fractionated throughout a 24-h period. The patients remain somnolent most of the time and bedridden in the advanced stages of the illness.

Sleep dysfunction in AD is very common and includes insomnia and sleep apnea syndrome with sleep fragmentation, hypersomnia related to intrinsic disease process, comorbid medical or psychiatric disorders or ingestion of medications, circadian rhythm sleep disorders including inversion of sleep rhythm and "sun downing," excessive

nocturnal motor activity including occasional REM behavior disorder (Box 41.3).

Box 41.3 Summary of Sleep Dysfunction in Alzheimer's Disease

- May occur in the early stage,
- More common and severe in advanced stages,
- Sleep onset in the early evening; waking up frequently or staying awake most of the night,
- Sleep architectural changes, including decreased sleep efficiency, reduced slow-wave sleep with eventual disappearance as the disease advances, increased awakenings after sleep onset, and reduced REM sleep in later stages,
- "Sundowning,"
- Fragmented and fractionated sleep throughout the 24-hour period with increased daytime napping,
- Sleep apnea: 33–53 %; more with *APOE4* allele, possibly also with MAO-A 4 repeat allele,
- Visual hallucinations with nocturnal agitations.
- In advanced stage, somnolent most of the time.

Sleep disorders in AD may increase cognitive and behavioral dysfunction. Such sleep disorders may arise directly from the disease itself, as a consequence of the degeneration of the brain stem and other centers that regulate sleep [31, 109], or indirectly from changes in sleep associated with aging (see Chap. 51) and comorbid conditions or medications (see Chap. 47). Sleep disorders can have a number of undesirable consequences, including increasing cardiovascular and even cerebrovascular morbidity as well as impairing daytime alertness and functioning [91, 105, 108].

A number of studies have examined the differences between demented patients and normal elderly individuals and have demonstrated higher prevalence of sleep apnea and poorer sleep quality when patients are compared to age-matched controls [121–131]. Although the results vary somewhat from study to study, these investigations have shown deterioration of sleep parameters, including reduced total length of sleep, decreased REM and slow-wave sleep, loss of phasic components (spindles and K complexes) of NREM sleep, and sleep-wake rhythm disturbances, in demented patients. Montplaisir et al. [128] documented EEG slowing during both wakefulness and REM sleep in AD patients. The authors suggested that degeneration of the nucleus basalis of Meynert, which is the main source of cholinergic input to the cerebral cortex, may be responsible for EEG slowing and REM sleep changes. This pattern of disorder is different from that of depressed elderly patients, who most clearly show poor sleep maintenance, often with increased REM sleep [128]. Most of the studies, however, have not used current diagnostic criteria for dementia and have lumped together patients with different forms of it. When more accurate diagnostic groupings were made, similar results were found for AD patients, usually defined by clinical course. Some studies have shown a clear association between greater sleep disturbance and impaired mental functioning or severity of dementia [132–136].

Some of the inconsistencies noted in the sleep architecture in AD patients may be related to the fact that in many studies, mild, moderate, and severe AD patients were grouped together and not necessarily analyzed separately. Another point to remember is that it is often difficult to separate the effects of the disease on sleep from the effects of medication, PLMS or sleep apneas, which are common in elderly patients. Additionally, sleep architectural alterations noted during overnight laboratory sleep studies may be partly environmentally determined, as AD patients may become confused, displaying features of sundowning, in the artificial and foreign environment of the laboratory.

Vitiello et al. [133, 134] and others [123, 124, 135–138] reported sleep disturbances in AD associated with a decrease in slow-wave sleep and an increase in nighttime awakenings. In a study of 45 control subjects and 44 mild AD patients, Vitiello's group [139] confirmed their previous findings of disturbed sleep-wake patterns in AD patients, but the phenomenon of sleep disturbances was not diagnostically useful for discriminating between those with a mild stage of AD and control subjects.

A meta-analysis by Benca et al. [132] clearly showed significant sleep disturbances in dementia. Reduced sleep efficiency, increased stage 1 NREM sleep, and increased number of awakenings are some of the prominent findings noted in the various studies [127, 128, 131–144]. In some studies, there is a relationship between the severity of sleep disturbance and the severity of dementia [139]. Contradictory findings have been noted regarding decrement of slow-wave sleep. Reduction of sleep spindles is noted by Prinz et al. [135] as well as by Montplaisir et al. [145]. REM sleep abnormalities have given inconsistent results (decreased in some studies [131, 139] but not in others [142]), and this discrepancy may have been related to the degree of severity of dementia. It should be kept in mind that more severe sleep disturbances have been noted in depression than in dementia, and sometimes differentiating these two conditions, particularly in the early stage of AD, may be difficult. Other sleep architectural changes in AD include sleep-wake cycle [145] and sleep rhythm [146, 147] and disturbances and alterations in physiologic delta waves [148]. These sleep quality changes may cause EDS [148, 149].

Sleep may be disturbed early in the disease process, and sleep disturbances are noted even in the presence of mild cognitive impairment [139, 150–153]. It has been recently shown that sleep loss may even precede AD symptoms by

many years similar to CSF biomarkers [154–156]. It has been suggested that sleep disturbances and cognitive dysfunction are positively correlated in AD—that is, sleep disturbances increase with severity of disease process [157]. Disruption in sleep-wake patterns, circadian rhythmicity, increased amount and frequency of nighttime wakefulness, and reduction of slow-wave sleep occur at the early stages of AD and worsen with disease progression. In later stages of AD, there is a reduction of REM sleep, increased REM latency, and alteration of the circadian rhythm resulting in daytime sleepiness. The daytime sleep, however, consists essentially of NREM stages 1 and 2 and does not compensate effectively for the loss of slow-wave sleep and REM sleep. Thus, daytime napping and somnolence increase as the disease progresses.

The phenomenon of sundowning is noted in many AD patients, contributing to sleep disturbance. Sundowning can be described as cyclic nocturnal agitation syndrome [110, 151–153] with inversion of sleep schedule (wakefulness at night and somnolence in the daytime). It is a predictor of faster cognitive decline [157], is most likely related to the severity of dementia, and remains a common cause of institutionalization in AD patients. Factors such as going to bed early, increased use of sedatives, advanced cognitive impairment, associated medical conditions, and circadian rhythm disturbances may all contribute to sundowning. Circadian rhythm disturbances are frequently seen and pronounced in AD [110, 152, 153, 158–163]. It has been suggested that an alteration in the biologic clock in the SCN and the pineal gland is considered to be the biologic basis for the circadian rhythm disturbances in AD. Wu and Swaab [158] found disruption of pineal melatonin secretion and pineal clock gene oscillations in AD patients. They noted even in the earliest AD stage a functional disruption of the SCN as manifested by decreased vasopressin RNA, a clock-controlled major output of the SCN. The functional disconnection between the SCN and the pineal gland noted in the earliest stage of AD seems to account for the pineal clock gene and melatonin changes accounting for the circadian rhythm disturbances in AD. They also noted decreased melatonin MT_1 receptor in the SCN in late-stage AD patients and therefore suggested that in the advanced stages of AD, supplementary treatment with melatonin may not improve the circadian rhythm disturbances. Wu and Swaab [159] previously suggested that circadian disorders, such as sleep-wake cycle disturbances, associated with aging and advanced stages of AD causing disruptive melatonin production and rhythms may result from presumed degeneration of the retina-SCN-pineal axis. They further suggested that reactivation of the circadian system (retina-SCN-pineal pathway) by the use of light therapy and melatonin supplementation to restore the circadian rhythm and relieve clinical circadian disturbances has shown promising results.

However, there are contradictory reports [160, 161]. Dowling et al. [160] tested the effectiveness of time to bright-light therapy given in the morning and early afternoon in 70 institutionalized patients with AD and controls. They did not find any significant differences in actigraphy-based measures of nighttime sleep or daytime wakefulness between the groups. They therefore concluded that one hour of bright-light treatment in patients with AD in the morning or early afternoon did not improve nighttime sleep or daytime wakefulness compared to the control group. In another study, Dowling et al. [161] tested the effect of morning bright-light therapy in 46 AD subjects fulfilling the NINCDS-ADRDA criteria in two nursing home facilities in California. They gave one hour of bright-light exposure (≥2500 lx) to the experimental group and gave usual indoor light (150–200 lx) to the control group. By means of actigraphy, they assessed nighttime sleep efficiency, total sleep time, and number of awakenings. They also determined circadian rhythm parameters from the actigraphy data using core cosinor analysis and nonparametric techniques. They concluded that morning bright-light exposure did not induce an overall improvement in measures of sleep or rest activity in all treated patients compared to control subjects. However, they found that only subjects with the most impaired rest activity rhythm responded significantly and positively to a bright (one hour) light therapy. However, in a more recent study using randomized controlled trial, McCurry et al. [164] found that walking, light exposure, and combination are effective in improving sleep in community-dwelling AD patients. Singer et al. [162] conducted a multicenter, placebo-controlled trial of melatonin for sleep disturbance in 157 individuals with AD recruited by 36 AD centers. They measured nocturnal total sleep time, sleep efficiency, wake time after sleep onset, and day-night sleep ratio during a 2- to 3-week baseline and 2 months of treatment with melatonin. The sleep measures were obtained from the actigraphic data. They did not find any statistically significant differences in objective sleep measures between baseline and treatment for any of the group. Therefore, they concluded that melatonin is not an effective agent for treating sleep disturbances in patients with AD. This observation by Singer et al. [162] agrees with more recent conclusion based on a review of randomized controlled trials by McClury et al. [165] that there is no evidence of benefit from melatonin treatment in AD patients. The results of these studies, therefore, contradict the earlier findings of Mishima et al. [163] of altered melatonin secretion rhythms in patients with AD having disturbed sleep-wake patterns.

Sleep apnea has been observed in approximately 33–53 % of demented patients with probable AD [131, 133, 152, 153, 166–173] (Fig. 41.14). Although sleep apnea may be associated with disease severity, no longitudinal studies have been conducted to determine whether sleep apnea increases the severity of disease in individual patients and whether sleep apnea may be associated with more rapid progression of the disease. Such a deleterious effect of sleep apnea is to be expected, as it is thought to increase the intellectual deficit of demented patients [128, 129]. Because

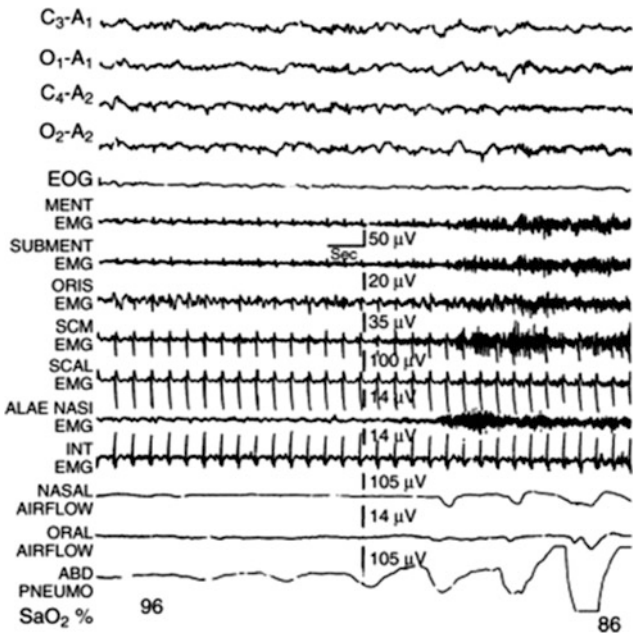

Fig. 41.14 Polysomnographic recording of a patient in an advanced stage of Alzheimer's disease shows a portion of mixed apnea during stage 2 NREM sleep accompanied by oxygen desaturation. Top four channels represent the electroencephalogram (EEG) (Key: international electrode placement system). Electromyograms (EMG) of mentalis (MENT), submental (SUBMENT), orbicularis (ORIS), sternocleidomastoid (SCM), scalenus anticus (SCAL), alae nasi, and intercostal (INT) muscles are shown. Also shown are nasal and oral airflow, abdominal pneumogram (ABD PNEUMO), and oxygen saturation ($SaO_{2\ \%}$). (EOG = electrooculogram.) Reproduced with the permission from Chokroverty [91]

sleep apnea may be treated by a number of modalities, it is possible that therapy may improve behavior and cognitive function. According to Smallwood et al. [131], the incidence of sleep apnea in male AD patients is similar to that in healthy elderly subjects. Reynolds et al. [167] reported a higher prevalence of sleep apnea in female AD patients during the later stage of the illness than in controls. These findings have been confirmed by Mant et al. [168]. The prevalence of sleep apnea is found to vary (70–80 % having an apnea-hypopnea index [AHI] of 5 or more and 38–48 % with an AHI of 20 or more in institutionalized demented patients) [174, 175]. However, in mild-to-moderate AD, the prevalence with AHI of 10 or more is up to 53 % of patients [176]. Bliwise [169] pointed out the high prevalence of comorbid cardiovascular, cerebrovascular, and pulmonary disease in the elderly population in the nursing home and outpatient memory clinics. These disorders may have played a causal role for sleep apnea and dementia. A key genotypic marker of AD is the apolipoprotein E4 (*APOE4*) allele. In recent years, the demonstration of an association between *APOE4*-genotype AD and sleep apnea has kindled interest in the possible association between sleep apnea and AD [169–173]. Gehrman et al. [172] suggested sleep apnea or sleep-disordered breathing (SDB) may be related to agitation in AD. These authors recorded sleep for one night and measured agitation with behavioral observations and ratings by nursing staff in 38 patients (29 women, 9 men) in a nursing home population. They found that SDB was very prevalent in this sample and was related to some types of agitation during the day but not in the evening and night. They further suggested that treatment of SDB may decrease agitation in these patients. In a later study by this group [173] utilizing 66 patients with mild-to-moderate AD in a home polysomnographic (PSG) study, the authors observed that the patients with SDB spent less time in REM sleep than those with no SDB, but they did not find any differences in other sleep stages. They concluded that decreased REM sleep may be due to the presence of SDB in AD. They further speculated that treating these patients' SDB may increase their amount of REM sleep, which may result in improved daytime functioning. Chong et al. [177] randomly assigned 39 community-dwelling elderly patients with mild-to-moderate probable AD with SDB to receive 6 weeks of therapy with continuous positive airway pressure (CPAP) titration or 3 weeks of sham CPAP followed by 3 weeks of therapeutic CPAP. They measured Epworth Sleepiness Scale (ESS) scores at baseline, 3 weeks, and 6 weeks to measure the changes in daytime sleepiness. Their results of reduction of ESS scores after therapeutic but not sham CPAP treatment supported the effectiveness of CPAP in reducing subjective daytime sleepiness in AD patients with SDB. Does CPAP slow cognitive decline in patients with comorbid Alzheimer diseases and sleep apnea? Preliminary studies support improvement or slowing of the progression of cognitive impairment as well as quality of sleep and architecture in AD patients [176, 178–181] although there are limitations [176, 182].

Ancoli-Israel et al. [176] studied 52 men and women with mild-to-moderate AD and OSA who were randomized to either therapeutic CPAP for six weeks or placebo CPAP for three weeks followed by therapeutic CPAP for three weeks in a double-blind placebo-controlled trial. The neuropsychologic test battery showed improvement in some of the cognitive functioning. The same group in a subsequent exploratory study [180] involving 10 patients with mild-to-moderate AD (five patients using CPAP for a mean of 13.3 months and five patients who discontinued CPAP use after the initial six-week randomized clinical trial of CPAP) showed less cognitive decline (based on a neuropsychologic test battery and sleep/mood questionnaires) in the group with sustained CPAP use. Recently, Troussiere et al. [181] in a single-blind, proof-of-concept trial involving 23 patients with mild-to-moderate AD and severe sleep apnea showed that those on CPAP (14 patients) had significantly slower decline in cognitive function over a three-year follow-up period. All these preliminary studies are encouraging but because of many limitations [176, 178, 182] (e.g., small sample size, too short a period of treatment exposure, selection bias, self-reported CPAP use, and failure

to adequately consider comorbid medical disorders), there is a need for a prospective randomized controlled trial including larger number of patients and a longer follow-up period.

Pseudodementia in elderly depressed patients presents a frequent diagnostic dilemma in differentiating depression from dementia of the Alzheimer's type. It has been noted that depressed elderly patients have shortened REM latency and increased REM density; in contrast, AD patients tend to have greater reduction in the amount of REM sleep and lower REM density [183, 184]. These findings, however, are not useful as a predictive indicator on a case-to-case basis.

Hallucinations may occur in AD patients but are noted much less frequently than in DLBD (see later). Sinforiania et al. [185] administered a sleep questionnaire in the presence of a caregiver to 280 patients in order to evaluate the relationship between hallucinations and sleep-wake cycle in patients with early-to-moderate AD. They noted hallucinations, mainly visual, in 12 % of the sample, and 69 % of the hallucinations occurred when the patient was awake. Vivid dreams were reported in 11 %, and violent sleep-related and dream-related behaviors (probable RBD episodes) were noted in 10 % of the subjects. The authors concluded that the higher occurrence of vivid dreams and RBD in AD patients with hallucinations compared with those without hallucinations indicates a potential role of disordered REM sleep in the occurrence of hallucinations in AD. It should be noted that in most of the reports, RBD has not been seen frequently in tauopathies such as AD. Although RBD is rare, REM sleep without atonia may be noted relatively frequently in patients with probable AD [186]. EDS is very common in AD, and in order to assess daytime sleep propensity in a cohort of patients with mild-to-moderate AD, Bonanni et al. [187] studied 20 drug-free AD patients meeting the NINCDS-ADRDA criteria for probable AD and a group of 12 healthy subjects free of dementia as controls. They used multiple sleep latency tests and overnight PSG recordings to evaluate daytime sleepiness. Their findings of significantly reduced daytime sleep latencies indicated an increased sleep propensity during the daytime in patients with mild-to-moderate AD. Park et al. [149] observed that AD patients with excessive daytime napping had more parkinsonian motor signs, suggesting that this subgroup may have an increased propensity for sleepiness resembling PD. The authors cautioned that longitudinal studies with objective measures are needed to determine whether a causal relationship exists between sleepiness and parkinsonism in AD.

The pathogenesis of sleep disturbances in AD is multifactorial, resulting from possible degeneration of neurons regulating sleep-wake cycles, SDB, and disruptive chronobiology. However, no longitudinal studies are currently available correlating sleep apnea with the severity or progression of the disease. Suprachiasmatic nuclei regulating circadian rhythm show degenerative loss of neurons in AD, which may explain inversion of rhythm in many patients. Other factors include normal age-related physiologic changes in sleep, medication effects, increased prevalence of PLMS causing arousal and sleep fragmentation in the elderly AD patients, comorbid RLS, environmental factors (e.g., artificial environment of the institution, laboratory, and nursing homes), and comorbid medical disorders (e.g., congestive cardiac failure, chronic obstructive pulmonary disease, pain from arthritis, nocturia, gastroesophageal reflux disease) or depression. Finally, there may be a genetically increased risk of sleep disruption in AD. Craig et al. [188] surveyed 426 AD patients diagnosed according to standard criteria and performed genotyping of APOE. They found that increased susceptibility to sleep disturbance is associated with genetic variation at the enzyme monoamine oxidase A.

In summary, it is known that sleep dysfunction is common in AD. It is unclear, however, whether a specific set of sleep abnormalities will be found to be associated with AD that are different from those observed in other dementias. Reynolds et al. [124] suggested that sleep dysfunction in AD may be related to the progression of the disease and may cause ongoing deterioration of the alertness, orientation, and cognitive function. Box 41.3 summarizes the sleep dysfunction in AD.

Dementia with Diffuse Lewy Body Disease

DLBD is a neurodegenerative disease characterized by onset of dementia (impaired executive function) within 12 months of onset of motor symptoms of parkinsonism such as akinesia or bradykinesia, postural instability, and rigidity without the characteristic parkinsonian tremor, associated with visuospatial dysfunction, recurrent visual hallucinations, fluctuating cognitive function, and hypersensitivity to neuroleptics. The clinical features of DLBD may be divided into three groups: core, suggestive, and additional features [189]. A recent international consortium on DLBD has resulted in revised criteria [190] for the clinical and pathologic diagnosis, incorporating new information about the core clinical features and improved measures for their assessment. The core features are typically cortical and subcortical cognitive impairment with worse visuospatial and executive dysfunction than AD [189]. In the early stage, the memory dysfunction may be relatively spared. Other core features include recurrent visual hallucinations, parkinsonism, and fluctuating attention. Suggestive features consist of RBD, severe neuroleptic sensitivity, and low dopamine transporter uptake in the basal ganglia on functional neuroimaging. Additional features supporting the diagnosis but occurring less commonly include repeated falls and syncope, transient loss of consciousness, severe

autonomic dysfunction, systematized delusions, olfactory and tactile hallucinations, depression, neuroimaging finding of relative preservation of medial temporal lobe structures, reduced occipital activity in functional neuroimaging, EEG slowing, and myocardial scintigraphy showing low uptake [189]. The pathologic criteria include the presence of Lewy bodies in limbic, paralimbic, and neocortical regions in addition to the midbrain substantia nigra, LC, and raphe nuclei. Senile plaques are present in the majority of individuals with DLBD, although neurofibrillary tangles are typically absent.

Studies inquiring about sleep disturbance in DLBD are few given its clinical overlap with AD and PD. Sleep disturbances in DLBD are very common and more prominent than in AD patients. The significant sleep disturbances in DLBD consist of insomnia, daytime hypersomnolence, RBD, sleep apnea, and nocturnal visual hallucinations. Presti et al. [191] in a recent postmortem examination of brains from DLBD patients observed that medullary respiratory neurons involved in respiratory rhythmogenesis and chemosensitivity are affected (decreased neuronal densities by immunocytochemical staining) in DLBD patients accounting for SDB [108, 191] including central apnea and sudden death during sleep and decreased ventilatory response [192] in these patients. Grace et al. [193] made a comparative study of sleep profiles in patients with DLBD and AD. They reported more overall sleep disturbances, more movement disorders in sleep, and more abnormal daytime sleepiness in DLBD patients in comparison with AD patients. RBD is very common in DLBD (present in 50–80 % of DLBD patients) and sometimes may be the initial presentation without other core diagnostic features [194–199]. Boeve and colleagues in a series of studies [40, 200–203] suggested that RBD is a manifestation of an underlying α-synucleinopathy (e.g., PD, DLBD, and MSA) and may be a forerunner or precursor of the disease. Neuropathologic studies by Uchiyama et al. [204] and Boeve et al. [197–203] supported the conclusion that idiopathic RBD may be a preclinical sign of DLBD. Disturbance of the circadian rhythm has been noted and is a potential factor underlying the nocturnal sleep fragmentation and daytime sleepiness in many AD and DLBD patients. Harper et al. [205] studied circadian variation of core body temperature and motor activity in a total of 32 institutionalized patients with probable AD by NINCDS-ADRDA criteria, nine of whom also met pathologic criteria for DLBD and in eight elderly male controls. They noted that patients with a postmortem diagnosis of DLBD manifested greater disturbances of locomotor activity circadian rhythms than patients with AD, which may reflect the greater sleep disturbances seen in this population. Bauman et al. [206] reported EDS with normal CSF hypocretin in 10 DLBD patients.

Sleep Disturbances in Frontotemporal Dementia

FTD is a type of cortical dementia and a tauopathy resembling AD, but there are many features differentiating these two entities. Sleep disturbances are noted in many FTD patients but have not been adequately characterized. The clinical features of FTD include core and supportive features [207]. Core features include insidious onset and progression, early loss of insight, social decline, personal conduct, and emotional blunting with relative preservation of perception, praxis, and memory. Supportive features include perseveration, hyperorality, impersistence, mental inflexibility, decline in personal hygiene, and altered speech and language dysfunction such as echolalia, mutism, reduced speech output, and lack of spontaneity in speech. Physical findings may include akinesia, rigidity, and appearance of primitive reflexes. Laboratory tests may include normal EEG, and neuropsychologic tests show frontal lobe impairment. Computed tomography (CT) and MRI of the brain may show frontal or temporal lobe atrophy.

In a retrospective review of the clinical records, Seeley et al. [208] studied the natural history of the temporal variant of FTD and divided FTD into three stages according to the progression of symptoms. Stage 1 is characterized by either semantic loss characterized by anomia with word-finding difficulties and repetitive speech or an early behavioral syndrome characterized by emotional distance, irritability, and disruption of sleep, appetite, and libido. In stage 2, appearing on an average after 3 years, patients have both semantic and behavioral syndromes. In stage 3, generally 5–7 years after onset, in addition to the above features, patients now have disinhibition, compulsions, impaired face recognition, altered food preference, and weight gain. The authors concluded that the temporal variant of FTD follows a characteristic cognitive and behavioral progression, suggesting early spread from one anterior temporal lobe to the other, and the latest symptoms implicate ventromedial frontal, insular, and inferoposterior temporal regions. However, they caution that precise anatomic correlates need to be confirmed. Liu et al. [209] compared the behavioral features in the frontal and temporal variants of FTD and performed volumetric measurements of the frontal, anterior temporal, and ventromedial frontal cortex and the amygdala in 51 patients with FTD and 20 normal controls as well as 22 patients with AD serving as dementia controls. They found that the group with the frontal variant of FTD showed more anxiety, apathy, and eating disorders, and the group with the temporal variant of FTD showed a higher prevalence of sleep disturbances, than patients with AD. The behavior between the two variants may be differentiated: There is greater apathy in the frontal variant and more sleep disturbances in the temporal variant of FTD. In 13 patients with FTD, actigraphic data suggested possible phase delay [210].

Some patients with FTD may have sleep-wake cycle abnormalities early in the course associated with sleep fragmentation and possible advanced sleep phase syndrome [211]. Coban et el [212] observed reduced orexin A plasma levels in cases of FTD possibly explaining EDS in these patients. Although RBD is rare in tauopathies, Lo Coco et al. [213] described a case of RBD (clinically and polysomnographically) in a case of FTD.

Sleep Dysfunction in Corticobasal Degeneration (CBD)

Corticobasal degeneration (CBD) is a rare tauopathy presenting with an atypical parkinsonian dementia syndrome characterized by asymmetric or unilateral rigidity, action or stimulus-sensitive myoclonus, apraxia, asymmetric or unilateral cortical sensory loss, and alien limb phenomenon, in which the patient cannot recognize his own affected limb, which may be performing apparently purposeful movements not intended by the patient. The pathologic hallmarks include large achromatic neurons and gliosis distributed asymmetrically in discrete frontal or parietal cortical and subcortical regions affected in PSP. Isolated case reports of sleep dysfunction such as insomnia, sleep-related respiratory disorders, PLMS, and RBD or REM without atonia are available [214–217].

Stroke and Sleep-Wake Disorders

Stroke is an acute neurologic deficit resulting from vascular injury to the brain and is the third leading cause of death and disability worldwide. Stroke is responsible for half of all acute neurologic hospital admissions in the USA [218]. Vascular injury could be ischemic (thrombotic or embolic) or hemorrhagic. In this section, we first describe sleep and breathing disorders as well as other sleep-wake dysfunction in cerebral hemispheric and thalamic strokes followed later by those resulting from brain stem stroke.

There are a few scattered reports of sleep complaints after stroke and several reports of SDB after cerebral infarction, but there is a dearth of well-controlled studies of the relationship between sleep disorders and cerebral vascular diseases [218]. Such studies are important from prognostic and therapeutic points of view.

Hemispheric Stroke

Sleep apnea or SDB and stroke

Sleep disruption and sleep complaints resulting from sleep-related breathing dysrhythmias have been reported in many patients with cerebral hemispheric stroke. Sleep apnea, snoring, and stroke are intimately related. Sleep apnea may predispose to stroke, and stroke may predispose to sleep apnea. There is increasing evidence based on case-control, epidemiologic, and laboratory studies that snoring and sleep apnea are risk factors for stroke. Confounding variables that are common risk factors for snoring, sleep apnea, and stroke (e.g., hypertension, cardiac disease, age, body mass index [BMI], smoking, and alcohol consumption) should be considered when attempting to establish relationships among snoring, sleep apnea, and stroke. A history of habitual snoring (established through questionnaire studies and interviews with a bed partner or other family members) is a clear risk factor for stroke. There is an increased frequency of sleep apnea in both infratentorial and supratentorial strokes. Sleep apnea may adversely affect the short-term and long-term outcomes in patients with stroke in terms of both morbidity and mortality. It is important to make the diagnosis of sleep apnea in stroke patients, as there is effective treatment for sleep apnea that can decrease the risk of future stroke.

Case-control and epidemiologic studies have established an association between hypertension and habitual snoring [219–222] and between habitual snoring and stroke [223–227]. The prospective study by Koskenvuo et al. [222], adjusting for other risk factors, found that habitual snorers have a significantly increased risk of new stroke or ischemic heart disease. Neau et al. [228] also found a significantly increased adjusted risk of stroke in habitual snorers. Spriggs et al. [229] found that in addition to increasing the risk for stroke, snoring adversely affected the prognosis after a stroke. In a prospective study, Bassetti et al. [230] used PSG to determine the frequency of habitual snoring and sleep apnea in 36 of 59 subjects within 12 days of acute hemispheric stroke or transient ischemic attack (TIA) and in 19 age- and sex-matched controls. Habitual snoring was reported in 58 % of patients with TIA or stroke, in addition to an increased frequency of sleep apnea in patients with TIA and acute stroke.

There is considerable evidence based on several recent large epidemiologic and many case-control studies showing an independent association between obstructive sleep apnea syndrome (OSAS) and stroke. Sleep apnea has been found in up to 72 % of patients with stroke. The pathogenesis is not clearly known, and most likely is multifactorial, involving sympathetic nervous system hyperactivity, activation of inflammatory molecular pathways, endothelial dysfunction, metabolic dysregulation, abnormal coagulation, dyslipidemia, and insulin resistance [231]. There are several well-established risk factors for the development of stroke, including arterial hypertension, cardiac disease, diabetes mellitus, smoking, and dyslipidemia. Although the evidence of association between OSAS and stroke is strong based on

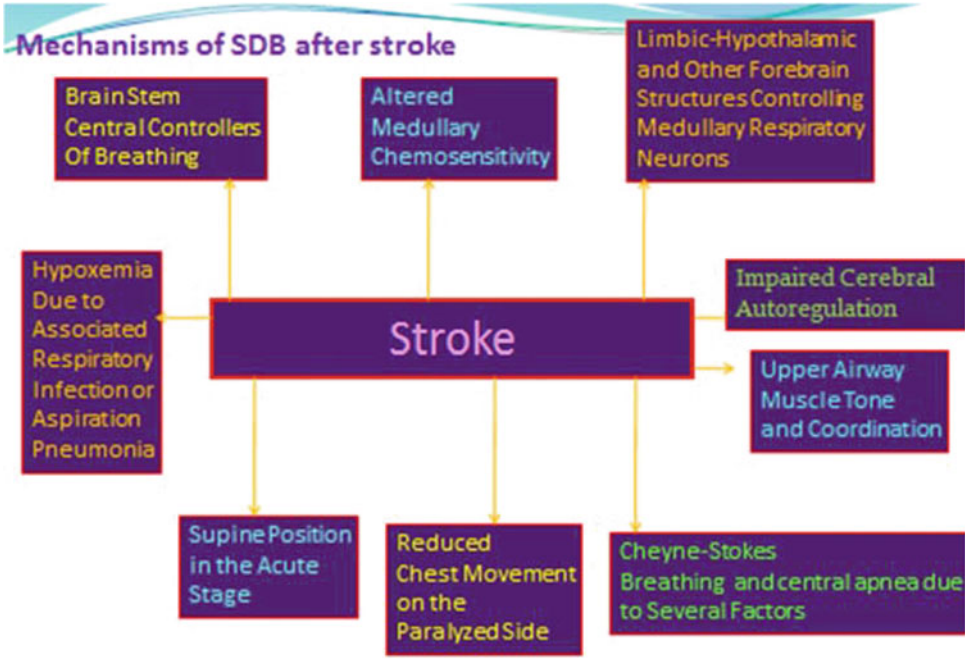

Fig. 41.15 Mechanisms of SDB after stroke

mainly cross-sectional, case-control, and some limited longitudinal studies, large-scale collaborative studies including patients with OSA controlled adequately for potential confounders are needed to evaluate the relationship between OSAS and stroke and the potential interactions between different basic mechanisms (Fig. 41.15). The Sleep Heart Health Study [232] is a cross-sectional study including a sample of 6424 individuals who underwent unattended overnight PSG at home. Sleep apnea was significantly associated with the development of stroke, coronary artery disease, and congestive cardiac failure independent of known cardiovascular risk factors.

As part of the Sleep Heart Health Study in a later report, Redline et al. [233] followed 5422 community-based subjects without stroke for a median of 8.7 years and reported in 2010 that 193 developed ischemic stroke with a significant positive association with AHI in men. Stroke risk was estimated to increase by 6 % for each one-unit increase in AHI in men with mild-to-moderate sleep apnea.

A higher prevalence of OSA has also been shown in patients with TIAs compared with controls by Bassetti and Aldrich [234]. Cross-sectional studies, however, cannot make a definite conclusion about the cause-and-effect relationship, and therefore, prospective longitudinal studies are needed. A prospective cohort study of patients admitted for stroke or TIA by Parra et al. [235] demonstrated a higher prevalence of OSA than in the general population. However, this was contradicted in a small case-control study involving 86 patients with TIA matched for age and sex with controls that showed no significant difference in the severity or prevalence of OSAS between the two groups [236]. A study by Wierzbicka et al. [237] involving 43 patients found a high prevalence of sleep apnea in patients with acute stroke and TIA. The authors suggested that overnight screening for SDB should be routinely performed in every patient admitted with stroke or ischemic attack. Grigg-Damberger [238], in a review article, made a similar suggestion and noted that such screening and treatment for OSAS should be incorporated into stroke prevention programs.

In an important observational cohort study, Yaggi et al. [239] performed PSG in 1022 consecutive patients enrolled in the study and verified subsequent events such as strokes and deaths. Proportional hazards analysis was used to determine the independent effect of OSAS on the composite outcome of stroke or death. At baseline, 697 patients (68 %) had a mean AHI of 35 as compared with 2 in controls. After a median follow-up period of 3.4 years, the OSAS syndrome was associated with stroke or death from any cause with a hazard ratio of 2.24. After adjusting for age, sex, smoking habits, alcohol consumption, BMI, and the presence or absence of diabetes mellitus, hyperlipidemia, atrial fibrillation, and hypertension, OSAS retained its statistically significant association with stroke or death with a hazard ratio of 1.97. The authors concluded that OSAS significantly increases the risk of stroke or death from any cause and the increase is independent of other risk factors. Several other studies confirmed an independent association between OSAS and stroke [240–244]. Harbison et al. [240] performed a prospective, uncontrolled observational study at week 2 and a repeat study in 50 patients at weeks 6–9 following stroke-utilizing sleep studies, modified ranking score, Barthel score, Scandinavian Neurological Stroke Scale, and

ESS score. They concluded that SDB improved in the first 6–9 weeks following stroke but remained highly prevalent. They made a surprising observation of the presence of SDB in patients with lacunar stroke. Marin et al. [241] did an observational study to compare the incidence of fatal and nonfatal cardiovascular events, including stroke, in simple snorers. They included patients with untreated OSAS, patients treated with CPAP titration, and healthy men recruited from the general population. The subjects were followed up at least once a year for a minimum of 10.1 years, and CPAP adherence was checked with a built-in meter. The study included 264 healthy men, 377 simple snorers, 403 patients with untreated mild-to-moderate OSAS, 235 with untreated severe disease, and 372 with the disease who were treated with CPAP. They found that patients with untreated severe disease had a higher incidence of both fatal cardiovascular events (deaths from myocardial infarction or stroke) and nonfatal cardiovascular events than did untreated patients with mild-to-moderate disease, simple snorers, patients treated with CPAP, and healthy participants. The authors concluded that in men, severe OSAS significantly increased the risk of fatal and nonfatal cardiovascular events and CPAP treatment reduced this risk. Munoz et al. [242]. performed a prospective 6-year longitudinal population-based study in subjects aged 70–100 years. After adjustment for confounding factors, the authors confirmed that patients with severe OSAS at baseline had an increased risk of developing stroke independent of known confounding factors. Artz et al. [243] also demonstrated after a cross-sectional longitudinal analysis of subjects from the general population that there was a strong association between moderate-to-severe SDB and prevalence of stroke independent of the confounding factors. These authors also provided the first prospective evidence that SDB preceded stroke and may contribute to the development of stroke. In a prospective 10-year follow-up study, Sahlin et al. [244] obtained overnight sleep recordings at a mean of 23 days after the onset of stroke in 132 patients. They found that the risk of death was higher among the 23 patients with obstructive apnea (AHI $\geq$ 15) than controls (AHI < 15), with an adjusted hazard ratio of 1.76 independent of all the confounding factors. There was no difference in mortality between central sleep apnea (CSA) patients and controls.

Several early studies [245–247] evaluated the role of CPAP in the treatment of patients with OSAS and found significant protection against new vascular events after ischemic stroke. Bassetti et al. [247] found a beneficial effect of CPAP in a small percentage of patients. In contrast, after a randomized controlled trial of CPAP in patients with stroke with an AHI of 30 or more, Hsu et al. [248] found no benefit from CPAP treatment. These authors advocated that CPAP treatment should be used for patients with stroke only if there are symptoms of SDB. Similar to the findings of Bassetti et al. [247], Palombani and Guilleminault [249] found that the majority of stroke patients with OSAS rejected CPAP treatment, and they suggested that better education and support of patients and families, and special training sessions, will be needed to improve adherence in such patients.

Obstructive sleep apnea is the most common form of SDB in stroke victims, and the prevalence in stroke patients exceeds the figure quoted for the general population [218, 236, 250–266]. Bassetti et al. [254] suggested that the presence of OSA should be suspected in men and elderly patients with diabetes mellitus and nighttime onset of TIA or stroke. The increased prevalence of OSAS in patients with TIA and stroke suggests that OSAS does not commonly precede but rather follows the onset of cerebrovascular events [255, 256]. It is notable that acute stroke may aggravate preexisting SDB or even may cause it de novo [255]. Improvement of SDB often occurs in the recovery phase after stroke [254, 256].

Mansukhani et al. [260] from Mayo Clinic in a prospective cohort study included 174 consecutive patients with acute ischemic stroke. Using Berlin Sleep Questionnaire, they identified 105 patients (60.4 %) with a high risk for OSA and seven patients (4 %) with a previous diagnosis of OSA. They found that those with a previous diagnosis of OSA were more likely to die within the first month after stroke and had worse functional outcome. Such comorbid OSA and stroke causing poor functional outcome [252, 257, 261] and increased poststroke mortality [231, 234] had been observed by earlier investigators.

In an important meta-analysis of 29 articles (2343 patients), Johnson and Johnson [262] observed that the percentage of stroke and TIA patients with OSA is up to 72 % (with an AHI of 5 or more) and up to 63 % (with an AHI of 10 or more), and the type of apnea is primarily obstructive (only 7 % had central apnea). They also made the following important observations: Comorbid OSA and stroke are more common in men than women and in older than younger subjects; nocturia may be a predictor and recurrent stroke may be an indicator.

In a recent review of stroke and sleep apnea, Davis et al. [263] cautioned that we may be neglecting a modifiable stroke risk factor. They provide evidence that sleep apnea is an important but under-recognized risk factor for incident and recurrent stroke which may adversely affect stroke recovery and that CPAP titration improves functional outcome after stroke. The authors further state that several preliminary randomized trials of CPAP therapy after stroke suggest diagnosing OSA in stroke patients may be best accomplished with portable devices, but these are less sensitive and specific for the diagnosis of OSA than a formal in-laboratory polysomnography (PSG). Many preliminary randomized trials of CPAP therapy for SDB in stroke

patients have shown improvement in stroke scales, motor recovery, symptoms of sleepiness, and depression, but some randomized trials have shown no difference in outcome [249]. Despite inconsistencies, Davis et al. [263] made the following important conclusions regarding CPAP therapy for sleep apnea in stroke: Increased CPAP adherence improves stroke recovery, but adherence remains a problem because of advancing age, severity of stroke causing facial paralysis, dysphasia, and impaired cognition [249, 254, 263–267]. However, better selection, patient education, and early CPAP treatment during hospitalization or as soon as the patient can tolerate may improve increasing adherence and treatment benefit.

In addition to OSA, patients with stroke may have central sleep apnea (CSA), including central periodic breathing and CSB Figure (Fig. 41.16) [268–272]. CSA and CSB may persist in 6–29 % of stroke patients and may adversely affect the recovery [252]. Nopmaneejumrusler et al. [272] suggested that in patients with stroke, CSA and Cheyne–Stokes respirations are associated with hypocapnia and occult left ventricular systolic dysfunction but are not related to the location or type of stroke. Hermann et al. [271] found central periodic breathing during sleep in 3 of 31 patients with first-ever stroke in the absence of cardiopulmonary dysfunction. They assessed the patients using PSG, MRI of the brain, and echocardiography. They concluded that central periodic breathing during sleep may be present in strokes involving the autonomic (insular) and volitional (cingulate and thalamus) respiratory networks and that breathing improved in all patients during stroke recovery. Bonnin-Vilaplana et al. [268] described CSB in patients with first-ever lacunar stroke. In a recent retrospective analysis of adaptive servoventilation (ASV) treatment for persistent CSA in postacute ischemic stroke patients without concomitant congestive cardiac failure, Brill et al. [269] observed that ASV was well tolerated and clinically effective in these patients.

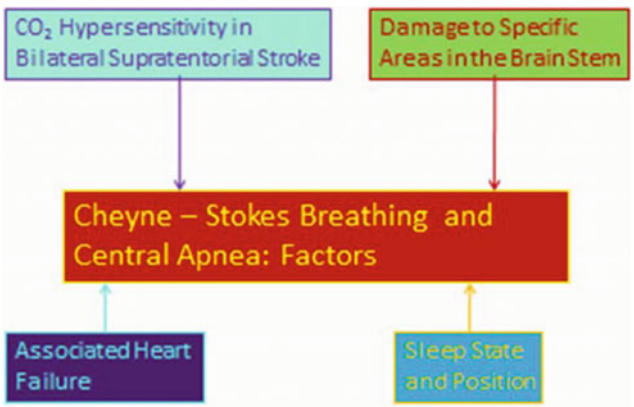

Fig. 41.16 Cheyne–Stokes breathing and central apnea: factors

Some studies have addressed circadian variations of stroke onset. In a study of 53 stroke patients, Kapen et al. [273] confirmed their previous reports of prevalence for the onset of stroke in the morning during a 6-hour period after awakening from sleep. This is similar to the peak incidence in the morning hours for myocardial infarction and sudden cardiac death. All of these conditions may be aggravated by a combination of circadian increase of corticosteroids and catecholamines, increased blood pressure and heart rate in the morning, and increased platelet "aggregability." (Normal subjects exhibit increased platelet aggregability in the early morning [274]. In several other studies, the incidence of stroke was highest during sleep at night [275] or during early morning hours after awakening from nocturnal sleep [276, 277]. In order to investigate circadian variations in situations at stroke onset, Omama et al. [278] analyzed 12,957 cases of first-ever stroke onset diagnosed from the Iowa Stroke Registry between 1991 and 1996 by CT or MRI of the brain. They noted that patients who had cerebral infarctions showed a bimodal pattern with a higher peak in the morning and a lower peak in the afternoon, whereas intracerebral hemorrhage and subarachnoid hemorrhage patients had the same bimodal pattern but with a lower peak in the morning and a higher peak in the afternoon. The authors concluded that sleep tends to promote ischemic stroke and suppresses hemorrhagic stroke. Another study from Japan [279] found that intracerebral hemorrhage during the sleep period may be more detrimental compared with the intracerebral hemorrhage during awake periods, causing larger hematoma and higher mortality rates.

Brain Stem Vascular Lesions

Brain stem vascular lesions include infarction, hemorrhage, arterial compression, and localized brain stem ischemia. Sleep disturbances have been described in brain stem infarction by Markand and Dyken [280] and several other authors [19, 21, 281, 282]. Polysomnographic findings generally consisted of increased wakefulness after sleep onset and decreased REM and slow-wave sleep. Several reports of EEG or PSG studies to document sleep disturbances have been described in patients with locked-in syndrome, which is characterized by quadriplegia associated with de-efferentation and results from ventral pontine infarction. Patients are generally aware of their surroundings and are conscious. They cannot speak because of facial muscle paralysis but can respond by moving the eyes, whose control is spared. Sleep EEG recordings of locked-in syndrome patients have been reported by Feldman [283], Freemon et al. [284], Markand and Dyken [280], Cummings and Greenberg [285], Oxenberg et al. [286], and Nordgren et al. [287]. The EEG findings in these reports generally

showed reduced or absent REM sleep and variable changes in NREM sleep, including reduction of slow-wave sleep and total sleep time. Oxenberg's group [286], however, described only minor alterations in the initial recording in contrast to the more marked alterations noted in the other reports. The authors thought that the difference could be related to the extent of the lesion. Feldman [283] found in his patient reduced REM, stage 4 NREM, and total sleep time. Markand and Dyken [280] noted in five of seven locked-in syndrome patients the total absence of REM sleep and variable changes in NREM sleep. Cummings and Greenberg [285] described one patient who had reduced slow-wave sleep and another with reduced NREM sleep and no REM sleep. Autret et al. [288] also found a reduction of REM and NREM sleep in four patients after medial pontine tegmental stroke.

The term, *Ondine's curse,* or the *syndrome of primary failure of automatic respiration,* was coined by Severinghaus and Mitchell [289] to describe three patients who experienced long periods of apnea even when awake but could breathe on command. They became apneic after surgery involving the brain stem and high cervical spinal cord and required artificial ventilation while asleep. When their consciousness was altered by nitrous oxide or thiopental, they became apneic. Carbon dioxide response to breathing showed low sensitivity. One patient died in apnea, and the two others improved in one week. The authors suggested that Ondine's curse resulted from damage to the medullary carbon dioxide chemoreceptors. It is notable that the term *Ondine's curse* was derived from the sea nymph in German mythology, whose curse rendered her unfaithful lover incapable of automatic respiratory function and caused his death. This eponymic syndrome generated considerable controversy and confusion [290]. The syndrome of Ondine's curse is usually caused by bilateral lesions anywhere caudal to the fifth cranial nerve in the pons down to the upper cervical spinal cord in the ventrolateral region. Levin and Margolis [282] described a 52-year-old man with unilateral medullary infarction, however, who lost automatic respiratory control. At autopsy, the lesion was found to extend from the left lower pons through the left lateral medullary tegmentum to the upper cervical spinal cord and to involve the left paramedian PRF. Thus, in some patients, automatic respiratory control can reside unilaterally in the pontomedullary tegmentum.

A case of inverse Ondine's curse syndrome in a patient with selective paralysis of voluntary respiration but preservation of automatic respiration was described by Munschauer et al. [291]. This was a 36-year-old man with sudden onset of quadriparesis and bulbar dysfunction in whom MRI demonstrated a well-demarcated lesion restricted to the ventral basilaris pontis. His hypercapnic ventilatory response and breathing during sleep were normal. Emotional stimuli producing laughter, crying, or anxiety appropriately modulated automatic respiration, but the patient could not voluntarily modify any respiratory parameters. The findings in this case suggested that descending limbic influences on automatic respiration are anatomically and functionally independent of the voluntary respiratory systems.

Bogousslavsky et al. [292] reported a clinical pathologic correlation in two patients who had central hypoventilation and unilateral infarct in the caudal brain stem. The authors suggested that unilateral involvement of the pontomedullary reticular formation and nucleus ambiguus is sufficient for generating a loss of automatic respiration, whereas associated lesion of the NTS may lead to more severe respiratory failure involving both automatic and voluntary responses [292].

Respiratory rate and pattern were studied by Lee et al. [19] by impedance pneumography in 14 patients with acute brain stem or cerebral infarction, and in a subsequent study, they reported on another 23 patients with acute brain stem infarction [21]. They found frequent abnormalities of respiratory pattern and rate in such patients, and these abnormalities became worse during sleep. The abnormal pattern included CSB and Cheyne–Stokes variant types of breathing, in addition to tachypnea and cluster breathing in some patients. In contrast to the observations of Plum et al. [11–13, 293] that such breathing patterns are associated with bilateral cerebral hemispheric and diencephalic lesions but rarely with lesions in the upper pons, Lee's group [21] observed Cheyne–Stokes respirations in patients with extensive bilateral pontine lesions. They suggested that the size and the bilaterality of the lesions determined the types of respiratory pattern abnormalities.

Devereaux et al. [281] reported sleep apnea that required ventilatory support in two women who breathed normally while awake. Aged 36 and 59 years, they had bilateral infarctions limited to the lateral medullary tegmentum. In one of these patients, the carbon dioxide response was markedly depressed. Although the authors stated that acute automatic respiratory failure did not generally evolve into a chronic alveolar hypoventilation syndrome, their second patient continued to have sleep-induced apnea after many months.

Sleep apnea after bulbar stroke was also described by Askenasy and Goldhammer [294]. Their patient had a left-sided Wallenberg syndrome (lateral medullary syndrome), and 2 nights' PSG recordings documented mostly obstructive or mixed apneas and hypopneas. This was a clinical diagnosis, and neuroimaging did not define the exact anatomy of the lesion. Their report, however, should direct attention to the possibility that unilateral brain stem lesions can cause sleep apnea syndrome. In such patients, it is important to diagnose and promptly treat ventilatory dysfunction during sleep.

Lassman and Mayer [295] described a 70-year-old woman with right lateral medullary infarction who developed recurrent episodes of life-threatening central

hypoventilation requiring diaphragm pacing with a phrenic nerve pacemaker and nocturnal mechanical ventilation via a tracheostomy.

Diencephalic Stroke

Freund [296] should probably be credited with the first report of patients with hypersomnolence following paramedian thalamic strokes. Thalamic stroke may cause ipsilateral loss of sleep spindles [297], and bilateral paramedian thalamic infarcts may be associated with hypersomnia [298, 299]. Bassetti et al. [299] evaluated 12 patients with MRI-proven isolated paramedian thalamic stroke and hypersomnia. The patients were evenly divided between groups of severe and mild hypersomnia. Nocturnal PSG findings included increased stage 1 NREM sleep, reduced stage 2 NREM sleep, and a reduced number of sleep spindles. Bassetti et al. [299], however, found intact REM sleep as well as circadian, ultradian, and homeostatic sleep regulation in their patients. The authors concluded that hypersomnia after paramedian thalamic stroke is accompanied by deficient arousal during the day and insufficient spindling and slow-wave sleep production at night. Their observation supported the hypothesis of a dual role of the paramedian thalamus for the maintenance of sleep-wake regulation.

In contrast, Guilleminault et al. [300] reported three patients with pseudohypersomnia and presleep behavior with bilateral paramedian thalamic lesions. These authors used long-term monitoring with an infrared video camera and polygraphic study to document that their patients did not develop the normal NREM cycling during the day; rather, the EEG indicated a mixture of low-amplitude theta and alpha frequency waves during the day, with "sleep-like behavior." The patients exhibited the behavioral aspects of sleep during the day, suggesting to Guilleminault et al. [300] that these subjects did not present hypersomnia but a "de-arousal" and were left in the transition between wakefulness and sleep. These authors [300] cited a report by Catsman-Berrevoets and von Harskamp [301] of a similar patient with compulsive presleep behavior and apathy due to bilateral thalamic stroke who responded to bromocriptine. There are a few other scattered cases reported of hypersomnolence following bilateral paramedian thalamic infarct [302–306]. Scammell et al. [307] described a narcolepsy-like syndrome with low CSF hypocretin-1 in a 23-year-old man after diencephalic stroke following the removal of a craniopharyngioma. Similar syndrome has been described by Castaigne et al. [298] after paramedian thalamic and midbrain infarcts.

Other Sleep-Wake Disorders in Stroke

Stroke may predispose to a number of other sleep disorders. Kleine–Levin syndrome can occur after multiple cerebral infarction [308]. Narcolepsy-cataplexy has been reported to follow cerebral hypoxia-ischemia [309].

Insomnia is commonly noted after cerebral infarction, but this may be partly due to the depression that typically follows stroke [310]. Bassetti and Hermann [264] reported an increased prevalence of sleep-wake disturbances in at least 20–40 % of stroke patients, mainly in the form of increased sleep need (hypersomnia), EDS, or insomnia. They listed several factors contributing to sleep-wake disorders in such patients, including depression, anxiety, SDB, complications resulting from stroke (e.g. nocturia, dysphagia, and urinary or respiratory infections), and medications. In another study by Palomaki et al. [311], the authors concluded that insomnia is a common complaint after ischemic stroke.

Total dream loss (Charcot–Wilbrand syndrome) after acute bilateral infarction of the deep occipital lobe as well as after parietal and deep frontal infarcts has been described by Bischof and Bassetti [312] and Solms [313].

Sleep architectural changes involving NREM and REM sleep have also been noted after cerebral hemispheric stroke [314–317].

There are a few scattered reports of cases of RBD and REM without atonia [318–320] after pontine stroke and rare cases of RLS/WED after lenticulostriate [321], lacunar [322], thalamic [323], and other subcortical and cortical stroke [324, 325].

Basal Ganglia Disorders

Sleep disturbances and sleep-related respiratory dysrhythmias are noted in many patients with basal ganglia disorders, but a systematic study to evaluate such dysfunction has not been undertaken in a large number of patients. A review of sleep and movement disorders is provided in Chap. 39.

Disorders of the Cerebellum

Cerebellar influence on the sleep-wakefulness mechanism has been clearly demonstrated in experimental animal studies by showing a mild decrement of NREM and an increment of REM sleep in cerebellectomized cats [326]. The role of the cerebellum in the respiratory control mechanism in sleep, however, is not known.

Olivopontocerebellar atrophy (OPCA) defines chronic progressive hereditary (usually dominant, occasionally recessive, rarely sporadic) cerebellar degeneration manifested by cerebellar-parkinsonian or parkinsonian-cerebellar syndrome and associated with atrophy of the pontine nuclei and cerebellar cortex and degenerative lesions of the olivopontocerebellar regions [327, 328]. There have been a few reports on sleep disturbances and sleep-related respiratory

dysrhythmias in OPCA (for sporadic OPCA or multiple system atrophy [MSA], see further on).

Cerebellar role in sleep has also been demonstrated by showing changes in the sleep-wake cycle after lesions of the fastigial nucleus and middle cerebellar peduncle as well as EEG changes after electrical stimulation or suppression of cerebellar nuclei [329, 330]. Further evidence is shown by significantly increased activity in the cerebellum during slow-wave sleep following functional magnetic resonance imaging [331]. Brain stem neurons, which are known to be degenerated in OPCA [328], lie close to the hypnogenic [67] and respiratory neurons [82–85]. Thus, dysfunction of respiratory control, in parallel with the somatic structural dysfunction in OPCA, may be expected. The known morphologic changes of OPCA [328] are adequate to explain the sleep disturbances and sleep apnea in this condition. Several authors [332–336] described EEG sleep alterations in degenerative cerebellar atrophy. Reduced or absent REM sleep, reduced slow-wave sleep, and increased awakenings are the essential PSG findings. In several cases of OPCA, REM sleep without muscle atonia accompanied by the typical features of RBD has been described [336, 337]. Jouvet and Delorme [38] produced REM sleep without atonia in cats by bilateral pontine tegmental lesions. A similar lesion in OPCA may be also responsible for RBD in this condition. OPCA has also been associated with hyposomnia [338].

Sleep apnea has been described in several cases of OPCA [335, 338–340]. Patients with sporadic OPCA associated with prominent autonomic failure are now classified as having MSA or Shy–Drager syndrome (see Sect. "Sleep and Breathing Disorders in Autonomic Failure" later in this chapter). Chokroverty et al. [339] described five patients with OPCA and sleep apnea. PSG study showed repeated episodes of central, upper airway obstructive, and mixed apneas during sleep; the apneic episodes lasted from 10 to 62 s, and the apnea index was 30–55. Pure central apnea was noted in three patients, but all three types of apnea were seen in two, and most of the apneic episodes occurred during NREM sleep stage 2. Thus, these findings suggested central neuronal dysfunction in an area where respiratory and sleep-waking systems are closely interrelated, such as the NTS and the pontomedullary reticular formation. Salazar-Grueso and associates [335] described a 37-year-old man with a 19-year history of autosomal dominant OPCA and EDS whose PSG demonstrated episodes of mixed and central (predominantly central) sleep apnea and no sleep spindles or REM sleep. Trazodone treatment normalized the sleep architecture and reduced the apneic episodes.

Occasionally, sleep disturbances are associated with other types of cerebellar lesions, although systematic studies are lacking. Bergamasco et al. [341] made a polygraphic study of a 13-year-old girl with a diagnosis of dyssynergia cerebellaris myoclonica (Ramsay hunt syndrome). An all-night sleep study showed no REM sleep and increased slow-wave sleep. The EEG showed multiple spike-and-wave discharges accompanied by myoclonic generalized seizures. There are reports of sleep disturbances including RLS and RBD in spinocerebellar ataxia (SCA) type SCA1, SCA2, SCA3, as well as increased prevalence of SDB in Friedreich's ataxia [329].

Brain Stem Tumor

Brain stem glioma with automatic respiratory failure was mentioned by Plum [13]. Ito et al. [342] described two children with brain stem gliomas and sleep apnea. Brain stem tumor may cause disorganization of the tonic and phasic events of REM sleep, as described in a patient whose pontine tumor caused a marked decrease in the atonia of REM sleep [343]. Lee et al. [344] reported a 74-year-old woman with recurrent acoustic neuroma at the cerebellopontine angle presenting as central alveolar hypoventilation. The patient had shallow breathing during sleep and had hypersomnolence during the daytime. Arterial blood gases showed increased $Paco_2$ and decreased partial pressure of arterial oxygen (Pao_2). Tumor resection eliminated hypersomnolence and respiratory failure. A patient seen by the senior author with a medullary tumor that caused severe hypoventilation during sleep required tracheostomy (unpublished observation). The central apneic episodes in the same patient became prolonged when the tracheostomy tube was occluded.

Other Brain Stem and Diencephalic Lesions

The metabolic and autonomic respiratory neurons and the lower brain stem hypnogenic neurons are located in the medulla. These neurons are influenced by the supramedullary respiration-controlling inputs and hypothalamic preoptic nuclei, as well as by the peripheral afferent inputs to the respiratory centers (see Chap. 9). Therefore, sleep and respiratory disturbances should be common manifestations of lesions in the brain stem, and many such cases have been described. Such disorders have included brain stem vascular lesions, tumors, traumatic lesions, multiple sclerosis (MS), bulbar poliomyelitis and post-polio syndrome, brain stem encephalitis, motor neuron disease affecting the bulbar nuclei, syringobulbia-syringomyelia, and Arnold–Chiari malformation [91]. In addition, several cases in which brain stem and diencephalic lesions caused narcolepsy-like syndrome have been described [307, 345–350]. All the characteristic features of narcolepsy are not seen in the cases. The causes have included infarction [307], trauma, tumors (including third ventricle tumor) [345], and arteriovenous malformation invading the third ventricle and affecting the

hypothalamus [347], and some cases have been associated with MS [348–350].

Brain stem ischemic damage may also cause respiratory dysfunction. Beal et al. [351] described a 19-year-old man who had failure of automatic respiration and other signs of brain stem dysfunction after nearly drowning. He had sleep apneas, and PSG study confirmed the presence of CSAs. During wakefulness, his breathing was normal. Hypercapnic ventilatory response was markedly impaired, but hypoxic ventilatory response appeared to be normal. Autopsy findings 8 months later, after sudden death, documented marked bilateral neuron loss in the tractus solitarius, ambiguus, and retroambigualis nuclei. This most likely resulted from anoxia or ischemia.

Parenti et al. [352] described two patients aged 38 and 53 years with CSA who died during sleep. At autopsy, the authors described acute bilateral hypoxic lesions at the level of the solitary tract nuclei.

Traumatic Brain Injury and Sleep Dysfunction

Traumatic brain injury (TBI) is defined as "an alteration in brain function or other evidence of brain pathology caused by an external force" [353]. It includes concussion, contusion, laceration, hemorrhage, and cerebral edema. After a severe TBI, brain stem function is severely compromised and the patient becomes comatose. There have been many EEG studies in patients with coma, and some patients may demonstrate sleep patterns such as spindles and K complexes. Such patterns are designated as *spindle coma* [354]. It is often stated that the presence of EEG sleep patterns indicates a favorable prognosis [355], but this may not be necessarily true. On recovering from the coma during this stage of rehabilitation, many patients may have sleep-wake disturbances. However, there have been no adequate studies addressing the sleep-wake abnormalities in such patients. This is surprising, considering that one editorial labeled TBI a silent epidemic [356]. There is a dearth of studies addressing sleep-wake abnormalities after minor brain injuries that did not result in coma but caused a transient loss of consciousness. Many of these patients experience the so-called postconcussion syndrome, characterized by a variety of behavioral disturbances, headache, and sleep-wake abnormalities.

Traumatic brain injury is a public health challenge and a leading cause of death and disability according to the World Health Organization (WHO) [357, 358]. There is a high prevalence of sleep-wake (S-W) dysfunction in TBI including mild TBI adversely impacting recovery, rehabilitation, and outcome [359], but unfortunately S-W dysfunction is not routinely screened in such patients [360]. An important point to remember is that TBI may trigger post-traumatic stress disorder (PTSD) and depression as well as increased sensitivity to pain in such patients promoting and aggravating sleep dysfunction [359]. TBI may cause insomnia, sleep-disordered breathing (SDB), hypersomnolence not due to SDB, circadian rhythm sleep disorders (CRSD), parasomnias, and sleep-related movement disorders (Fig. 41.17). In the past 15 years, there has been an explosion of studies using both self-report and objective methods to characterize sleep dysfunction in TBI [358–381].

In a meta-analysis involving 21 studies including 1706 subjects with mild, moderate, and severe TBI, Mathias and Alvaro [359] reported that overall, 50 % of subjects had some form of sleep disturbance and 25–29 % had a specific sleep disorder (insomnia [29 %], hypersomnia [28 %], obstructive sleep apnea [25 %], PLMS [19 %], and post-traumatic narcolepsy [4 %]). These rates are significantly higher than those seen in the general population. The authors suggested routine screening for sleep dysfunction in TBI patients for optimal treatment and favorable outcome and recovery. Similar suggestion was made by Mollayeva et al. [360] in a later review. In a prospective longitudinal study in 51 consecutive TBI patients, Kempf et al. [371] showed that three years after TBI, two out of three patients had a significant S-W disturbance, particularly post-traumatic hypersomnia, and only 10 % of patients had insomnia.

Verma et al. [365] studied 60 TBI patients (40 % mild, 60 % moderate-to-severe; three months to two years post-trauma) from a sleep clinic and observed the following S-W disorders: sleep apnea (30 %), parasomnias (25 %) including REM sleep behavior disorder (RBD) or increased EMG tone during REM sleep (13 %), sleepwalking (8 %), nightmares (7 %), sleep paralysis (5 %), nocturnal enuresis (5 %), nocturnal eating disorder (3 %), and post-traumatic narcolepsy (3.3 %).

There are several studies investigating the frequency of sleep disorders in TBI patients with hypersomnia and insomnia. Baumann et al. [381] prospectively assessed CSF hypocretin-1 levels in 44 consecutive patients with acute TBI. They found abnormally lower hypocretin-1 levels in 95 % of patients with moderate-to-severe TBI compared with controls. Later on, this group of authors [382] enrolled 96 consecutive patients within the first 4 days after TBI, attempting to delineate the frequency and clinical characteristics of post-traumatic sleep-wake disorders. Six months later, they studied 65 of these patients using questionnaire, CT scan of the brain, CSF hypocretin-1 levels, overnight PSG, and MSLT and actigraphy. They found new-onset sleep-wake disorders following TBI in 72 % of these patients, objective EDS in the MSLT in 25 %, post-traumatic hypersomnia (increased sleep need of 2 or more hours within 24 h compared to the pre-TBI period) in 22 %, and insomnia in 5 %. They found low CSF

hypocretin-1 levels in 4 of 21 patients 6 months after TBI compared to 25 of 27 patients in the first few days after TBI. The patients with post-traumatic sleep-wake disorders also had impaired quality of life. The authors suggested that sleep-wake disturbances are common and involvement of the hypocretin system is possible in the pathophysiology of post-traumatic hypersomnia.

Castriotta et al. [383] evaluated 87 adult patients at least 3 months after TBI using overnight PSG, MSLT, ESS, and neuropsychologic testing. They found a high prevalence of sleep disorders (46 %) and of EDS (25 %) in subjects with TBI. Sleep dysfunction in these patients included a high prevalence of OSA (23 %), post-traumatic hypersomnia (11 %), post-traumatic narcolepsy (7 %), and PLMS (7 %). Ouellet and coinvestigators [384] evaluated 452 subjects aged 16 years and older with minor-to-severe TBI utilizing a questionnaire related to quality of sleep. They found overall insomnia symptoms in 50.2 % and diagnostic criteria for an insomnia syndrome in 29.4 %. Risk factors for insomnia included mild TBI and high levels of fatigue, depression, and pain. Ouellete and Morin [385] studied 14 patients with mild-to-severe TBI compared to 14 healthy good sleepers using a sleep diary and 2 nights of overnight PSG. The authors found a higher proportion of stage 1 sleep in the TBI participants than in controls, but the percentages of stage 2, slow-wave, and REM sleep did not differ between the two groups. TBI patients, however, had more awakenings lasting longer than 5 min and a shorter REM sleep latency. The authors concluded that these results were similar to those found in patients with either primary insomnia or insomnia comorbid with depression.

Schreiber et al. [386] observed alterations in both timing and sleep architecture in 26 adult patients with a past history of minor head trauma (no structural brain imaging findings). In contrast, Gosselin and investigators [387] observed only subjective complaints but no objective sleep architectural abnormalities in 10 athletes with a history of sport-related concussion within the past year compared with 11 nonconcussed athletes. In a subsequent investigation, this group [388] confirmed their previous observations of a lack of abnormal sleep macroarchitecture in mild TBI patients but observed an increase of EEG beta power which could be attributed to brain injury or other factors such as anxiety or pain.

Post-traumatic hypersomnia has been listed in the third edition of the International Classification of Sleep Disorders (ICSD-3) under the heading "Hypersomnia due to a medical disorder" [389]. Guilleminault et al. [390] evaluated 20 patients with post-traumatic hypersomnia using PSG and the MSLT. The causes were multiple, including cases secondary to sleep apnea syndrome. TBI may cause central and upper airway obstructive sleep apnea by inflicting functional or structural alterations of the brain stem respiratory control system. It is important to remember, however, that many patients may have sleep apnea syndrome before sustaining TBI.

EDS in adults with TBI was also reported prospectively in case series of subjects by Castriotta and Lai [391]. These investigators found a high prevalence of sleep apnea-hypopnea syndrome, PLMS, and post-traumatic hypersomnia as well as post-traumatic narcolepsy. Post-traumatic narcolepsy in mild-to-moderate head injury in nine patients was also reported by Lankford et al. [392] utilizing overnight PSG and MSLT.

Hypersomnia or increased sleep need per 24 hours is noted in TBI in association with EDS, by the group led by Baumann [364] who suggested the term pleiosomnia for the increased need for sleep following TBI indicating an increased pressure for sleep. In a recent review of 12 cases of recurrent hypersomnia following TBI, Billiard and Podesta [370] attributed two directly to TBI. Collen et al. [374] retrospectively studied 116 soldiers with combat-related TBI and reported EDS in 85.2 % of the participants. These combat veterans also had a high rate (90.5 %) of comorbid psychiatric disorder (e.g., PTSD, anxiety, and depression).

Okawa et al. [393] described disturbance of circadian rhythms in severely brain-damaged patients. Patten and Lauderdale [394] reported a case of delayed sleep phase syndrome in a 13-year-old boy after a minor head injury sustained in a motorcycle accident (5 min' loss of consciousness followed by headache and drowsiness without other objective neurologic findings). Quinto et al. [395] reported a case of a delayed sleep phase syndrome (DSPS) in a 48-year-old man after TBI. There is another report of post-traumatic DSPS in a 15-year-old girl treated successfully with 5 mg melatonin [396]. In a more recent study, Ayalon et al. [397], using actigraphy, salivary melatonin, oral temperature measurement, and PSG, evaluated 42 patients with mild TBI and found circadian rhythm sleep disorders (DSPS in eight, irregular sleep-wake pattern in seven) in 36 % (15 patients).

The pathophysiology of post-traumatic S-W dysfunction remains unclear but most likely results from a complex interaction of anatomic, physiologic, environmental, and psychologic (e.g., anxiety, depression, and maladaptive habits) factors, as well as neurotransmitters and neuromodulators including hypocretin levels and hormonal changes, circadian rhythms, age, pain, and genetic predisposition.

In summary, TBI of any severity (mild, moderate, severe) may cause a variety of sleep-wake disorders with a much higher prevalence than in general population, impacting on quality of life and final outcome of rehabilitative and other therapies (schematically shown in Fig. 41.17).

Demyelinating Lesion in the Brain Stem

Sleep disturbances are very common in MS and may be seen in over 50 % of patients [398–454]. Surprisingly, there is a

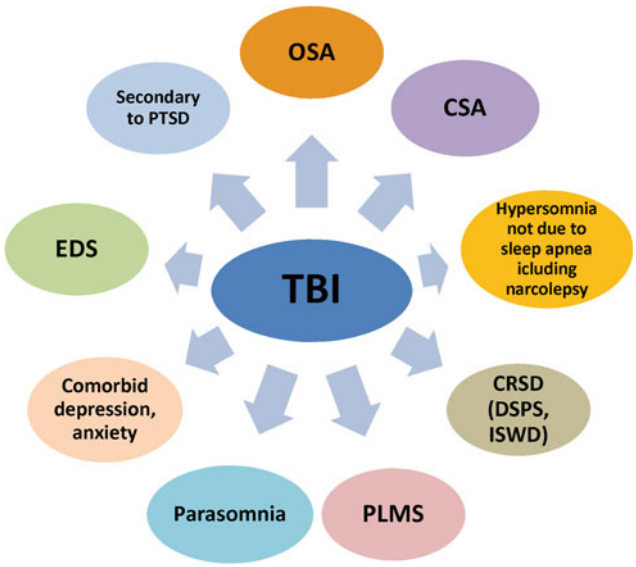

Fig. 41.17 Sleep dysfunction in traumatic brain injury TBI)

lack of adequate evaluation and characterization of such dysfunction in a systematic manner using subjective and objective measures in MS patients. Most MS patients suffer from an unexplained fatigue (see Chap. 42). An important reason for such fatigue may be an unsuspected sleep disorder, such as SDB or insufficient nocturnal sleep. Sleep disturbances in MS may include insomnia, hypersomnia, SDB, narcolepsy, restless legs syndrome (RLS)-PLMS, and RBD [398–454]. We do not know whether such sleep disturbances have an adverse impact on the natural history of MS (Fig. 41.18). Also, we have insufficient knowledge about the effects of treatment of MS with immunomodulating therapies on sleep-wake disturbances (see further on). It is not known whether sleep-wake disorder is related to the severity of the illness as there have not been adequate studies in a large number of MS patients complaining of sleep-wake disorder correlating with Kurtzke's expanded disability scale score.

Sleep-Disordered Breathing in MS

In individuals with MS, a demyelinating plaque may involve the hypnogenic and respiratory neurons in the brain stem, giving rise to sleep disturbance and SRBDs. A few such cases have been described in MS patients. An unusual patient, a 38-year-old man who had a clinical diagnosis of acute demyelinating lesion in the cervicomedullary junction, was described by Newsom Davis [398]. The patient had an autonomous breathing pattern, but he could neither take a voluntary breath nor stop breathing, thus illustrating the apparent independence of the mechanisms controlling metabolic and behavioral respiratory control systems. A patient reported by Rizvi et al. [399], whose brain stem dysfunction was consistent with MS, became apneic when asleep but was able to breathe when awake. His hypercapnic and hypoxic ventilatory responses were normal. Boor and associates [400] described a 40-year-old patient with paralysis of automatic respiration. During relaxation, the patient had recurrent apnea, but the breathing was stable when the patient was alert. The discovery at postmortem examination of a large, demyelinating lesion in the central medulla involving the medullary respiratory neurons explained the respiratory failure.

There are other reports of SDB [401–407] in MS, including failure of automatic respiration (Ondine's curse) [408] with sudden respiratory arrest and nocturnal death, CSA, hypoventilation, and paroxysmal hyperventilation. It is important to consider such a possibility when patients complain of EDS, fatigue, and disturbed sleep associated with snoring. Figures 41.19 and 41.20 show a sample of the hypnogram and overnight PSG recording from a 51-year-old woman with a history of MS showing frequent obstructive, mixed, and central apneas and hypopneas during both NREM and REM sleep associated with mild-to-moderate oxygen desaturation and frequent arousals, as well as REM sleep dysregulation with longer REM sleep in the early part of the night.

Fig. 41.18 Types of sleep dysfunction and factors: multiple sclerosis

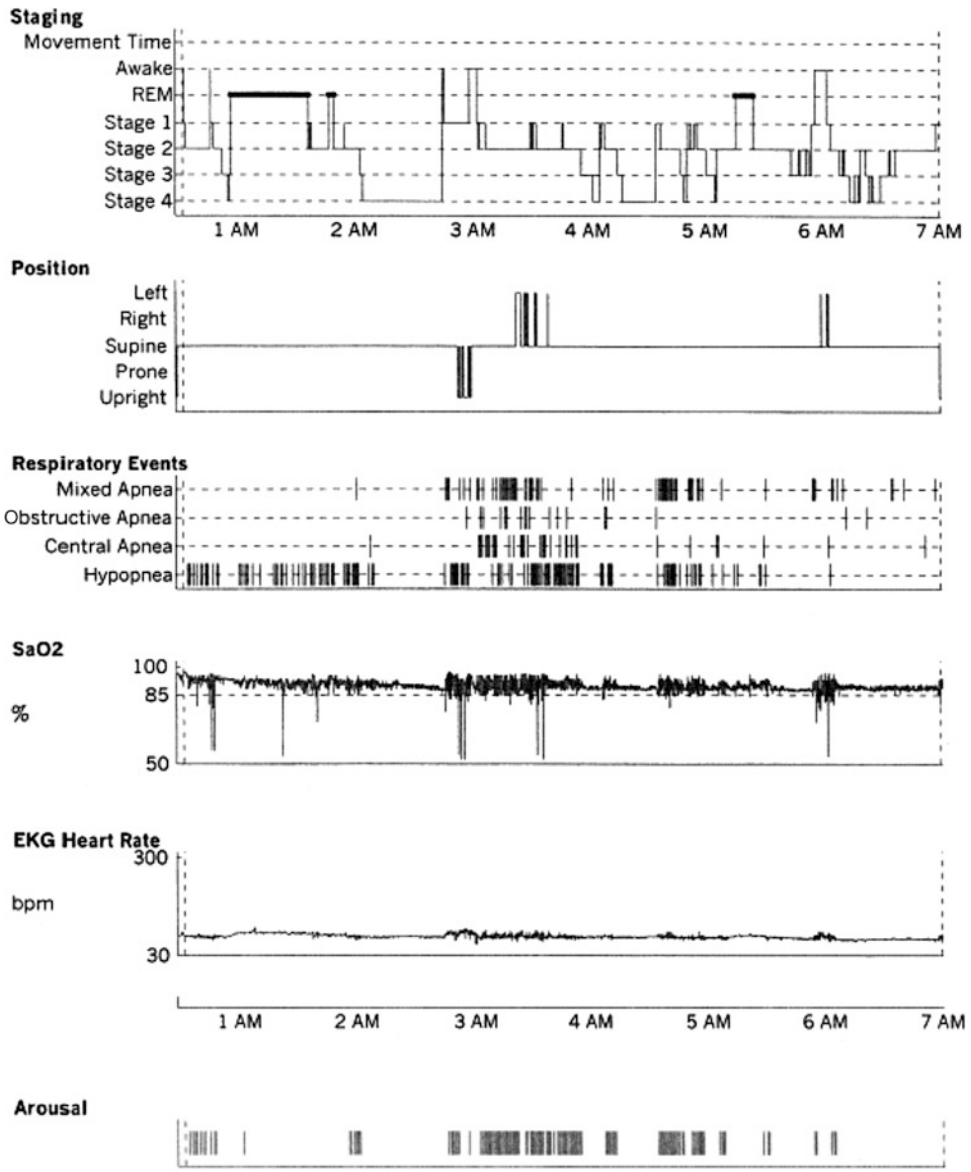

Fig. 41.19 A case of SDB in a 51-year-old woman with a history of multiple sclerosis diagnosed 7 years ago. Her sleep difficulties started approximately 3 years ago and are described as frequent night awakenings, sleepwalking, and brief episodes consisting of sudden sleepiness or impairment of consciousness resulting in falls and multiple fractures but never accompanied by jerky movements of the limbs, tongue biting, or incontinence, with spontaneous recovery in 5–10 min without residual confusion. These episodes occur during the early morning hours as well as during the day. Her neurologic examination is significant for the presence of decreased visual acuity and impaired saccades bilaterally, horizontal nystagmus on looking to the left, intention tremor (left more than right) on finger-to-nose testing, mild ataxia in the lower extremities on heel-to-shin testing, tandem ataxia, and impaired joint and position sense in the toes bilaterally. She was clinically evaluated with a differential diagnosis of SDB related to multiple sclerosis, narcolepsy-cataplexy secondary to multiple sclerosis, and sleepwalking. Unusual nocturnal seizures remained unlikely given the clinical features, the several negative electroencephalograms, and the negative long-term epilepsy monitoring. This hypnogram is significant for REM sleep distribution abnormality (the longest REM in the early part of the night); frequent, obstructive, mixed, and central apneas and hypopneas both during NREM and during REM sleep; mild-to-moderate O_2 desaturation; and frequent arousals. Sleep-related respiratory dysrhythmias due to brain stem involvement are a common finding in multiple sclerosis patients. Reproduced with the permission from Chokroverty et al. [455]

Insomnia in MS

In addition to sleep-related breathing abnormalities, other sleep difficulties have been commonly reported in MS patients, including insomnia and EDS [401, 402, 431–435, 440, 441]. Insomnia is the most common sleep problem in MS with an overall prevalence of more than 40 %. Tachibana et al. [431] evaluated 28 consecutive patients with MS,

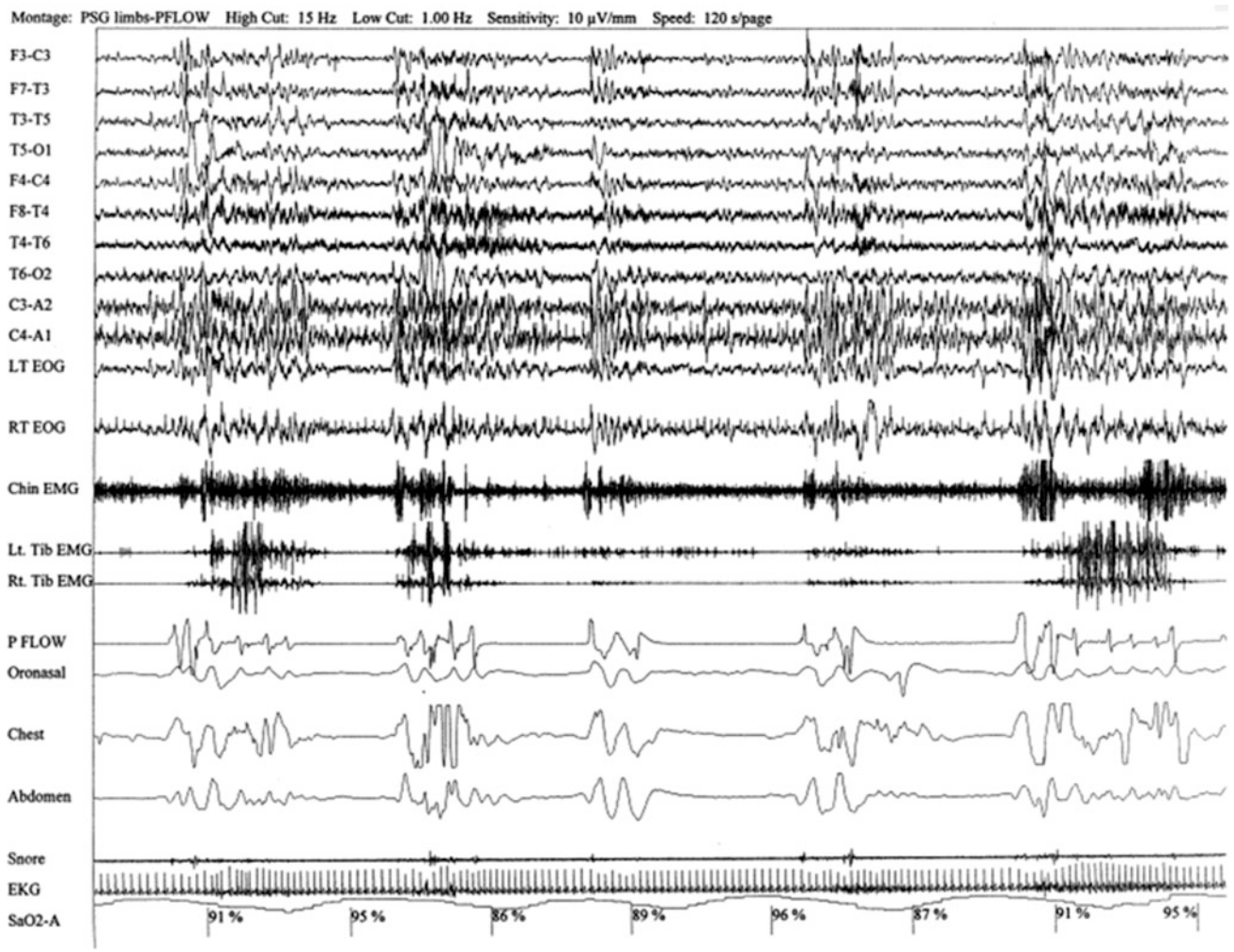

Fig. 41.20 A 120-s excerpt from an overnight polysomnographic recording (same patient as in Fig. 41.19) showing repeated central apneas with O_2 desaturation. An increase in muscle tone is noted on chin (chin EMG) and tibialis anterior (Tib.) electromyography (EMG) channels following some central events. Electroencephalogram (EEG): top 10 channels. *Lt.* left; *Rt.* right; *EOG* electrooculograms; *P Flow*, peak flow; oronasal thermistor; chest and abdomen effort channels; snore monitor; *EKG* electrocardiography; SaO_2, oxygen saturation by finger oximetry. Reproduced with the permission from Chokroverty et al. [455]

15 of whom had sleep problems that included difficulty initiating sleep, frequent awakenings, difficulty maintaining sleep, habitual snoring, and nocturia. All-night oximetric study showed sleep-related O_2 desaturation in three patients, two of whom had sleep apnea on PSG investigations. The authors concluded that sleep disturbance in MS is common but poorly recognized. Ferini-Strambi et al. [401] performed PSG studies in 25 MS patients and compared the results with 25 age- and sex-matched controls. They found reduced sleep efficiency with increased awakenings during sleep and an excess of PLMS in patients as compared with the controls. The cross-sectional study of Veauthier et al. [404] quoted 25 % prevalence of insomnia in MS patients, but most other studies in MS did not consider standardized diagnostic criteria confounding a methodological limitation. Sleep disturbance causing repeated arousals and sleep fragmentation is thought to be a contributing factor for MS-related fatigue [402, 436] (see also Chap. 42). An important cause of insomnia in MS is comorbid depression, which has a high prevalence (up to 50 %); it is important to recognize depression as treatment may improve sleep dysfunction and quality of life [417–419, 428, 430, 443–446, 454].

RLS-PLMS has a high prevalence in MS patients and in the general population [420, 435]. RLS-PLMS is an important cause of insomnia in these patients. Manconi et al. [435] studied 156 MS patients using a structured questionnaire and assessing the ESS; about one-third of their subjects satisfied the criteria for RLS. These authors noted that the primary progressive form of MS was more representative of the RLS group, which showed a higher ESS score than those without RLS. In a later multicenter Italian REMS study, Manconi et al. [447] reported that the prevalence of RLS was

19 % in MS and 4.2 % in controls. They identified the following risk factors: older age, longer duration, primary progressive MS form, higher disability, and the presence of leg jerks at sleep onset.

A recent meta-analysis by Schurks and Bussfeld [420] covering 24 studies estimated fourfold higher risk of RLS in MS patients than in those without MS. Manconi and collaborators [421] based on diffusion tensor MRI study suggested that cervical cord damage was a significant risk factor for RLS in MS which agrees with previous suggestion by Hartmann et al. [422]. A disconnection between brain stem and spinal cord due to interruption of ascending or descending pathways from the cervical spinal cord may be provided as an explanation for RLS in these patients [409].

Fatigue, Sleep Dysfunction, and MS

Most patients with MS suffer from an unexplained fatigue (see also Chap. 42). In the studies by Attarian et al. [436], Kaynak et al. [402], and others [415], there is a significant correlation between fatigue and disrupted sleep with sleep fragmentation, alteration of sleep macrostructure and microstructure, poor quality of life, and depression.

Other Sleep Disturbances in MS

Hypersomnolence with low CSF hypocretin-1 levels in primary and secondary narcolepsy [423–425, 438, 449, 450–453] and RBD [439] have also been observed in some MS patients. Plazzi et al. [439] described a 25-year-old woman with MS who presented with RBD as an initial presentation of MS, and this subsequently resolved after treatment with adrenocorticotrophic hormone. No MRI documentation, however, of brain lesions was provided. More recently, Tippmann-Peikert et al. [426] reported a 51-year-old woman with acute MS and RBD showing a large MS plaque (MRI T2 signal) in the dorsal pons similar to the lesion site causing RBD-like behavior in cats. One study [427] estimated prevalence of RBD in MS as 1.4 %.

Medications Causing Sleep Disturbance in MS

Treatment of MS with immunomodulating therapies such as interferon and methylprednisolone may cause sleep disturbances in the form of hypersomnolence, increasing fatigue, insomnia, and depression [454, 456]. The newer medications such as glatiramer acetate (Copaxone) or mitoxantrone (Novantrone) have not been found to cause sleep disturbance in MS, but adequate studies have not been undertaken. Insomnia, however, has been reported with laquinimod treatment in MS patients [457]. No specific information is available for natalizumab and fingolimod [409]. There is a report [458] showing that compared with oral baclofen, intrathecal infusion to treat severe spasticity in MS patients improved sleep continuity without affecting respiratory function.

Quality of Life and Sleep Dysfunction in MS Patients

Merlino et al. [440] studied 120 MS patients to assess the prevalence of sleep dysfunction in MS and to evaluate various factors affecting sleep quality and quality-of-life indicators. These authors found poor sleep in 47.5 % of the patients and concluded that poor sleep is an independent predictor of impaired quality of life, directing our attention to assessment and treatment of sleep dysfunction in MS patients to improve the quality of life. They also confirmed significantly higher mean Kurtzke MS disability scores among poor sleepers than among good sleepers, supporting an earlier report by Lobentanz et al. [446] but contradicting other reports [431, 432, 439] showing no correlation with these scores.

Mechanisms of Sleep Dysfunction in MS

Sleep-wake disturbances in MS may result from a variety of factors (see Fig. 41.18) as listed below: discomfort from immobility, spasticity and pain, nocturia, abnormal motor activities (e.g., RLS-PLMS, muscle spasms, and parasomnias), anxiety, depression, sleep-disordered breathing, anatomic locations of MS plaques (e.g., location of lesions affecting sleep-wake regulatory regions in brain stem, hypothalamus, and other brain areas), immunologic and cytokine abnormalities, and genetic predisposition (in some cases).

Bulbar Poliomyelitis and Post-polio Syndrome

In the acute and convalescent stages of poliomyelitis, respiratory disturbances commonly get worse during sleep. Some patients are left with the sequelae of respiratory dysrhythmia, particularly sleep-related apnea or hypoventilation requiring ventilatory support, especially at night. Another group of patients decades later develop symptoms that constitute *post-polio syndrome*. Sleep disturbances and sleep apnea or hypoventilation are also noted in post-polio syndrome. Medullary respiratory and hypnogenic neurons are involved directly in the poliovirus infection, and this explains the patients' symptoms.

Bulbar Poliomyelitis

Hypoventilation syndrome in bulbar poliomyelitis was first documented quantitatively by Sarnoff et al. [459]. They described four patients who could breathe voluntarily on

command but hypoventilated during periods of sleep and quiescence. The authors described irregular rate and rhythm of respiration, incoordination of the muscles of respiration, and hypoventilation resulting from decreased sensitivity of the respiratory center to $Paco_2$ as a result of direct involvement of the respiratory center by the poliomyelitis virus. Two of their patients benefited from electrophrenic respiration.

An extensive report on the clinical and physiologic findings in 20 of 250 poliomyelitis patients with central respiratory disturbances was given by Plum and Swanson [16]. These patients' respiratory disturbances could not be explained by involvement of the spinal motor neurons or airway obstruction. In acute bulbar poliomyelitis, the disordered breathing progressed through three successive stages. Stage I was characterized by disorder of respiratory rhythm during sleep, when breathing became irregular in rate and depth with periods of apnea ranging from 4 to 12 s. During stage II, normal breathing required increasing effort and concentration, and strong auditory or painful stimuli were necessary to maintain respiratory rhythmicity. At this stage, the patients had impaired chemosensitivity of the central respiratory centers as evidenced by a reduction in ventilation and carbon dioxide retention after O_2 inhalation. Sleep exacerbated the breathing difficulty, and there were longer periods of apnea. The respiratory homeostasis was lost entirely in stage III, and there was no ventilatory responsiveness to reflex, chemical, or other neuronal stimuli. The respiratory pattern was chaotic, with varying periods of apnea. The patients required ventilatory support to maintain respiratory homeostasis. Severe inflammatory changes and small areas of necrosis in the ventrolateral reticular formation of the medulla were noted in two patients on neuropathologic examination.

The breathing abnormalities in this series rarely lasted more than 2 weeks, but two patients had sleep-related irregular respiration that persisted many months after acute poliomyelitis. These two patients also demonstrated impaired hypercapnic ventilatory response and hypoventilation during administration of 100 % O_2. The physiologic abnormalities suggested severe and permanent dysfunction of the medullary respiratory neurons. In several convalescent spinal poliomyelitis patients, the authors also observed subnormal ventilatory response to carbon dioxide with reduction of maximum breathing capacity or vital capacity to less than 50 % of predicted normal values. These findings implied that peripheral mechanisms that cause restriction of chest movements may also contribute to impaired ventilatory response to carbon dioxide.

Post-polio Syndrome

Post-polio syndrome is manifested clinically by increasing weakness or wasting of the previously affected muscles and by involvement of previously unaffected regions of the body, fatigue, aches and pains, and sometimes symptoms secondary to sleep-related hypoventilation, such as EDS and tiredness [460, 461]. The exact mechanism of post-polio syndrome is not known. Some of the symptoms (e.g., EDS and fatigue) could result from sleep-related hypoventilation or apnea and sleep disturbances [462]. Thus, it is important to be aware of sleep apnea in such patients. This syndrome has been described in patients who had poliomyelitis decades earlier. Guilleminault and Motta [463] reported on five such men who had a history of bulbar poliomyelitis 16 years earlier. All had EDS, and PSG study documented numerous episodes of apneas, which were predominantly central but also mixed and upper airway obstructive types associated with O_2 desaturation. Their longest apneas were seen during REM sleep. It is important to know that these patients resemble those with primary sleep apnea syndrome. Presumably, the lesions in these cases involved the medullary respiratory neurons, and thus, central lesions were responsible for all three types of apneas. The patients' symptoms improved and daytime somnolence decreased after ventilatory assistance at night.

Steljes et al. [462] performed PSG examinations on 13 post-polio patients, 5 of whom used rocking beds for ventilatory assistance and 8 of whom had no ventilatory assistance. Patients who required ventilatory assistance demonstrated severe sleep disturbances with decreased total sleep time, reduced sleep efficiency, and decreased percentages of stage 2 NREM sleep, slow-wave sleep, and REM sleep, but increased awakenings and percentage of stage 1 NREM sleep. Respiratory abnormalities in these patients consisted of hypoventilation, apneas, and hypopneas associated with significant O_2 desaturation. These patients did not respond to CPAP treatment with the rocking bed, but they showed improvement in sleep structure and respiratory function after mechanical ventilation via nasal mask. Five of the eight patients who required no ventilatory assistance also showed impairment of sleep architecture similar to the other group, but the findings were less severe. All but one patient from the second group had obstructive or mixed apneas, which were treated successfully with nasal CPAP. One patient with mixed apnea and marked hypoventilation improved after treatment with nasal ventilation by mask.

Polysomnographic and pulmonary function studies by Bye et al. [464] and Ellis et al. [465] documented respiratory failure and sleep hypoxemia, particularly during REM sleep, in patients with post-polio respiratory muscle weakness. Sleep studies by Ellis' group [465] under controlled conditions without respiratory support showed repeated arousals with disruption and fragmentation of the REM-NREM cycle. In a retrospective review of medical records from 108 consecutive patients with post-polio syndrome and sleep

disturbances encountered during an 11-year period at the Mayo Clinic, Hsu and Staats [466] reported PSG findings from 35 patients fulfilling the inclusion criteria. All patients had hypersomnolence as the most common presenting symptom, and the authors identified three patterns of sleep disturbances: OSA, hypoventilation, and a combination of both. They concluded that SDB is a late sequela of poliomyelitis. Dean et al. [467] from the National Institutes of Health reported the PSG findings in 10 patients with clinical signs of post-polio syndrome. They noted disruption of sleep architecture due to sleep apnea (both central and obstructive), which was more frequent in patients with bulbar involvement who had more central than obstructive apneas. Bruno [468] reported abnormal movements during sleep studies (e.g., random myoclonus, brief ballistic and slow grasping movements, and PLMS) in seven poliomyelitis survivors. A physiologic study to understand the sequence of events during REM sleep in 13 patients with post-polio syndrome by Siegel et al. [469] from the National Institutes of Health measured latencies to the onset of the first occurrence of muscle tone reduction, the first sawtooth waves, and the first REMs in 13 patients with post-polio syndrome. The latencies for the entire group were longer than those of the normal volunteers, and the latencies for the bulbar group were significantly longer than those for the nonbulbar group of post-polio patients. The authors concluded that prolongation of these latencies may be due to prolonged recruitment time for neurons in the pontine tegmentum as a result of damage from the poliomyelitis virus in the past.

In a more recent report, Marin et al. [470] observed 10 fulfilling the diagnostic criteria for RLS/WED (2 men, 8 women; mean age of 42.5 years) among 35 post-polio patients in the outpatient clinics. They noted a concomitant occurrence of both RLS and post-polio patients suggesting a possible common underlying mechanism for both conditions. This is a small sample without controls, and epidemiologic studies including larger samples are needed to confirm this relationship. Silva et al. [471] in a brief report described some nonspecific sleep architectural changes, increased PLMS, and apnea-hypopnea index in overnight polysomnographic studies obtained from 60 randomly selected post-polio patients. The authors concluded these abnormalities reflected a dysfunction of the surviving motor neurons in the brain stem. There have been no new advances in the management of post-polio patients [472].

Syringobulbia-Syringomyelia

Some patients with syringobulbia-myelia may have alveolar hypoventilation and sleep-related apneas or irregular breathing and stridor. Haponik et al. [473] described such a case. The patient was a 35-year-old woman whose polygraphic examination showed 370 upper airway obstructive apneas lasting 10–170 s associated with hypoxemia during 7 h of NREM stages 1 and 2 sleep. The patient died 9 months after the onset of the illness, and neuropathologic examination disclosed a syrinx that extended from the lower third of the medulla to the upper thoracic spinal cord. Nogues et al. [474] studied 30 patients with syringomyelia, including 17 with syringobulbia, using overnight PSG and pulmonary function tests that also included hypercapnic ventilatory response; they found SDB (central, mixed, and obstructive apneas) in 1 of 13 patients with syringomyelia and 13 of 17 patients with syringobulbia. Impaired hypercapnic ventilatory response was noted in patients with syringobulbia. They found that symptoms of dysphagia and dysphonia rather than the size of the cavity on MRI or muscle weakness were predictive of SDB. These authors [475] also reported PLMS during NREM stages 1 and 2 in 16 of 26 patients with syringomyelia and periodic limb movements in wakefulness in three of these patients. The EMG latency delay between the upper and lower limb muscles suggested conduction along slowly conducting propriospinal pathways, indicating spinal cord hyperexcitability similar to the propriospinal propagation of PLMS in some RLS patients [476]. An occasional report [477] of postural tachycardia syndrome (see later) in syringomyelia and cardiovascular autonomic [478] impairment associated with sleep apnea in syringomyelia and syringobulbia suggest involvement of brain stem and spinal autonomic neurons. In a recent review published in 2012, Massimi et al. [479] stated that in the last three decades, only 41 cases of abrupt onset of syringomyelia associated with Chiari malformation type 1, respiratory failure (29 %), and cardiac autonomic dysfunction have been reported.

Sleep Dysfunction and Encephalitis

Cohn and Kuida [480] and White et al. [481] described alveolar hypoventilation, CSA, EDS, and subnormal hypercapnic ventilatory response after western equine encephalitis. The respiratory center was thought to have been damaged by the virus. Iranzo et al. [482] reported six patients with nonparaneoplastic limbic encephalitis associated with antibodies to voltage-gated potassium channels. Five of these patients had RBD associated with the onset of limbic encephalitis and in three of these immunosuppression resulted in the resolution of RBD in parallel with remission of the limbic syndrome. The authors suggested that RBD may be seen in the setting of voltage-gated potassium channel antibody-associated limbic encephalitis, which may be related to an autoimmune-mediated mechanism.

Sleep dysfunction, including total insomnia, NREM and REM parasomnia, has been described in many other types of autoimmune (antibody-mediated) encephalopathies [483–485] (e.g., anti-NMDA-receptor encephalitis and several limbic encephalitis subtypes). Distinctive clinical features including sleep disorders along with neuroimaging and

electrophysiologic findings may indicate specific antibody-mediated encephalitis. A novel encephalopathy (a tauopathy) associated with cell surface autoimmunity (IgLON5) causing a novel NREM and REM parasomnia (RBD) with OSA has been recently described [486].

Arnold–Chiari Malformation

Arnold–Chiari malformation, particularly types I and II, may cause SDB, predominately CSA but also upper airway OSA, and central hypoventilation, including sudden respiratory arrest during sleep or postoperatively [487–489]. A repeat PSG in 6 of 12 patients out of 16 consecutive patients with Arnold Chiari malformation type I showed a decrease in the central apnea index following decompression surgery [490]. In a study by Sergio et al. [491] reporting 103 patients with Arnold–Chiari malformation (36 with type I and 67 with type II), a video-PSG study showed RBD in 23 and SDB in 65 (predominantly with CSA syndrome in 61 of the 65 patients). More recently, PSG documented a high prevalence of sleep apnea (both central and obstructive) in 16 children with Chiari type II [492] and eight out of 22 children with Chiari type I [493] malformations who showed significant improvement of central apneas after surgical decompression. Figures 41.21 and 41.22 show a hypnogram and a 120-second excerpt from a PSG recording from a 52-year-old man with Arnold–Chiari malformation type I. The hypnogram findings suggest REM sleep-related hypoventilation, and the PSG tracing shows obstructive apneas and hypopneas.

Diseases of the Spinal Cord

In spinal cord disorders, sleep disturbances occur as a result of sleep-related respiratory dysrhythmias causing sleep apneas, hypopneas, or hypoventilation associated with hypoxemia and repeated arousals. The voluntary or behavioral respiratory control system descends via the corticospinal tracts, and the metabolic or automatic respiratory control system descends via the reticulospinal tracts; the two systems are integrated in the spinal cord (see also Chap. 11). The behavioral system is located in the dorsolateral quadrant of the cervical spinal cord [13, 14] and the automatic respiratory system in the ventrolateral quadrant. These two systems control the final common respiratory pathways of the spinal respiratory motor neurons, which send impulses along the phrenic and intercostal nerves to the main respiratory muscles. The anterior horn cells in the third, fourth, and fifth cervical spinal cord segments give rise to phrenic nerves, and the intercostal nerves originate from the ventral rami from the anterior horn cells in the thoracic spinal cord. It is known that transection of either the dorsolateral or the ventrolateral quadrant of the spinal cord may independently affect the voluntary and the automatic respiratory control systems [79]. Most reports, however, refer to transection of the ventrolateral tracts giving rise to dysfunction of the metabolic respiratory control system. Direct involvement of the lower motor respiratory pathways, either in the anterior horn or in the phrenic and intercostal nerves, may also give rise to respiratory dysfunction. Three patterns of respiratory dysfunction have been summarized by Krieger and Rosomoff [494]: (1) efferent motor impairment (e.g., phrenic nerve paralysis causing diaphragmatic weakness) associated with reduced vital capacity, (2) impaired hypercapnic ventilatory response without significant chest wall or diaphragmatic weakness and with normal vital capacity, and (3) a mixture of these two abnormalities. The lesions that cause such dysfunction in the spinal cord may include spinal surgery, spinal trauma, amyotrophic lateral sclerosis (ALS), syringomyelia, cervical spinal cord tumor, and cervical myelitis (demyelinating or nonspecific myelitis).

Spinal Surgery

Several cases of sleep apnea have been described after spinal surgery [494–496]. Krieger and Rosomoff [495] also described sleep apnea after high cervical cordotomy. These authors observed respiratory dysfunction within 24–48 h of bilateral percutaneous cervical cordotomy in 10 patients [494]. Although the authors concluded that the ascending reticular fibers in the ventrolateral segment of the spinal cord that relay afferent impulses to the medullary respiratory center had been damaged in their patients, it is most likely that selective damage to the descending automatic respiratory control fibers in the ventrolateral quadrant of the spinal cord was the lesion responsible. In two other patients, Krieger and Rosomoff [495] described sleep apnea that required assisted ventilation at night for several days after anterior spinal surgery at C3-4 interspace. Lahuerta et al. [496] performed high cervical cord percutaneous cordotomy for pain management in 12 patients, all of whom died during sleep postoperatively, presumably from respiratory dysrhythmia. These patients had lesions involving the anterolateral funiculus in the C2 segment, where respiratory fibers are intermingled with ascending pain fibers. Thus, these reports clearly document Ondine's curse as a sequela of high cervical spinal cord lesions.

Spinal Trauma

OSA has been described in patients with cervical spine fractures [497] or high spinal cord injury [498, 499]. Guilleminault [500] described eight victims of neck trauma who showed sleep apnea, hypoxemia, and EDS and suggested that mild compression of the lower medulla and upper cervical spinal cord might cause respiratory disturbances during sleep after severe whiplash injury or odontoid fractures. In another report, Stockhammer et al. [501]

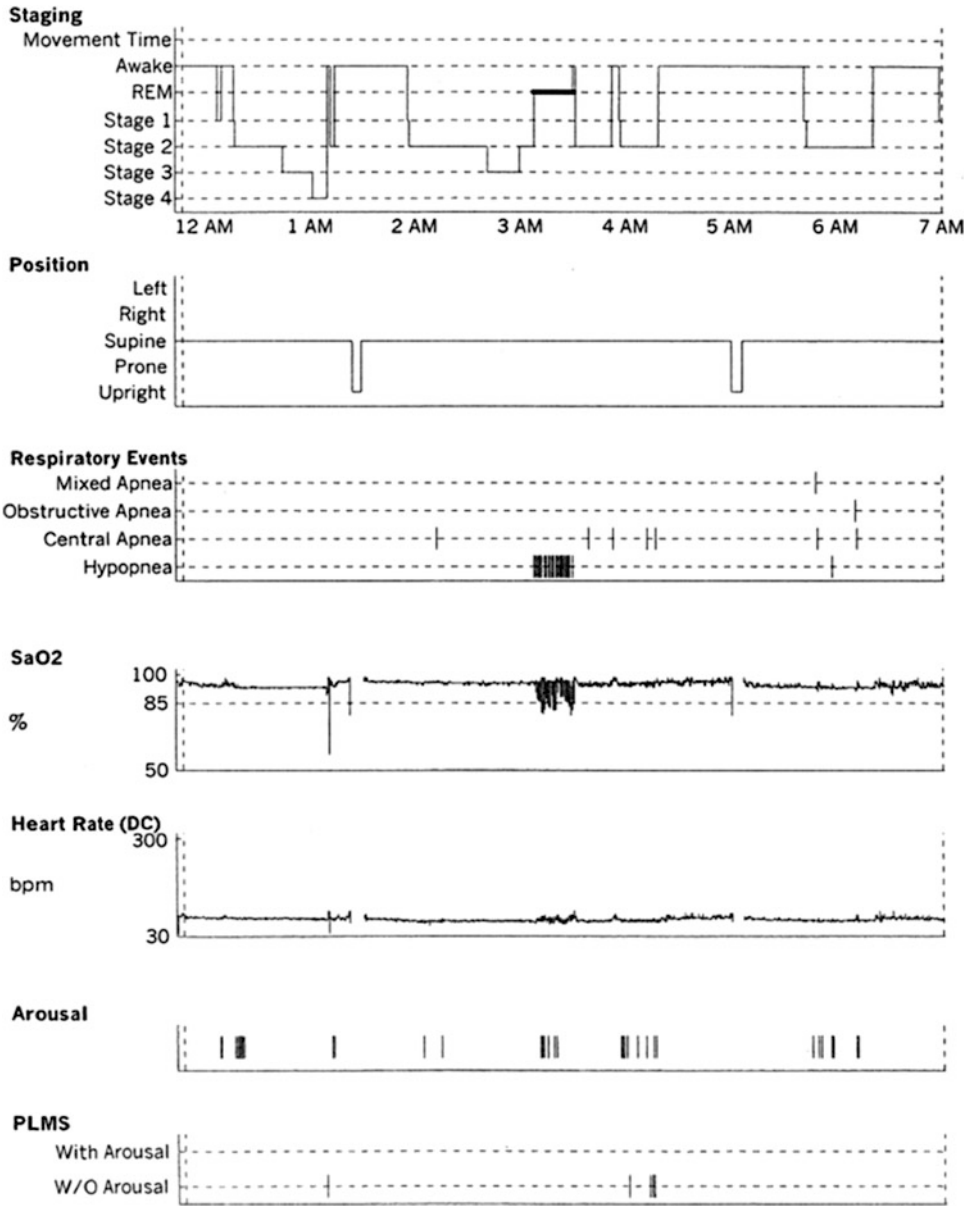

Fig. 41.21 A case of Arnold–Chiari malformation and SDB in a 52-year-old man with a history of tiredness and excessive daytime sleepiness for many years but no cataplexy, sleep paralysis, or hypnagogic hallucinations. At the age of 27 years, he complained of gait problems, and magnetic resonance imaging examination revealed Arnold–Chiari malformation type 1. His neurologic examination is significant for the presence of a coarse horizontal nystagmus, minimal right lower facial weakness, minimal right wrist extensor muscle weakness, minimal-to-mild ataxia in upper and lower extremities on coordination testing, and the presence of ataxia on tandem gait. This hypnogram shows a few periods of apneas and hypopneas accompanied by mild-to-moderate oxygen desaturation and arousals limited exclusively to a single REM sleep period recording during the night. A supine posture is maintained throughout the polysomnographic recording. These findings are suggestive of REM sleep-related hypoventilation. Central sleep apnea, obstructive sleep apnea, and hypoventilation have all been described in patients with Arnold–Chiari malformation, likely from brain stem involvement. Reproduced with the permission from Chokroverty et al. [455]

documented sleep apnea syndrome in 55 % men and 20 % of women in a series of 50 randomly selected patients with tetraplegia resulting from spinal cord injuries. The authors concluded that the incidence of sleep apnea syndrome is high in tetraplegia, especially in older men with large neck circumference and long-standing spinal cord injuries. More recent reports also emphasized a high prevalence of sleep dysfunction and sleep-disordered breathing (SDB) [502–506] in spinal cord injury. Sleep complaints are frequent in spinal cord injury patients and may include difficulty in falling asleep, repeated awakening, impaired sleep quality, increasing use of sleeping medication, snoring, and daytime

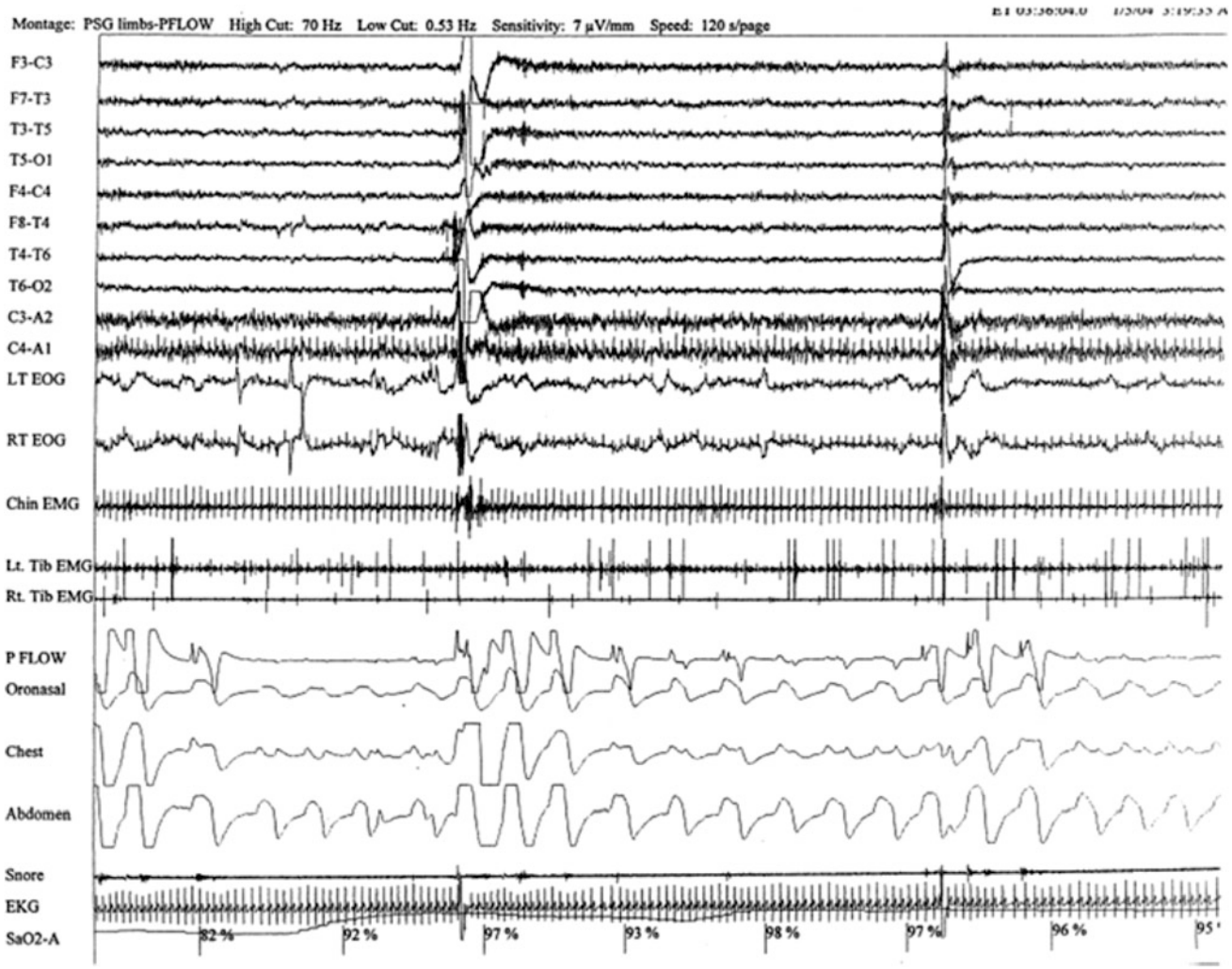

Fig. 41.22 A 120-s polysomnographic excerpt from REM sleep (same patient as in Fig. 41.21) showing one obstructive apnea followed by two sequential hypopneas. Oxygen desaturation of 82 %, likely from a prior respiratory event, is recorded at the onset of the epoch. The first two events are followed by an arousal response, and the epoch does not include the complete recovery phase of the third event. Phasic eye movements of REM sleep are noted on the electrooculogram (EOG) channels in the early part of the epoch. Phasic muscle twitches of REM sleep are noted on both tibialis anterior electromyography (Tib. EMG) channels. Chin EMG channel shows electrocardiography artifact. Electroencephalogram (EEG): top 10 channels. *Lt.* left; *Rt.* right; *P Flow* peak flow; oronasal thermistor; chest and abdomen effort channels; snore monitor; EKG, electrocardiography; SaO_2, oxygen saturation by finger oximetry. Reproduced with permission from Chokroverty et al. [455]

napping [503, 507]. Proserpio et al. [502] in a prospective observational study evaluated 35 patients with spinal cord injury (15 tetraplegics and 20 paraplegics) within the first year after injury. They noted OSA in nine (25.7 %) and PLMS in 10 (28.6 %) patients. In their patients, the frequency of OSA was higher in tetraplegics than paraplegics, similar to high prevalence of SDB in tetraplegics reported previously by Berlowitz et al. [508]. Another important observation in this study is the high prevalence of OSA after cervical cord injury. Finally, the absence of daytime sleepiness related to OSA in their patients is in line with similar previous observation [505] and that noted in heart failure patients with SDB [507].

There are a few scattered reports of PLMS associated with paraplegia due to spinal cord injury or other spinal cord lesions [509–512]. The authors of these papers concluded that the PLMS resulted from disinhibition of the spinal locomotor generator. It should be noted that the question of the spinal cord as the generator for PLMS remains highly speculative and controversial. In a recent preliminary neurophysiologic study in a subgroup of spinal cord injury patients, Ferri et al. [513] observed a cerebral and autonomic response to leg movements in 45 % of patients with acute spinal cord injury suggesting the potential presence of surviving spinal or extraspinal connections.

Sleep and Breathing Disturbances in Neuromuscular Disorders

Sleep disturbances in neuromuscular disorders are most commonly due to respiratory dysrhythmias secondary to involvement of the respiratory pump, which includes the diaphragm, the intercostal and other accessory muscles of respiration, and the upper airway muscles (genioglossus, palatal, pharyngeal, laryngeal, hyoid, and masseter muscles). Adverse effects on the motor neurons, the phrenic and intercostal nerves, or the neuromuscular junctions of the respiratory and oropharyngeal muscles, and primary muscle disorders affecting these muscles are responsible for respiratory dysrhythmia and sleep dysfunction [91, –519]. The most common complaint is EDS resulting from repeated arousals and sleep fragmentation due to transient nocturnal hypoxemia and hypoventilation in addition to sleep-related respiratory dysrhythmias. Some patients, particularly those with painful polyneuropathies, muscle pain, muscle cramps, and immobility due to muscle weakness, may complain of insomnia. The most common neuromuscular disorders causing SDB and sleep dysfunction include motor neuron disease (ALS); myasthenia gravis, including myasthenic syndrome; acute inflammatory demyelinating polyradiculoneuropathies (Landry/Guillain–Barré/Strohl syndrome); muscular dystrophies, including myotonic dystrophy; inflammatory myopathies; and congenital myopathies (Box 41.4 and Fig. 41.23). Many of these conditions are treatable; others show relentless progression, but even in these conditions, quality of life may be improved with prolongation of the natural course of the illness by timely and adequate treatment of SDB. It is therefore important for physicians taking care of patients with neuromuscular disorders to have a basic understanding of these disorders and a high index of suspicion for SDB in such patients so that patients can be either referred to specialists or treated adequately in a timely manner.

Box 41.4 Common Neuromuscular Disorders Causing Sleep-Disordered Breathing and Sleep Dysfunction

- Motor neuron disease (amyotrophic lateral sclerosis [ALS]),
- Polymyositis and post-polio syndrome,
- Myasthenia gravis,
- Myasthenic syndrome,
- Acute inflammatory demyelinating polyradiculoneuropathy (Landry–Guillain–Barré syndrome),
- Muscular dystrophies including myotonic dystrophies types 1 and 2 (DM1 and DM2),
- Inflammatory myopathies (polymyositis and dermatomyositis),
- Congenital myopathies.

Sleep-disordered breathing is commonly associated with insidiously developing chronic respiratory failure in neuromuscular disorders, especially in the advanced stages, but is often unrecognized and untreated [91, 513–519]. The most common SDB in neuromuscular disorders is sleep-related, especially REM-related, hypoventilation. Both central and upper airway obstructive apneas also occur. Bulbar muscle weakness in many patients may cause increased upper airway resistance, but adequate studies have not been undertaken to identify its true prevalence in neuromuscular

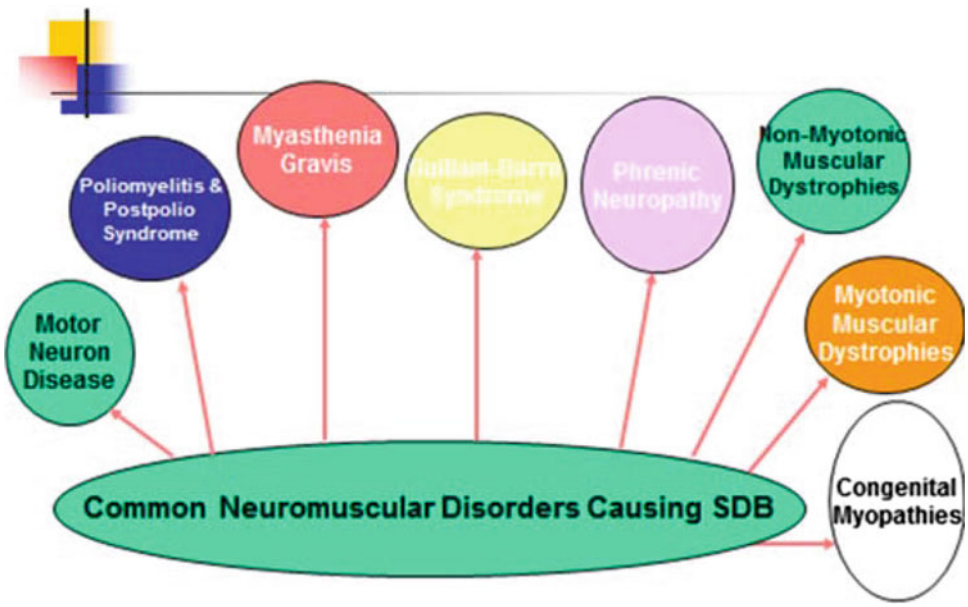

Fig. 41.23 Types of neuromuscular disorders

disorders. Paradoxical breathing (movements of the thorax and abdomen in opposite directions) may be seen in patients with upper airway OSA and upper airway resistance syndrome. This is different from paradoxical inward movement of the abdomen with epigastric retraction instead of protrusion during inspiration as seen in patients with diaphragmatic paralysis. Nocturnal hypoventilation giving rise to hypoxemia and hypercapnia during sleep in the initial stage of neuromuscular disorders causes chronic respiratory failure; the abnormal blood gases may later present even during the daytime.

Mechanism of SDB and Respiratory Failure in Neuromuscular Diseases

Respiratory failure is defined as an inability of the lungs to effectively exchange gas and maintain normal acid-base balance as a result of failure of the respiratory system anywhere from the medullary respiratory controllers to the chest bellows and the lungs, including the upper airways. As a result of this failure, there is reduction in Pao_2 and increased $Paco_2$. A Pao_2 of less than 60 mm Hg and a $Paco_2$ of more than 45 mm Hg at sea levels are commonly considered criteria for respiratory failure. Most neuromuscular disorders cause ventilatory failure, which is defined as inadequate alveolar ventilation with reduced tidal volume causing low Pao_2 and high $Paco_2$.

Respiratory failure in neuromuscular disorders begins during sleep, followed by gradual or relentless progression unless interrupted by ventilatory support at night. A variety of physiologic changes occur in the central control of breathing and in the respiratory muscles during sleep (see Chap. 11) that are responsible for initiating respiratory failure in sleep in patients with neuromuscular disorders. Additionally, there may be a comorbid upper airway obstruction not related to neuromuscular disorders. However, in many of these patients, the upper airway muscles are also affected, causing upper airway OSA. The accessory muscles of respiration maintain breathing during NREM sleep in patients with weakness of the diaphragm, the main muscle of ventilation; however, during REM sleep, there is hypotonia or atonia of these accessory muscles, and ventilation then depends exclusively on the diaphragm. Therefore, in patients with diaphragmatic weakness, ventilation is severely affected during REM sleep, causing REM hypoventilation. This is the first stage of respiratory failure in neuromuscular disorders (Fig. 41.24). As the disease advances to the second stage, the accessory muscles of respiration are affected severely, thus causing ventilatory disturbance during NREM sleep [513, 520]. In the final stage (stage 3) of neuromuscular disorders, ventilation is affected even during the daytime, causing altered blood gases (e.g., hypoxemia and hypercapnia) during wakefulness. Stage 2 of respiratory failure may be related to either progression of the neuromuscular disorder or superimposed intercurrent infection (e.g., pneumonia), or both.

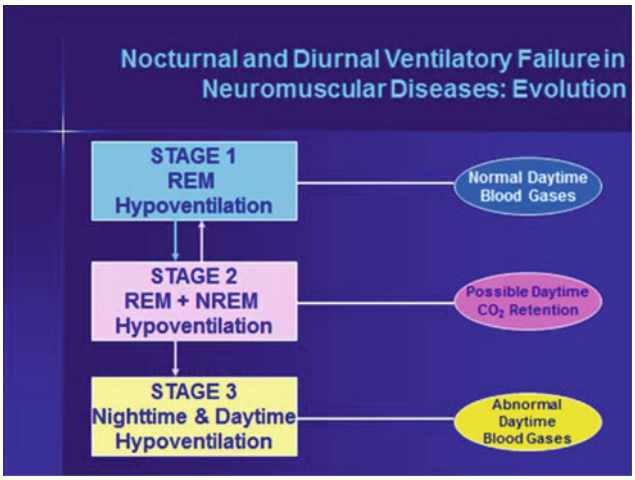

Fig. 41.24 Stages of NMD

Several authors aimed at identifying daytime predictors of SDB and nocturnal hypoventilation and its onset [521–523]. These authors concluded that progressive ventilatory restriction in neuromuscular diseases correlates with respiratory muscle weakness and can be predicted from daytime lung and respiratory muscle function. Inspiratory vital capacity (IVC) and maximum inspiratory muscle pressure (PI_{max}) are the two important predictors of the onset of respiratory failure [521, 522]. IVC of less than 60 % and PI_{max} of less than 4.5 kPa predicted onset of REM hypoventilation, IVC of less than 40 % and PI_{max} of less than 4.0 kPa predicted both REM and NREM hypoventilation, and IVC of less than 25 % and PI_{max} of less than 3.5 kPa predicted daytime respiratory failure. However, Lyall et al. [523] and Morgan et al. [524] suggested that the noninvasive maximal sniff pressure measurement is more sensitive than vital capacity and static maximal inspiratory muscle pressure in patients with ALS and in assessing the risk of ventilatory failure. Carratu et al. [525] in a later preliminary study in 31 ALS patients confirmed that maximal sniff nasal inspiratory pressure (SNIP) lower than 60 CMH_20 may be an early predictor of SDB in ALS. It has also been suggested that a significant fall of vital capacity from the erect to the supine position (70 % or less of the predicted value) indicates the presence of diaphragmatic weakness [526–528]. A fluoroscopy will confirm the weak movement of the dome of the diaphragm during inspiration. A serial blood gas determination is important in detecting impending respiratory failure. It should be remembered that a normal daytime Pao_2 and $Paco_2$ does not exclude REM-related hypoventilation.

In patients with weak respiratory muscles, regardless of cause, the waking breathing difficulties may worsen during

sleep. While patients are awake, both voluntary and metabolic respiratory controls are intact and central respiratory neurons increase the rate of firing or recruit additional respiratory neurons to maintain ventilation adequately to drive weak respiratory muscles [91]. During sleep, however, voluntary control is absent and respiration is dependent entirely on the metabolic control system. Respiratory neurons are thus vulnerable during sleep, aggravating the ventilatory problems and causing more severe hypoventilation and even apneas and hypopneas. Functional impairment of the sensitivity of the central respiratory neurons, causing decreased metabolic respiratory control, may also give rise to apnea-hypopnea during both REM and NREM sleep. Oropharyngeal (upper airway) muscle weakness coupled with REM-related hypotonia or atonia of the muscles may contribute to possible upper airway OSA.

In summary, breathing disorders causing sleep-related hypoventilation in neuromuscular disorders may be related to the following factors:

1. Weakness of the respiratory and chest wall muscles causing impaired chest bellows,
2. Increased work of breathing due to altered chest mechanics and reduced forced vital capacity caused by weakness of the chest wall muscles and diaphragm so that breathing is less efficient,
3. Hyporesponsive chemoreceptors, which may be secondarily acquired or related to altered afferent inputs from skeletal muscle spindles, causing functional alteration of the medullary respiratory neurons,
4. Weakness of upper airway muscles that increases upper airway resistance, adding respiratory muscle load or even upper airway OSA from complete closure of the upper airway,
5. Decreased minute and alveolar ventilation during sleep,
6. REM-related marked hypotonia or atonia of all the respiratory muscles except the diaphragm, causing increased diaphragmatic workload,
7. Respiratory muscle fatigue due to increased demand on the respiratory muscles during sleep, particularly REM sleep,
8. Kyphoscoliosis secondary to neuromuscular disorders, causing extrapulmonary restriction of the lungs with impairment of pulmonary functions, breathlessness, sleep apnea, and hypoventilation,
9. Failure of central control of ventilation,
10. Alteration of respiratory reflexes in upper airway and lung receptors and arousal responses.

All these factors may lead to ventilatory failure in neuromuscular disorders initially at night in the early stage. As a result of alveolar hypoventilation and ventilation-perfusion mismatching, hypoxemia and hypercapnia occur, giving rise to chronic respiratory failure even during the daytime at an advanced stage of the illness (Fig. 41.24).

Clinical Approach

The initial approach to clinical diagnosis of acute respiratory failure, as may occur in patients with acute inflammatory demyelinating polyradiculoneuropathies (e.g., Guillain–Barré syndrome) or myasthenic crisis, is quite obvious. Patients may have irregular, rapid, shallow, or periodic breathing, intermittent cessation of breathing, and cyanosis. However, recurrent hypoventilation in neuromuscular disorders may present insidiously and may initially remain asymptomatic [514, 515, 529–531]. A high index of clinical suspicion is needed. Clinical clues include the presence of EDS, nocturnal restlessness, frequent unexplained arousals, daytime fatigue, shortness of breath, orthopnea (breathlessness in supine position), morning headache, intellectual deterioration and failure to thrive and declining school performance in children. Signs of impending cor pulmonale include insomnia, morning lethargy, headache, and unexplained leg edema. Patients with neuromuscular disorders manifesting these clinical features should be investigated to uncover nocturnal hypoventilation in order to prevent adverse consequences of chronic respiratory failure, such as congestive cardiac failure and cardiac arrhythmia. Special attention during physical examination should be paid to uncover bulbar and respiratory muscle weakness, use of accessory muscles of respiration, and paradoxical breathing. Neuromuscular disorders causing SDB, respiratory failure, and sleep disturbance include ALS or motor neuron disease, primary muscle diseases, acute and chronic inflammatory demyelinating polyneuropathies, hereditary sensorimotor neuropathy, phrenic neuropathy, and neuromuscular junctional disorders (Fig. 41.23).

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis is the most common degenerative disease of the motor neurons in adults, affecting the spinal cord, brain stem, motor cortex, and corticospinal tracts. It is characterized by a progressive degeneration of both upper and lower motor neurons manifesting as a varying combination of lower motor neuron (e.g., muscle weakness, wasting, fasciculation, dysarthria, and dysphagia) and upper motor neuron (e.g., spasticity, hyper-reflexia, and extensor plantar response) signs. The readers are referred to the revised El Escorial and Awaji criteria for diagnosing ALS [532]. ALS can cause profound sleep disturbances associated with EDS as a result of repeated arousals and sleep fragmentation due to nocturnal hypoventilation, recurrent episodes of sleep apnea, hypopnea, hypoxemia, and hypercapnia. Insomnia related to other factors, such as

decreased mobility, muscle cramps, anxiety, and difficulty in swallowing, may be present in some patients. SDB in ALS may result from weakness of the upper airway, diaphragmatic, and intercostal muscles due to involvement of the bulbar, phrenic, and intercostal motor neurons. In addition, degeneration of central respiratory neurons may occur, causing central and upper airway OSAs. Generally, respiratory failure in ALS occurs late, but occasionally this may be a presenting feature requiring mechanical ventilation [529, 533]. Diaphragmatic weakness resulting from the degeneration of phrenic neurons is noted frequently in ALS and is mainly responsible for nocturnal hypoventilation, initially during REM sleep [514, 515]. Newsom Davis' group [534] described eight patients with diaphragmatic paralysis resulting from a variety of motor disorders. One of their patients had Kugelberg–Welander syndrome. The following features may be helpful in the diagnosis of diaphragmatic paralysis:

1. Breathlessness and EDS, suggesting alveolar hypoventilation,
2. Paradoxical inward movement of the abdomen with epigastric retraction instead of protrusion during inspiration,
3. An elevated diaphragm on chest radiography and paradoxical movement or decreased excursion of the diaphragm on fluoroscopy,
4. Documentation of a very sensitive measurement showing a lack of change in the transdiaphragmatic pressure during a maximum inspiration,
5. Diaphragmatic electromyographic (EMG) findings,
6. Respiratory function tests with the evidence of a restrictive pattern,
7. Blood gases showing hypoxemia and hypercapnia, suggesting alveolar hypoventilation,
8. Documentation of sleep-related breathing abnormalities on PSG.

Sleep-related respiratory dysrhythmia is a common complication of ALS causing central and obstructive sleep apneas, sleep hypoventilation, and respiratory failure associated with daytime hypersomnolence [514, 515, 535–538]. Overnight polygraphic recording documenting both central and upper airway obstructive apneas (Fig. 41.25) associated with severe oxygen desaturation, and alveolar hypoventilation taken from a PSG tracing of one of our (SC) ALS patients is shown here.

Ferguson et al. [535] studied 18 ALS patients with mild-to-severe bulbar muscle involvement and 10 age-matched control subjects. Most patients complained of difficulty initiating and maintaining sleep. All patients and controls had overnight PSG study, and 13 ALS patients had a second night of PSG study. ALS patients had more arousals and stage changes per hour, more stage 1 NREM sleep, and shorter total sleep time than controls. ALS patients had mild SDB with greater AHI than controls. It is notable that SDB was similar in ALS patients with or without respiratory muscle weakness. The SDB consisted of REM-related nonobstructive and central apneas. In an early study, Minz et al. [536] described PSG findings in 12 ALS patients, six men and six women. Four patients had both central and obstructive apneas. Sleep structure was normal in eight, but the others had frequent awakenings.

Howard et al. [537] described 14 patients with motor neuron disease associated with respiratory dysfunction. Eleven received respiratory support, including CPAP and intermittent positive pressure ventilation (IPPV) at night with considerable benefit. In a recent report, Lo Coco et al. [538] studied 100 consecutive ALS patients and 100 age- and sex-matched control subjects using PSQ and ESS as well as overnight PSG in 12 patients and the ALS Functional Rating Scale—Review (ALSFRS-R) in all patients. Fifty-nine percent of patients and 36 % of controls had sleep disturbances. The most common nighttime sleep complaints by patients with ALS included nocturia (54 %), sleep fragmentation (48 %), and nocturnal leg cramps (45 %). PSG showed decreased sleep efficiency and fragmented sleep architecture. These authors demonstrated that ALS patients had significant impairment of quality of sleep which correlated with the severity of illness (reduced ALSFRS-R score), daytime somnolence, ESS score, and depression. This is an important study challenging the clinicians to be aware of sleep-wake problems in ALS patients, because timely intervention could lead to better quality of life for these patients.

There have been several reports focusing on the role of noninvasive IPPV at night on the quality of life and the prognosis (see later in the Sect. "Treatment of Sleep and Respiratory Dysfunction Secondary to Neurologic Disorders").

Other Types of Motor Neuron Diseases

SDB causing sleep disturbance and daytime symptoms has also been noted in other types of motor neuron diseases, such as Kugelberg–Welander syndrome, a variant of juvenile-type motor neuron disease, as well as spinal muscular atrophy types 1 and 2 in children and adolescents [539–542].

Spinal muscular atrophy (SMA) consists of a group of recessively inherited neuromuscular disorders resulting from mutations of the survival motor neurons (SMN-1) gene on chromosome 5q [515]. Based on the age of presentation and

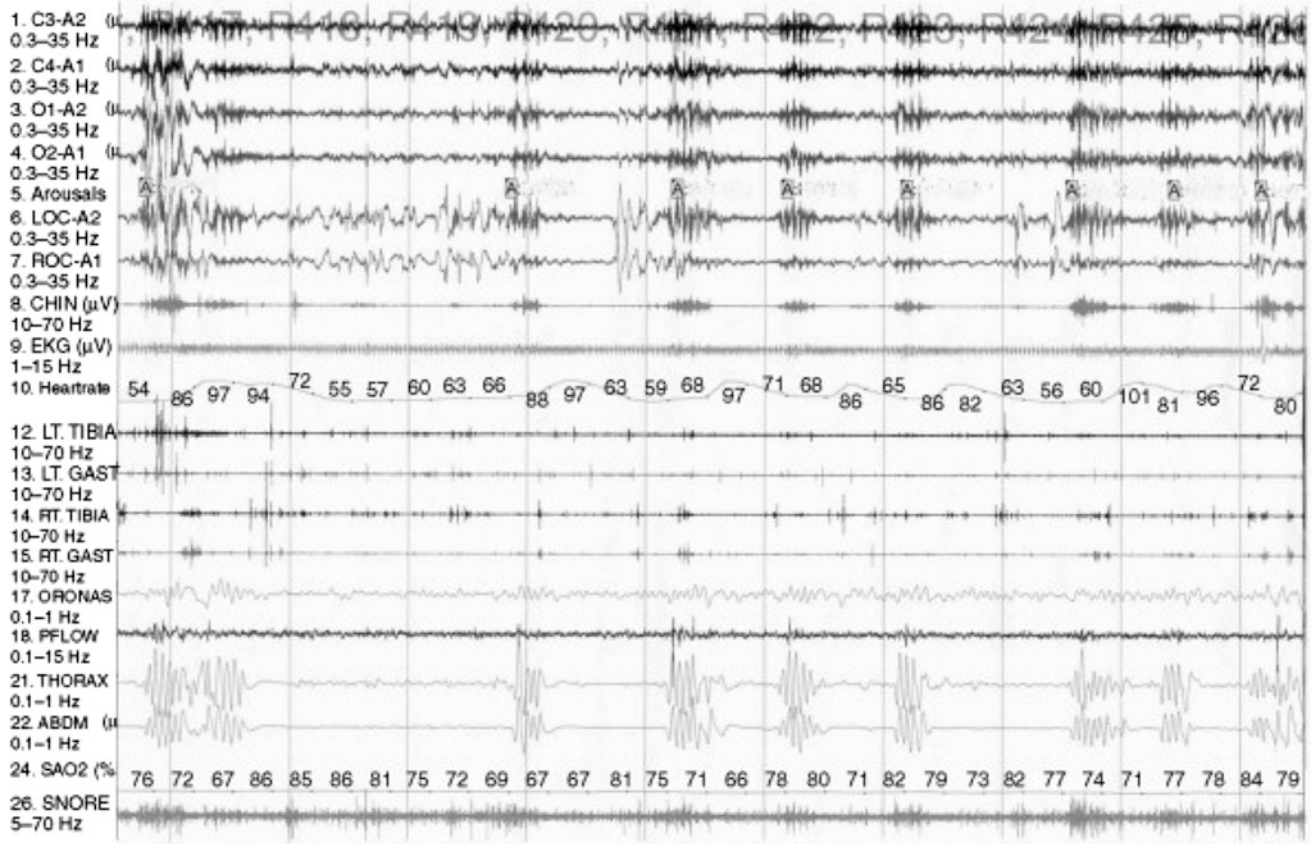

Fig. 41.25 Overnight polysomnographic recording from a patient with amyotrophic lateral sclerosis presenting with upper and lower motor neuron signs, including bulbar palsy, showing recurrent periods of central apneas many of which are prolonged, followed by irregular ventilatory cycles (resembling ataxic breathing; see Fig. 41.7) accompanied by severe oxygen desaturation and sleep hypoxemia during REM sleep. *Top four channels* represent the electroencephalogram. *EEG* international electrode placement system, *ABDM* abdominal breathing effort; *CHIN* submental electromyogram (EMG); *EKG* electrocardiogram; *LOC* left electrooculogram; *LT.GAST* left gastroenemius EMG; *LT.TIBIA* left tibialis EMG; *ORONAS* oronasal airflow; *PFLOW* nasal pressure recording for airflow; *ROC* right electrooculogram; *RT.GAST* right gastroenemius EMG; *RT.TIBIA* right tibialis EMG; *SAO_2%,* oxygen saturation [%] by finger oximetry; *SNORE* snoring recording; *THORAX* thoracic breathing effort

the number of functioning copies of the SMN-2 gene, SMA has been divided into four subtypes: SMA-1 (acute infantile type also called Werdnig–Hoffman disease), SMA-2 (chronic infantile form), SMA-3 (juvenile form or Kugelberg–Welander disease), and SMA-4 (adult onset). Those with a greater number of copies of the SMN-2 gene begin later in life and have less severe symptoms. Nocturnal noninvasive IPPV eliminates SDB, improves sleep quality, and prolongs survival in children with SMA types 1 and 2 [539, 541, 542].

Polyneuropathies

The cardinal manifestations of polyneuropathies are bilaterally symmetric, distal sensory symptoms and signs, and muscle weakness and wasting (affecting the legs more often than the arms). Peripheral neuropathies may be caused by a variety of heredofamilial and acquired diseases. Disorders of the phrenic, intercostal, and other nerves supplying the accessory muscles of respiration can cause weakness of the diaphragm, intercostal, and accessory respiratory muscles, giving rise to breathlessness on exertion, hypoxia, and hypercapnia. These respiratory dysrhythmias become worse during sleep. Sleep disturbances in polyneuropathies may result from painful neuropathies, partial immobility owing to a paralysis of the muscles, or SBD.

Acute inflammatory Neuropathy

The most common cause of respiratory dysfunction in polyneuropathy is acute inflammatory demyelinating polyradiculoneuropathy (Landry–Guillain–Barré–Strohl syndrome). The characteristic clinical manifestations consist of predominantly motor deficits associated with rapidly progressive ascending paralysis beginning in the legs and manifesting maximally in 2–3 weeks. In approximately 20–

25 % of cases, severe respiratory involvement has been reported, and the critical period is usually the first 3–4 weeks of the illness. It is important to recognize and treat the ventilatory dysfunction. Even the mild respiratory dysrhythmia during wakefulness may worsen during sleep, causing sleep apnea and hypoventilation. Patients with Guillain–Barré syndrome (GBS) may also have vivid dreams and hallucinations with abnormalities of sleep structure in the form of sleep-onset REM, REM sleep without atonia, RBD, and autonomic dysfunction, which have been described in approximately one-third of the GBS patients admitted to an intensive care unit [543]. In a prospective questionnaire-based study [544], more than half of GBS patients had sleep disturbance characterized by delayed sleep onset, sleep fragmentation, and decreased total sleep time, particularly during the first week of hospitalization with subsequent improvement. The question of long-term persistence of SDB in GBS remains undecided until further research [545].

Charcot–Marie–Tooth Disease

Charcot–Marie–Tooth (CMT) disease is the most common inherited neuropathy which has been separated into two main groups: a demyelinating form (CMT1) and an axonal form (CMT2) which has several subtypes (e.g., CMT2A…CMT 2G). Patients with CMT 2C are especially prone to develop vocal cord palsy, possibly due to laryngeal nerve involvement, as well as diaphragmatic dysfunction, hypoventilation, and sleep apnea [546], presumably due to phrenic neuropathy. Sleep dysfunction in CMT results mainly from comorbid sleep apnea [547–552] which may occur in both CMT1 and CMT2 subtypes and restless legs syndrome/Willis–Ekbom disease (RLS/WED) [549, 553–558].

RLS/WED, Polyneuropathies, and Sleep Dysfunction

RLS is seen most commonly in CMT2 but has also been noted in CMT1 type. Gemignani et al. [553, 555–558] observed that RLS associated with sleep dysfunction was more prevalent in subgroups of patients with painful polyneuropathies (both retrospective and prospective studies) compared with controls, suggesting small fiber neuropathy and central sensitization. In contrast, Lim et al. [559] based on their studies of 56 patients with primary RLS/WED and 36 age- and sex-matched controls, using quantitative sudomotor axon reflex test (QSART) and sensory testing concluded that abnormal sensory perception in RLS/WED patients resulted from an impairment of central somatosensory processing rather than small fiber neuropathy.

Other Neuropathies and Sleep Dysfunction

In addition to GBS, a high prevalence of RLS/WED with sleep dysfunction has been described also in chronic inflammatory demyelinating polyneuropathy (CIDP) [557, 560, 561] and those with painful polyneuropathies [556, 558, 559]. On rare occasion, multifocal motor neuropathy (MMN), a distinctive acquired demyelinating neuropathy with conduction block, may present with sleep hypoventilation (presumably due to bilateral phrenic neuropathy) which may be successfully treated with a combination of intravenous immunoglobulin (IVIG) and nocturnal bilevel positive ventilation therapy [562]. OSA associated with chronic sleep dysfunction itself may be a risk factor for axonal polyneuropathy due to recurrent intermittent hypoxemia [563, 564].

Phrenic neuropathies of diverse etiologies associated with neuropathies and plexopathies may cause SDB and sleep difficulty as a result of diaphragmatic dysfunction [514, 515]. Trauma, inflammatory polyneuropathy, and infiltrative lesions (e.g., neoplasms) may cause phrenic neuropathy. Phrenic nerve injury causing SDB with sleep dysfunction has also been noted as a complication of cardiothoracic surgeries [515, 565].

Primary Muscle Diseases (Myopathies)

Myopathies are primary muscle disorders characterized by weakness and wasting of the muscles resulting from a defect in the muscle membrane or the contractile elements that is not secondary to a structural or functional derangement of the lower or upper motor neurons [91, 514]. The characteristic clinical presentation consists of symmetric, proximal muscle weakness and wasting in the upper or lower limbs without sensory impairment or fasciculations. The causes include hereditary muscular dystrophies with or without myotonia; glycogen storage diseases; myoglobinuric myopathies; congenital nonprogressive myopathies with distinct morphologic characteristics; and various acquired metabolic, inflammatory, and noninflammatory myopathies. Some of these patients may report breathing disorders during sleep or worsening of the respiratory dysfunction during sleep. Generally, respiratory disorders show manifestations in the advanced stage, but a small number of patients may present with respiratory failure at an early stage. In many such patients, the true incidence of the sleep disturbances and sleep-related respiratory dysrhythmias cannot be determined without a systematic PSG study. Factors responsible for breathing disorders associated with hypoventilation and sleep apnea in these patients may be summarized as follows [91, 514, 515]: impairment of chest bellows owing to weakness of the respiratory and chest wall muscles,

increased work of breathing, and functional changes in the medullary respiratory neurons that could be due to hyporesponsive or unresponsive chemoreceptors acquired secondarily. The other suggestion for carbon dioxide hyposensitivity is altered afferent input from the skeletal muscle receptors [528]. Sleep disturbances generally occur in muscle disorders secondary to sleep-related respiratory dysrhythmias. Alveolar hypoventilation, both during wakefulness and sleep, should be diagnosed early in these patients to prevent dangerous or fatal hypoventilation during sleep or during administration of drugs, general anesthetic agents, and respiratory infections [91, 514]. Complaints of daytime hypersomnolence and breathlessness should direct attention to the possibility of SDB in these patients.

Muscular Dystrophy

The most common type of muscular dystrophy (nonmyotonic) associated with respiratory dysrhythmia-related sleep dysfunction is Duchenne's muscular dystrophy (DMD) and its variant, Becker muscular dystrophy (BMD). DMD is an x-linked recessive disorder with mutation of the dystrophin gene causing sarcolemmal membrane instability. Dystrophin is absent in DMD but is reduced in BMD. DMD is a relentlessly progressive disorder of muscle weakness, involving initially the pelvifemoral muscles resulting in an inability to stand and walk with confinement to a wheel chair within a few years. Respiratory failure with repeated awakenings at night and EDS occur in the late stage of the disease associated with alveolar hypoventilation and obstructive sleep apnea (OSA). Hypoventilation results from respiratory muscle weakness and scoliosis with restrictive pulmonary deficit, whereas OSA is secondary to upper airway muscle weakness.

Sleep-related respiratory dysrhythmias (both obstructive and central apneas) accompanied by O_2 desaturation and daytime hypersomnolence have been described in many patients with Duchenne's muscular dystrophy [517, 566–571]. Although respiratory failure is most commonly noted in Duchenne's muscular dystrophy, sometimes it also occurs in the more advanced stages of Becker's, limb-girdle, and facioscapulohumeral muscular dystrophies [514, 515, 517].

Smith and associates [567] described 14 patients with Duchenne's muscular dystrophy who had sleep apneas or hypopneas associated with marked O_2 desaturation. These authors stated that the severity of SDB in Duchenne's muscular dystrophy could not reliably be ascertained from daytime pulmonary function studies and asserted that sleep studies are essential.

Howard et al. [568] described nocturnal hypoventilation and respiratory failure in 84 patients with primary muscle disorders that included Duchenne's, Becker's, limb-girdle, and facioscapulohumeral muscular dystrophies; adult-onset acid maltase deficiency; myotonic dystrophy; polymyositis; congenital myopathies; and rigid spine syndrome. All patients needed ventilatory support in the form of negative or positive pressure ventilation or tracheostomy.

Khan and Heckmatt [569] studied 21 patients aged 13–23 years with Duchenne's muscular dystrophy and 12 age-matched controls using 2 consecutive nights of PSG. They noted apneas, 60 % of which were obstructive in nature, with hypoxemia in 12 patients. The respiratory care of patients with Duchenne's muscular dystrophy has been summarized in a consensus statement developed by the American Thoracic Society [534].

In a more recent study, Polat et al. [572] studied 35 children (12 with DMD and 23 controls) using PSG and they noted sleep-wake-related symptoms in 50 % of their patients. In an earlier study [517], similar symptoms were seen in up to 42 % and OSA in 16.6 %. These authors concluded that being wheelchair-bound or having scoliosis did not predict SDB, and so these patients should be investigated with PSG recording because if DMD patients are found to have SDB, treatment with nocturnal noninvasive positive pressure ventilation will improve the quality of life and longevity. In one of the largest studies [573] of 32 children with DMD by Suresh et al., OSA was noted in 31 % and these authors also recommended PSG for wheelchair-bound patients. They noted a bimodal presentation with OSA occurring in the first decade, whereas hypoventilation was seen more commonly in the second decade.

SDB including hypoventilation and OSA has been described in limb-girdle muscular dystrophy [574–576] (several subtypes are described based on distinct molecular abnormalities) and facioscapulohumeral muscular dystrophy [577, 578], the third most common form of muscular dystrophy after DMD and myotonic dystrophy, but not in a systematic manner.

Khan et al. [579] described eight children 6–13 years of age with congenital myopathy, congenital muscular dystrophy, and rigid spine syndromes with respiratory failure. PSG documented nocturnal hypoxemia and severe hypoventilation. Sleep disturbances included repeated awakenings. Sleep complaints and sleep-related periodic respiratory dysrhythmias are also common in other congenital myopathies such as nemaline rod myopathy, centrotubular and central core disease, merosin deficiency myopathy, and congenital muscular dystrophy [579–584]. Most of these present in childhood, but sometimes there is delayed presentation in adulthood [579–581] (see further on).

Myotonic Dystrophy

Dystrophica myotonica, or myotonic dystrophy type 1 (DM1), is an adult-onset, dominantly inherited muscular dystrophy associated with myotonia. DM1 is a multisystem disorder due to a trinucleotide expansion mutation (CTG

sequence) on the DMPK gene on chromosome 19, frontal baldness, cataract, endocrinopathy, and neuropsychologic deficit. Benaim and Worster-Drought [585] were most probably the first to describe alveolar hypoventilation in myotonic dystrophy. Alveolar hypoventilation associated with hypoxemia, as well as impaired hypercapnic and hypoxic ventilatory responses, may be present in both the early and the late stages of the illness. Several authors [517, 586–590] performed polygraphic studies that showed central, mixed, and upper airway obstructive sleep apneas, and sleep-onset REM was noted in some patients. The latter finding may have been due to sleep deprivation secondary to sleep-related respiratory disturbances. Two fundamental mechanisms account for the SDB in this illness: (1) weakness and myotonia of the respiratory and upper airway muscles and (2) an inherited abnormality of the central control of ventilation, most likely related to a common generalized membrane abnormality of the muscles and other tissues, including brain stem neurons that regulate breathing and sleep [587–591].

Sleep studies by Bye et al. [464] in four patients with myotonic dystrophy showed REM sleep-related O_2 desaturation and sleep disorganization. Several other authors have described alveolar hypoventilation, daytime somnolence, and periodic breathing in patients with myotonic dystrophy in single case reports and small and large series [517, 587–604].

Begin et al. [599] found a high prevalence of chronic alveolar hypoventilation in a series of 134 patients with myotonic dystrophy. The authors suggested that the central ventilatory control mechanism is abnormal in myotonic dystrophy patients, contributing to chronic alveolar hypoventilation. These authors concluded that the chronic alveolar hypoventilation resulted from a combination of inspiratory muscle weakness and loading. In addition, the presence of EDS suggested reduced central ventilatory drive or sleep apnea in these patients. The clinicopathologic study by Ono et al. [602] of one patient with myotonic dystrophy, alveolar hypoventilation, and hypersomnia supported the hypothesis postulated by Begin et al. [599]. On postmortem examination of this patient, Ono et al. [602] observed significant neuronal loss and gliosis in the midbrain and pontine raphe, as well as the pontomedullary reticular formation.

Park and Radtke [601] reviewed seven patients with myotonic dystrophy referred to their sleep disorder center. All patients had PSG. Five patients were subsequently given an MSLT. Each of the five who had an MSLT showed the evidence of moderate hypersomnia. Three of these five patients had two sleep-onset REM episodes, only one of whom showed the evidence of sleep apnea in the overnight PSG study. Human leukocyte antigen (HLA) typing was negative for DQW2, but DQW1 was present in two patients. The authors reviewed the literature available (they published their own paper in 1995) and found 86 patients, including their seven patients, with myotonic dystrophy who also had hypersomnolence. Ten percent of the reported patients with hypersomnolence had documented alveolar hypoventilation. Respiratory center hypoexcitability or myotonic muscle weakness is thought to be responsible for alveolar hypoventilation. Correction of hypoventilation does not always lead to improvement of EDS [597, 601]. SDB events were noted in 57 % of the reported patients with EDS, and both central and obstructive sleep apneas were observed. The presence of sleep-onset REMs in these patients supported the hypothesis of a primary CNS abnormality as the cause of EDS [601]. EDS in myotonic dystrophy patients often occurs in the absence of sleep apnea [600, 601]. EDS in their patients [601] responded to methylphenidate treatment. Martinez-Rodriguez et al. [603] measured CSF hypocretin-1 levels in six patients with myotonic dystrophy type 1 complaining of excessive daytime sleepiness who were HLA-DQB1*0602 negative and found to have significantly lower hypocretin-1 levels compared to the control values. The authors concluded that the dysfunction of the hypothalamic hypocretin system may be responsible for hypersomnia in myotonic dystrophy type 1. However, other authors [604, 605] did not find low CSF hypocretin levels in DM1 patients.

In summary, SDB including OSA and nocturnal hypoventilation, EDS, and REM sleep dysregulation are frequently noted in DM1 patients. There is reasonable explanation for the mechanism of sleep-related breathing disorder as stated above. However, an explanation for REM sleep dysregulation and EDS is not always obvious. In a case-control study including 40 DM1 patients and 40 controls, Yu et al. [590] observed EDS in 80 % of patients (ESS score was more than 10 in 31.4 %, and MSLT mean latency was less than 8 min in 12.5 %) and one SOREM in the majority of the patients, whereas two or more SOREMs were seen in about one-third of the patients. These authors also found higher REM density in patients than in controls. REM sleep dysregulation with two or more SOREMs or increased REM density in DM1 patients was also noted by Park et al. [601], Martinez-Rodriguez and coinvestigators [603], and Gibbs et al. [606]. It has been suggested that EDS and REM sleep dysregulation in DM1 patients are not necessarily related to SDB but may be due to an intrinsic CNS dysfunction involving sleep-wake-regulating neurons [590, 593, 600, 601, 604, 607].

Sleep disturbances have also been reported in proximal myotonic myopathy (PROMM), also known as myotonic dystrophy type 2 (DM2). PROMM is an autosomal dominant multisystem disorder caused by a CCTG repeat expansion in intron 1 of the zinc finger protein 9 gene (*ZNF9*), which is differentiated from myotonic dystrophy type 1 by the absence of a chromosome 19 CTG trinucleotide repeat that is associated with type 1 [608, 609].

DM2 has many overlapping clinical features with DM1 such as cataracts, myotonia, cardiomyopathy, autosomal dominant inheritance, diffuse muscle aches and pains, and insulin resistance, but differs from DMI in more proximal distribution of muscle weakness, later onset of the illness, slower progression, and genetic testing. Sleep disturbances including SDB and hypersomnolence have been described in many DMI patients (see above), but a description of sleep problems has been characteristically absent in DM2 until recently. In a brief report, the senior author described sleep disturbances in two sisters, aged 51 and 53, with PROMM [610, 611]. The patients had difficulty initiating sleep, EDS, snoring, frequent awakenings, and movements during sleep. Overnight PSG study showed decreased sleep efficiency, increased number of arousals, and sleep architecture abnormalities. One patient had absent REM sleep, and the other patient had dissociated REM sleep characterized by phasic REM bursts associated with EEG patterns showing sleep spindles and alpha intrusions. These sleep abnormalities in PROMM suggested involvement of the REM-NREM-generating neurons as part of a multisystem membrane disorder. Subsequently, our (SC) group reported more patients with DM2 showing SDB [612] and one with REM behavior disorder [613]. Many other investigators in case series and scattered case reports of DM2 reported a variety of sleep dysfunction including SDB, PLMS, EDS, RLS, and insomnia [614–618]. However, no systematic study involving a large number of DM2 patients with longitudinal follow-up is available. The MRI findings of white matter hyperintensity in T_2-weighted images in six patients from three families with PROMM described by Hund et al. [619] suggested brain involvement in PROMM, but the relationship between the sleep disturbances and the MRI abnormalities remains to be determined.

Acid Maltase Deficiency and Other Glycogen Storage Disorders

Alveolar hypoventilation has been described in several cases of mild-to-moderate myopathy associated with adult-onset acid maltase deficiency, a variant of glycogen storage disease, also known as Pompe disease. Pompe disease (or glycogen storage disease type II) is an autosomal recessive, serious, and often fatal disorder of glycogen metabolism. It is due to mutations in the acid alpha-glucosidase (GAA) gene, absence of which causes cardiorespiratory failure in the first year, whereas reduced GAA activity gives rise to progressive respiratory failure later in life [620, 621]. The disease may present in the early stage with diaphragmatic weakness causing hypoventilation, initially during REM sleep and later causing respiratory failure even during the daytime. Presence of macroglossia and significant tongue weakness should direct attention to upper airway dysfunction causing OSA. It is important to make the correct diagnosis early by performing electromyographic (EMG), biochemical, histochemical, or morphological examination of muscle biopsy samples, determination of low GAA activity in skin fibroblasts or blood samples, respiratory function, and genetic testing as specific treatment is now available. The Federal Drug Administration (FDA) in the USA and the European Authority recently approved alglucosidase alfa (recombinant human GAA, Myozyme, Genzyme Corporation, Cambridge, MA, USA) as enzyme replacement therapy (ERT) for the treatment of Pompe disease (biweekly intravenous infusion of 20 mg/kg body weight) [620, 621]. Subsequent clinical data suggest that ERT delays progression of symptoms, but many patients will require additional ventilator support, especially during sleep [620].

Bye et al. [464] described REM sleep-related hypoxemia and sleep disorganization in acid maltase deficiency. An adult patient with acid maltase deficiency with severe OSA and respiratory failure was reported by Margolis et al. [622]. Despite ventilatory support, the patient died. At postmortem examination, profound muscle replacement by fibrofatty tissue was noted in the tongue and diaphragm. The authors suggested that severe tongue weakness due to fatty metamorphosis associated with macroglossia contributed to the upper airway obstruction in this patient. The brain was not examined at the autopsy.

Other Varieties of Congenital Myopathies

Riley et al. [566] described alveolar hypoventilation in two patients with congenital myopathies (one with nemaline myopathy and the other with a myopathy of uncertain type). The patients' ventilatory response to carbon dioxide was absent, and the authors suggested that the alveolar hypoventilation may have been due to a primary defect in the central chemoreceptor control of breathing. Their other suggestion was that the sensory stimuli from skeletal muscle receptors (e.g., muscle spindles) may have played a role in the blunted hypercapnic ventilatory response by altering afferent input to the CNS. There are other reports of sleep hypoventilation in congenital myopathy [464, 579, 622– 624].

Miscellaneous Myopathies

Obstructive sleep apnea with sleep-related hypoxemia and sleep disturbances have also been described in patients with polymyositis [464, 517, 568, 625] including inclusion body myositis [626] and mitochondrial encephalomyopathy [627–630].

Neuromuscular Junction Disorders

Myasthenia gravis, myasthenic syndrome, botulism, and tick paralysis are several neuromuscular junction disorders

characterized by easy fatigability of the muscles, including the bulbar and other respiratory muscles, owing to failure of neuromuscular junctional transmission of the nerve impulses. The most important of these conditions is *myasthenia gravis*, an autoimmune disease characterized by a reduction in the number of functional acetylcholine receptors in the postjunctional region. Acute respiratory failure is often a dreaded complication of myasthenia gravis, and patients need immediate assisted ventilation for life support [91, 514, 515]. The respiratory failure, moreover, may be mild during wakefulness but may deteriorate considerably during sleep.

An important study by Quera-Salva et al. [631] reported the pulmonary function and PSG studies of 16 women and 4 men whose mean age was 40 years and who were diagnosed and treated for myasthenia gravis. Polysomnographic findings included moderately disturbed nocturnal sleep with an increase in stage 1 NREM and decreased slow-wave and REM sleep. Eleven patients had an RDI of 5 or higher. They had central, obstructive, and mixed apneas and hypopneas accompanied by decreased O_2 saturation. All patients with REM sleep-related apneas or hypopneas had disturbed nocturnal sleep with a sensation of breathlessness. Twelve patients had insufficient sleep owing to awakening in the middle of the night and early morning hours with a sensation of breathlessness. Four of the 12 patients also had daytime hypersomnolence. The authors suggested that those patients of advancing age, moderately increased BMI, abnormal pulmonary function results, and daytime abnormal blood gas concentrations are at particular risk for SDB. Since this report, there have been a few other reports of SDB in patients with myasthenia gravis [632–635].

Manni et al. [632] studied breathing patterns during sleep in 14 patients with mild generalized myasthenia gravis. Polysomnographic study documented infrequent central apneas, mainly during REM sleep, in five patients associated with O_2 desaturation. Putman and Wise [633] described a 54-year-old woman with myasthenia gravis and episodes of shortness of breath, which were more severe at night. The flow-volume loops suggested extrathoracic airway obstruction. They also surveyed a total of 61 myasthenia gravis patients referred to their pulmonary function laboratory during 42 months. They found a pattern of extrathoracic upper airway obstruction in 7 of the 12 patients who had flow-volume loops. Nicolle et al. [634] randomly selected 100 patients with myasthenia gravis out of 400 patients from their database. They found a prevalence of OSA of 36 % based on PSG study in 50 patients compared to an expected prevalence of 15–20 % of the general population. The prevalence of OSAS (those with daytime sleepiness) was 11 % compared to 3 % in the general population. The authors suggested that it is important to inquire about OSA symptoms in myasthenia gravis patients for adequate management of fatigue in these patients. Prudlo et al. [635] investigated sleep and breathing in 19 myasthenia gravis patients utilizing two consecutive overnight PSG studies. These authors found clinically relevant SDB in terms of OSA (defined as an RDI of > 0/h) in only four patients, who had also a few central apneas. The authors failed to confirm the high occurrence of central respiratory events during sleep and also failed to find a causal relationship between medically stable myasthenia gravis and OSA. Thus, some investigators observed more central than obstructive apneas [632], whereas others noted predominantly obstructive apneas. The final answer remains to be determined. Some investigators [636] reported a high prevalence of patient-reported sleep disturbance which was correlated with disease severity, while some other researchers [637] reported a high prevalence of RLS in MG compared with controls.

Fernandes Oliveira and coinvestigators [638] made a meta-analysis of 17 cross-sectional observational or clinical studies assessing the quality of sleep in MG patients published between 1970 and 2014. They found that the literature is limited and the evidence for sleep dysfunction in MG is inconclusive because some studies reported poor sleep quality, EDS, RLS, and SDB in patients with MG, whereas others did not report such associations. The authors recommended further research to investigate sleep dysfunction in MG.

Myasthenic syndrome, or Lambert–Eaton syndrome, is a disorder of the neuromuscular junction in the presynaptic region and is often a paraneoplastic manifestation, mostly of oat cell carcinoma of the lungs. Patients complain of muscle weakness and fatigue involving the limbs accompanied by decreased or absent muscle stretch reflexes and characteristic electrodiagnostic findings that differentiate this from myasthenia gravis. Very few data exist on SDB and sleep dysfunction in Lambert–Eaton myasthenic syndrome.

Botulism caused by *Clostridium botulinum* and tick paralysis caused by the female wood tick *Dermacentor andersonii* may also cause neuromuscular junctional transmission defects, which are due to released toxin, and may cause respiratory failure and sleep dysfunction, but adequate studies have not been performed.

Sleep and Breathing Disorders in Autonomic Failure

Anatomically and functionally, sleep, breathing, and the autonomic nervous system (ANS) are closely interrelated [91, 639–644]. To understand the sleep and breathing disorders in autonomic failure, it is important to understand the functional anatomy of sleep, control of breathing, and the central autonomic network. A brief review of the functional anatomy of sleep is given in the beginning of this chapter, and the neurophysiology of sleep is also described

extensively in Chaps. 5 and 8. Functional neuroanatomy of respiration, control of breathing during sleep and wakefulness, and the central autonomic network with its integration of sleep and breathing are reviewed briefly in Chap. 11.

In all of these conditions, respiratory muscles may be affected and patients may require assisted ventilation. They can exhibit sleep hypoventilation and sleep apnea. Profound functional changes occur during sleep in circulation, respiration, thermoregulation, and the gastrointestinal and urogenital systems due to alterations in autonomic outflow [639, 640] (see also Chap. 11). Thus, sleep has an important effect on the functions of the ANS, and dysfunction of the ANS may have significant impact on human sleep. Sleep and breathing disorders have in fact been described in many patients with autonomic failure. It is also important to remember that the peripheral respiratory receptors, the central respiratory neurons, and the hypnogenic neurons in the preoptic-hypothalamic area and the region of the NTS in the medulla are intimately linked by the ANS, making it easy to comprehend why sleep and breathing disorders should be associated with autonomic failure.

Autonomic failure (AF) may be classified into primary and secondary types. Primary autonomic failure (without known cause) includes pure autonomic failure without any somatic neurologic deficits (Bradbury–Eggleston syndrome), multiple system atrophy (MSA) formerly known as Shy–Drager syndrome, postural tachycardia syndrome (PoTS), familiar dysautonomia, and autoimmune autonomic neuropathy or acute pan-dysautonomia. The most well-known condition with autonomic failure in which sleep and respiratory disturbances have been reported and well described is MSA with progressive autonomic failure. In a consensus statement [645] in 1996 sponsored by the American Autonomic Society and the American Academy of Neurology, *multiple system atrophy* is the favored term, replacing *Shy–Drager syndrome.* MSA defines a sporadic, adult-onset progressive disorder characterized by autonomic dysfunction, parkinsonism, and ataxia in any combination. *Striatonigral degeneration* is the term used when the predominant feature is parkinsonism. The term *sporadic olivopontocerebellar atrophy* is used when cerebellar features are present. Finally, when autonomic failure is the predominant feature, the term *Shy–Drager syndrome* is often used. Familial dysautonomia, a recessively inherited primarily autonomic failure, is also known to be associated with disturbances of breathing and sleep. Congenital central hypoventilation syndrome (CCHS) (see Chap. 33), another autosomal dominant familial disorder due to mutations of PHOX 2B gene, has recently been considered to be a disorder of autonomic regulation, although classified in the ICSD-3 [101] under the category of "Sleep-related Hypoventilation Disorders." A large number of neurologic and general medical disorders are associated with prominent secondary autonomic failure. In many patients with diabetic autonomic neuropathies, amyloid neuropathy, and GBS, sleep and sleep-related respiratory disturbances have been noted. In many neurologic conditions, sleep and respiratory disturbances are secondary to the structural lesions involving the central hypnogenic or respiratory neurons. Some examples of neurodegenerative diseases with autonomic failure and sleep dysfunction are PD (see Chap. 39) and DLBD with dementia (see earlier section) and fatal familial insomnia (FFI), a rare prion disease with severe sleep disturbances and dysautonomia (see later in this chapter). Finally, some primary sleep disorders, such as chronic insomnia disorder, narcolepsy-cataplexy and upper airway OSAS, a very common primary sleep disorder, may be associated with autonomic deficits.

Multiple System Atrophy with Progressive Autonomic Failure (Shy–Drager Syndrome)

In 1960, Shy and Drager [646] described a neurodegenerative disorder characterized by autonomic failure and MSA. Since their description, there have been many reports [87, 91, 99, 640, 647–660] of the condition, which has generally come to be known as *Shy–Drager syndrome* or *multiple system atrophy with progressive autonomic failure.* MSA defines a sporadic adult-onset progressive disorder of multiple systems characterized by autonomic dysfunction, parkinsonism, and cerebellar ataxia in various combinations (Box 41.5). A second consensus conference held in 2007 published new diagnostic criteria for definite, probable, and possible MSA (Box 41.6) [656].

Box 41.5 Salient Clinical Manifestations of Multiple System Atrophy [77]

A. Autonomic Features

1. Cardiovascular
   - Orthostatic hypotension,
   - Postprandial hypotension,
   - Postural syncope,
   - Postural dizziness, faintness, or blurring of vision,
   - Orthostatic intolerance.

2. Genitourinary
   - Urinary bladder dysfunction (incontinence, hesitancy, frequency, nocturia),
   - Impotence in men.

3. Sudomotor
   - Hypohidrosis or anhidrosis,

4. Gastrointestinal
   - Gastroparesis,

- Intermittent diarrhea or constipation (intestinal or colonic dysmotility),
- Abnormal swallowing (esophageal dysmotility).

5. Ocular
   - Horner's syndrome,
   - Unequal pupils.

B. Nonautonomic Manifestations

1. Parkinsonism
   - Rigidity,
   - Bradykinesis or akinesis,
   - Postural instability.
2. Cerebellar dysfunction
   - Ataxic gait,
   - Scanning speech,
   - Dysmetria,
   - Dysdiadochokinesia,
   - Intention tremor.
3. Upper motor neuron signs
   - Extensor plantar responses,
   - Hyper-reflexia
   - Spasticity.
4. Lower motor neuron signs
   - Muscle wasting,
   - Fasciculations.
5. Respiratory
   - Sleep apnea-hypopnea,
   - Other respiratory dysrhythmias,
6. REM sleep behavior disorder
7. Cognitive decline (5–26 %)
8. Normal sensation.

Box 41.6 Criteria for the Diagnosis of Multiple System Atrophy (MSA) Based on Second Consensus Statement [617]

Definite MSA

- A sporadic, progressive adult-onset (>30 years of age) disease with neuropathologic demonstration of α-synuclein-positive glial cytoplasmic inclusions in the CNS,
- Evidence of neurodiagnostic changes in striatonigral or olivopontocerebellar structures.

Probable MSA

- A sporadic, progressive adult-onset (>30 years of age) disease with the evidence of autonomic dysfunction (e.g., orthostatic fall of blood pressure by at least 30 mm Hg systolic or 15 mm Hg diastolic within 3 min of standing, urinary incontinence, or erectile dysfunction in men)
- Parkinsonian features (e.g., bradykinesia, rigidity, tremor, and postural instability) that are poorly levodopa responsive, or
- Cerebellar features (e.g., gait and limb ataxia, scanning dysarthria, and cerebellar type of oculomotor dysfunction).

Possible MSA

- A sporadic, progressive adult-onset (>30 years of age) disease with parkinsonian features or cerebellar features or
  evidence of at least one autonomic dysfunction (orthostatic fall of blood pressure should be significant, which may not meet the level required for probable MSA).
- Presence of at least one of the following additional features (either a clinical or a neuroimaging abnormality):
  – stridor and hyper-reflexia with Babinski sign.

Possible MSA-P

- Parkinsonian or cerebellar features; dysphagia within 5 years of motor onset; olivopontocerebellar or putaminal atrophy on brain MRI; FDG-PET hypometabolism in putamen, brain stem, or cerebellum.

Possible MSA-C

- Cerebellar features; presynaptic nigrostriatal dopaminergic denervation on SPECT or PET scan; olivopontocerebellar or putaminal atrophy on MRI; FDG-PET hypometabolism in putamen, brain stem, or cerebellum.

CNS central nervous system; *FDG-PET* fluorodeoxyglucose positron-emission tomography; *MRI* magnetic resonance imaging; *PET* positron-emission tomography; *SPECT* single-photon-emission computed tomography.

Patients frequently manifest sleep and respiratory disturbances. Initially, they present with autonomic failure of both the sympathetic and the parasympathetic systems. They may present with symptoms related to orthostatic hypotension (e.g., postural dizziness and faintness or even frank loss of

consciousness in the erect posture), urinary sphincter dysfunction (e.g., frequency, urgency, hesitancy, dribbling, and overflow incontinence), hypohidrosis or anhidrosis, and impotence in men. After 2–6 years, patients lapse into the second stage, showing some combination of cerebellar, extrapyramidal, upper motor neuron, and lower motor neuron dysfunction, including bulbar deficits. Most patients manifest a parkinsonian-cerebellar syndrome. In some, atypical parkinsonian features (e.g., bradykinesia, rigidity, and postural instability) predominate; in others, pancerebellar dysfunction predominates. There has been an increasing evidence of cognitive decline in MSA [661, 662]; however, cognitive deficits are poorly recognized in this condition and in fact are listed as nonsupportive diagnostic features in the latest consensus diagnostic criteria [656] for MSA. In the later stages of the illness, a variety of respiratory and sleep disturbances add to the progressive disability. Occasionally, respiratory dysfunction, particularly dysrhythmic breathing in wakefulness that becomes worse during sleep, manifests in the initial stage of the illness [663]. In the final stage, progressive autonomic and somatic dysfunctions are compounded by respiratory failure. Ventilatory disturbances now may be present in both wakefulness and sleep. Pathologically, there are various combinations of striatonigral degeneration, OPCA, and degeneration of the autonomic neurons. A distinctive neuropathologic alteration in MSA is thought to be the presence of argyrophilic oligodendroglial cytoplasmic inclusions in the cortical motor, premotor, and supplementary motor areas; extrapyramidal and corticocerebellar systems; brain stem reticular formation; and supraspinal autonomic systems and their targets [653]. This inclusion-bearing oligodendroglial degeneration may cause or contribute to the manifestations of clinical symptoms in MSA. In fact, Wenning et al. [654] recently hypothesized that MSA is a primary oligodendrogliopathy, followed by the secondary selective neurodegeneration. In fact, a prion-like transfer of α-synuclein from neurons to oligodendrocytes has been suggested to be playing a crucial role in the pathogenesis and progression of MSA [659].

Sleep Disturbances

Patients with autonomic failure (primary or secondary) often have sleep dysfunction. There is a bidirectional relationship between disorders of ANS and sleep [644, 664, 665]: Sleep disorders may affect ANS functions, and ANS disorders may affect physiology of sleep. Because of this close associated, every patient presenting with AF should be questioned about sleep dysfunction; similarly, one should be vigilant about a possible autonomic impairment in a primary sleep disorder and look for clues to AF.

Sleep dysfunction is very common in MSA and includes insomnia with sleep fragmentation; EDS and RBD, which may occasionally be the presenting feature [666, 667]; and sleep-related respiratory dysrhythmias. RBD is very common, being present in 80–95 % of MSA patients [200, 664–677]. The characteristic clinical features of RBD include intermittent loss of REM-related muscle atonia and appearance of a variety of abnormal motor activities during sleep. The patient presents a violent dream-enacting behavior during REM sleep, often causing self-injury or injury to the bed partner. RBD may precede the illness or may present concomitantly or after the onset of MSA [664–677]. Positron-emission tomography (PET) and single-photon-emission computed tomography (SPECT) studies by Gilman et al. [671] suggested that RBD in MSA is related to nigrostriatal dopaminergic deficit. In other cases, RBD in MSA may be due to the neuropathologic changes in the brain stem REM-generating neurons.

The most common sleep disorders in MSA result from a variety of sleep-related respiratory dysrhythmias similar to those described in other neurologic conditions (see Fig. 41.9). The most common types of respiratory dysrhythmias consist of sleep apnea and hypopnea associated with repeated arousals and hypoxemia [85, 87, 91, 663, 664, 671, 678, 692], dysrhythmic breathing [87, 91, 663], and laryngeal stridor due to laryngeal abductor paralysis [647, 648, 684, 689–692]. Less commonly, apneustic breathing [679] and inspiratory gasping [85, 90, 647, 684] may occur. Hypersomnia often results from nocturnal sleep disruption. Sudden nocturnal death in patients with MSA in some cases probably is due to respiratory arrest and other cardiorespiratory abnormalities. Sleep-related respiratory dysrhythmias in MSA are present in almost 100 % of the cases in the advanced stages of the illness. Polysomnographic studies may show the following: a reduction of total sleep time, decreased sleep efficiency, increased number of awakenings during sleep, a reduction of slow-wave and REM sleep, absence of muscle atonia in REM sleep in those with RBD, and a variety of respiratory dysrhythmias. Laryngeal stridor and excessive snoring resulting from laryngeal abductor paralysis have been described in cases of MSA by several groups [648, 680, 682–684, 689–692]. The nocturnal stridor can be inspiratory, expiratory, or both and can cause upper airway obstruction during sleep. The stridor may result in a striking noise likened to a donkey's braying [87, 648]. Williams's group [682] noted this abnormality in 8 of 12 cases. The stridor can be relieved by tracheostomy. The group led by Guilleminault [685–687] described eight patients with predominantly upper airway OSA associated with O_2 desaturation.

In our early study of four patients with MSA [99], we observed periodic central apnea in the erect position

(Fig. 41.12) and CSB in one patient during the last stage of the illness. Impaired hypercapnic ventilatory response and mouth occlusion pressure response in the supine position in one patient suggested impairment of the metabolic respiratory system, whereas normal hypercapnic and hypoxic ventilatory responses in another patient (in the presence of an abnormal respiratory pattern resembling that noted by Lockwood [678]) suggested that the chemoreceptor control and respiratory pattern generator were probably subserved by different populations of neurons rendered selectively vulnerable in MSA. The neuropathologic findings in the same patient with impaired chemoreceptor response—neuronal loss and astrocytosis in the pontine tegmentum—suggested involvement of the respiratory neurons in the brain stem. In a later study [85, 87], we described 10 other patients with MSA who showed central apnea, including CSB or Cheyne–Stokes variant type breathing and upper airway obstructive and mixed apneas accompanied by O_2 desaturation, predominantly during NREM sleep stages 1 and 2 and REM sleep (Fig. 41.26). During sleep, seven patients had central apnea, two had upper airway OSA, and three had mixed apneas. The AHI varied from 20 to 80; the duration of apneas ranged from 10 to 65 s. The variation in the heart rate during apneic and eupneic cycles was not seen in these patients with the evidence of cardiac autonomic denervation. This finding was in contrast to the bradyarrhythmias and tachyarrhythmias noted during apnea and immediately after resumption of normal breathing in patients with primary sleep apnea syndrome [88]. Four patients had several episodes of central apneas during relaxed wakefulness; it was as if the respiratory center "forgot" to breathe. Two patients had inspiratory gasps and two required tracheostomy for respiratory dysrhythmia. All-night PSG studies in two patients revealed the following sleep abnormalities in addition to recurrent episodes of sleep apneas accompanied by O_2 desaturation: marked reduction of NREM sleep stages 3 and 4 and REM sleep, increased awakenings after sleep onset, snoring, and excessive body movements and frequent arousal responses in the EEG. In 8 of 10 patients, dysrhythmic breathing occurred mostly during sleep, although in 4 of these 8 it was also present during wakefulness; this finding suggests that this type of respiratory dysrhythmia is very common in MSA. These observations are in agreement with the suggestion of McNicholas et al. [663] that such findings imply an impaired respiratory pattern generator in these patients.

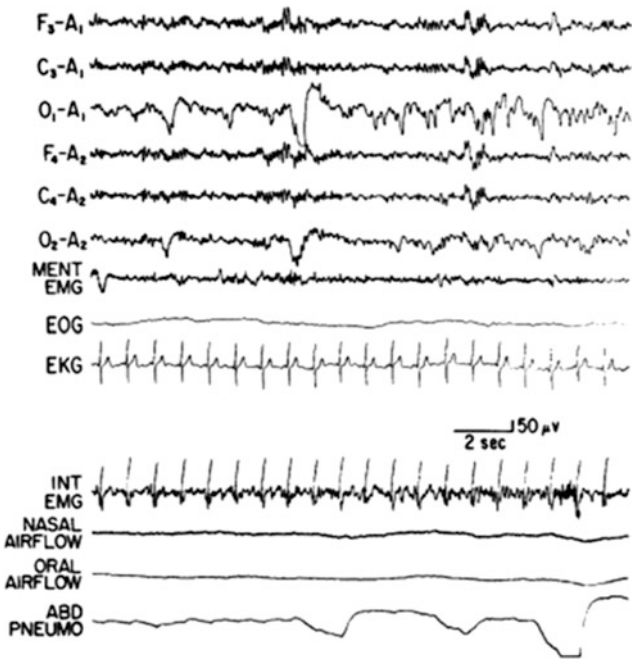

Fig. 41.26 A portion of an episode of mixed apnea during stage 2 NREM sleep associated with oxygen desaturation in a patient with multiple system atrophy. The electroencephalogram (EEG) is shown in the top six channels. Also shown are electromyography (EMG) of the mentalis (MENT) and intercostal (INT) muscles, electrocardiogram (EKG), nasal and oral airflow, and abdominal pneumogram (ABD PNEUMO). Reproduced with the permission from Chokroverty [91]

Mechanisms of Ventilatory Dysrhythmia

There is ample evidence in the literature [85, 87, 108, 646–648, 653–655, 657, 659, 660] of pathologic involvement of the pontine tegmentum, reticular formation, NTS, nucleus ambiguus, hypoglossal nucleus, and, in some patients, anterior horn cells of the cervical and thoracic spinal cord. Lockwood [678] and Chokroverty et al. [99] correlated the physiologic and clinical findings of respiratory dysrhythmias with a direct involvement of the regions of the brain stem that contain the respiratory neurons. In addition, physiologic studies of respiratory control [99, 663] showing impairment of hypercapnic and hypoxic ventilatory and mouth occlusion pressure responses indirectly suggested an impairment of the metabolic respiratory control system. Vagal and sympathetic denervation in these patients is firmly established [327, 644, 646, 659, 660]. The pathogenic mechanisms for the respiratory dysrhythmia include all that had been postulated in the beginning of this chapter for the respiratory dysrhythmias in neurologic disorders. Additional mechanisms for the respiratory dysrhythmia in MSA have been suggested [85]: interference with the forebrain, midbrain, and pontine inputs to the medullary respiratory neurons causing dysrhythmic and apneustic breathing; involvement of the direct projections from the hypothalamus and central nucleus of the amygdala to the respiratory neurons in the NTS and nucleus ambiguus; affection (loss of neurons) [644, 693] of the parabrachial nucleus (PBN) and the adjacent Kölliker–Fuse nucleus (KFN) in the pons which are responsible for respiratory rhythmogenesis and control of upper airway

resistance and have reciprocal connections with the medullary respiratory neurons including laryngeal motoneurons of the nucleus ambiguus; involvement of the vagal afferents from the lower and upper airway receptors, which would reduce the input to the central respiratory neurons, causing respiratory dysrhythmia; sympathetic denervation of the nasal mucosa causing increased nasal resistance, thus promoting upper airway obstructive apnea; and discrete neurochemical alterations that may interfere with the normal regulation of breathing.

There is experimental evidence that noradrenaline, serotonin, and dopamine play distinct roles in the control of breathing [644, 694]. Patients with MSA have been found to have low levels of dopamine and noradrenaline in the basal ganglia, the limbic-hypothalamic regions including the septal nuclei, and the LC [695]. Furthermore, these patients may also have specific catecholamine enzyme deficits in the brain and sympathetic ganglia [696]. SPECT findings by Gilman et al. [697] suggested decreased pontine cholinergic projections to the thalamus contributing to OSA in MSA. Finally, in a series of postmortem studies of brains obtained from patients with MSA, Benarroch and colleagues reported depletion of catecholaminergic neurons in the ventrolateral medulla [698], A5 noradrenergic neurons [699], cholinergic neurons in the medullary arcuate nucleus [700], corticotrophin-releasing factor neurons [701] in the putative pontine micturition center, mesopontine cholinergic neurons in the PPT and LDT nucleus [702, 703], ventrolateral medullary neurokinin 1 receptor-like immunoreactive neurons [704], chemosensitive glutamatergic and serotoninergic neurons in the arcuate nucleus in the ventral medullary surface as well as serotoninergic neurons in the medullary raphe [705], serotoninergic neurons in the pontomedullary raphe [706], and neurons in the ventrolateral nucleus ambiguus innervating the heart and dorsal vagal nucleus-innervating enteric neurons [707], loss of hypocretin (orexin) hypothalamic neurons [708], and loss of PBN and KFN in the pons [709]. Loss of these cell groups may contribute to the respiratory disturbances, including loss of automatic respiration and other autonomic dysfunction involving various systems in MSA [644, 693, 709].

Vetrugno et al. [710] performed video-PSG study in 19 consecutive MSA patients and documented RBD in 100 % of the patients, stridor in 42 %, OSA in 37 %, and PLMS in 88 %. Plazzi et al. [668] documented RBD in 90 % of 39 consecutive MSA patients. RBD preceded in 44 %, appeared concomitantly in 26 %, and followed the onset of MSA symptoms in 30 % of the patients. They also noted OSA, stridor, and PLMS in some patients. Ghorayeb et al. [711], based on a standard sleep questionnaire, reported a variety of sleep disorders in 70 % of 57 unselected patients with MSA: sleep fragmentation (52.5 %), vocalization (60 %), RBD (47.5 %), and nocturnal stridor (19 %). They noted that severity of motor symptoms, disease duration, comorbid depression, and the duration of levodopa treatment correlated with sleep problems. Silber and Levine [712], after reviewing 42 patients with MSA (17 with nocturnal stridor and 25 without stridor), concluded that survival is shorter in those with stridor than in those without stridor. There are several other reports of stridor, particularly nocturnal stridor and sudden nocturnal death resulting presumably from laryngeal obstruction, in some MSA patients. Iranzo et al. [713] reported sleep disturbances in all 20 patients with MSA and vocal cord abduction dysfunction in 14 (70 %) of their 20 patients in a prospective study. Following CPAP treatment, laryngeal stridor and obstructive apneas were eliminated in three patients. Iranzo et al. [714] followed 13 MSA patients with stridor for months and reported beneficial effects of long-term CPAP therapy. In addition to improvement in the quality of sleep, these authors found similar median survival in patients with and without stridor. In a later study of 22 MSA patients, Ghorayeb et al. [715] found 3 with OSA without stridor and 15 with stridor alone or accompanied by apnea. They administered CPAP treatment in 12 of these patients. Two, however, died shortly after CPAP titration and one died 17 months later. Five patients discontinued the use of CPAP because of discomfort, and only four continued CPAP with improvement of sleep and daytime alertness. The authors concluded that the severity of motor impairment at the time of initial CPAP is the most significant factor for long-term CPAP acceptance.

Postural Tachycardia Syndrome

PoTS, also known as orthostatic intolerance syndrome, is an entity still in search of an identity, and the clinical manifestations are still evolving. Sleep dysfunction, which is often an important complaint of patients with PoTS, has largely been neglected in the literature [716]. The clinical diagnostic criteria for PoTS include symptoms of orthostatic intolerance accompanied by heart rate of 120 beats/min or more, or a heart rate increment of 30 beats/min or more on changing from supine to upright position within 5 min of standing or head-up tilt [717]. The symptoms of orthostatic intolerance include faint feelings, dizziness, palpitations, nausea, tremulousness, anxiety, and visual blurring on standing without significant orthostatic hypotension. The other symptoms of these patients include extreme fatigue, diffuse muscle aches and pains, and upper and lower gastrointestinal symptoms, as well as sleep dysfunction [718, 719]. Some patients may complain of sleep-onset or maintenance insomnia, whereas others may have daytime hypersomnolence or circadian rhythm disorders. Some patients may complain of fatigue, which is a very common

manifestation and may be difficult to differentiate from EDS. Sleep-onset and maintenance insomnia in patients with PoTS may be related to inadequate sleep hygiene, diffuse muscle aches and pains, and anxiety. Daytime hypersomnolence may be secondary to OSA, sleep deprivation at night, or depression in some patients. Circadian rhythm disorder in an occasional patient suggests a dysfunction of the circadian clock in the SCN.

Bagai et al. [720] using only a battery of questionnaires without any objective data in 44 patients with PoTS and 46 controls reported higher subjective daytime sleepiness, fatigue, and poor health-related quality of life. In a subsequent study [721], the same group using wrist actigraphy as an objective measure of sleep studied 36 patients with PoTS and equal number of healthy controls and observed significantly reduced sleep efficiency (SE), self-reported (subjective) sleep problems (restless sleep), and morning tiredness in PoTS patients. The authors suggested that sleep-onset latency mismatch between subjective and objective data is indicative of paradoxical insomnia (sleep state misperception). Furthermore, their other observations of increased upright plasma norepinephrine levels correlating with actigraphic sleep-onset latency may have contributed to a hyperarousal state and consequent insomnia.

In an important study, Mallien and coinvestigators [722] obtained overnight PSG and heart rate variability (HRV) using a fast Fourier transform (FFT) algorithm in addition to subjective scales in 38 PoTS patients and 31 healthy controls. The only significant abnormality in the PSG is higher percentage of stage N2 in patients than in controls; one patient had predominantly REM-related obstructive sleep apnea. The authors suggested that the increased amount of stage N2 is similar to that noted in patients with insomnia disorder which they provided as a supportive evidence for PoTS patients having a primary sleep disorder. This suggestion, however, may not be acceptable to the entire sleep community. Their other finding of reduced HRV during different sleep stages in PoTS patients may have indicated either a cardiac dysautonomic neuropathy or a hyperadrenergic state [719].

In contrast, Pengo and collaborators [723] did not find any abnormal PSG findings in 37 patients with PoTS seen in a single sleep clinic nor any objective daytime sleepiness assessed by MSLT. However, HRV studied by the FFT analysis showed an association between enhanced parasympathetic nervous system activation at night and subjective daytime sleepiness assessed by ESS, implying an altered ANS in PoTS patients.

Previously, Thieven et al. [724], after retrospectively reviewing 152 medical records, noted that 31.6 % of PoTS patients had sleep disturbances and 48 % had severe fatigue.

Thus, objective data (PSG finding) have been inconsistent. The subjective findings, however, of EDS and fatigue have been noted consistently in PoTS patients. Similar to pathophysiologic mechanisms, the pathogenesis of fatigue and subjective EDS in patients with PoTS remains controversial.

It is important to pay attention to sleep dysfunction in these patients as treatment combining pharmacologic therapy (short-term hypnotic or selective serotonin reuptake inhibitor) and nonpharmacologic treatment (sleep hygiene, stimulus control therapy, relaxation techniques, appropriately timed bright-light exposure, or CPAP in appropriate patients) may be beneficial in such patients. An adequate number of patients with PoTS using both subjective and objective (e.g., PSG and actigraphy) data with longitudinal follow-up have not been studied prospectively to understand the pathophysiology of sleep dysfunction in this syndrome.

Familial Dysautonomia (Riley–Day Syndrome)

Riley–Day syndrome is a recessively inherited disorder associated with autonomic failure. The condition usually presents in childhood and is peculiar to the Ashkenazi Jewish population. This neurodevelopmental disorder results from IKBKAP gene mutation [725] causing marked reduction of IKAP protein in the CNS which is responsible for the clinical manifestation. The clinical features consist of a variety of autonomic and somatic manifestations [726–728]: autonomic, neuromuscular, cardiovascular, gastroesophageal, skeletal, renal, and respiratory abnormalities; absence of the fungiform papillae of the tongue; defective lacrimation and sweating; vasomotor instability and fluctuation of blood pressure (postural hypotension and paroxysmal hypertension); relative insensitivity to pain; and absent muscle stretch reflexes. Sleep dysfunction, associated with both CSAs and OSAs, has been described in most of these patients [729]. Sleep abnormalities consist of increased awakenings; delayed sleep onset, including prolonged REM sleep onset (but reduced REM sleep time); and sleep apneas. Patients with familial dysautonomia often have prolonged breath-holding spells, owing to defective responses of central respiratory neurons to changes in $Paco_2$.

Gadoth et al. [729] performed PSG recordings in 13 patients (7 women and 6 men aged 5–31 years) with familial dysautonomia to investigate the role of ANS in sleep and breathing disorders in this condition. All had sleep apneas (an average of 73.5/night), 11 had central apnea, and 2 had OSA. REM latency was prolonged, with decreased amount of REM in some patients, and adults also had increased sleep latency. All had orthostatic hypotension, and cardiac responses during apnea were absent, indicating cardiac autonomic denervation.

Guilleminault et al. [687] described two adolescent girls with familial dysautonomia who had respiratory

irregularities. One also had esophageal reflux during sleep that gave rise to sleep disturbances due to frequent awakenings. McNicholas et al. [94] described dysrhythmic breathing in a patient with familial dysautonomia similar to the irregular breathing noted in patients with MSA. Carroll et al. [730] obtained cardiorespiratory home monitoring during sleep and wakefulness in 25 children with familial dysautonomia and 25 age- and sex-matched controls. They found higher daytime respiratory variability compared with controls, suggesting alterations in central rhythm generating circuits associated with reduced parasympathetic drive in patients. An infant with familial dysautonomia with episodic somnolence lasting for 4–15 h during the neonatal period has also been reported [731].

Secondary Autonomic Failure

Many medical and neurologic conditions have associated autonomic neuropathies with or without peripheral neuropathies, but in most of these conditions, sleep and respiratory dysfunctions have not been adequately studied [87, 732–734]. However, there are many reports of such studies in diabetic polyneuropathies associated with autonomic neuropathy. This combination of somatic and autonomic neuropathies has been observed in some patients with acute inflammatory polyradiculoneuropathy (GBS), amyloidosis, and paraneoplastic autonomic neuropathy.

Rees et al. [735] observed 30 or more apneic episodes (in two patients mainly central and in one predominantly obstructive) during sleep at night in three of eight patients with diabetic autonomic neuropathy. In contrast, eight diabetes patients without autonomic neuropathy exhibited no sleep-related respiratory dysrhythmias. The authors speculated that sudden cardiorespiratory arrests that have been noted in some patients with diabetes may be related to autonomic failure and sleep apneas.

Mondini and Guilleminault [736] obtained PSG recordings for 12 type 1 and seven type 2 diabetes. They found obstructive and central apneas and an irregular pattern of breathing in five of 12 type 1 patients. They noted OSA in only one of seven type 2 diabetes. Autonomic neuropathy was present in all three type 1 patients with diabetes.

The findings of Catterall et al. [737], however, do not support the findings reported above of patients with diabetic autonomic neuropathy. They studied eight patients who had autonomic neuropathy and eight who did not and found no significant difference in frequency of apnea between the two groups.

Bottoni et al. [738] described obstructive sleep apnea/hypopnea with a frequency of more than 30 % in adult, nonobese diabetes with autonomic neuropathy independent of the severity of their dysautonomia.

Neurodegenerative Disease with Autonomic Failure and Sleep Dysfunction

Two neurodegenerative diseases, PD and DLBD, are associated with autonomic failure and sleep disturbances [739–745]. They are considered synucleinopathies, which are a group of disorders with abnormal deposition of α-synuclein in the cytoplasm of neurons or glial cells.

In PD, sleep dysfunction is present in 70–90 % of cases, with progressive impairment with the progression of the disease (see Chap. 39). Sleep disturbances and sleep-related respiratory dysrhythmias are common in patients with PD, especially those with the evidence of autonomic failure [103]. Distinguishing L-dopa-responsive idiopathic PD with autonomic failure from L-dopa-nonresponsive MSA with predominant parkinsonism and dysautonomia may be difficult but important for prognosis and treatment.

Symptomatic orthostatic hypotension, including syncope, occurs in up to 30 % of patients with DLBD [739–744], sometimes as the presenting feature. Other dysautonomic features in DLBD may include urogenital disturbance.

Fatal familial insomnia (see further on) is also associated with significant dysautonomia, particularly sympathetic hyperactivity.

Cardiac Arrhythmias and Autonomic Deficits in Obstructive Sleep Apnea Syndrome

Several varieties of cardiac dysrhythmias are noted in patients with OSAS as a result of changes in the ANS. These are described in Chap. 47.

Other Primary Sleep Disorders with Autonomic Dysfunction

Autonomic dysfunction has been reported in insomnia disorders, narcolepsy-cataplexy, idiopathic RBD (iRBD), sleep terror, RLS/WED, and idiopathic hypersomnia. In all of these conditions, autonomic dysfunction is mild generally and is not a major contributor of morbidity.

In insomnia, sympathetic hyperactivity (as manifested by increased LF component in the EKG spectral analysis, increased urinary excretion of catecholamine, and increased resting pulse rate) may partly account for the hyperarousal hypothesis in this condition [102].

Klein et al. [746] studied autonomic function in 15 consecutive patients with narcolepsy and 15 matched controls prospectively using a variety of scales (e.g., SCOPA-AUT, Parkinson's disease nonmotor symptoms [PDNMS], and others) and found frequent dysautonomia in all domains except sexuality in the patients. Limitations of this study

include small sample size, inability to exclude medication effect, and the absence of objective autonomic function tests. An impaired autonomic control of the cardiovascular system in narcolepsy has been mentioned in a review chapter by Calandra-Buonaura and Cortelli [664].

Patients with idiopathic hypersomnia may have symptoms suggestive of autonomic dysfunction, such as orthostatic intolerance, perception of temperature dysregulation, cold hands, and feet [101]. The presence of ANS abnormality has often been quoted as a differentiating feature from narcolepsy, but as stated above, narcoleptics may also have subtle ANS dysfunction.

Mahowald and Schenck [747] first directed our attention to the possibility of ANS dysfunction in iRBD by pointing out that the heart rate did not rise appropriately during abnormal movements and stage transitions in RBD patients. Subsequently, several studies have documented ANS dysfunction in scattered case series. Ferini-Strambi et al. [748] in a multicenter case-control study reported the presence of autonomic symptoms in the largest series covering PSG-confirmed 318 cases of iRBD and 137 healthy controls from 13 centers in 10 countries. They used a validated scale (SCOPA-AUT) consisting of 25 items to assess the autonomic function in multiple domains and concluded that iRBD patients have significantly more problems with gastrointestinal, urinary, and cardiovascular functioning than controls. These data may be used as prodromal markers for eventual neurodegeneration in these patients.

Miscellaneous Neurologic Disorders

Sleep Apnea in Narcolepsy Syndrome

The narcolepsy syndrome is manifested by an irresistible desire to fall asleep at inappropriate times. Such attacks last a few seconds to as long as 20–30 min. They are often accompanied by cataplexy or other characteristic ancillary manifestations of narcolepsy (see Chap. 38). Narcolepsy may be associated with other comorbid sleep disorders such as RBD, OSA, PLMS, sleep-related eating disorder, sleepwalking, and nightmares. It is often associated with an increased BMI, which predisposes to the development of OSA. Narcoleptics have on average a BMI 10–20 % higher than the normal population [749]. A reduced metabolic rate, decreased motor activity, and abnormal eating behavior [750] have been suggested as possible explanations. SDB is found in 10–20 % of patients [751, 752].

Guilleminault's group [753] first reported CSA that lasted 20–90 s (during REM and NREM sleep) accompanied by O_2 desaturation in two patients with pure narcolepsy. In a later report, Guilleminault et al. [754] described 20 additional cases of narcolepsy with sleep apnea, which was predominantly central, although 5 also had mixed and obstructive apneas. The authors speculated that a dysfunction of the CNS structures that control sleep and respiratory centers was responsible for the combined syndrome of sleep apnea and narcolepsy. Laffont et al. [755] also described central, obstructive, and mixed apneas in 5 of 18 narcolepsy patients. Chokroverty [752] made polygraphic observations in 16 patients with narcolepsy syndrome, 11 of whom showed central apneas and 5 upper airway OSAs during both REM and NREM sleep stages associated with O_2 desaturation (Figs. 41.10 and 41.27).

Sansa et al. [756] in a later report made an important observation after studying 133 consecutive patients in a university sleep clinic with narcolepsy diagnosed with PSG and MSLT. They noted that 33 patients (24.8 %) had OSA with an AHI of > 10. Ten of these patients were initially diagnosed with only OSA, and narcolepsy diagnosis was delayed by several years until evaluation for residual sleepiness after adequate CPAP therapy. In the remaining 23 patients, both OSA and narcolepsy were diagnosed concurrently. The authors concluded that OSA occurs frequently in narcolepsy and this may delay the diagnosis of narcolepsy by several years, and the physicians should be vigilant about comorbid narcolepsy in OSA patients in whom EDS persists

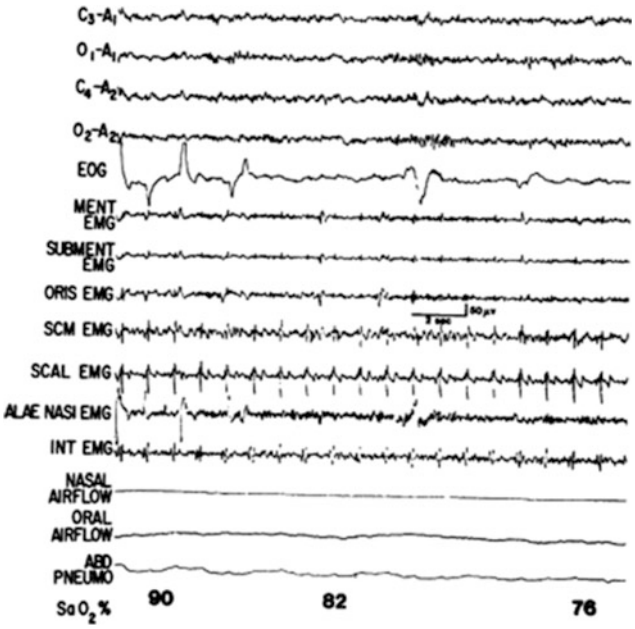

Fig. 41.27 Polysomnographic recording of a patient with narcolepsy showing four channels of the electroencephalogram (EEG); vertical electrooculogram (EOG); electromyograms (EMG) of mentalis (MENT), submental (SUBMENT), orbicularis oris (ORIS), sternocleidomastoid (SCM), scalenus anticus (SCAL), alae nasi, and intercostal (INT) muscles; nasal and oral airflow; abdominal pneumogram (ABD PNEUMO); and oxygen saturation (SaO_2%; ear oximeter). The patient has central apnea during REM sleep (only 18–30 s are shown). Note decrease of SaO_2 from 90 to 76 % during apnea

despite adequate CPAP therapy. Pizza et al. [757] also documented a high prevalence of SDB (11 out of 35 consecutive patients, i.e., 31 %) in narcolepsy type 2. The authors listed older age and higher BMI compared with those without SDB as the risk factors for OSA.

The possibility of coexisting sleep apnea should be considered in a patient with narcolepsy, particularly when the patient is again complaining of EDS after initial improvement on stimulant therapy. OSA should be suspected in such a patient, particularly with increasing age as prevalence of OSA increases in the elderly. Patients with comorbid narcolepsy and sleep apnea should receive treatment for both conditions.

Kleine–Levin Syndrome

An episodic disorder characterized by periodic hypersomnolence and bulimia was described first by Kleine [758] and later by Levin [759] occurring mostly in adolescent boys (but also described in girls). Critchley [760, 761] gave a comprehensive description after analysis of 15 cases from the literature and 11 personal cases. The episodes usually occur three to four times per year, and each episode lasts days to weeks. During the sleep "attacks," patients sleep 16–18 h a day or more, and on awakening, they eat voraciously. Other behavior disturbances during the episode may include dull appearance, withdrawal, confusion, hallucinations, inattentiveness, memory impairment, and hypersexuality. In a later report, Billiard and Cadilhac [762] in 1988 reviewed 123 cases collected from the literature. The condition is generally sporadic and self-limited (although not always) and disappears by adulthood. Occasional familial cases have been described [763, 764]. Polysomnographic studies show normal sleep cycling or nonspecific findings, and MSLTs show the evidence of pathologic sleepiness without sleep-onset REM [765–767]. In a report on 10 patients, Huang et al. [768] observed a reduction of slow-wave sleep in the initial half of the symptomatic period and mild sleepiness in the MSLT, with two or more sleep-onset REM periods (SOREMPs) in 7 of 17 patients. Occasional atypical presentations with episodic alteration in sleep (hypersomnia and insomnia) and appetite (hyperphagia and anorexia) responding to carbamazine treatment have been reported [769].

In the third edition of ICSD [101], the eponym Kleine–Levin syndrome is considered the preferred name for recurrent and periodic hypersomnia which now includes menstrual related hypersomnia which is very rare and may be a variant of Kleine–Levin syndrome except that it occurs just before or during menses. Box 41.7 lists the ICSD-3 criteria for Kleine–Levin syndrome all of which must be fulfilled to meet the diagnostic criteria of Kleine–Levin syndrome. In a recent review, Arnulf [770] summarized Kleine–Levin syndrome as a rare neurologic disorder affecting adolescent boys more frequently than girls, manifested by relapsing-remitting episodes of hypersomnolence, apathy, cognitive impairment, psychiatric and behavioral disturbances (e.g., anxiety, delusions, and hallucination), and altered environmental perception characterized by derealization. The authors considered these as core symptoms superseding previously emphasized triad of hypersomnia, hyperphagia, and hypersexuality (the latter two symptoms are noted in about 50–70 % of cases). Functional imaging studies (e.g., SPECT and PET scans) have shown hypoperfusion of hypothalamus, mesial temporal and frontal lobes consistently, and less frequently of thalamus [771, 772]. EEG has shown diffuse slowing in 70 % and normal findings in 30 % of cases during episodes. Arnulf's group published the data from their most recent analysis of a new series of 120 patients with typical primary Kleine–Levin syndrome seen between 2006 and 2012 [773]. This analysis essentially confirmed their previous [770, 774, 775] conglomeration of symptom in addition to some new features (e.g., more frequent birth and developmental abnormalities than controls and those with prolong episodes lasting longer than one month [seen in 34 patients]), had shorter sleep time with higher anxiety level and agitation during the episodes, but in between these episodes needed more naps, felt tired, and had higher anxiety-depression score. They analyzed the evolution of the disease in 53 patients and found that the frequency of episodes decreased in 63 % but increased in 10 % of the patients after five years. Almost half of the patients had decreased performance at school or at work, and some especially those with prolonged episodes were left with some long-term residual symptoms challenging the concept of Kleine–Levin syndrome being a benign disorder.

Box 41.7 ICSD-3 Diagnostic Criteria for Kleine–Levin Syndrome: All five must be met [101]

1. At least two recurrent episodes of hypersomnolence, each lasting for two days to five weeks,
2. Episodes recur at least every 18 months,
3. In between the episodes, alertness, mood, and cognitive function are normal,
4. During episodes, one of the following must be present:
   - Cognitive dysfunction,
   - Altered perception,
   - Hyperphagia or anorexia,
   - Behavioral disinhibition (e.g., hypersexuality).
5. The above behavior is not better explained by another sleep, neurologic, medical, or psychiatric disorder or ingestion of medication.

The pathophysiology [770, 771, 774, 775] is unknown but points to a localized but multifocal encephalopathy during recurrent episodes as evidenced by EEG and functional imaging findings (see above). Another intriguing neuroimaging finding is the demonstration of interictal thalamic hyperactivation using functional magnetic resonance imaging (fMRI) during working memory performance [776] on a group but not on an individual basis. The authors suggested that this might be considered a compensatory mechanism in those with high working memory capacity. The syndrome may have been caused by genetic, environmental, autoimmune, inflammatory, or metabolic factors singly or in combination. CSF hypocretin-1 levels have been essentially normal [770] as are serum cytokine levels [777].

Drug treatment of Kleine–Levin syndrome has been unsatisfactory [770]. All the drug trials had been nonplacebo-controlled open-label, but there have been no randomized controlled trials (RCTs) for this condition. For symptomatic treatment during episodes, stimulants and wake-promoting agents (e.g., amphetamines, methylphenidate, modafinil, and armodafinil) had been tried with minimal success in eliminating or shortening the hypersomnolence episodes. For eliminating the recurrent episodes, prophylactic treatment has been tried with some success. Lithium (requires close monitoring as the range of therapeutic and toxic doses is narrow) has been most successful in about 50–60 % of cases followed by the treatment with valproic acid [770, 778, 779]. Carbamazepine was successful in occasional patients. Amantadine, an antiviral agent which is also used in Parkinson's disease, had been successful in some patients if given at the beginning of an episode. There is a single case report of success with sodium oxybate (4 g) treatment [780]. In view of the reports of Kleine–Levin syndrome being triggered by upper respiratory or other infections, clarithromycin, an antibiotic with GABA A receptor antagonistic properties, was tried in an occasional patient with success [781], but further studies in larger number of patients are needed to verify the usefulness of this approach.

Idiopathic Recurrent Stupor

In 1992, Tinuper et al. [782] coined the term *idiopathic recurrent stupor* (IRS) for a condition characterized by recurrent episodes of stupor in all of these patients, in whom no metabolic, toxic, or structural brain dysfunction was noted. A characteristic EEG during an episode of stupor in these patients showing nonreactive, diffusely distributed fast rhythms (14–16 Hz) was described. Benzodiazepine-like activity identified as endozepine-4 in plasma and CSF was markedly elevated in all patients. The clinical manifestations and the EEG abnormalities rapidly reversed to the normal state after administration of flumazenil (0.5–1.0 mg intravenously), a benzodiazepine receptor antagonist. Endozepines also accumulate in hepatic coma, in which flumazenil injection causes transient arousal [783]. In 1998, however, the original authors who described IRS [784] reported a case of covert lorazepam intoxication misdiagnosed as endozepine stupor and called attention to the need to perform refined toxicologic analyses (mass spectroscopy with high-performance liquid chromatography) in order to exclude with certainty the presence of exogenous benzodiazepines, in particular lorazepam, that may mimic the action of endozepines. Subsequent reports also highlighted the need to exclude fraudulent exogenous benzodiazepines, in particular lorazepam administration, in cases of comas associated with fast EEG activities and response to flumazenil [785], and have cast doubts on the true existence of a syndrome of recurrent comas due to endozepine accumulation. Since 1998 report casting doubt on the true existence of this syndrome, no new cases of apparent IRS have been attributed to an endrogenous molecule with benzodiazepine-like bioactivity [785]. The Bologna group who first described IRS warned in a recent report [786] that a diagnosis of IRS should not be made without performing sophisticated toxicological tests to exclude exogenous benzodiazepines; otherwise, this may lead to inappropriate treatment which may have legal implications for the treating physicians.

Idiopathic Hypersomnia

Idiopathic hypersomnia (IH), a condition of excessive somnolence, has no known cause. A disorder of the CNS has been suspected but not proved [787]. The syndrome has been described under a variety of labels, including nonrapid eye movement narcolepsy; idiopathic central nervous system hypersomnia; and mono- or polysymptomatic idiopathic hypersomnia; *idiopathic hypersomnia* is the preferred term. IH closely resembles narcolepsy syndrome. The ICSD-3 [101] defines the disorder as a condition characterized by EDS or irrepressible need to sleep without cataplexy lasting for at least three months that is associated with a total 24-h sleep time of 660 min or more (typically 12–14 h) documented by 24-hour PSG monitoring or by wrist actigraphy for seven days and sleep log. Bedrich Roth [788], who actually coined the term *idiopathic hypersomnia*, described a monosymptomatic form manifested only by EDS and a polysymptomatic form characterized by EDS, nocturnal sleep of abnormally long duration, and signs of "sleep drunkenness" upon awakening. The onset of the disease is generally around the same age as narcolepsy (15–30 years). The sleep pattern, however, is different from that of narcolepsy. The patient generally sleeps for hours, and the sleep is not refreshing. Because of EDS, the condition may be mistaken for sleep apnea or narcolepsy. However, the patient does not give a history of cataplexy, snoring, or repeated awakenings throughout the night. Sleep drunkenness is often

seen in these patients and may manifest as sleep inertia or automatic behavior with amnesia for the events. Physical examination uncovers no abnormal neurologic findings. The condition is disabling and generally lifelong, although spontaneous remissions have been noted in a few patients [101]. In a retrospective review of 77 patients with IH, Anderson et al. [789] stated that clinical features were heterogeneous and of variable severity, similar to the suggestion made by Aldrich [790]. It has been suggested [791] that occasional patients with IH may be misdiagnosed as having adult-onset attention deficit/hyperactivity disorder (ADHD) based on a self-reported ADHD questionnaire. The condition may be familial, but in the absence of rigorous studies, mode of inheritance cannot be determined [101].

The differential diagnosis of the condition should include other causes of EDS (see Chap. 3) including insufficient sleep syndrome. Polysomnographic monitoring shows generally normal sleep structure and sleep cycling with normal REM latency and prolonged total sleep time. Sforza et al. [792] based on the spectral analysis of the EEG found reduced power of slow-wave activity due to reduced amount of slow-wave sleep, suggesting that the homeostatic sleep regulatory mechanism is preserved, but the sleep pressure indicated by slow-wave activity is reduced. The MSLT shows mean sleep latency of 8 min or less but typically longer than in narcolepsy and less than 2 SOREMPs or none if a SOREMP was noted on the preceding overnight PSG. A recent report [793] of actigraphic assessment of patients with drug naïve narcolepsy type 1 (39), idiopathic hypersomnia (24), and controls (30) documented some distinguishing features among these central disorders of hypersomnolence based on significant differences in nighttime and daytime parameters. CSF hypocretin-1 levels are normal, in contrast to reduced levels in the majority of patients with narcolepsy-cataplexy syndrome [101, 794].

In this condition, no consistent HLA association has been found in contrast to narcolepsy [101]. The treatment of IH is unsatisfactory and is somewhat similar to the stimulant treatment for narcolepsy. The behavioral approach of sleep hygiene techniques has been advised, but these do not have a significant impact on the disease. Compared with patients with classic narcolepsy with cataplexy, stimulants are less effective in those with IH. There are still unresolved and pending issues in terms of precise clinical characteristics, treatment response, and neurobiology of idiopathic hypersomnia [101].

Central Sleep Apnea and Sleep Hypoventilation Syndromes

These entities including sleep and breathing at high altitudes have been described in Chap. 33.

Sleep and Increased Intracranial Pressure

Increased intracranial pressure (ICP) may result from a variety of neurologic disorders (e.g., tumor, large infarction, intracranial hemorrhage, head trauma, focal abscess, and diffuse encephalitis). Cooper and Hulme [795, 796] found that the ICP of patients with intracranial lesions rose during REM and stage 2 NREM sleep. This was probably due to a combination of factors [797–799] (e.g., variations in cerebral blood flow, neurogenic reflex, cerebral vasoconstriction, and enhanced brain metabolism). These observations have been confirmed by the findings of Munari and Calbucci [800] in 16 head trauma patients. In a study of children with craniosynostosis, Gonzalez et al. [801] observed both increased ICP and upper airway obstruction. They performed PSG studies along with continuous monitoring of ICP during sleep in 13 children with the syndrome of craniosynostosis and 7 control patients with isolated unicoronal synostosis only. In 11 of 13 patients with this syndrome, they found upper airway obstruction, and 8 of those 11 had frank OSAs. The other group of children showed no signs of upper airway obstruction during sleep. The causal relationship between upper airway obstruction and raised ICP in these children, however, remains undetermined. In a later report, Stephensen et al. [802] measured ICP levels during wakefulness and sleep in 29 adults with noncommunicating and 26 adults with communicating hydrocephalus. They found that ICP is normal in most adults with hydrocephalus; however, ICP is higher during sleep than during periods of wakefulness in the supine position and is not correlated with either symptoms or the rate of improvement after surgery. In idiopathic intracranial hypertension (IIH) in adults, SDB may be noted in many patients [803–808]. The conclusion in some studies is based on the findings from nonconsecutive case series [807], Berlin questionnaire without a control group, and retrospective, validated questionnaire-based study with matched controls. It is notable that OSA itself may cause increased intracranial pressure during apneic episodes due to associated hypoxia and cerebral vasodilation, and this has been thought to play a role in the pathogenesis of IIH in men with coexisting OSA [806]. Many of these prior studies did not have a control group. However, in a more recent study, Thurtell et al. [807] reversed their prior [808] conclusion based on overnight PSG study in 24 patients (20 women and 4 men) with coexisting IIH and OSA, and controls derived from population-based model matched for age, sex, and menopause status. These authors noted OSA in 8 patients (33.3 %) which is not significantly different from the control group. It was, however, unclear whether the presence or treatment of OSA would have influenced the clinical course of IIH. The authors recommended larger prospective, controlled study to evaluate the relationship between OSA and IIH.

Headache Syndromes

Headaches and sleep complaints are common and have a bidirectional relationship [809]. Sleep disturbance (e.g., OSAS) may cause headache, and headache itself may cause sleep disturbances. The relationship between headache and sleep disorders is somewhat complex and remains ill-understood [810]. Sleep-related headaches include most daytime headache conditions, which also occur during sleep or on awakening in the morning. The ICSD-3 [101] includes migraine, cluster headache, chronic paroxysmal hemicrania (CPH), and hypnic headache syndrome (HHS) under "Sleep-related Headaches." Other causes of sleep-related headaches (secondary headaches) include medical (e.g., hypertension), neurologic (e.g., tumor and head trauma), psychiatric (e.g., depression), and primary sleep disorders (e.g., OSAS). Migraine headache can, of course, occur during both the day and night. There are several reports on headache and sleep disorders in the literature, but many of them are retrospective analyses and do not clearly eliminate other confounding factors.

Migraine headaches are common episodic headaches characterized by nausea, vomiting, photophobia, and phonophobia; they are generally unilateral and associated with throbbing pain. Dexter and Weitzman [811] made the first PSG recording in patients with chronic migraine and cluster headaches and found a clear relationship between REM sleep and attacks of headache. Attacks occurred during REM or within 9 min after it terminated. In later studies, Dexter [812] also found a relationship between NREM stages 3 and 4 and REM sleep and arousals with migraine headaches. Kelman and Rains [813] evaluated 1283 migraineurs from 1480 consecutive headache patients attending a tertiary headache clinic. They reported that over half of the migraineurs reported difficulty in initiating and maintaining sleep, and the migraine headaches were triggered by sleep disturbance in 50 % of patients. "Awakening headaches," or headaches awakening them from sleep, were reported by 71 % of patients. The authors concluded that there is a substantial sleep-migraine relationship, those patients who slept 6 h per night exhibited more severe headache, and sleep complaints were more frequent during chronic episodic attacks. Gori et al. [814] after evaluating 100 patients suffering from migraine without aura noted a preferential timing for occurrence of migraine attacks during the night and early morning hours. Engstrom et al. [815] evaluated sleep quality by sleep questionnaires and diaries, and PSG from 53 migraine and 20 tension-type headache (TTH) patients as well as 34 controls in a blinded exploratory study. They reported more sleep-related symptoms and anxiety in all headache groups: TTH and migraineurs with daytime onset had more daytime tiredness and increased slow-wave sleep as seen after sleep deprivation, whereas those with migraine headache during sleep had increased awakening during sleep.

Cluster headaches are unilateral severe headache in the periorbital or temporal region lasting for 15 min to 3 h. As the name suggests, the headaches occur in clusters of one to three per day over a period of 1–2 months. Most of the patients have one cluster period each year, and the headache tends to occur at the same hour each day. A characteristic feature of cluster headache is the presence of autonomic features such as lacrimation, conjunctival injection, nasal congestion, rhinorrhea, and the evidence of Horner's syndrome (e.g., the absence of forehead and facial sweating, ptosis, and small pupils). Cluster headaches are thought to be REM-related [812, 816, 817], by some but not by all investigators [818]. Sometimes, cluster headaches may be triggered by NREM sleep [819].

CPH [101, 820, 821] is probably a variant of cluster headache. CPH is grouped under trigeminal autonomic cephalalgias [822] which are primary headache disorders associated with cranial parasympathetic autonomic symptoms (e.g., conjunctival injection, lacrimation, rhinorrhea, nasal congestion, ptosis, and eyelid edema). This is chronic in 80 % but episodic in 20 % of cases [820]. The attacks of CPH occur unilaterally involving orbital, supraorbital, or temporal region and are briefer (2–30 min) and more frequent (1–40 per day) and more in women (3 W:1 M) than cluster headaches. CPH is most commonly associated with REM sleep [101, 821], and it responds to indomethacin but in some cases may respond to calcium channel blockers [820, 823]. Significant disruption of sleep architecture (decreased total and REM sleep time accompanied by increased number of awakenings during REM sleep) has been described in patients with CPH [101, 821]. After a nocturnal polygraphic study, Conelli et al. [824] reported that CPH headache episodes were preceded by a sustained increase in blood pressure. There are occasional reports of the coexistence of OSAS and cluster headache with improvement of headache after CPAP titration [825, 826]. An earlier report by Kudrow et al. [827] also found a high prevalence of CSA or OSAS in patients suffering from cluster headaches, especially episodic headaches.

The relationship between chronic headache and early morning headache has remained somewhat controversial. Patients with upper airway OSAS are thought to have an increasing incidence of morning headache as compared with controls [828–830], and improvement in morning headache has been reported after treatment of OSAS [831]. Dexter [828] reported PSG-documented sleep apnea in 11 patients with chronic recurring headache syndrome. After surgical reconstruction in six patients with obstructive apneas, PSG demonstrated marked improvement in sleep apnea and

considerable improvement in headache symptoms. In contrast, Aldrich and Chauncey [832] as well as Poceta and Dalessio [833], after a survey, found that the complaint of morning headache was no different in patients with OSAS than in those with other sleep disorders. The Copenhagen Male Study [834] (included 3323 men aged 54–74 years), however, found that heavy snoring was an independent risk factor for headache. Ulfberg et al. [835] confirmed the association between heavy snoring, OSA, and headache in both men and women based on a questionnaire survey as well as sleep apnea screening that included 4 h of sleep on the back of a static charge-sensitive bed and finger oximetry. In a later report of 432 patients with a variety of sleep disorders studied with two nights of PSG comparing with 30 controls, Goder et al. [836] noted an increased frequency of morning headaches not only in OSAS but also in other sleep disorders. The authors concluded that morning headache might be associated with decreased total sleep time, sleep efficiency, and amount of REM sleep and an increase in the wake time during the preceding night.

Paiva et al. [837] evaluated 49 subjects successively seen in a headache clinic during a 6-month period with the predominant complaints of nocturnal or early morning headache. Based on the questionnaire and overnight sleep recordings, the authors found that headache was related to a specific sleep disorder (e.g., OSAS, PLMS, sleepwalking, and sleep paralysis) in 55 % of these subjects. They also found that treatment of these sleep disorders ameliorated the headaches. These findings confirmed the earlier observations of Paiva et al. [838] that morning or nocturnal headaches were frequent indicators of a sleep disturbance.

HHS is a rare benign headache syndrome of the elderly that usually occurs after the age of 50 years and awakens the patient from sleep at a consistent time each night like an alarm clock and hence the name alarm clock headache [101, 839–841]. The headache is either generalized or lateralized, lasting for at least 15 min (with range up to 180 min) and occurring at least 15 times per month. This may occur one to three times during the night and tends to occur during REM sleep but may also occur during stage N3 sleep [101]. In a recent serial PSG study [842] on four consecutive nights in six patients with hypnic headache capturing 22 attacks, six arouse from REM sleep and 16 from different NREM sleep stages. Five patients had an increased apnea-hypopnea index indicating OSA on some nights but not the majority of nights. The underlying pathophysiology of HH is unknown, but a hypothalamic involvement seems likely [843]. HHS is differentiated from chronic cluster headache by its generalized distribution, age of onset, and the lack of autonomic manifestations. The disorder often responds to lithium, indomethacin, or caffeine treatment.

Another variety of unusual headache syndrome is "exploding head syndrome," which usually occurs in the transition from wake to sleep, abruptly arousing the patient with a feeling of an explosion or a sensation of bursting of the head [844–846]. The condition is benign, and most likely represents a type of "sleep starts" and is classified in ICSD-3 under "Other Parasomnias" [101]. Polysomnographic recordings [847, 848] showed that the syndrome occurred during both wakefulness and REM sleep. In occasional cases, treatment with clomipramine may be effective [847].

The exact pathophysiologic mechanism for association of headache and sleep is not known, but Dodick et al. [849] suggested a role for the hypothalamus, serotonin, and perhaps melatonin. The PET scan finding of hypothalamic activation in cluster headache [850] and the therapeutic response of melatonin [851] in migraine and other headache types lend some support to the suggested mechanism of Dodick et al. [849]. The principles of treatment of sleep-related headaches include first the correct diagnosis of the type of the headache, investigations (including PSG recordings) to exclude other causes of headaches, practice of commonsense measures for sleep hygiene, treatment of underlying sleep disorders, and symptomatic treatment for specific headache using standard medications [852].

Familial and Sporadic Fatal Insomnia

Lugaresi and associates [853] originally described FFI in a family (14 affected members in three generations) as an autosomal dominant, rapidly progressive neurologic illness characterized by insomnia and dysautonomia that terminated in death. Later, they found that two families with FFI harbored a mutation (associated with the substitution of aspartic acid with asparagine) at codon 178 of the prion protein (PrP) gene *PRNP,* located on chromosome 20 [854, 855]. FFI therefore belongs to the so-called prion diseases, characterized by the accumulation of a pathologic isoform of the PrP that becomes resistant to the action of the proteases and called PrPres or PrPsc (sc for scrapie). It should be noted that the same mutation at codon 178 of *PRNP* is present in both FFI and familial CJD (178fCJD). These two conditions, however, are separated by the methionine-valine polymorphism at codon 129 on the mutated allele of *PRNP,* a common polymorphism that codes either for methionine or for valine: FFI is invariably associated with methionine, while 178fCJD is associated with valine [856–859]. This genetic difference is expressed in a different type of PrPres being accumulated in the brain of affected individuals, whereby FFI brains accumulate a 19-kDa (type 2) PrPres, while 178fCJD brains accumulate a 21-kDa (type 1) PrPres [856].

Prion diseases can occur as infectious, sporadic, and hereditary forms and are transmissible. Accordingly, FFI has been transmitted to experimental animals [860, 861], in

particular to transgenic mice expressing a chimeric human-mouse *PRNP* [862]. A sporadic form of fatal insomnia (called sporadic fatal insomnia [SFI]) has also been described, characterized by the same clinicopathologic features of FFI and by type 2 PrPres and also transmissible, but in the absence of the defining *PRNP* 178 codon mutation [863, 864]. Upon transmission of either FFI- or SFI-derived brain inoculates, the experimental animal accumulates the same type of PrPres and displays pathologic features comparable to those found in the donor brain, thus demonstrating that prion strains encipher and propagate the diversity of prion diseases [862]. FFI represents the third most frequent hereditary prion disease and has been reported worldwide [865, 866]. Age of onset of FFI is at about 51 years, but cases with young age of onset (23 and 24 years) are described. The clinical course runs from 7 to 72 months, with a mean of 18 months. A two- to threefold longer disease course (together with some differing clinical features) has been related to the presence of a valine 129 *PRNP* codon polymorphism on the *non*mutated allele (heterozygote methionine/valine 129 *PRNP* codon FFI patients) [867].

Clinical manifestations of FFI and SFI include impaired control of the sleep-wake cycle, including circadian rhythms; autonomic and neuroendocrine dysfunction; and somatic neurologic, cognitive, and behavioral manifestations [868, 869]. Profound sleep disturbances and, in particular, severe insomnia are noted from the very beginning of the illness. Patients seldom complain of drowsiness and may look drowsy with expressionless faces and lowered eyelids but present an inability to nap during the day and to fall asleep at night. Moreover, at the onset of the disease, patients become increasingly taciturn and apparently indifferent to their surroundings and even their fate (apathy). Neuropsychologic studies reveal an early progressive impairment of attention and vigilance, leaving relatively intact intellectual skills so long as consciousness is preserved [870]. Polysomnographic study [853, 871, 872] shows the early loss of sleep spindles and K complexes which are markedly and progressively reduced and are absent in the later stage of the illness. The loss of sleep spindles and slow-wave sleep is so severe and permanent that these EEG activities cannot even be induced by IV administration of barbiturates or benzodiazepines, drugs that usually cause spindles and slow waves to appear in the EEG [873]. The sleep cycle organization and stage shifts are altered from the very beginning, and there is no orderly transition from wake to sleep or from one sleep stage to the other. The dominant EEG pattern until the most advanced disease stages is characterized by a mixed stage between stage 1 (dominant theta activity and slow eye movements) with interspersed short, often recurring in clusters, REM sleep episodes, lasting for a few seconds or minutes only with or without muscle atonia. When left alone, both during the day and during the night, patients present stereotyped, simple, calmer, automatic, well-organized motor gestures mimicking daily life activity such as eating, drinking, dressing, combing the hair, washing, or manipulating nonexistent objects. If questioned at the end of these behaviors, patients often link these gestures to an oneiric scene, and the motor activity appears to be clearly related to the oneiric content (oneiric stupor) [869, 874]. The terminal stage of the illness is characterized by progressive slowing of the EEG, and the patients remain in a coma. It is remarkable that the quasi-periodic sharp-wave EEG activities typical of CJD are not recorded in FFI, except in some patients with long evolution just before death.

Insomnia is associated with sympathetic activation in the form of hypertension, tachypnea and tachycardia, hyperhidrosis, and slight pyrexia. Autonomic function tests show the evidence of sympathetic hyperactivity with preserved parasympathetic activity [853, 874–876], resulting in persistent elevation of plasma catecholamines with further increase after upright tilt of the table [877]. There is consistent elevation of blood pressure, heart rate, and core body temperature, and the nocturnal fall in blood pressure that occurs in normal individuals is lost from the early stages of the illness [876, 877].

Neuroendocrine functions [875, 876, 878, 879] in FFI show a dysfunction of the pituitary-adrenal axis as manifested by striking elevation of serum cortisol but normal adrenocorticotrophic hormone and persistently elevated serum norepinephrine levels, associated with abnormal secretory patterns of growth hormone, prolactin, and melatonin: Growth hormone showed no nocturnal secretory peaks, while the circadian rhythm of prolactin persisted. Circadian fluctuations of prolactin, however, tended to disappear with disease progression, and likewise, the nocturnal rise in melatonin was progressively lost [878]. Fifty-two days of actigraphic monitoring in one patient showed up to 80 % increased motor activity with a loss of circadian rhythmicity, and indirect calorimetry revealed a remarkable 60 % metabolic increase in 24-h energy expenditure [880].

The somatic neurologic manifestations are present in all cases, particularly in the later stage of the illness, and consist of dysarthria and dysphagia, ataxia [881], the evidence of pyramidal tract dysfunction, and myoclonus. The disease progresses rapidly, and in the final stage of the illness, the patients may also have breathing disturbances and mutism and then end in coma and death. CSF analysis for the 14-3-3 protein, a good marker of prion diseases, detects increased levels in only half of FFI patients. CSF hypocretin-1 levels are normal in FFI [882].

Neuropathologically, the hallmark of FFI is severe atrophy of the thalamus, particularly the anterior ventral and dorsomedial thalamic nuclei, and of the inferior olives, associated with variable involvement of the cerebral cortex, striatum, and cerebellum [853, 883, 884]. In the thalamus,

the loss of neurons is particularly striking, averaging 80 % of neurons and associated with reactive astrogliosis [883, 884]. There are no prominent spongiform changes, which are usually found in prion diseases, but a mild-to-moderate spongiform degeneration in the cerebral cortex has been noted in subjects with the longest duration of symptoms. These pathologic features in FFI are at variance with those found in 178fCJD, where spongiosis and cortical involvement predominate [858]. Moreover, deposition of PrPres in FFI brains is also characteristic, occurring to a much lesser degree than in sporadic CJD, especially in the neo- and limbic cortex and in those patients with prolonged disease course [885]. The amounts of PrPres indeed correlate with disease duration, though not in the thalamus, where deposition of PrPres is only moderate and unrelated to disease duration. This could probably reflect a selective thalamic vulnerability in FFI [886]. Severe hypometabolism of the thalamus along with a mild hypometabolism of the cingulate cortex was shown also by means of an in vivo fluorodeoxyglucose PET study in seven FFI patients by Cortelli et al. [887]. Hypometabolism of other brain regions depended on the duration of symptoms, being more widespread in the methionine-valine heterozygotes at *PRNP* codon 129, who also had a more prolonged course. Comparison with the neuropathologic changes showed that the metabolic changes were more widespread than the pathologic alterations, correlating with the amount of abnormal PrPres deposited in the different brain areas [887]. In a fluorodeoxyglucose PET study [888] of 9 asymptomatic carriers of the FFI mutation, 10 noncarriers belonging to the same family and 19 age-matched controls studied over several years, together with spectral EEG and PSG, the PET, and all other examinations, were normal at the beginning of the study. Four of the mutation carriers developed typical FFI during the study, but PET and other results remained normal for 63, 56, 32, and 21 months before disease onset. Selective thalamic hypometabolism was found in the thalamus 13 months before the onset of symptoms, while spectral EEG analysis disclosed changes indicative of impaired thalamic sleep spindle formation. Following clinical disease onset, hypometabolism was found in the thalamus in all three patients examined. These findings were considered to demonstrate that the neurodegenerative process associated with FFI begins in the thalamus at close to one year before the clinical presentation of the disease [888].

The study of FFI has opened a new era in the molecular biology of the prion proteins and their genes, being instrumental in the discovery of different prion strains in humans [856] and in establishing that prion strains alone encode prion disease diversity [862, 889]. FFI has also been proposed as a model disease for sleep pathophysiology [890], rekindling the role of the thalamus in sleep-wake-regulating mechanisms [871–873, 886, 891] Geminiani et al. [891] by demonstrating that the thalamus is essential for the generation of slow-wave sleep and also suggesting a role for prions in sleep regulation. The consideration that FFI has clinical features in common with diseases such as delirium tremens and Morvan's chorea, an autoimmune limbic encephalitis, has finally led to the concept of "agrypnia excitata" [892], a clinical condition characterized by disruption of the sleep-wake cycle, a continuous day and night motor, sympathetic and aminergic overactivity, and episodes of oneiric stupor, related to changes in the thalamolimbic circuitry [893, 894]. In agrypnia excitata, loss of slow-wave sleep occurs in the face of preserved light stage 1 NREM sleep (stage N1), a fact that has been taken as evidence that NREM sleep is not a continuous process starting from stage 1 and progressing to stage 3, but that light sleep probably represents an independent state of sleep and should not be combined with deep sleep into a unique NREM sleep process [892, 895].

Laboratory Investigations

The laboratory tests should be directed at a diagnosis of the primary neurologic disorder and an assessment of sleep disturbances resulting from the neurologic illness.

Laboratory Tests for the Primary Neurologic Disorders

It is beyond the scope of this chapter to delve into details of neurodiagnostic tests to assess the neurologic condition that gives rise to sleep and SRBDs, so readers are referred to some excellent neurologic texts available [896–899]. Laboratory tests must subserve the findings of the history and physical examination, as discussed in Chap. 26. Laboratory tests are essential for diagnosis, prognosis, and treatment of the primary neurologic disorders. These investigations can be broadly divided into neurophysiologic tests, neuroimaging studies, examination of the cerebrospinal fluid, and general laboratory tests, including blood work and urinalysis. Special procedures such as tests to uncover autonomic deficits; neuroimmunologic, neurovirologic, or neurourologic investigations; and brain biopsy are required to detect some neurologic disorders.

Neurophysiologic Tests

Neurophysiologic tests include electroencephalography (**EEG**), evoked potential, nerve conduction studies (NCS), and electromyography (EMG). EEG, including 24-h ambulatory and video-EEG examinations, is necessary to detect seizure disorder and may also be useful in

metabolic-toxic-nutritional encephalopathies and dementing illnesses (e.g., AD and CJD). Evoked potential studies include sensory (somatosensory, brain stem auditory, and visual evoked responses) and motor-evoked potentials and may be indicated in certain neurologic disorders, particularly demyelinating diseases such as MS. NCS and EMG are necessary for diagnosis of various neuromuscular disorders, including neuromuscular junction diseases.

Neuroimaging Studies

These studies include anatomic and physiologic studies which are essential when a neurologic illness is suspected to cause sleep disturbance.

Cerebral angiography, including digital subtraction arteriography and magnetic resonance angiography (MRA), may be necessary to investigate for strokes. Computer tomography (CT) and magnetic resonance imaging (MRI) are important studies for structural lesions of the CNS (e.g., tumors, infarctions, and vascular malformations). CT and MRI are also helpful in patients with demyelinating and degenerative neurologic disorders that can be responsible for sleep and SDBs. Diffusion tensor MR imaging, MR tractography, functional MRI (fMRI), DAT scanning used with single-photon-emission computed tomography (SPECT) for detecting dopamine transporter (DAT) uptake in the basal ganglia in suspected parkinsonian syndromes, and MR spectroscopy are other imaging studies which may be helpful in diagnosing and monitoring neurologic diseases responsible for sleep dysfunction.

Positron-emission tomography (PET) dynamically measures cerebral blood flow, O_2 uptake, and glucose utilization and is helpful in the diagnosis of dementing, degenerative (e.g., PD), and seizure disorders. It is very expensive, however, and is not available in most centers. SPECT, which dynamically measures regional cerebral blood flow, may be useful for patients with cerebral vascular disease, AD, or seizure disorders. PET and SPECT studies can also be performed to investigate D_2 receptor alterations in RLS-PLMS as well as narcolepsy and RBD [900–906], which may show reduced striatal presynaptic dopamine transporter uptake. Functional MRI can be useful to study the generators and the areas of activation in RLS-PLMS [907]. Doppler ultrasonography is an important test for investigation of stroke due to extracranial vascular disease. Myelography other than CT and MRI is important for diagnosis of diseases of the spinal cord.

In selected patients, fiber-optic endoscopy may be performed to locate the site of collapse of the upper airway, and cephalometric radiographs of the cranial base and facial bones may be obtained to assess the posterior airway space or maxillomandibular deficiency (see Chap. 32). These are important when surgical treatment is planned. For research and clinical investigations, cross-sectional areas of the upper airway during wakefulness may be measured by CT and MRI [908–915]. Some imaging studies measured upper airway during sleep dynamically [916, 917].

Finally, MIBG cardiac scintigraphy [918] may show reduced cardiac uptake, and midbrain transcranial sonography [919, 920] may show hyperechogenicity as preclinical markers for neurodegeneration in RBD.

Cerebrospinal Fluid Examination and Other Laboratory Tests

Cerebrospinal fluid examination is important for the diagnosis of meningoencephalitis, Lyme disease, and MS, all of which may give rise to sleep disturbances. Hematologic tests and biochemical studies of blood and urine, as well as tests to assess the endocrine, pulmonary, and cardiac disorders, are essential to uncover general medical disorders that may result in metabolic or toxic encephalopathies.

Laboratory Tests to Investigate Sleep and Sleep-Related Breathing Disorders

Polysomnography

The importance of PSG in the diagnosis of sleep and SDBs is discussed in Chaps. 26 and 32. Sleep can adversely affect breathing, and conversely, respiratory dysrhythmias can have deleterious effects on sleep (see Chap. 11). Both alterations can affect the severity and course of a neurologic illness, causing such sleep disturbances, and so the sleep architecture should be studied. The technique of PSG is described in detail in Chap. 17. For indications and PSG findings in sleep disorders, see Chap. 26.

Video-PSG is important for monitoring patients suspected of having epilepsy or parasomnias that may be associated with certain neurologic disorders (see Chaps. 26, 44 and 50).

Electroencephalography, Including 24-h Ambulatory EEG

Multiple channels of EEG recordings are essential to document focal and diffuse neurologic lesions and to accurately localize epileptiform discharges in patients with seizure disorders (see Chap. 18). Electroencephalography, including 24-h ambulatory EEG, is essential if epilepsy is suspected, as it can cause sleep disturbances that may sometimes be mistaken for parasomnias or sleep apneic episodes. For further details, see Chaps. 26 and 32. If the results of the EEG recording, including long-term monitoring, and neuroimaging findings are discordant in localizing the focus or in making a

diagnosis of seizure in a patient strongly suspected to have it, the patient should be referred to a specialized epilepsy center for intracranial recordings. Recently, for better localization and identification of the epileptic focus as part of presurgical screening, high-density EEG (HD-EEG) technique has been introduced [921]. HD-EEG or dense-array EEG can overcome the spatial limitation of standard EEG in more precise localization of an epileptic focus.

Electrodiagnosis of the Respiratory Muscles

Electromyography of the upper airway, diaphragmatic, intercostal, rectus abdominis, or other abdominal accessory expiratory muscles (see Chaps. 11 and 18) may detect effects on these muscles in neurologic diseases [88, 922–927]. In patients with MSA with laryngeal stridor, it is important to perform laryngeal EMG to detect laryngeal paresis [928].

Phrenic nerve [929] and intercostal nerve conduction study [930] may detect phrenic and intercostal neuropathy, which may cause diaphragmatic and intercostal muscle weakness in some patients with neurologic disorders. Needle EMG of the diaphragm may reveal diaphragmatic denervation, which would suggest neurogenic dysfunction of the diaphragm [931–933].

Multiple orofacial muscle EMGs, in addition to the standard chin EMG, may help assess upper airway muscle hypotonia (see Chap. 18). Multiple muscle EMGs, including tibialis anterior, additional forearm, other limb, and trunk muscle EMGs, are essential for diagnosis of RLS, PLMS, some parasomnias (e.g., RBD), and other sleep-related physiologic and pathological movements.

Multiple Sleep Latency Test

The MSLT is an important test to effectively document EDS, and narcolepsy is the single most important indication for performing MSLT. The presence of two sleep-onset REMs (SOREMs) on four or five nap studies (SOREMs in the preceding overnight PSG may substitute for one MSLT SOREMs) and sleep-onset latency of 8 or less minutes strongly suggest a diagnosis of narcolepsy [101, 934] (see Fig. 41.3). Abnormalities of REM sleep regulatory mechanisms (e.g., OSAS, insufficient sleep syndrome, and use of REM-suppressant medications) or circadian rhythm sleep disturbance may also lead to REM sleep abnormalities during MSLT. Further details about the recording technique and the indications of MSLT are described in Chap. 22.

Maintenance of Wakefulness Test

The maintenance of wakefulness test (MWT) is a variant of the MSLT measuring the subject's ability to stay awake. It also consists of four to five trials of remaining awake recording every 2 h. Each trial is terminated if no sleep occurs after 40 min or immediately after the first 3 consecutive epochs of stage 1 NREM sleep or the first epoch of any other stage of sleep [934]. If the mean sleep latency is less than 8 min, it is then considered an abnormal test; values greater than this but less than 40 min are of uncertain significance. The MWT is less sensitive than the MSLT as a diagnostic test for narcolepsy but is more sensitive in assessing the effect of treatment (e.g., CPAP titration in OSAS and stimulant therapy in narcolepsy). The MWT 40-minute protocol is also indicated to assess an individual's ability to remain awake when his/her inability to remain awake constitutes a public or personal safety issue. For further details, see Chap. 23.

Actigraphy

Actigraphy is an activity monitor [935] or motion detector, designed to record acceleration or deceleration of body movements, that indirectly indicates the stage of sleep or wakefulness (see Fig. 41.27). This complements the sleep diary or sleep log data. It is a small watch-like device generally worn on the wrist, but that can also be worn at the ankle, for 1–2 weeks. The actigraph stores the activity data in epoch-by-epoch samples in its internal memory until the end of the recording period, when it is downloaded to a computer to pool the data graphically and generate a report of the sleep-wake pattern. It is assumed that sleep is represented by long periods with very little to no movement. Actigraphy is a cost-effective method for the assessment of sleep-wake pattern. It can assess sleep-wake schedules in normal and sleep-disordered patients. Actigraphy is very useful in the diagnosis of circadian rhythm sleep disorders (see Fig. 41.28), paradoxical insomnia (sleep state misperception; see Fig. 41.12), and other types of insomnia. It also can be used to detect and quantify PLMS and other sleep-related movements. However, it is not suitable for the assessment of SDB events. Sometimes, it is difficult to assess the sleep-wake schedule in subjects who may feign a sleep problem. Several models are commercially available. Actigraphy and overnight PSG sleep measures are highly correlated in clinical studies. For additional information about actigraphy, see Chap. 39.

Pulmonary Function Tests

Pulmonary function tests (PFTs) assess respiratory and ventilatory muscle function. PFTs include measurement of lung volumes (quantities of air within the lungs) and lung capacities (derived from lung volumes), arterial blood gases, Pa_{O_2} and Pa_{CO_2} obtained by arterial (radial or femoral) puncture, arterial oxygen saturation by finger oximetry, and end-tidal CO_2 or

transcutaneous CO_2. Spirometry is the most important pulmonary function test, measuring most of the lung volumes and capacities except residual volume, functional residual capacity, and total lung capacity, which require nonspirometry techniques (e.g., gas dilution technique). The important spirometric measurements [525–530, 620, 621, 936] are forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and the ratio of FEV_1 to FVC. In order to obtain valid spirometric measurements, it is important to have patient cooperation and good patient-technician interaction. Values are expressed as percentage of predicted. Values of FVC, FEV_1, and peak expiratory flow of less than 80 % predicted are considered abnormal. A value of less than 70 % predicted for the ratio of FEV_1 to FVC is abnormal. The characteristic abnormalities in neuromuscular disorders include decreased FVC, FEV_1, and total lung capacity but increased residual volume. The airway obstruction shows less-than-predicted values of the ratio of FEV_1 to FVC, whereas restricted lung disease will show an increase in the ratio of FEV_1 to FVC combined with an absolute reduction in FVC and FEV_1. Box 41.8 lists the lung volumes and lung capacities, which are schematically shown in Fig. 41.28.

Box 41.8 Lung Volumes and Capacities

Lung Volumes

- Tidal volume (TV): volume (ml) of air per normal inspiration or expiration,
- Inspiratory reserve volume (IRV): volume of air during maximal inhalation following a normal breath,
- Expiratory reserve volume (ERV): volume of air during maximal exhalation following a normal breath,
- Residual volume (RV): volume of air remaining after maximal exhalation.

Lung Capacities (derived from lung volumes)

- Vital capacity (VC): volume of air that can be exhaled maximally after maximal inspiration (IRV + TV + ERV),
- Inspiratory capacity (IC): inspiratory reserve volume plus tidal volume (IRV + TV),
- Functional residual capacity (FRC): volume of air remaining after a normal expiration (ERV + RV),
- Total lung capacity (TLC): vital capacity plus residual volume (VC + RV).

Before a significant reduction in lung volume is appreciated, respiratory muscle strength must be severely reduced because pressure/volume characteristics of the respiratory system are not linear. Thus, static respiratory pressure measurements are often used to assess the respiratory muscle strength: for example, maximal inspiratory pressure (PI_{max}) and maximal expiratory pressure (PE_{max}) [937]. However, these measurements require the cooperation of patients, and the normal values have large ranges and variability that may be related to factors such as lung volume, type of mouthpiece, variable effort, and learning. In patients with bulbar muscle weakness, it may not be possible to measure PI_{max} and PE_{max}. In order to reduce the effects of these variables in the measurements of PI_{max}, investigators have used respiratory pressures during the maximal sniff maneuver [523, 524]. The maximal sniff pressure may be measured using transdiaphragmatic, esophageal, or nasal methods. Nasal pressure is often measured rather than esophageal pressure because it is much less invasive.

The definitive test for alveolar hypoventilation is an analysis of arterial blood gases showing hypercapnia and hypoxemia [518, 531]. In the early stage of neuromuscular disorder, awake arterial blood gas values remain normal; only in advanced stages with chronic respiratory failure, will these values be abnormal. To detect abnormal nocturnal arterial blood gases and hypoventilation, an indwelling arterial catheter needs to be placed throughout the night, which is invasive and rather impractical. Therefore, some investigators advocate noninvasive monitoring of arterial oxygen saturation and $Paco_2$ only to detect hypoventilation; however, there are pitfalls to this line of investigation [531]. There is limitation to the usefulness of finger oximetry alone because of the hyperbolic shape of the oxyhemoglobin dissociation curves, which may show minor oxygen desaturation in the presence of significant hypoventilation and reduced Pao_2. The noninvasive end-tidal and transcutaneous carbon dioxide tension measurements are also unreliable and correlate poorly with actual $Paco_2$.

Chemical control of breathing may be impaired if neurologic disease causes dysfunction of the metabolic respiratory controllers [9]. Such impairment may be detected by hypercapnic ventilatory response ($VE/Paco_2$), hypoxic ventilatory response (VE/Pao_2), and mouth occlusion pressure ($P_{0.1}$) response, with or without loading [9]. Central respiratory drive and the inspiratory muscle strength independent of pulmonary mechanical factors are reflected in the $P_{0.1}$ response.

PFTs can exclude intrinsic bronchopulmonary disease, which may affect SDBs [936]. For additional detail on PFTs, see Chap. 20.

Chest Fluoroscopy

In patients suspected to have diaphragmatic paralysis, chest fluoroscopy in addition to the measurement of transdiaphragmatic pressure using esophageal and gastric balloons

inserted through the nasogastric route may be necessary [938–940]. The chest radiography is noninvasive and permits visualization of the diaphragm dome but provides little information regarding diaphragm function. Chest fluoroscopy of the diaphragm provides real-time examination of the start of diaphragm dome motion but carries the disadvantage of exposure to ionizing radiation and poor sensitivity and specificity.

Other Laboratory Tests

Any suspected medical disorders that may be causing patient's insomnia or hypersomnia should be investigated with appropriate laboratory tests which may include blood and urinalysis, ECG including Holter monitoring, echocardiogram, chest radiography, and other tests to exclude pulmonary, cardiovascular, gastrointestinal, endocrine, and renal disorders. Autonomic function tests may be required in autonomic failure cases causing SDB and other sleep disturbance.

Narcolepsy patients may require histocompatibility leukocyte antigen (HLA) typing as most of the patients with narcolepsy are HLA DR2DQI and DQB1*0602 antigen positive (see Chap. 38). This is, however, not a specified test for narcolepsy as a high percentage of rheumatologic disorder, and some (12–21 %) normal individuals are also DR2 positive. Another important test for diagnostic problem cases of narcolepsy is the measurement of CSF hypocretin-1 levels which are found to be low (<110 pg/ml) in narcolepsy type 1 patients who are DQB1*0602 positive (see also Chap. 38). In patients with narcolepsy type 2 and in some other neurologic disorders, CSF levels may be low normal.

Minnesota Multiphasic Personality Inventory (MMPI) testing may be needed to assess the baseline personality trait in some psychiatric patients complaining of EDS.

In patients with RLS, in addition to neuroimaging tests as described above, EMG and NCS are important to exclude polyneuropathies or lumbosacral radiculopathies, and other lower motor neuron disorders that may be associated with RLS or cause symptoms resembling idiopathic RLS. Other important laboratory tests in patients with RLS include those necessary to exclude diabetes mellitus, uremia, anemia, and other associated conditions. It is particularly important to obtain levels of serum iron (including serum ferritin and transferrin), serum folate, fasting blood glucose, blood urea, and creatinine. In a subgroup of patients with RLS, serum iron and ferritin levels are found to be low (ferritin < 50–70 mg/ml), and correction of these abnormalities may improve the condition. The role of nerve biopsy remains controversial, and in the vast majority of patients, it is not necessary, but may be obtained for research purpose and when there is a strong suspicion of polyneuropathy.

Box 41.9A and Box 41.9B outline the laboratory tests to assess the sleep disorders.

Box 41.9A Diagnostic Tests to Assess the Sleep Disorder

- Diagnostic workup for the primary or comorbid condition causing sleep disturbance
- Laboratory tests for the diagnosis and monitoring of sleep disorders:
  - Overnight polysomnography (PSG),
  - High-definition video-PSG,
  - Multiple sleep latency tests (MSLT),
  - Maintenance of wakefulness test (MWT),
  - Actigraphy.
- Video-PSG with multiple muscle montage
- Laboratory tests for suspected seizure disorders
  - Standard electroencephalography (EEG),
  - Video-EEG monitoring for suspected seizure disorders,
  - Video-PSG with special seizure montage.
- Imaging studies:
  - Upper airway imaging for obstructive sleep apnea syndrome,
  - Neuroimaging studies of the brain (e.g., computed tomography, magnetic resonance imaging [MRI], MR angiography, diffusion tensor MRI, and MR tractography) and cerebral angiography in cases of suspected neurologic illness causing sleep disorder,
  - Positron-emission tomography and single-photon-emission computed tomography of the brain in special situations,
  - Cardian MIBG scintigraphy and midbrain transcranial sonography in idiopathic RBD to uncover preclinical markers for neurodegeneration,
  - Fiber-optic endoscopy and cephalometric radiographs of the cranial base and facial bones to locate site of the upper airway collapse and to assess the posterior airway space in OSA patients.
- Miscellaneous tests:
  - Standard blood and urine analysis,
  - Pulmonary function tests including arterial blood gases (ABGs) in cases of suspected bronchopulmonary and neuromuscular disorders causing sleep-disordered breathing,
  - Histocompatibility leukocyte antigen for suspected narcolepsy (HLA DQB1*0602),
  - Cerebrospinal fluid hypocretin-1 levels in suspected narcolepsy,
  - Serum iron, ferritin levels, and transferrin for patients with RLS/WED,

- Electromyography and nerve conduction studies to exclude comorbid or secondary RLS/WED,
- Cardiological investigations including electrocardiogram (EKG), Holter EKG, and echocardiogram,
- Endocrine tests,
- Autonomic function tests in patients with suspected autonomic and sleep-related breathing disorders.

Box 41.9B Home Sleep Apnea Testing (HSAT)

- Indications
  - May be alternatives for the initial diagnosis of OSA in patients with a high pretest probability for the condition.

- Contraindications to HSAT
  1. Patient is 18 years of age or younger,
  2. Moderate or severe chronic obstructive pulmonary disease (COPD)—FEV1/FVC less than or equal to 0.7 and FEV1 less than 80 % of predicted,
  3. Moderate or severe congestive heart failure (CHF)—NYHA class III or IV,
  4. Cognitive impairment (inability to follow simple instructions),
  5. Neuromuscular impairment,
  6. Suspicion of a sleep disorder other than OSA (e.g., central sleep apnea, narcolepsy, restless legs syndrome, circadian rhythm disorder, parasomnias, and periodic limb movement disorder),
  7. Previous technically suboptimal home sleep study (2 nights of study attempted),
  8. Previous 2-night home sleep study which did not diagnose OSA in a patient with ongoing clinical suspicion of OSA,
  9. Patient is oxygen dependent for any reason,
  10. History of cerebrovascular accident (CVA) within the preceding 30 days,
  11. History of ventricular fibrillation or sustained ventricular tachycardia.

Treatment of Sleep and Respiratory Dysfunction Secondary to Neurologic Disorders

Treatment is discussed under two broad categories: (1) therapy for the primary neurologic illness and (2) therapy for the secondary sleep disturbance.

Treatment of Primary Neurologic Illness

First and foremost is accurate diagnosis of the primary neurologic disorder. This is followed by vigorous treatment and monitoring of the neurologic illness. Such treatment may improve the sleep disturbances. It is beyond the scope of this volume to discuss the treatment of primary neurologic disorders, and readers are referred to some excellent texts [896–899].

Treatment of Sleep Disturbances Including Sleep-Related Breathing Disorders

Sleep disturbances in neurologic disorders include hypersomnia, insomnia, circadian rhythm sleep disturbances, parasomnias, and other sleep-related movement disorders. Treatment of these complaints is discussed in several chapters in this volume (see Chaps. 32–38, 40–42, 44, 46–50, and 55). In this section, treatment of hypersomnia that results mainly from sleep-related respiratory dysrhythmias in neurologic disorders is discussed. In the following sections, general principles of treatment for sleep disturbances in dementias and PD not related to the respiratory dysrhythmias are briefly reviewed.

The objective of treatment of SRBDs is twofold: (1) to improve the quality of life by improving the quality of sleep and (2) to prevent life-threatening cardiac arrhythmias, pulmonary hypertension, and congestive cardiac failure related to SDB. The quality of sleep may be improved by eliminating repeated apneas during sleep and thus preventing repeated arousals, sleep fragmentation, nocturnal hypoxemia, and daytime hypersomnolence. The treatment modalities for sleep-related respiratory dysrhythmias resulting from neurologic illness may be divided into five categories: (1) general measures, (2) pharmacologic agents, (3) mechanical devices, (4) supplemental O_2 administration, and (5) surgical treatment (Box 41.10).

Box 41.10 Treatment of Sleep-Related Breathing Disorders in Neurologic Illness

General Measures

- Avoid alcohol and sedative hypnotics, especially in the evening.
- Reduce body weight if overweight.
- Avoid sleep deprivation.
- Avoid supine sleeping position.
- Participate in regular exercise program if possible.

Pharmacologic Agents

- Protriptyline, medroxyprogesterone acetate, or SSRIs in mild cases (mostly ineffective),
- Nasal corticosteroids for OSA in children (minimal benefit),
- Acetazolamide in central apnea at high altitude,
- Modafinil as an adjunct treatment in a subset of OSA patients with residual sleepiness and in some patients with myotonic dystrophy.

Mechanical Devices

- Continuous positive airway pressure (CPAP) titration,
- Bilevel positive airway pressure (BPAP) titration,
- Auto-CPAP,
- Assisted servoventilation,
- Intermittent positive pressure ventilation,
- Dental appliances, including mandibular advancement device,
- Tongue retaining device.

Supplemental O_2 Administration

Surgical Treatment

- Bariatric surgery,
- Diaphragm pacing or electrophrenic respiration,
- Hypoglossal nerve stimulation,
- Tracheostomy (rarely performed nowadays).

OSA obstructive sleep apnea; *SSRIs* selective serotonin reuptake inhibitors.

General Measures

General measures of treatment include reduction or elimination of risk factors that can aggravate sleep-related respiratory dysrhythmias. Avoidance of alcohol and sedative hypnotic drugs [941] (e.g., benzodiazepines, barbiturates, and narcotics) that can depress breathing during sleep is an important step in eliminating the risk factors. Alcohol is known to increase the frequency and duration of apneas, probably by two mechanisms [942–944]: (1) selective depression of the genioglossus and other upper airway muscles and (2) impairment of the arousal response by raising its threshold. For obese patients, weight loss is another important step in eliminating risk factors for sleep-related respiratory dysrhythmia. Other general measures include avoidance of sleep deprivation and supine sleep position and maintenance of a regular exercise program as much as possible from a practical point of view in the neurologically afflicted patient.

Pharmacologic Treatment

This therapy remains unsatisfactory [945]. The agents that have been tried with partial success for mild-to-moderate sleep apnea are protriptyline, medroxyprogesterone acetate, acetazolamide, selective serotonin reuptake inhibitors (SSRIs), and nasal corticosteroids for children. Protriptyline may be used in a dose of 5–20 mg at bedtime. Suppression of REM sleep; a specific alerting property; increased upper airway muscle tone; and conversion of apnea to hypopnea are cited as mechanisms of action of this drug [941, 946]. Anticholinergic effects and cardiac arrhythmias are the limiting side effects of this drug.

Medroxyprogesterone acetate has been tried in many patients with sleep apnea, but the results have been

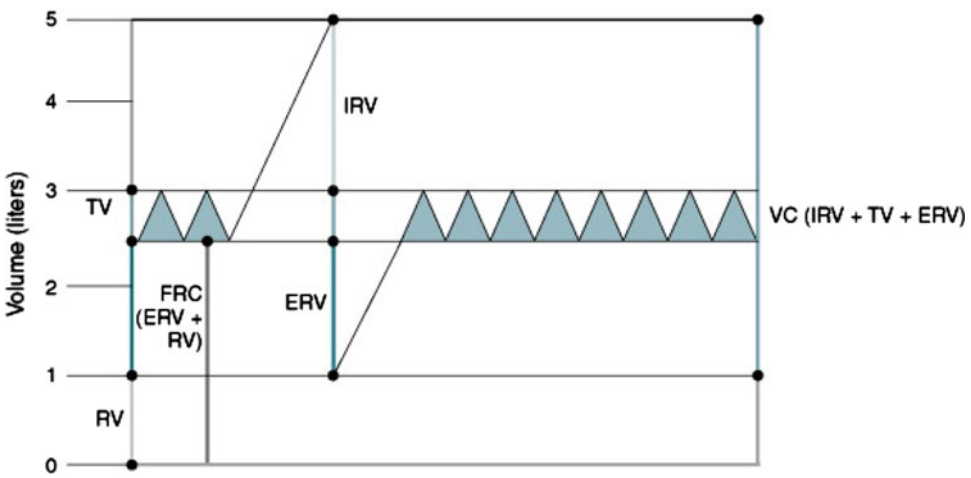

Fig. 41.28 Schematic diagram to show lung volumes and capacities. *ERV* expiratory reserve volume; *FRC* functional residual capacity; *IRV* inspiratory reserve volume; *RV* residual volume; *TV* tidal volume; *VC* vital capacity.)

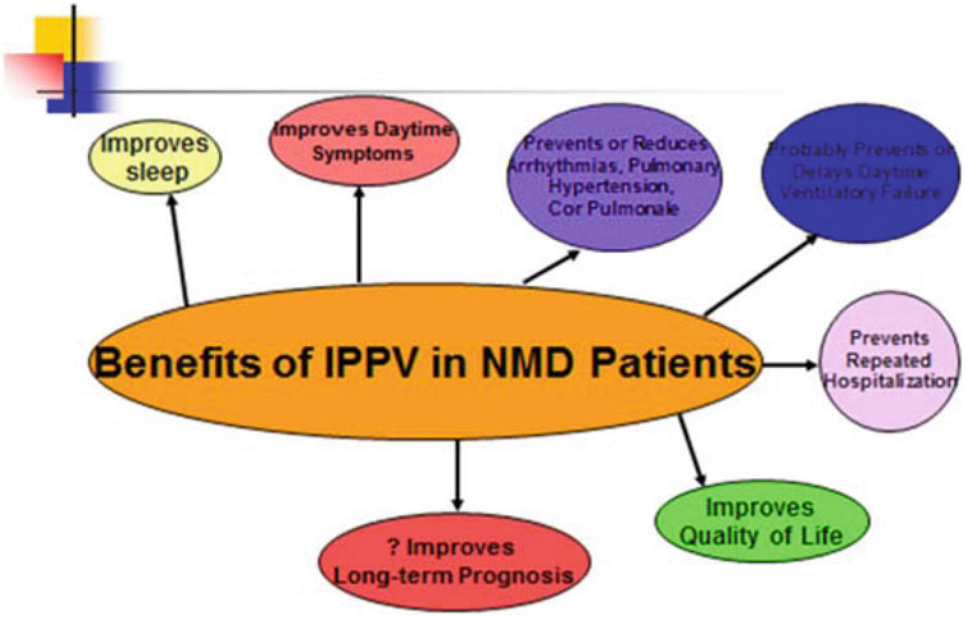

Fig. 41.29 Schematic to show benefits of IPPV

disappointing [947–949]. It is thought to act by increasing ventilatory drive. Impotence in men is a limiting side effect, and there are other side effects [950].

Acetazolamide has been used with some success in central apnea, but development of obstructive apnea or aggravation of orthostatic hypotension owing to its diuretic and natriuretic effects should be kept in mind during treatment. Acetazolamide is a carbonic anhydrase inhibitor and will produce metabolic acidosis, causing a shift in the P_{ACO_2} apnea threshold, and it has been used with some success to treat central apnea at high altitude [951–955].

There have been isolated reports of the use of selective serotonin reuptake inhibitors in mild cases and topical nasal corticosteroids for OSAS in children with minimal benefit. In a subset of OSAS patients on CPAP titration (see later), complaining of residual daytime sleepiness, modafinil or armodafinil, a novel wake-promoting agent, has been used with success as an adjunct treatment [956–964]. Modafinil has also been used successfully for myotonic dystrophy patients with hypersomnia unrelated to alveolar hypoventilation or sleep apnea [965–967]. Modafinil may be initiated at 100 mg/day, increasing to a maximum of 400 mg/day to be taken in two divided doses. Armodafinil may be used as a single dose (longer-acting agent than modafinil of 150–250 mg one totwo hours before or after breakfast). Methylphenidate and amphetamines may also be used if modafinil is not effective.

CSA, including CSB, associated with heart failure requires aggressive pharmacologic treatment for heart failure (e.g., beta-blockers, digoxin, and diuretics) and, if needed, heart transplantation (see Chap. 47).

Mechanical Devices

Nasal Continuous Positive Airway Pressure

An important therapeutic advance in the treatment of OSAS, CPAP is described in detail in Chap. 34. It should be given a trial in neurologic disease patients with upper airway OSAs associated with intermittent CSAs or with mixed apneas. Such treatment often improves the quality of sleep and reduces daytime symptoms by eliminating or reducing sleep-related obstructive or mixed apneas and O_2 desaturation. The role of nasal CPAP for CSA is highly controversial. The Stanford University group [968] found CPAP helpful for central apnea patients who had associated OSA or who showed sleep fragmentation and repeated sleep-wake changes. In a subgroup of patients with CSA with insomnia who may show narrowing or occlusion of the upper airway via fiber-optic scope, nasal CPAP reversed the CSA [969, 970]. In addition to nasal or full-face CPAP with or without expiratory pressure relief (1–3 cm), other devices that found to be useful include bilevel positive airway pressure (BiPAP) delivering higher pressure during inspiration and lower pressure during expiration, auto-CPAP, and auto-BiPAP titration. Auto-CPAP and auto-BiPAP machines automatically titrate pressure according to specific algorithms set by each manufacturing agency to detect abnormal breathing events. The role of these autodevices in better adherence than standard CPAP remains to be determined despite reducing mean pressure requirement by 2 cm compared to fixed pressure CPAP. For further details, see Chap. 34.

Treatment of Cheyne–Stokes Breathing and Central Sleep Apnea

Patients with CSB-CSA should be given a trial with CPAP or BIPAP titration to improve ventilation in addition to pharmacologic treatment with acetazolamide or theophylline. Some patients may require oxygen inhalation and gas modulation with inert carbon dioxide through the nasal mask or with added dead space to positive pressure titration [971, 972]. Another treatment besides CPAP-BIPAP that has been found to be useful in patients with CSB-CSA and complex sleep apnea includes adaptive servoventilation [973–983]. The role of adaptive servoventilation in terms of long-term prognosis, however, remains to be determined. Recent European trial suggested increased mortality after ASV titration for CSA-CSB in systolic heart failure with reduced (≤45 %) ejection fraction [984]. See also Chap. 47 and contradictory correspondence with response from the original authors [985].

Neuromuscular Disorders and Other Ventilatory Supports

In the past, the mainstay of treatment for patients with neuromuscular disorders associated with SDB including hypoventilation was invasive ventilation through a tracheostomy (see later in this section), but this has now been largely replaced by noninvasive measures of ventilatory support consisting of negative and positive pressure ventilators [531, 986, 987]. These ventilators were developed during the early polio epidemics in the 1950s and the 1960s. Negative pressure ventilators include "iron lung" or tank respirators, the "rain coat" or "pneumowrap ventilator," and the cuirass or "tortoise shell" [986, 988–992]. Although the tank respirator is the most effective negative pressure ventilator, applying negative pressure to the entire body below the neck, it is bulky and limits the patient's acceptance [986, 990]. Furthermore, negative pressure ventilators may cause upper airway OSA with oxygen desaturation both in normal subjects [993] and in patients with neuromuscular diseases [994]. The contemporary standard of care for chronic ventilatory failure in neuromuscular disorders is noninvasive intermittent positive pressure ventilation (IPPV) using a nasal mask or prongs. Positive pressure ventilation includes CPAP, BiPAP, and IPPV. For upper airway OSAS, nasal CPAP is the ideal treatment. Following such treatment, sleep quality and daytime hypersomnolence often improve due to the reduction or elimination of sleep-related obstructive or mixed apneas and oxygen desaturation. However, such treatment has not been very useful in patients with relentlessly progressive disease; therefore, the role of CPAP in such diseases requires additional study. Some patients may not be able to tolerate the same high pressure during both inspiration and expiration and feel comfortable using BIPAP, which uses higher inspiratory than expiratory positive airway pressure.

The beneficial effect of nocturnal IPPV may be summarized as follows: improved nocturnal gas exchange as reflected in Sao_2 and transcutaneous CO_2 as well as improved daytime arterial blood gases; mild improvement of total sleep duration without significant improvement of quality of sleep; improved FVC and PI_{max}; reduced number of days of hospitalization; and improved quality-of-life measures and long-term survival. Figure 41.29 schematically outlines the benefit of IPPV in neuromuscular disorders.

The benefits of noninvasive ventilation through a nasal mask for 6–8 h during sleep in neuromuscular disorders have been clearly shown in many studies [464, 519, 530, 995–1025]. IPPV generally uses no expiratory positive pressure, but in some patients, positive end-expiratory pressure up to 5 cm may be required. In some patients during initial nights of IPPV, there may be upper airway closure for the first time [520, 1026] during the expiratory phase. The mechanism for such closure may include driving CO_2 below the inspiratory threshold and marked reduction of muscle tone as a result of REM rebound. Treatment of these patients is by the addition of a positive end-expiratory pressure valve by maintaining a positive pressure (up to 5 cm) during expiration. Noninvasive IPPV can be used even in those patients with bulbar muscle weakness utilizing the full-face mask. Either pressure-cycled ventilators delivering air at a fixed pressure or volume-cycled ventilators delivering a fixed volume of air may be used. Many clinicians prefer pressure-cycled ventilators to deliver IPPV, but there is variation in individual patient response [1025]. There does not seem to be a difference between these two types of ventilators in terms of long-term survival [1027] and short-term studies showing correction of hypoventilation [1028]. The volume-cycled ventilators deliver tidal volume, and pressure-cycled ventilators deliver fixed pressure (usually 10–20 cm H_2O) set by the clinician. One of the following three ventilator modes may be used: control mode, wherein the ventilator starts and ends inspiration according to prescribed settings; assist-control mode, wherein either the patient's effort or a programmed setting initiates inspiration; and spontaneous assist, wherein the patient's effort starts and ends inspiration. In the spontaneous mode, a backup respiratory rate is set up.

Cochrane Database updated review in 2014[1023] noted two trials comparing pressure-cycled ventilation (PCV) with volume-cycled ventilation (VCV). VCV was associated with less sleep time spent with an arterial O_2 saturation below

90 % and a lower apnea-hypopnea index per hour. There was only one trial in this report [1029] with 16 participants which found no difference in mortality between PCV and VCV.

Long-term follow-up and prospective randomized controlled trials in neuromuscular disorders such as ALS are limited. In one of the largest prospective, although not randomized, blinded studies, Mustafa et al. [1008] proved the efficacy of noninvasive ventilation in ALS patients. There were striking improvements in blood gases and a variety of quality-of-life measures following noninvasive ventilation within one month that were maintained for up to 12 months in 26 patients with ALS showing respiratory muscle weakness. These authors also studied in parallel 15 age-matched patients without respiratory muscle weakness but with similar severity of ALS. These ALS patients showed improvement in quality-of-life measures despite progression of the disease. It was also shown that noninvasive ventilation in patients had no impact on most quality-of-life measures for caregivers and did not increase caregiver burden or stress. In another study [1011], 26 patients with congenital neuromuscular or chest wall diseases having daytime normocapnea and nocturnal hypercapnia were randomized either to nocturnal noninvasive ventilation or to a control group without ventilatory support. These authors found increased mean Sao_2 and decreased mean percentage of the night with peak transcutaneous CO_2 tension in the group using noninvasive ventilation as compared with controls. The authors suggested that such patients may benefit from nocturnal IPPV before daytime hypercapnia ensues. In the only randomized controlled trial, Bourke et al. [998] assigned 22 patients to noninvasive ventilation and 19 patients to standard care when these ALS patients developed orthopnea with PI_{max} less than 60 % of predicted value or symptomatic hypercapnia. They found a median survival benefit of 205 days with improvement in quality-of-life measures in patients receiving noninvasive ventilation. In patients with severe bulbar involvement, however, survival benefit was not noted, but there was improvement in sleep-related symptoms. A survival benefit was also observed by Pinto et al. [999] and Kleopa et al. [1005]. Improvement in nocturnal ventilation and sleep quality following IPPV has been noted by several authors in patients with nocturnal respiratory failure as a result of restrictive or neuromuscular disorders [1026, 1030, 1031]. In the Cochrane Database updated review covering 10 eligible trials with 179 participants, Annane et al. [1029] stated that there is a clear evidence of alleviation of chronic hypoventilation in neuromuscular disorders in the short term. In their review covering four small studies involving mainly motor neuron disease, prolonged survival and reduced number of hospitalizations were noted. In both motor neuron disease and Duchenne's muscular dystrophy, survival benefit after using mechanical ventilation versus no ventilation is established. However, the authors concluded that further larger studies are needed to assess the long-term benefit of different types and modes of ventilation to determine morbidity, mortality, and quality of life in all other neuromuscular and chest wall disorders. Sancho et al. [1032] also observed prolonged survival of 22 patients with amyotrophic lateral sclerosis following both noninvasive and tracheostomy IPPV.

Indications for Intermittent Positive Pressure Ventilation

A European consensus conference in 1993 listed the following criteria for long-term noninvasive nasal ventilation for patients with neuromuscular disorders [1033]: presence of clinical symptoms associated with $Paco_2$ level of ≤45 mm Hg, Pao_2 <60 mm Hg in the daytime arterial blood gas analysis, or pronounced nocturnal oxygen desaturation. The patient's obstructive symptoms and arterial blood gases should be monitored. A later US consensus conference in a 1999 report listed the criteria for IPPV for patients with neuromuscular disorders (Box 41.11) [1034]. First, the diagnosis must be established via history and physical examination followed by appropriate laboratory tests. The patients should have received treatment for associated (e.g., OSAS diagnosed by performing PSG studies) or underlying conditions. The suggested indications for use of noninvasive ventilation include clinical symptoms and one of the three physiologic criteria (see Box 41.11). A follow-up in 1–3 months for the assessment of compliance and monitoring awake arterial blood gases is also suggested. Overnight oximetry may be helpful for monitoring such patients.

Box 41.11 1999 US Consensus Conference: Indications for IPV in Chronic respiratory failure [1034]

- Appropriate clinical symptoms

- PLUS one of the three physiologic criteria:
  - $PaCo_2$ ≥45 mmHg,
  - Nocturnal oxygen desaturation (by finger oximetry) of ≤88 % for five consecutive minutes,
  - PImax of <60 % cm H_2O or FVC <50 % of predicted value in cases of progressive neuromuscular diseases.

Abbreviations: *$PaCo_2$* arterial partial pressure of carbon dioxide; *PImax* maximum inspiratory muscle pressure; *FVC* forced vital capacity.

In 2009, the American Academy of Neurology published updated practice parameter [1035] for initiation of IPPV in the care of patients with amyotrophic lateral sclerosis (Box 41.12). The American Academy of Sleep Medicine (AASMS) Task Force made recommendations for titration guidelines for noninvasive positive pressure ventilation

[1036]. It should be remembered that different neuromuscular disorders evolve and progress at different and varying speeds depending on the etiology of the disease process and other associated variables, and therefore, the setup guidelines may need further modifications depending upon the disease process involved.

Box 41.12 American Academy of Neurology Practice Parameters updated (2009) for IPPV in the care of ALS patients [1035]

- PImax of <60 cm H_2O,
- FVC <50 % of predicted value,
- Pnsn <40 cm H_2O,
- Nocturnal SaO_2 <90 % for a cumulative time of >1 min in the presence of orthopnea.

Abbreviations: *PImax* maximum inspiratory muscle pressure; *FVC* forced vital capacity; *Pnsn* nasal sniff pressure.

There have been some attempts to document daytime predictors that will indicate nocturnal hypoventilation and hence the need for IPPV, and these have been discussed previously in this chapter. Katz et al. [1037] studied 46 children with progressive neuromuscular diseases and observed that subjects (15 %) with nocturnal hypoventilation had FVC <70 % and FEV_1 <65 % which the authors considered as predictors of nocturnal hypoventilation. In a recent study of obesity hypoventilation syndrome from Saudi Arabia, Bahammam [1038] concluded that serum sodium bicarbonate (HCO_3) may be a predictor of nocturnal hypoventilation. There is no controlled study implementing these predictors to evaluate the progression of disease and efficacy of treatment, but finger oximetry is the most widely used. In addition, transcutaneous or end-tidal CO_2 concentration can also be used. Electromyography of the accessory respiratory muscles may help in indicating the evidence of ventilatory failure; however, repeat PSG study remains the best test for evaluating quality of sleep and effectiveness of IPPV. Guilleminault and Shergill [516] suggested that even if there is no change in clinical symptoms, a PSG is recommended at least once a year as respiratory changes can occur without accompanying clinical symptoms. There are, however, no standard guidelines for this recommendation.

The complications of IPPV are similar to those noted with CPAP or BIPAP (see Chap. 34). One particularly annoying complication is nasal stuffiness or rhinorrhea, which may be relieved by using a warm humidifier or nasal corticosteroids. Some patients complain of claustrophobia when using a nasal mask, particularly those with breathing problems. In such patients, a nasal pillow instead of a nasal mask may be useful. Leaks around the mask causing arousals, sleep fragmentation, and subsequent decrease in efficacy of IPPV are also common, and correction of these leaks is important to improve the sleep quality and architecture. Long-term use of a nasal mask can lead to a maxillary hypoplasia in young subjects. Children using nasal ventilation should be seen monthly to adjust mask size, particularly in the first 2 years of life, as a child's face grows quickly during infancy and childhood. Furthermore, airways develop and remodel during this time, and repetition of nocturnal PSG has been suggested approximately every 3 months [516].

Mechanism of Improvement Following IPPV

Several mechanisms have been suggested but not proven for improving SDB and related symptoms in patients with neuromuscular disorders following noninvasive IPPV [518, 530, 531, 1039, 1040]. Improvement of respiratory muscle fatigue and restoration of the sensitivity of the respiratory center to carbon dioxide are the two important mechanisms cited. Changes in pulmonary mechanics (e.g., increasing lung volumes, improvement of lung compliance, and reduction of dead space) may also contribute to improvement in symptoms and gas exchanges (Fig. 41.29).

Oxygen Supplementation

The role of supplemental oxygen therapy using low-flow oxygen (1–2 L/min) in the treatment of SDB in neurotomy-muscular diseases remains controversial. According to most investigators, oxygen therapy in restrictive thoracic disorders caused by neuromuscular diseases is ineffective and may be dangerous, leading to marked CO_2 retention [1041].

Supplemental O_2 therapy may decrease the severity of OSA in certain patients [1042]. The recommended treatment of nocturnal hypoxemia is the administration of O_2 at a low flow rate (1–2 L/min) via a nasal cannula (see Chap. 47). Oxygen administration may not be safe for all patients with sleep apnea syndrome. Motta and Guilleminault [1043] and Chokroverty et al. [1044] observed prolongation of apneas after O_2 administration during sleep in patients with OSAS and obesity hypoventilation syndrome. Gay and Edmonds [1045] directed our attention to the possible exacerbation of hypercapnia after administration of low-flow O_2 in patients with neuromuscular disorders. In eight patients with neuromuscular disease and diaphragmatic dysfunction (patients with polymyositis, ALS, or inflammatory motor neuropathy), mean $Paco_2$ increased considerably after administration of low-flow supplemental O_2 (0.5–2.0 L/min). Four patients needed subsequent nocturnal assisted ventilation. The authors suggested that nocturnal assisted ventilation can be considered for patients with O_2-sensitive hypoventilation. In such patients, it may be possible to safely administer O_2 during the daytime. AASM made recommendations [1036] for supplemental oxygen during noninvasive IPPV titration.

Surgical Treatment

This consists of bariatric surgery, hypoglossal nerve stimulation, diaphragmatic pacing or electrophrenic respiration and tracheostomy (see Box 41.10).

Hypoglossal Nerve Stimulation

Recently, hypoglossal nerve stimulation by an implanted device has been tried in 126 patients who had difficulty in accepting or toleratin CPAP with reduction of mean AHI from 32 to 15.2/hour at 12 months' follow-up. Aderse effects included and soreness and abrasions of the tongue [1046].

Diaphragmatic Pacing or Electrophrenic Respiration

Sarnoff et al. [1047] first used electrophrenic stimulation in patients with poliomyelitis in 1951, but the technical difficulties at that time prevented its regular use for such treatment. Glenn and associates [1048] improved the technique and extensively studied electrophrenic respiration by diaphragm pacing (DP). This form of treatment is used successfully in patients with respiratory center involvement with CSA syndrome. Superimposed OSA may complicate the procedure, which may then require both electrophrenic respiration and tracheostomy for treating such patients. Glenn's group [1048] used such treatment successfully in three groups of neurologic disease patients: those with respiratory center involvement, either direct or through interruption of the afferent or efferent neurons to the respiratory center; those with high cervical spinal cord lesions; and those with primary alveolar hypoventilation (PAH). Chervin and Guilleminault [1049] reviewed the topic of DP. The authors stated that the "gold standard" of treatment of hypoventilation due to neurologic (including neuromuscular) disorders is BIPAP or IPPV. For those patients who require ventilatory assistance during both the day and the night, however, DP is advantageous. The indications for DP include those patients with partial or total ventilatory failure, either during sleep or continuously. The causes for hypoventilation include neurologic disorders proximal to the phrenic motor neurons. The causes include both idiopathic CSA syndrome and CCHS in infants. Most of the patients on long-term DP require minimal or no additional ventilatory support, and most show improvement in the quality of life.

Complications of DP include precipitation of upper airway OSA requiring CPAP or tracheostomy in many patients, damage to the phrenic nerve, diaphragmatic damage due to fatigue, equipment malfunction, surgical complications, neuromuscular junction failure, local infection, and interference with cardiac pacemakers. Finally, DP is an invasive procedure. Despite the complications and disadvantages, DP is the preferred procedure for those requiring ventilatory assistance during both the day and the night. In June 2008, the US Food and Drug Administration (FDA) approved the $NeuR_x$ Diaphragm Pacing System (DPS) only for spinal cord injury (SCI) patients who depend on ventilators because of a paralyzed diaphragm. This approval was based on data obtained from a multicenter clinical trial [1050]. In September 2011, the FDA approved DP for amyotrophic lateral sclerosis (ALS) patients under a "Humanitarian Device Exemption" provision [1051]. In a 2009 multicenter study report involving laparoscopic diaphragm pacing in 88 patients (50 SCI and 38 ALS), Onders et al. [1052] have shown freedom from ventilators in SCI patients and delayed need for ventilators in ALS patients increasing their survival. In later studies, the same group [1053, 1054] demonstrated that DP can be used to overcome instability of breathing, improve sleep, and positively influence survival in ALS patients. The FDA subsequently approved DP for ALS patients.

Tracheostomy

Tracheostomy remains the only effective measure for emergency treatment of patients with marked respiratory dysfunction with severe hypoxemia, patients with sudden respiratory arrest after resuscitation by intubation, and patients with severe laryngeal stridor due to laryngeal abductor paralysis. This used to be the definitive treatment for patients with severe OSAS, but it has been largely replaced by CPAP or BIPAP since they became available. On improvement after emergency tracheostomy, patients may later be weaned from the tracheostomy. Permanent tracheostomy may still be needed for patients with neuromuscular diseases: those with central respiratory drive abnormalities showing persistently elevated $Paco_2$ despite using noninvasive IPPV; those who are unable to handle oropharyngeal secretions and show continued deterioration of neuromuscular disorders with very brief periods of spontaneous ventilation; and those patients with sleep apnea who fail to improve after nasal CPAP and nasal ventilation [528, 986]. In such patients, ventilatory assistance is provided at night with plugging of the tracheostomy tube during the daytime, or the patient may use a commercially available portable ventilator continuously if needed, using the assist-control mode [979]. Potential complications of tracheostomy and the care needed for maintenance of the tracheostomy should be discussed in detail with the patients and their families. Besides its invasiveness, the complications of tracheostomy include disfigurement, difficulty with speaking, tracheal stenosis, and tracheomalacia [531, 1055].

Treatment of Sleep Disturbances in Alzheimer's Disease and Related Dementias

Treatment of acute confusional states associated with dementia is described in Chap. 51. In this section, general principles of

treatment of sleep disturbance in patients with dementia are outlined [1056]. Box 41.13 lists certain general principles of treatment. Medications that could have an adverse effect on sleep and breathing should be reduced in dose or changed. Associated conditions that could interfere with sleep (e.g., pain due to arthritis and other causes) should be treated with analgesics. Depression is often an important feature in patients with AD, and a sedative antidepressant may be helpful. Frequency of urination in such patients may result from infection or enlarged prostate and may disturb sleep at night. Appropriate treatment should be directed toward such conditions. Patients should be encouraged to develop good sleep habits. They should be discouraged from taking daytime naps and should be encouraged to exercise (e.g., walking during the day). They should not drink caffeine before bedtime or in the evening. For sleeplessness, a nonbenzodiazepine agonist such as zolpidem (including zolpidem CR) and eszopiclone as well as a melatonin receptor agonist (e.g., ramelteon) are commonly prescribed for a short period (see Chap. 37). For nocturnal agitation and sundowning, the patient should be treated with antipsychotics, including the newer agents (haloperidol, 0.5–1.5 mg; thioridazine, 10–100 mg; risperidone, 1–1.5 mg; olanzapine, 5–10 mg; quetiapine, 12.5–100 mg) (see Chap. 46). In a recent review, McCleery et al. [1057] found no RCTs (and therefore, presumed to have no clear evidence) for commonly prescribed hypnotics (e.g., benzodiazepine and nonbenzodiazepine drugs) in patients with AD. However, after analyzing all RCTs, these authors found three drugs (e.g., melatonin, trazodone, and ramelteon) which had undergone RCTs to treat sleep dysfunction in AD. They found no evidence of benefit on sleep for melatonin in AD with moderate-to-severe dementia and ramelteon in AD with mild-to-moderate dementia, but noted some evidence of benefit on sleep for low dose (50 mg) of trazodone at bed time.

Box 41.13 Treatment of Sleep Disturbance in Alzheimer's Disease and Related Dementias

- **General Measures**
  - Reduce or eliminate medications that may contribute to sleep disturbance or sleep apnea.
  - Treat associated depression or anxiety and other comorbid conditions (e.g., pain causing sleep disturbances).
  - Eliminate alcohol and caffeine in the evening.
  - Institute regular sleep-wake schedule and sleep hygiene as much as possible.
  - Avoid daytime naps.
  - Encourage regular exercise (e.g., walking).
  - Attend to environmental factors.
- **For insomnia**, try a nonbenzodiazepine agonist (e.g., zolpidem and eszopiclone) or melatonin receptor agonist (e.g., ramelteon).
- **For insomnia associated with depression**, sedative antidepressants (e.g., mirtazapine and trazodone) may be used.
- **For extreme agitation or nocturnal confusional episodes**, try small doses of antipsychotics, such as haloperidol (0.5–1.0 mg/day), risperidone (1–1.5 mg/day), or quetiapine (12.5–100 mg/day).
- **Timed exposure** to bright light in the evening and in the morning may be helpful.

In some patients, timed exposure to bright light may be helpful [1058–1061]. In limited studies, Satlin et al. [1058] and Okawa et al. [1059, 1060] reported improvement in nighttime sleep and a decrease in daytime sleepiness after bright-light exposure in the evening. These findings were confirmed in some later reports [158, 159, 1062–1066]. In contrast, Dowling et al. [1067] did not find any improvement in nighttime sleep or daytime wakefulness (actigraphically documented) following morning exposure to bright light (2500 lx) for 1 h in a group of institutionalized AD patients compared to controls. However, in a later study, Dowling et al. [1067] observed that a combination of nighttime melatonin (5 mg) and bright-light (2500 lx) exposure for 1 h the next morning improved daytime activity levels and wake time in a group of institutionalized AD patients but not those receiving placebo and bright light only. Further studies are needed to confirm these observations. In a RCT of exercise (walking), light therapy, and combination in 132 AD patients, McCurry et al. [1068] evaluated sleep by wrist actigraphy. They concluded that walking, light exposure, and combination of both walking and light therapy were all effective in improving sleep. Salami et al. [1065] reviewed 38 studies (majority included mild-to-moderate AD) which used PSG, actigraphy, sleep logs, and rating scales as outcome measures to evaluate sleep. These authors concluded that most treatments for sleep disturbance were ineffective. Pharmacologic agents produced inconsistent results, but bright-light therapy (BLT) among all nondrug treatments had the best results. In a RCT evaluating effect of BLT versus standard light therapy on agitation and sleep in demented patients, Burns et al. [1066] concluded that BLT was a potential alternative to drug treatment in agitated dementia.

Treatment of Sleep Disturbances in Patients with Parkinson's Disease

Sleep has not been consistently improved in patients with PD following antiparkinsonian medications. In those patients with reactivation of parkinsonian symptoms during sleep at night, adjustment in the timing and choice of

medication may be helpful. Dopamine agonists or longer-acting preparations of levodopa at bedtime may benefit sleep in some patients. Antihistamines such as diphenhydramine may promote sleep in addition to their modest antiparkinsonian effect. A small dose of carbidopa-levodopa at bedtime with a second dose later at night when the patient awakens may sometimes help those with insomnia. Nocturnal dyskinesias related to levodopa causing insomnia may respond to a reduction in the dopamine agonists or the addition of a small dose of a benzodiazepine or nonbenzodiazepine agonist as mentioned previously. In patients with psychosis and severe nocturnal hallucinations, clozapine or newer drugs such as olanzapine may be used with considerable benefit. During clozapine treatment, the usual precautions of monitoring blood counts and testing liver functions should be taken. Sleep disorders (e.g., insomnia, hypersomnia, RBD, OSA, and RLS-PLMS) are common but have been a challenge to treat these; however, several options are available for many of these [1069]. Patients with PD associated with RBD should be treated with a small dose of clonazepam (0.5–1 mg) or melatonin (3–12 mg) nocte. Patients with PD with OSAS associated with oxygen desaturation and repeated arousals should be treated with CPAP titration. In some patients with insomnia, judicious short-term use of hypnotics may be recommended. Rios et al. [1070] conducted a randomized pilot study in 18 patients with insomnia (divided into three groups: six on doxepin 10 mg; six on CBT with BLT; and six on placebo). Using insomnia scales, clinical global impression, sleep diaries, and actigraph as outcome measures, the authors concluded that doxepin and CBT improved insomnia in PD; however, the authors cautioned that these results must be confirmed in future full RCTs. Some patients with PD showing the phenotype of narcolepsy with EDS not associated with OSAS may be treated with a small dose (100 mg in the morning) of modafinil or armodafinil (150–250 mg) one to two hours before or after breakfast (not approved by the FDA), although the results have been inconsistent [1071–1074]. Modafinil data regarding treatment of EDS in PD in several small controlled studies generated conflicting results, but data from open trials and case reports suggested limited benefit [1075]. Some of these studies showed improvement in subjective sleep ratings, but the results have been inconsistent or without any benefit in objective sleep studies. The American Academy of Neurology [1076], the American Academy of Sleep Medicine [1077], and European Federation of Neurological Society [1078] guidelines all recommended the use of modafinil in PD for treating EDS to improve subjective perception of sleepiness based on conflicting data from modafinil clinical trials in PD [1075].

Conclusion

The science of sleep is beginning to advance and probe even deeper into the significance and pathogenesis of sleep and its disorders. Dement [1079] stated aptly that sleep medicine focuses on the sleeping brain and on all phenomena and pathologic effects that derive therefrom. Progress in research involving molecular neurobiology and neurophysiology of sleep, chronophysiology, chronobiology, and functional imaging of the brain (e.g., functional MRI, PET, and SPECT scanning) holds great promise to unravel the mysteries of sleep even further and to direct our attention to finding more promising therapies for the unfortunate millions suffering from chronic disorders of sleep and wakefulness.

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Fatigue in Clinical Practice

42

Sushanth Bhat and Sudhansu Chokroverty

Introduction

Practitioners of sleep medicine often encounter patients complaining of fatigue. Patients and clinicians may use the terms "fatigue" and "sleepiness" interchangeably, but while fatigue may be secondary to excessive daytime sleepiness, and both symptoms may result from disorders of sleep, they are distinct and often have different causes, significances, and treatments. Fatigue is often described as a pervasive sense of tiredness or lack of energy impacting quality of life, and excessive daytime sleepiness (EDS) signifies a pressure to sleep or an inability to stay awake. In contrast, a patient with EDS complains of episodes of involuntarily eye closure, lapses into episodes of microsleep with inattention, yawning, and succumbing to irresistible attacks of sleepiness. It falls to the practitioner to distinguish between these two symptoms, so that appropriate investigations can be performed and management strategies initiated.

Fatigue is underreported by patients, underrecognized by clinicians, and often lumped together with other symptoms of the underlying disease. Fatigue-related complaints are often nebulous and vague, and therefore dismissed as psychosomatic [1, 2]. Treatment strategies for fatigue are not standardized, making management challenging. Prevalence rates for chronic fatigue in the general population vary, ranging from 13.6 to 30.5 % [3, 4] and suffer from a lack of a universally accepted standard definition [5]. While fatigue has generally been thought of as trouble initiating and sustaining motor tasks despite intact motor strength, patients complaining of fatigue may be describing this as muscle weakness, inability to sustain muscle contraction (muscle fatigability), exercise intolerance, inability to concentrate, perceived cognitive deficits (mental fatigue), excessive daytime sleepiness (EDS), apathy, and a loss of motivation. Many of these symptoms suggest underlying medical, neurological, sleep-related or psychiatric etiologies that may only be identified by eliciting a thorough history and performing a detailed physical examination. Several validated and reliable tools (e.g., the Fatigue Severity Scale [FSS] in Table 42.1 [6], the Checklist Individual Strength and the Abbreviated Fatigue Questionnaire [AFQ] [7, 8]) are available for identification of fatigue in the clinical setting.

This chapter focuses on the causes and management of fatigue in primary sleep, neurological, and general medical and psychiatric disorders, with a brief overview of the proposed mechanism (the neurophysiological basis) of fatigue.

Identifying the Sites of Fatigue

Classification of fatigue as being of peripheral or central origin has aided the development of neurophysiological models [9]. Both peripheral and central fatigue can be demonstrated using models that measure the force generated by muscle during maximum voluntary contraction (MVC) (Fig. 42.1).

Peripheral fatigue occurs as a result of failure of the motor unit (the anterior horn cell, the motor axon, the neuromuscular junction, and the muscle fibers innervated by this). The recording and comparison of force generated by electrical stimulation of muscle before and after exercise helps identify peripheral fatigue. Typically, after a pre-exercise electrical stimulation, the subject performs a maximum voluntary contraction (MVC) for a pre-determined period of time, generally 30–60 s, which is measured with a force transducer. A subsequent post-exercise electrical stimulation is then performed, and the force generated is compared to the pre-exercise tracing. Lower amplitudes of the waveform and slower relaxation phases as compared with pre-exercise findings are characteristic of peripheral fatigue [10,

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Table 42.1 Fatigue severity scale

Patients choose a number from 1 to 7 that shows their degree of agreement with every statement, where 1 indicates strongly disagree and 7 indicates strongly agree
• My motivation is lower when I am fatigued • Exercise brings on my fatigue • I am easily fatigued • Fatigue interferes with my physical functioning • Fatigue causes frequent problems for me • My fatigue prevents sustained physical functioning • Fatigue interferes with carrying out certain duties and responsibilities • Fatigue is among my three most disabling symptoms • Fatigue interferes with my work, family, or social life

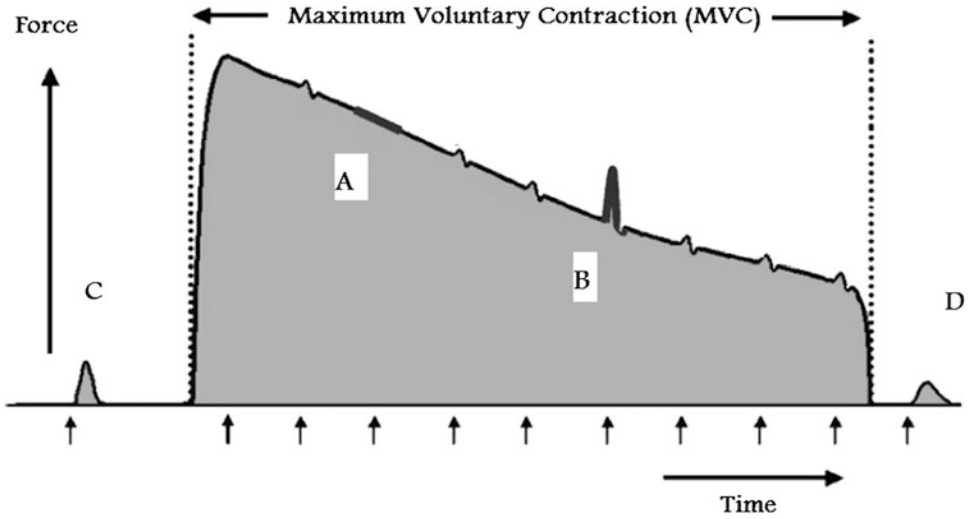

Fig. 42.1 Peripheral fatigue can be studied by measuring the maximum voluntary contraction (MVC) of muscle as recorded by a force transducer. Note the normal linear decrease in force generated is attributable to peripheral fatigue. Superimposed tetanic stimulation (denoted by the *arrows*) is used to detect the presence of central fatigue. Absence of significant twitch amplitude (*A*) suggests the absence of central activation failure (CAF), whereas a large twitch amplitude (*B*) suggests the presence of CAF. A pre-MVC tetanic contraction (*C*) and post-MVC tetanic contraction (*D*) are compared. The lower amplitude and slower relaxation phase of the post-MVC contraction is suggestive of the development of peripheral fatigue. (Reprinted with permission from Bhat and Chokroverty [44] and modified with permission from Zwarts et al. [11]

11]. On the other hand, central fatigue is generated in the central nervous system (CNS), namely the brain, spinal cord and descending central motor pathways, or at unidentified "pre-motor cortex" sites. This is assessed by measuring central activation failure (CAF), which suggests suboptimal CNS output to the motor unit. CAF can be measured by analyzing the force generated during MVC and providing superimposed electrical stimulation. The resulting twitch interpolation is then analyzed; the absence of significant change in twitch amplitude suggests full voluntary contraction and no central fatigue, whereas a large superimposed twitch amplitude suggests significant CAF. Several studies using transcranial magnetic stimulation (TMS) in patients with CNS lesions support the concept of a supraspinal site of fatigue in these conditions [12–14], and some authors have proposed a focal reduction in cortical excitability following a fatiguing motor task as the basis for such central fatigue [15, 16].

The localization of the seat of central fatigue remains elusive, and many diverse areas influencing motor output, such as the prefrontal cortex, multiple subcortical areas including the hypothalamus, the brainstem, the cerebellum, and neuronal systems subserving arousal and attention (i.e., ascending reticular activating system and the limbic system) have been investigated in this regard. Neuroimaging has not been able to identify a single anatomical substrate correlating with fatigue [17–20]. Functional magnetic resonance imaging (fMRI) studies in patients with fatigue have shown greater motor task-related activation of the contralateral cingulate area and more diffuse cervical cord recruitment [21–23] compared to controls, whereas positron emission tomography (PET) scans in patients with fatigue have demonstrated cerebral hypometabolism [24]. The clinical significance of these early findings remains unclear, and most patients with fatigue likely have involvement of multiple central and peripheral areas.

Cognitive or mental fatigue, defined as a failure to endure sustained mental tasks, a deficit of self-motivation, and

overall debilitation not attributable to motor weakness, may occur with or without concomitant physical fatigue and is more challenging to identify, measure, and localize than physical fatigue. While a recent report suggested that the posterior hypothalamus may be involved in cognitive fatigue [25], this finding has yet to be replicated by other studies. Similarly, while several authors have proposed various cognitive and motor-task processing parameters to measure cognitive fatigue, large-scale validation studies are lacking [26–28].

Fatigue in Specific Conditions

Chronic Fatigue Syndrome (see also Chapter 47)

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis, is a poorly understood, ill-defined and yet potentially debilitating condition characterized by severe chronic fatigue lasting a minimum of six months and usually accompanied by myriad nonspecific systemic symptoms. Its full impact is difficult to estimate, with prevalence reports varying greatly from 0.002 to 11.3 % in primary care practices [29]. Most reports indicate that it is more common in women than in men, minority groups, and lower socioeconomic and educational classes, and is often comorbid with psychiatric and personality disorders [30, 31]. Our understanding about this condition is constantly evolving, and at present there is no uniform agreement about the criteria for diagnosis of CFS; while the Center for Disease Control (CDC) diagnostic criteria (Table 42.2) are generally widely accepted, they are limited by being highly dependent on patient self-reporting. The US Institute of Medicine recently recommended that the disorder be renamed "systemic exercise intolerance disease" and has proposed new diagnostic criteria, including three core symptoms that must be present: Impaired day-to-day functioning because of fatigue, malaise after exertion (physical, cognitive, or emotional) and unrefreshing sleep, and at least one of the following two additional symptoms: cognitive impairment or orthostatic intolerance [32]. This proposal awaits acceptance by the medical community at large.

Attempts to identify the etiology of CFS have been futile. A post-viral etiology has long been proposed, and many patients complain of relatively acute onset of fatiguing symptomatology after a flu-like illness, but no organism has been consistently identified [33]. A few early studies provided some evidence for both central and peripheral immunological dysfunction in CFS [34–36], but more research is necessary to determine the clinical significance of these preliminary results [37]. The anatomical site of dysfunction in CFS is similarly uncertain. Numerous neurophysiological studies have failed to establish a peripheral cause of fatigue in CFS [38]. While studies have shown that there is a delay in information processing speed in patients and central dysfunction with CFS [39], MRI and single-photon emission computerized tomography studies have not identified consistent structural or functional markers [40].

Nearly half of the patients with CFS have a coexistent primary sleep disorder (mainly obstructive sleep apnea syndrome [OSA], as well as chronic insomnia and periodic leg movements during sleep [PLMS]), and 45 % have a coexistent psychiatric disorder (mostly mood and anxiety disorders) [41]. The diagnosis of either a sleep or psychiatric disorder, however, does not rule out coexistent CFS [42]. While sleep complaints such as unrefreshing sleep, EDS, and insomnia are common in patients with CFS, objective sleep architectural abnormalities are usually not demonstrable on polysomnography [43].

The optimal treatment of CFS is unclear. Immunological treatments (e.g., high-dose glucocorticoids and intravenous immunoglobulin [IVIG] therapy) have not been found to be beneficial [44]. Similarly, evidence for benefit from stimulants, antidepressants, and wakefulness-promoting agents (e.g., modafinil) is mixed [45]. Several studies, however, have consistently shown the superiority of nonpharmacological interventions in CFS, such as cognitive behavioral therapy (CBT) and low impact, graded aerobic exercise [46].

Fatigue in Primary Sleep Disorders

One of the unique challenges in treating patients with primary sleep disorders is distinguishing between fatigue and EDS [47]. Both symptoms are common bedfellows; nevertheless, as stated before, the distinction is important, because the two symptoms warrant different investigations and management strategies. The practitioner must help the patient to distinguish between fatigue and EDS based on historical clues. Several validated questionnaires, however, are available, aiding the distinction, such as the Epworth Sleepiness Scale (ESS) for EDS and the FSS for fatigue.

Most patients with untreated primary sleep disorders experience fatigue. Younger age, female gender, and a high number of awakenings and arousals have been shown to be predictive characteristics for fatigue [48]. Fatigue occurs in up to 42 % of patients OSA [49] and improves with continuous positive airway pressure (CPAP) treatment [50]. While fatigue in patients with OSA is related to the presence of depressive symptoms [51], it has not been found to correlate with the severity of OSA or with objective measures of EDS (such as multiple sleep latency testing [MSLT]), demonstrating once again that sleepiness and fatigue are distinct symptoms [52]. Similarly, although fatigue occurs in up to 63 % of patients with narcolepsy [53], it does not correlate with the degree of EDS; however, both symptoms respond to treatment with modafinil [54]. Both restless legs syndrome (RLS, recently renamed

Table 42.2 Center for Disease Control (CDC) criteria for the diagnosis of chronic fatigue syndrome (CFS)

In order to be diagnosed with chronic fatigue syndrome, a patient must satisfy two criteria:
1. Have severe chronic fatigue for at least six months or longer with other known medical conditions (whose manifestation includes fatigue) excluded by clinical diagnosis and 2. Concurrently have four or more of the following symptoms: • post-exertional malaise • impaired memory or concentration • unrefreshing sleep • muscle pain • multi-joint pain without redness or swelling • tender cervical or axillary lymph nodes • sore throat • headache

Willis-Ekbom disease [WED]) and PLMS have been found to correlate with sleep disruption and fatigue [55]. Circadian rhythm disorders, especially shift work disorder, are associated with both EDS and fatigue, independent of mood disorders [56], possibly related to lower morning serum cortisol levels [57]. Insomnia, either as a primary disorder or as a symptom of another sleep disorder or medical condition, is commonly associated with fatigue. Nonpharmacological interventions, such as CBT and exercise programs, improve sleep quality as well as fatigue-related symptoms [58].

Fatigue in Neurological Disorders

Fatigue in Peripheral Nervous System (PNS) Disorders

Fatigue in Neuromuscular Junction Disorders

Neuromuscular junctional disorders are characterized by the failure of transmission across the neuromuscular junction and may be presynaptic (e.g., Lambert-Eaton myasthenic syndrome) or postsynaptic (e.g., myasthenia gravis). This results in muscle fatigue of peripheral origin. However, patients with myasthenia gravis experience additional cognitive fatigue following completion of demanding cognitive work, suggesting a component of central fatigue [59]. Supplementation of Vitamin D may benefit fatigue in patients with myasthenia gravis showing Vitamin D deficiency [60].

Fatigue in Neuropathies and Myopathies

Chronic, persistent fatigue occurs in many patients with acquired immune-mediated neuropathies (e.g., Guillain–Barre syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, and monoclonal gammopathies). Some authors have suggested that fatigue in these patients is related to axonal loss [61], but neurophysiological studies of the peripheral nerves are often normal, suggesting that central mechanisms are at play [62]. Medically supervised home exercise programs may be beneficial in these patients [63]. Modafinil has shown some benefit in alleviating fatigue in patients with hereditary motor sensory neuropathy type 1 (also known as Charcot–Marie–Tooth Disease-1), the most common inherited neuropathy [64]. Metabolic myopathies are characterized by the occurrence of "exercise intolerance," cramping, painful contractions, and myalgias after exercise, while being asymptomatic at rest. This exercise intolerance may occur in the absence of motor weakness or abnormal physical findings, and may be perceived as fatigue by patients. Genetic testing is often required for diagnosis. Similarly, patients with inherited channelopathies (hypokalemic and hyperkalemic periodic paralysis, myotonia congenita, paramyotonia congenita, and Andersen–Tawil syndrome) present with paroxysmal attacks of periodic generalized weakness as well as muscle fatigability brought on by exposure to cold, carbohydrate-rich meals, exercise or rest, depending on the exact disorder. Except for the hypokalemic periodic paralysis, these patients also have myotonia on EMG and can be diagnosed by genetic testing. Muscle weakness in these disorders may last from a few minutes to a few hours during each attack, with a normal neurological examination finding including normal strength testing in between the attacks. The symptoms are often treated with acetazolamide, although the exact mechanism of action of this agent in these conditions is unknown [44]. Fatigue has also been described in a large number of patients with a variety of inherited myopathies such as facioscapulohumeral dystrophy and myotonic dystrophy [65]. Both fatigue and excessive daytime sleepiness are common with myotonic dystrophy type 1 (DM1), most likely due to prominent sleep dysfunction that accompanies sleep-disordered breathing, numerous microarousals, and PLMS. DM1 patients have short sleep latencies on MSLT as well as sleep onset REM periods (SOREMPs), suggesting a narcoleptic phenotype [66].

Fatigue in CNS Disorders

Fatigue in Anterior Horn Cell Disorders

Fatigue is very common in disorders of the motor unit and pyramidal cells. In patients with amyotrophic lateral sclerosis (ALS), both central and peripheral fatigue seem to be present.

Patients with ALS show evidence of CAF on MVC studies, as well as less intramuscular phosphocreatine depletion and less fatigue of stimulated tetanic force during exercise compared to controls, suggesting that central fatigue plays a major role in this condition [67]. Peripheral fatigue has been demonstrated in muscles that show no evidence of denervation-related injury, suggesting that motor weakness and fatigue in ALS are distinct entities. Maladaptation of cortical processes related to degeneration of inhibitory GABAergic intracortical circuits is a feature of ALS that significantly correlates with the development of fatigue and weakness [68]. Sleep disruption is a contributory factor as well [69].

Fatigue occurs in over three quarters of patients with post-polio syndrome (PPS); young patients with PPS with shorter polio duration, more pain, and higher body mass index tend to be more fatigued and have a lower quality of life [70]. Both central and peripheral causes seem to be at play, with neuromuscular junction failure as well as defects of attention and information processing having been demonstrated [71, 72]. Neuroimaging studies have also shown that more than half of the patients with PPS-related fatigue have CNS white matter lesions [73]. EDS (causing secondary fatigue) may also result from sleep fragmentation, PLMS, OSA, hypoventilation, or a combination of these factors [74]. Treatment is unsatisfactory; amantadine, modafinil, and IVIG have all been studied, but no consistent benefit has been found [75]. The role of CBT and exercise programs is currently being investigated [76].

Fatigue in Multiple Sclerosis

Fatigue is a cardinal feature of multiple sclerosis (MS), reported by over 80 % of patients [47], but its etiology remains a matter of debate. Hypothalamic dysfunction, hypothalmo-pituitary axis hyperactivity, elevated adrenocortoctrophic hormone levels, lower waking cortisol levels and dopamine imbalance, and increased circulating proinflammatory cytokines have been all been implicated in causing fatigue in MS [77–81]. While certain agents used to treat MS, in particular interferons, may themselves worsen fatigue, glatiramer acetate and natalizumab have shown some efficacy in alleviating MS-related fatigue [82, 83]. The role of sleep dysfunction in MS patients with fatigue is being increasingly recognized. Insomnia, OSA, RLS, and PLMS are all very common in patients with MS and, when present, are associated with fatigue. Treating comorbid sleep disorders in MS patients improves fatigue [84]. Management of fatigue in MS has proven to be challenging. Pharmacological agents such as modafinil and amantadine have been tried with varying success. As with fatigue in general, MS-related fatigue improves with nonpharmacological measures (e.g., exercise programs and CBT) [85].

Fatigue in Parkinson's Disease

A majority of patients with Parkinson's disease (PD) complain of sleep disturbances and fatigue, which is associated with several motor and nonmotor symptoms [86]. Positron emission tomography (PET) scan findings in PD suggested that fatigue in this disorder is associated with reduced serotonergic function in the basal ganglia and limbic structures, and probably also dopaminergic dysfunction in the insular cortex [87]. Sleep dysfunction is common in PD (including insomnia, circadian rhythm abnormalities, RLS/PLMS, nocturnal bradykinesia and discomfort, sleep fragmentation, comorbid sleep apnea, and REM behavior disorder), and both sleep disorder and depression appear to be independent predictors of PD-related fatigue and EDS [88]. Fatigue may respond to treatment of comorbid mood disorders, levodopa therapy [89] as well as nonpharmacological interventions such as (e.g., CBT and exercise programs) [90].

Post-stroke Fatigue

Post-stroke fatigue affects more than half of the patients who suffer strokes and is associated with poor long-term functional outcome and physical health [91]. While post-stroke fatigue is often accompanied by depression, deficits in processing speed and memory appear to be independent of depressive symptoms [92]. It has been proposed that post-stroke fatigue is related to decreased motor cortex excitability [16], and serum glucose and homocysteine levels may play a role [93]. No neuroimaging findings predict post-stroke fatigue, and it does not appear to correlate with degree of neurological deficit. Younger patients with infratentorial infarctions and concomitant post-stroke depression appear to be most at risk for developing post-stroke fatigue [94]. There are no guidelines for treating post-stroke fatigue. Antidepressants, though commonly prescribed to post-stroke patients, have not been conclusively proven to be beneficial, and the role of CBT, exercise, and medications like modafinil and amantadine remains uncertain in this setting [95, 96].

Fatigue in Traumatic Brain Injury

Traumatic brain injury (TBI) results in a variety of long-term consequences, including sleep complaints such as insomnia and daytime sleepiness, cognitive impairment, mood disorders and fatigue, with the degree of initial injury being a poor predictor of the severity of post-TBI impairment [97, 98]. Fatigue, in particular, is present in nearly half of all patients post-TBI, does not appear to significantly improve with time, and seems to be independent of depression or EDS [99]. The natural history of fatigue in TBI remains unclear, but CBT,

lifestyle modification, pharmacologic treatments with modafinil and melatonin, and light therapy have been suggested as possible interventional strategies [100].

Fatigue in General Medical Conditions

Chronic fatigue occurs in a wide variety of medical conditions such as anemia, autoimmune disorders (e.g., systemic lupus erythematosus [SLE], sarcoidosis), chronic infectious diseases such as HIV and Lyme's disease, cardiopulmonary disorders (chronic obstructive pulmonary disease [COPD], congestive heart failure [CHF], interstitial lung disease), rheumatological disorders like fibromyalgia, and cancer. Endocrinological disorders such as hypothyroidism and hypothalamo-pituitary axis dysfunction are other causes of chronic fatigue. In addition, it may be a side effect of a wide variety of medications, most commonly beta-blockers, anxiolytics (e.g., benzodiazepines and barbiturates), antiepileptics (valproic acid, carbamazepine, and levetiracetam), antipsychotics, dopaminergics, proton pump inhibitors, chemotherapeutic agents, and beta interferons.

Fatigue in Cardiopulmonary Disease

Fatigue in COPD

The prevalence of daily fatigue in COPD has been reported as high as 80 %, and nearly half of COPD patients describe it as their most disabling symptom, affecting cognitive, physical, and psychosocial well-being and quality of life. It worsens with underlying disease severity and predicts higher hospitalization rates [101, 102]. The etiology of fatigue in COPD is incompletely understood, but is most likely multifactorial. Exercise intolerance in patients with COPD has been shown to be predictive of fatigue [103]. In addition, coexistent mood disorders and sleep disorders such as RLS [104] and sleep-disordered breathing (in particular the combination of COPD and OSA, known as the "overlap syndrome," a common cause of severe nocturnal hypoxemia, sleep disruption, and subsequent EDS) increase the likelihood of fatigue. Severe COPD is also associated with complaints of insomnia and nonrestorative sleep [105]. Treatment of fatigue in COPD is closely linked to the improvement of pulmonary status and comorbid sleep and mood dysfunction. Multidimensional programs that include pharmacotherapy to improve lung function, pulmonary rehabilitation, and CBT for insomnia have shown promising results [106].

Fatigue in Heart Failure

Fatigue is an important symptom in patients with heart failure (HF) including approximating 70–90 % of all patients which adds to the overall debilitation caused by orthopnea, peripheral edema, nocturnal cough, and exertional dyspnea. Fatigue is indicative of a poor prognosis in HF, but a consistent relationship between fatigue and degree of cardiac dysfunction has not been demonstrated [107, 108]. The proposed causes of fatigue in HF include impaired peripheral perfusion during exercise, reduced oxidative capacity of skeletal muscle, impaired muscle strength, and possibly reflex mechanisms associated with alterations in the metabolism of skeletal muscle. However, fatigue may persist despite optimization of cardiac output [109]. Comorbid sleep disorders contribute to fatigue in HF, with sleep-disordered breathing (including primary central apneas and Cheyne–Stokes respirations), nocturia, and insomnia being the most common. In addition, pharmacotherapy of HF, especially with beta-blockers, has been linked to fatigue. Fatigue and depression occur independently in HF [110]. Nonpharmacological interventions such as individualized exercise training programs for all patients with stable CHF may combat fatigue [111].

Fatigue in Chronic Renal Failure

The debilitating fatigue experienced by patients with chronic renal failure and end-stage renal disease (ESRD) is likely due to multiple chronic metabolic and physical derangements, such as anemia, cachexia, and abnormal calcium and phosphate metabolism. Nearly half of the patients on hemodialysis complain of major fatigue, often associated with depression and poor sleep quality [112]. Primary sleep disorders such as OSA and RLS/PLMS may lead to both insomnia and EDS, worsening fatigue [113]. Optimal treatment of fatigue in ESRD patients on hemodialysis is unclear, but may include strengthening of social support, exercise programs, erythropoietin, and L-carnitine supplementation [114].

Fatigue in Other Medical Conditions

The fatigue seen with chronic anemia often responds to erythropoietin-stimulating agents and blood transfusions as necessary. In several autoimmune conditions such as SLE and Sjögren's syndrome, fatigue is a prominent syndrome that is resistant to treatment and may be caused by underlying inflammatory states [4]. Chronic fatigue is a major symptom of fibromyalgia, along with abundant musculoskeletal and joint pains, depressive symptoms, and sleep disturbances, and as thus significant clinical overlap with CFS, with which it often coexists [115].

Cancer-Related Fatigue

Cancer-related fatigue is frequent, often severe and multifactorial. Its etiology is poorly understood and possibly related to changes in the underlying cytokine profile [116]. Older patients as well as those undergoing chemotherapy or radiation therapy, bone marrow transplantation, and treatment with biological response modifiers are particularly at risk [117]. Nutritional status and comorbid sleep and mood disorders play a significant role [118], and addressing these issues may alleviate fatigue to a certain extent. Anemia is a major underlying cause of fatigue in cancer patients, and several studies have shown that fatigue responds to improvements in hemoglobin levels in anemic patients with a variety of malignancies, both on and off chemotherapy [119]. Erythropoietin-stimulating agents, antidepressants, wakefulness-promoting agents, and psychostimulants have all been shown to improve subjective fatigue [120]. Daily exercise and CBT may also be beneficial [121, 122]

Fatigue and Psychiatric Disorders

Patients with primary psychiatric disorders (such as attention deficit-hyperactivity disorder, major depressive disorder, bipolar disorder, generalized anxiety disorder, substance intoxication and withdrawal, and post-traumatic stress disorder) usually suffer from significant fatigue. Sleep dysfunction, particularly insomnia and daytime somnolence, is also very common with psychiatric disorders, worsening fatigue. In addition, depression is a comorbid condition in a variety of neurological and medical conditions as discussed above, and when present, tends to be a risk factor for the development of fatigue. Unfortunately, fatigue in this setting is often resistant to treatment with antidepressants. The exact role of graded exercise therapy, CBT, psychostimulants, and wakefulness-promoting agents such as modafinil remains unclear [123].

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Sleep, Coma, Vegetative and Minimally Conscious States

43

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Abbreviations

DOC	Disorders of consciousness
REM	Rapid eye movement
NREM	Non-rapid eye movement
VS/UWS	Vegetative state/unresponsive wakefulness syndrome
MCS	Minimally conscious state
EMCS	Emergence from minimally conscious state
LIS	Locked in syndrome
MRI	Magnetic resonance imaging
PET	Positron emission tomography
EEG/TMS	Electroencephalography/transcranial magnetic stimulation
DMN	Default mode network
BOLD	Blood oxygen level-dependent
SWS	Slow-wave sleep

Introduction

Consciousness is a multifaceted and ambiguous concept, which is often the focus of passionate philosophical, ethical, social, religious and medical discussions. Even though there have been many attempts to define consciousness, no definition has been universally accepted [1, 2]. Here, we will define consciousness as what is lost during dreamless sleep and what is gained after waking up [3]. As such, consciousness is a matter of both waking states and experience, so that the less awake we get, the less aware we become of our surroundings and ourselves. From the scientific point of view, consciousness has been simplistically reduced into two main components: awareness and wakefulness [4] (Fig. 43.1). Awareness refers to the ability to live experiences of any kind, and these subjective experiences comprise sensations, thoughts, emotions, memory, imagination and other major psychological processes [2]. Awareness seems to be anatomically related to structures in the fronto-parietal cortex [4]. However, at present, there is no singular marker of conscious awareness but its presence can be clinically deduced from a range of behaviours and motor outputs (e.g. responses to command, visual pursuit) which indicate that an individual can perceive self and surroundings [5]. Wakefulness (also referred to as vigilance or arousal) is related to the level of alertness, and it can be considered as the potential to experience awareness. It is anatomically related to structures in the brainstem, hypothalamus and basal forebrain, and it is clinically evidenced by opening of the eyes [2]. Wakefulness holds considerable control over awareness; an increase in arousal is usually accompanied by an increase in conscious

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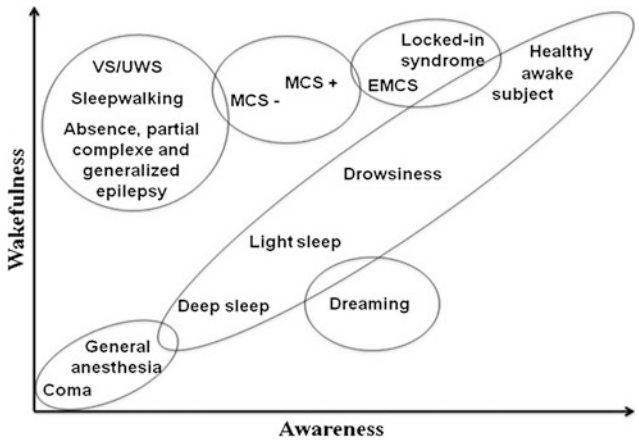

Fig. 43.1 The two main components of consciousness: wakefulness and awareness. In most pathological and physiological states, the two components are linearly correlated along the spectrum of consciousness. In some cases, however, they are dissociated. Vegetative state/unresponsive wakefulness syndrome, VS/UWS; minimally conscious state, MCS and emergence of MCS (EMCS). Adapted from [4]

experience, leading to a linear correlation of the two components along the spectrum of consciousness [2]. However, in some cases, these two components are dissociated. On the one hand, during vivid dreams, wakefulness is impaired, whereas awareness is spared. On the other hand, in the vegetative state (VS), now also called the unresponsive wakefulness syndrome (UWS) [6], in the minimally conscious state (MCS) and also in some more transient altered states of consciousness such as some kind of seizures and somnambulism, wakefulness is spared, while awareness is impaired [7–9]. These latter dissociated states, as opposed to unconscious states like deep sleep, acute coma and general anaesthesia (which are characterized by the absence of both wakefulness and awareness), offer us an important opportunity to disentangle the components of consciousness, and hence, to identify the neural correlates of (un)awareness [4].

Here, we review the clinical entities of disorders of consciousness (DOC) following brain injury (coma, VS/UWS and MCS) and the knowledge on (un)consciousness obtained by studying these patients, mainly focusing on functional neuroimaging and neurophysiological studies. We will then see how these neuroimaging techniques can detect covert awareness in this challenging patient population and, finally, we will further consider the converging points between loss of consciousness in pathological states such as DOC and in physiological states such as deep sleep.

Disorders of Consciousness

In the last decades, the development of emerging medicine and life-saving techniques has resulted in a progressively increased number of patients surviving after sustaining severe brain damage. Ever since, we witnessed a range of clinical entities of DOC never encountered before. DOC are among the most challenging and poorly understood conditions of modern medical care. The main difference between DOC and other states of unconsciousness, such as sleep, pharmacological anaesthesia and epileptic seizures, stems in the prolonged impaired awareness following severe brain damage. After a severe brain injury, a patient can spend some time in a coma, a condition characterized by the lack of both awareness and wakefulness, as evidenced by the closed eyes. Coma may arise after structural or metabolic lesions of the brainstem reticular system or after widespread bilateral cerebral damage [10]. The condition of coma usually does not last longer than 4 weeks, after which patients either evolve to brain death (i.e. permanent loss of brainstem functions), or completely recover consciousness or evolve to a VS/UWS [11]. VS/UWS is a condition of wakefulness, as evidenced by the opened eyes, without clinical evidence of awareness. This means that patients in a VS/UWS show only reflex behaviour, without any sign of voluntary conduct [4]. VS/UWS can be acute and reversible, as a transition before progressing to higher levels of awareness, or chronic and irreversible [12]. It has been proposed that the VS/UWS is permanent after 12 months following traumatic brain injury (TBI) and 3 months following non-traumatic insults, and therefore, chances for recovery are poor [13]. However, patients with late spontaneous recoveries have challenged these proposed time boundaries, and as such, the connotation of the VS/UWS has been revisited [14]. It has been recently recommended to substitute the term 'permanent' by the aetiology of the injury (traumatic or non-traumatic) and the length of time since onset, as these factors have been shown to influence outcome [15]. Patients from VS/UWS may evolve into a MCS, which may be the endpoint of their improvement or a temporary stage on the way to further recovery of consciousness [16]. MCS is a related diagnostic category recognized in 2002 [16]. It differs from the VS/UWS by the presence of discernible, yet inconsistent, non-reflex behaviours as a response to visual, auditory, tactile or noxious stimuli [16]. Although some patients in MCS may show intentional signs of communication [17], by definition they are not able to communicate accurately with their environment. The typical lesion profile consists of grade II or III diffuse axonal injury with multifocal cortical contusions, sometimes accompanied by thalamic involvement. In comparison with patients with VS/UWS, these patients show relatively preserved long-range thalamo-cortial pathways, which could explain why patients in a MCS retain some capacity for cognitive processing [15]. Diagnosis of MCS is clinically based on discernible and reproducible evidence of conscious awareness such as visual pursuit, simple command following, intelligible yes-no response and/or behaviours that are selected triggered by specific environmental stimuli. Example of the latter is the smiling of a patient only when looking at

his/her mother and not other persons. The responses of these patients are typically inconsistent. That is, as the behaviour of interest may occur infrequently or may be ambiguous, serial assessment is often required to capture signs of awareness. The heterogeneity of MCS has been recently recognized, and it has been proposed to subcategorize this entity into MCS PLUS and MINUS [18]. The differentiation was based on the level of complexity of the observed behavioural responses, such as the ability to understand language and therefore to follow simple commands [19]. Patients may emerge from MCS (EMCS) once they regain the ability to reliably communicate and/or use objects in a functional manner [16]. The temporal limits of irreversibility have not been proposed yet for MCS. Although there is some evidence suggesting that patients in a MCS have better chances of recovery than patients in VS/UWS, at present we are not in a position to possibly refer to chronic MCS [20]. Some patients, mainly after a focal brainstem injury, may evolve from coma to a locked-in syndrome (LIS). This is not properly speaking a DOC; however, it is worth to be mentioned in this context, as it is easily and often misdiagnosed as a DOC. This clinical entity results from a lesion in the brainstem extensively impairing the cortico-spinal and cortico-bulbar tracts, which classically leads to complete paralysis of voluntary muscles except for oculomotor muscles in a fully regained consciousness. These patients, therefore, are able to communicate solely through their eyelids movements [21]. Rarely, all voluntary muscles are impaired, including extrinsic eye muscles (complete LIS) making even more challenging the diagnosis of this patient category [22].

Neural Correlates of Awareness

Studies using conventional brain structural imaging have shown highly variable and heterogeneous results in patients with DOC, suggesting that awareness cannot be unequivocally related to a specific brain region [23]. Nonetheless, neuropathological findings seem to associate VS/UWS to profound damage to the subcortical white matter and the major relay nuclei of the thalamus [24, 25], supporting a role of the thalamus and cerebral cortex in the genesis of awareness. Using positron emission tomography (PET) during resting state, it has been shown that awareness is not related to a global brain metabolism [26], but instead to the preservation of a large-scale fronto-parietal network encompassing the polymodal associative cortices [27], and its connections with thalamic nuclei. This was suggested by the recovery of this thalamo-cortical activity in a VS/UWS patient who had recovered consciousness [26]. In VS/UWS, where awareness is impaired while wakefulness is spared, PET studies showed that patients were characterized by a reduced global metabolism compared with healthy subjects, but notably, the recovery of consciousness did not necessarily coincide with resumption of global metabolic activity [17]. Resting-state PET voxel-based studies have further demonstrated that impairment of awareness was related to impairments in specific brain areas, consisting of a large-scale fronto-parietal network encompassing the polymodal associative cortices (Fig. 43.2) [27]. In addition, a peculiar disconnection between primary sensory areas and higher order associative cortices, which are thought to be required for conscious perception [4], has been demonstrated in VS/UWS patients during passive auditory and noxious stimulations [28]. In contrast, function in known arousal structures including the reticular formation in the brainstem, the hypothalamus and the basal forebrain appeared to remain relatively intact in patients with VS/UWS [10]. In this context, recent PET studies during resting-state and passive paradigms have detected relative hyperactivity in the reticular formation of the brainstem in VS/UWS in contrast to hypo-activity between the reticular formation and the precuneus compared to controls, suggesting the existence of a functional link between the arousal system and the associative cortices in the genesis of perception awareness [29]. In line with their clinical condition, MCS patients showed a partial preservation of this large-scale associative fronto-parietal network [30]. More important, PET studies employing passive noxious stimuli have elicited the activation of association areas related to pain processing in MCS patients in a similar network as in normal controls, suggesting a potential pain perception capacity in this patient category [31]. Similar findings of fronto-parietal deactivation have been found in other conditions of impaired awareness, such as in somnambulism as well as in absence and complex partial (mainly in the temporal lobe) seizures [7–9], whereas temporal lobe seizures without loss of consciousness were not accompanied by these widespread changes [8]. The above-mentioned studies have suggested a key role of an extensive fronto-parietal associative cortex for the emergence of awareness. The higher order associative fronto-parietal network mentioned above, commonly impaired during altered states of consciousness, has been recently functionally subdivided into two different networks: external awareness and internal awareness network [32]. The first one, also called task-positive network, is a lateral fronto-parietal network routinely exhibiting activity increases during attention-demanding cognitive tasks. The second, better known as default mode network (DMN), is a mesial fronto-parietal network commonly involved in self-related processes [33]. These two networks are functionally anti-correlated, (that is, when one network is activated the other one is not, and vice versa) and clearly linked to spontaneous mentation [32]. Several studies using even-related functional magnetic resonance imaging (fMRI) experiments have, in fact, demonstrated that awareness of the environment and awareness of the self have different

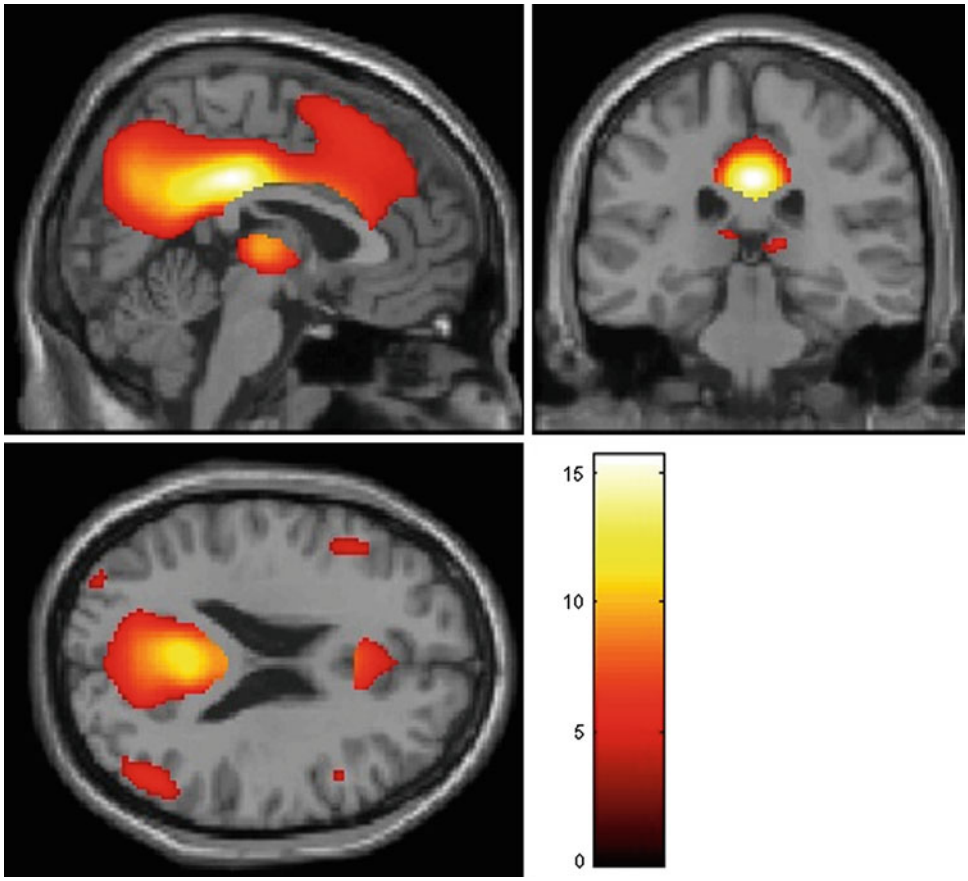

Fig. 43.2 Brain areas where metabolism is impaired in vegetative/unresponsive wakefulness syndrome (VS/UWS) patients compared to controls (areas in *red*), superimposed in a 2D image, axial, coronal and sagittal view. FWE p 0.05 corrected

anatomical substrates, namely the external and internal awareness network, respectively. For example, by giving subjects somatosensory laser stimuli on the back of their hand, it has been shown that at a certain intensity, one stimulus could be perceived only when the external awareness network was activated. Conversely, a stimulus at the same intensity could not be consciously perceived when the internal awareness network was activated, suggesting a role for the baseline brain activity fluctuations in the consciousness perception of the external world [34]. A number of auto-referential stimuli, furthermore, pointed to the critical role of the midline structures (DMN) for self or internal awareness [35–38]. In addition, the decreased anti-correlation of these two networks in unconscious states, such as anaesthesia [6], deep sleep [39] and DOC patients [40, 41], suggests somehow the functional contribution of this anti-correlated pattern to conscious cognition [42]. Frequently and increasingly used in the analysis of DOC, resting-state fMRI is a non-invasive technique which investigates the spontaneous temporal coherence in blood oxygen level-dependent (BOLD) fluctuations related to the amount of synchronized neural activity existing between different location of the brain (i.e. functional connectivity or correlation) in the absence of input or output tasks [43]. Besides the external and internal awareness networks mentioned above, several other resting-state networks of high spatial consistency across subjects have been detected, such as the auditory network, visual network, salience network and cerebellum network [44]. Among those, the DMN is the one that has mostly attracted the scientific attention. The DMN, in fact, has been thought to be implicated in cognitive processes and consciousness, probably because of its link to internally oriented cognitive content, such as mind wandering and autobiographical memory recall [45–47]. Recent resting-state fMRI studies have detected decreased DMN connectivity in patients in coma, VS/UWS and MCS [48]. Such reduced connectivity was shown to be correlated to the level of consciousness, mostly affecting the precuneus, a brain area considered to be a critical hub within this network [10]. Similar decreases in DMN connectivity were observed in healthy controls during sedation, general anaesthesia [6] and deep sleep [49]. However, other studies have shown the persistence of coherent DMN connectivity in some patients with VS/UWS as well as in a case of anesthetized monkey [50], in contrast with its complete absence in a case of brain death [41]. The above evidence suggests that the DMN may not be a mere reflection of conscious mental activity and that other phenomena may indeed play a role in the relation between consciousness and the DMN. For example, it was recently reported that along

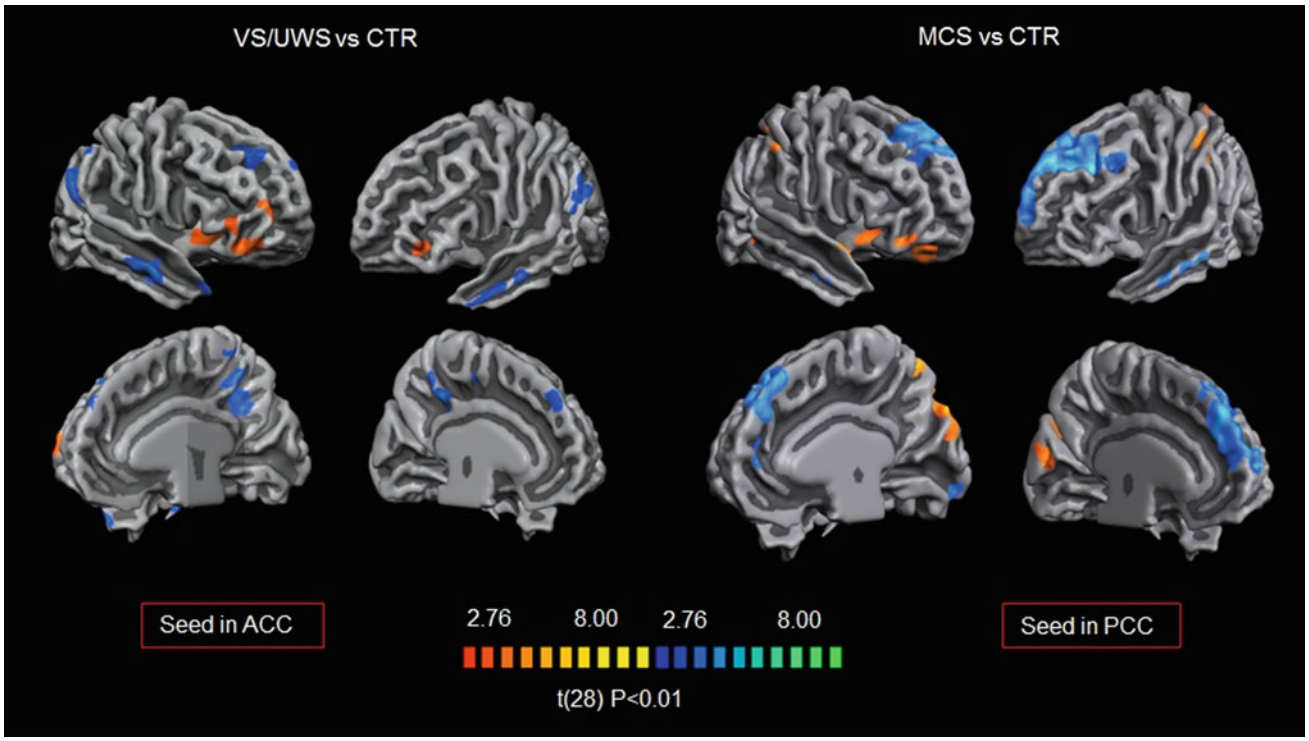

Fig. 43.3 In vegetative state/unresponsive wakefulness syndrome (VS/UWS), the anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC) are hypo-connected to the default mode network (DMN, in *blue*) and hyper-connected to the fronto-insular cortex (in *red*). Superimposed on a 3D template, lateral and mesial sagittal view. Correlation from random effect ($p < 0.01$) and clustered corrected ($p < 0.05$) results based on general linear model maps with seed region of interest comparing VS/UWS to healthy controls. Adapted from [51]

with decreased DMN connectivity, DOC patients showed an increased "pathological" correlation, compared to healthy controls, between the DMN and regions belonging to the external awareness network (hence normally anti-correlated in conscious controls), such as the insula and dorsolateral prefrontal cortex (Fig. 43.3), and stronger in VS/UWS than in MCS patients [51]. This pathological hyper–connectivity suggests the role of a network unbalance sustaining unconsciousness possibly caused by a natural brain topology reorganization strategy of functional connectivity [51]. Taking this into account, hypo–connectivity is therefore only an aspect of a possibly multifaceted and more complex dysfunctional architecture of brain connectivity in altered consciousness, and not necessarily the global hallmark of these conditions. This being also recently supported by the detection of hyper-connectivity patterns also in states of pharmacological coma, such as general anaesthesia [52]. Recently, more networks at resting state have been investigated in DOC, such as the bilateral fronto-parietal or executive control networks, salience, sensorimotor, auditory, visual systems and the cerebellar network. It was found that besides the DMN, the bilateral executive control networks and the auditory system were also significantly less identifiable (in terms of spatial and neural properties) in patients with DOC compared to healthy controls and showed consciousness-level-dependent decreases in functional connectivity across the spectrum of DOC. Furthermore, with machine learning classification trained on the identification of these ten networks as neuronal or not, it was even possible to separate healthy controls from patients in DOC and VS/UWS with high accuracy [53, 54]. One of the near-perspective future challenges will be to interpret resting-state patterns according to studied population in order to unravel the relationship (correlation and anti-correlation) between the resting-state networks in different level of consciousness, and to better comprehend its functional and clinical meaning in general and at also at single-subject level, leading to a more accurate diagnosis [42].

Functional Neuroimaging and Detection of Awareness in Disorders of Consciousness

Detection of potential awareness in uncommunicative brain-damaged patients raises important ethical and medical concerns, regarding end-of-life decisions and palliative treatment [5]. Clinicians are offered with various clinical scales to detect sings of awareness at the bedside [55]. The Coma Recovery Scale-Revised (CRS-R) [17] is one of the most sensitive tools to diagnose and differentiate between patients in VS/UWS and MCS because it assesses all the defining criteria for MCS, such as visual pursuit and

command following [56]. Nonetheless, not only is it made of different behavioural components, but it also includes directives to look for these behaviours. For example, when visual pursuit was tested by means of a moving object, a moving person and a moving mirror, more patients tracked their image in the mirror compared to the other two stimuli and were hence considered to be in a MCS [57]. Similarly, to score sound localization with the CRS-R, the patients need to orient their head or eyes towards the source of the sound. When the patients' own names were used, more patients oriented their head or eyes towards the examiner compared to the meaningless sound of a ringing bell [58]. These studies imply that self-referential stimuli are more effective to explore patients' responsiveness and can influence the diagnostic process [also see 59]. Nevertheless, it is worth stressing that what one can actually assess at the bedside of the patient is responsiveness. As responsiveness represents only an indirect evidence of consciousness (i.e. the lack of responsiveness does not necessarily imply lack of consciousness) reliance on these behavioural markers presents significant challenges and may lead to misdiagnoses. Clinical studies have shown that up to 40 % of patients with a diagnosis of VS/UWS may in fact retain some level of awareness [60–62], and the main causes of misdiagnosis are associated with patient's disabilities, such as paralysis and aphasia, fluctuation in arousal level, difficulty differentiating reflexive from involuntary movements, the presence of drugs' side effects and the non-use of standardized and sensitive clinical scales such as the CRS-R. One way to approach the problem is to detect awareness independently of responsiveness, that is to measure patients' brain responses and activation during sensitive experimental manipulations (which do not require motor responsiveness) and compare them with that of healthy controls. If the cerebral activation pattern is indistinguishable between the two groups, then one has good reasons to believe that the extracted statistical maps reflect the same construct [63]. Possible concerns about the degree of confidence on functional neuroimaging results are recently raised, especially when one considers that it is not possible to have subjective reports by the patients [e.g. 64]. In addition, our limited understanding of the complex dynamic neuronal mechanisms underlying consciousness and its reluctance to quantification in the absence of communication [65] makes it difficult to establish any strong claim about consciousness in non-communicating patients. Nevertheless, the use of these technologies (such as neuroimaging and electrophysiology) has shed light on the grey zones between the different clinical entities of consciousness and has revealed that not all patients considered as VS/UWS are actually unaware [20, 66]. Due to the excellent spatial resolution that is offered by functional magnetic resonance (fMRI) and PET, here we will focus on studies employing these neuroimaging methods referring to the main paradigms used to detect residual consciousness in patients with DOC: active and passive paradigms.

Active paradigms refer to mental imagery tasks which measure wilful modulation of brain signal in specific brain areas, aiming to detect ability to follow command. Command-following abilities in patients with DOC is of major importance as its presence or not can distinguish, respectively, the clinical entities of MCS and VS/UWS, with related ethical and medical issues. Hence, active paradigms in fMRI can be used to detect potential command-following abilities in those patients that are not able to show it through their motor behaviour, improving possible misdiagnosis in this category of patients that could occur when based only on the clinical approach.

In the fMRI setting, two main paradigms have been shown to activate robustly and reproducibly specific brain regions, namely imaging of playing a tennis match (encompassing mainly supplementary motor areas) and imaging visiting his/her own house (encompassing mainly parahippocampal cortex) [67]. When these paradigms were employed in a behaviourally unresponsive patient, the activation pattern of this patient was indistinguishable from that in a healthy control, showing that this patient was actually capable of understanding and following these mental imagery commands [67]. Thus, the behavioural diagnosis was challenged and the patient was no longer considered to be in a VS/UWS. Moreover, a few months after the fMRI finding of activation pattern, the same patient emerged out of the VS/UWS also clinically. We can say, therefore, that in this case functional imaging could detect signs of awareness in the patient earlier than the bedside clinical assessment. Nevertheless, this was the first evidence of dissociation between extreme behavioural motor impairment and identifiable preserved higher cognitive abilities detectable only by functional imaging techniques. A further study examined this phenomenon on a much larger cohort of patients, aiming at detecting the frequency of preserved awareness in behaviourally unresponsive patients [68]. It turned out that of 54 patients with DOC, five (3 VS/UWS and 2 MCS—two which did not show any signs of consciousness at behavioural assessment) were able to wilfully modulate their brain activity; furthermore, one behaviourally diagnosed VS/UWS patient was able to use this technique to communicate by correctly responding with yes (by imagining playing tennis) or no (by imagining visiting the rooms of his house) to autobiographical questions during the fMRI scanning [68]. Thus, this study showed that the case described by Owen et al. in 2006 was not an isolated case, and that approximately 17 % of patients diagnosed as in VS/UWS after behavioural assessment can follow commands when such commands showed a change in BOLD response, rather than overt motoric behaviour. Other mental tasks for detecting response to command in patients with

DOC have been employed. For example, by employing fMRI during covert picture naming as a command-following task in a cohort of patients with DOC, complete network expected for the task as in normal controls was evidenced in the patient with LIS, in two of five MCS patients and in one of two VS/UWS patients [69]. By instructing patients behaviourally considered in a VS/UWS to move their hand, Bekischtein et al. [70] detected activation in the premotor cortex contralateral to the instructed hand, consistent with movement preparation. Similarly, by employing a hierarchical mental imagery (imaging playing tennis and swimming) fMRI approach, Bardin et al. [71] detected residual cognitive capacities in patients with DOC, confirming the dissociation between bedside and fMRI-based command-following and communication abilities. More recently, a further study using selective auditory attention showed that three behaviourally unresponsive patients (two MCS and one VS/UWS) were able to convey their ability to follow commands, and one in VS/UWS was even able to use attention to correctly communicate answers to several binary questions [72], pointing out how different tasks, which allow to overcome the motor unresponsiveness of brain-injured patients by tackling different cognitive aspects, might detect residual covert awareness in this patient category. However, legitimate concerns about the degree of confidence in these methods have emerged. Mental imagery paradigms rely on the fact that a patient can understand the commands and is able to wilfully execute them. In fact, there are many cases when this is not possible, even if the patient retains some degree of consciousness. For example, a patient might not understand the task because he is deaf or aphasic, a patient might not be compliant due to the side effect of medications interfering with vigilance or motor ability or simply because he is sleepy at the moment of the mental imagery task, given that the fluctuation level of vigilance is very often shown in several cases of MCS. Indeed, out of 31 MCS patients described in the study by Monti et al. [68], only one was able to wilfully modulate his brain activity, and out of six cases of behaviourally MCS described by Bardin, only four showed contingent brain activation in the fMRI. Hence, it is worth stressing that absence of command-related brain activation does not allow to infer that awareness is not present [71], and this could lead to possible false-negative results [73]. In order to overcome some of the above-mentioned limitations, residual cognitive function in patients with DOC can be further assessed employing passive and resting-state paradigms.

Passive paradigms measure brain responses to external sensory stimulation (e.g. auditory, somatosensory and visual) while the subject is not performing any task. As previously mentioned, the administration of auditory stimuli in VS/UWS patients elicited PET activation in the primary auditory cortex of these patients, whereas a wider spread of activation in the secondary auditory cortex and associative cortices, contingent to their clinical condition, was detected in MCS patients [74]. By using PET, painful stimulation of the median nerve elicited the entire 'pain matrix' (including the anterior cingulate cortex and insular areas) in patients with MCS, whereas only activation in the lower level subcortical areas was detected in VS/UWS patients [28, 31], indicating that MCS patients are more likely to experience the administered stimuli as painful, with related practical and clinical issues regarding the use of painkillers in this patient category. Similarly, in a passive visual fMRI task, that is presenting pictures of different emotional valences, visual activation similar to healthy controls was found in MCS patients [75]. More recently, a visual cognition study applied to a MCS patient showed brain activations undistinguishable from those observed in healthy and aware controls, suggesting that the patient retained the ability to access his own visual representations [76]. The above studies once again confirm the importance of the associative areas for the emergence of awareness and showed an overlap between clinical and neuroimaging findings. However, the possible dissociation between clinical and neuroimaging assessment has been also shown by means of passive paradigms. For example, a study combining PET and fMRI and using a more complex auditory task (manipulating words at different levels of auditory intelligibility and semantic ambiguity) detected a residual auditory and speech processing in a patient behaviourally considered to be in a VS/UWS [77]. Also, a passive auditory fMRI study using narratives played forward and backwards showed one of three patients in a VS/UWS, and one of four MCS patients showed similar brain activation as that elicited in normal controls [78]. Another salient auditory stimulus which has been preferred because of its attention-grabbing properties is the patient's own name. It has been in fact reported that the subject's own name (SON) activated the cerebral cortex more extensively than non-self-referential emotional stimuli in patients with MCS [30] and the SON spoken by a familiar voice (SON-FV), as opposed to an unfamiliar voice, elicited stronger event-related potential (ERP) responses [79]. Furthermore, it is shown that the SON showed higher sensitivity to elicit sound localization reflex in DOC patients [58]. The SON-FV, therefore, has been used in order to maximize the chances of detecting residual brain function in DOC patients using fMRI. With a SON-FV paradigm, two of seven patients in UWS and all four patients in MCS not only showed activation of the primary auditory cortex but also in higher order associative auditory areas, which are thought to be implicated in the conscious processing of the incoming stimuli. Notably, these two patients in UWS subsequently recovered to MCS, as observed three months after their fMRI scan. This pointed out the possible prognostic value of such fMRI paradigm [80]. Taken together, these paradigms

have shown that auditory, visual and somatosensory activation is restricted to lower level sensory regions in patients in UWS, while brain activation is widespread in MCS reaching higher level associative areas. In some cases, they have shown activation in higher level associative areas in patients behaviourally diagnosed as VS/UWS, suggesting the potential of this tool to detect covert awareness in behaviourally unresponsive patients or, at least in some cases, before the clinical manifestations of the recovery. The passive paradigms can often overcome some limitation of the previously described active task, such as the possibility that a patient is aphasic and therefore unable to understand a task. However, in other cases, such as when a patient has sensory deficits (e.g. deafness or impaired vigilance possibly related to drug side effects), these paradigms might bring false-negative results and other acquisitions should be used, such as the resting-state fMRI. The use of neuroimaging techniques during resting state in patients with DOC has been more specifically described in the previous paragraph.

Electroencephalography (EEG) and transcranial magnetic stimulation (TMS)

Like fMRI, EEG recordings in patients with DOC can evaluate different aspects of cognitive residual function and provide means to communicate with the outside world without motor output. Standard recordings in the neurological department offer a first global view of the brain function of a patient and can detect abnormal activity and therefore guide treatment [81]. In resting conditions, various EEG paradigms have made an effort to differentiate between the clinical entities of patients with DOC. After a severe brain injury, of whatever origin, the EEG can be altered and may display abnormalities. A visible common effect is a slowing of the brain activity proportional to the severity of the injury. Therefore, the predominant rhythm is no longer posterior alpha (related to the awake stages in healthy adult individuals) but diffuse theta or delta (normally present in the slow stages of sleep in healthy adult individuals). In some cases, alpha or theta activity can be observed, but its activity differs from a normal adult alpha activity [82]. Measures of signal complexity such as the bispectral index (a measure of the depth of anaesthesia) were shown to discriminate between unresponsive and MCS patients at the group level [83]. The bi-spectral index was also positively correlated with behavioural scores of awareness at the time of testing and was associated with outcome at one-year post-trauma. However, at the single-subject level, establishing a diagnosis solely based on a single standard EEG is difficult since the patterns are not specific to the aetiology and the same subject can have different patterns in a short interval of time. A study based on patients in persistent VS/UWS concluded that it was not possible to reliably use EEG as a diagnostic tool due to its heterogeneous and varying aspects [84]. Despite the limited diagnostic role of standard EEG recordings, prognostic statements are possible but challenging as the same pattern can be found in varying brain pathologies. EEG information needs to be constantly integrated by the clinical information in order to have plausible insights into the prognosis [81]. In this context, active command mental paradigms combined with EEG [85–87] appear to be useful in the diagnosis of DOC. They have, in fact, allowed both detection of voluntary brain function in VS/UWS and functional communication in patients with complete LIS. A recent study showed that out of 16 studied patients, three were in VS/UWS on the basis of repeated specialist behavioural assessments, and were found to be aware and capable of substantially and consistently modulating their EEG responses upon command [87]. However, as pointed out above, no diagnostic information can be inferred from a negative result, as it does not necessarily imply the lack of consciousness. Indeed, patients behaviourally in a MCS might still not be able to understand and follow instructions. In this context, EEG combined with TMS (TMS/EEG) may be especially useful to assess the level of consciousness in DOC patients, because it does not rely on a subject's ability to process sensory stimuli, or to understand and follow instructions. TMS/EEG allows to stimulate a subset of cortical neurons in a non-invasive way, and to measure the effects produced by this perturbation in the whole brain [88, 89]. For patients in VS/UWS, when stimulating a superficial region of the cerebral cortex, TMS induced either no response or a simple response and a local EEG response, indicating an impairment of effective connectivity [90, 91], similar to the one observed in deep sleep and anaesthesia [89, 92]. In contrast, for patients in MCS, TMS triggered more complex EEG activations that sequentially involved different cortical areas, similar to activations showed in healthy awake subjects. Of note, an MCS patient assessed during a period of no responsiveness still showed complex and widespread brain responses to TMS, even though he did not demonstrate any behavioural sign of consciousness during clinical assessment [91]. Furthermore, an empirical measure of brain complexity, the perturbational complexity index (PCI), which measures the amount of information contained in the integrated response to a direct TMS perturbation, has recently been introduced [88]. The PCI was tested on a large data set of TMS-evoked potentials recorded from healthy subjects during wakefulness, dreaming, non-rapid eye movement (NREM) sleep, and different levels of sedation induced by different anaesthetic agents as well as from brain-injured patients who had emerged from coma (overall, 208 sessions in 52 subjects). PCI provided a data-driven metric that can discriminate level of

consciousness in single subjects under different conditions of consciousness: wakefulness; dreaming; the LIS; the MCS; the EMCS; intermediate levels of sedation; NREM sleep; midazolam-, xenon- and propofol-induced loss of consciousness; and the VS/UWS [88]. It appears that not a single unconscious subject (regardless of its aetiology) has a PCI above 0.31, and no awake healthy subject has a PCI below 0.44. This allows a single-subject approach, necessary for a clinical use of this tool. Because this technique is handy, not invasive, does not require patients' cooperation and works at the single-subject level, it appears to be a promising tool for the diagnosis of patients with DOC [88].

Sleep and Disorders of Consciousness: Differences and Crossing Points

Sleep and consciousness are intimately connected in several ways, showing many neurophysiologic and neuroimaging similarities and differences. Sleep disruption is very common after a TBI [93], often affecting quality of life and outcome/prognosis. Although numerous studies have been conducted on the association between sleep disorders and individuals with TBI, sleep is not routinely assessed in this population [94], and there are paradoxical reports regarding factors associated with sleep disturbance in TBI population [95]. Estimates of the prevalence of post-TBI sleep disturbances range between 30 and 84 % [93]. This so wide range is probably due to differences in the criteria (e.g. formal diagnosis or not), definitions (i.e. broad vs. specific) and measures (e.g. subjective vs. objective) used to assess sleep alterations, as well as heterogeneity of the samples studies, including symptomatic/asymptomatic individuals, or different severity of TBI [93]. Moreover, defining sleep in severely brain-injured patients is a problematic issue, considering the wide spectrum of neurophysiologic and imaging alterations in these patients [96], often irrespective of the injury severity [93, 97]. As for DOC assessment, neurophysiologic evaluation represents a valuable tool for clinical characterization and prognosis evaluation, being sometime more accessible than functional imaging modalities [73]. However, the definition of wakefulness and sleep in DOC is tricky because instrumental findings recorded in these patients may be correlated to different cellular mechanisms than those found in normal physiological sleep. Moreover, recording good-quality signals is not easy due to artefacts caused by skin and skull lesions, involuntary movements, vegetative or autonomous deregulation and electrical artefacts from life-supporting devices [96].

In healthy subjects, sleep is typically led by the search for a safe place and a progressive reduction of alertness and motor tone/activity. In DOC, the occurrence of these conditions is often unavailable. In particular, environmental factors in the intensive care unit like ventilator modes, the continuous exposure to light, noise and nursing activities or the chronic pain and discomfort suffered by these patients can cause considerable sleep disruption. As far as EEG patterns, normal sleep is characterized by well-defined cycles and microstructures (e.g. K-complexes, spindles), and is finely and continuously checked by homeostatic and circadian factors. In DOC, the existence of such elements and such regulators are a matter of debate [96]. Although these existing differences between normal and DOC sleep, and the lack of sleep staging criteria for DOC patients, several clinical and electrophysiological evidences like eye opening and the presence of a sleep–wake cycle suggest the importance of sleep disruption in the DOC spectrum [98]. The occurrence of phasic REMS [99] or the presence and density of sleep spindles [96] represent important parameters to define different comatose states and to speculate on the prognosis [100–102].

The transition from coma to VS/UWS is defined by spontaneous eye opening and the reappearance of sleep–wake cycles. According to this statement, several studies have analysed the presence of sleep–wake cycles in DOC, reporting their presence/absence in persistent VS/UWS patients, with no obvious difference in their clinical status [98]. REM sleep appeared to be the one sleep element that most adequately correlated with clinical scores, and a significant prognostic sign in DOC [103]. In a recent study [99], all of the 10 MCS patients enrolled show phasic REM sleep, a pattern associated with dreaming in healthy subjects, and therefore, with a differential diagnosis value in the VS/UWS. In another study [104], all MCS patients showed an alternating NREM/REM sleep pattern, though no slow-wave sleep or REM sleep stages could be identified in VS/UWS patients. Other authors focused on REM sleep in VS/UWS showing the presence of nystagmus in wakeful and REM stages [105] or the degradation of REM events [106]. As far as sleep microstructure, the presence of K-complexes has a marginal role, considering their high prevalence in these patients; sleep spindles, instead, showed a higher correlation with clinical scores and with DOC outcome [100, 107]. These NREM elements can possibly be present, slowed or absent in both MCS and VS/UWS patients, independently from their aetiologies. The correlation between the number of standard spindles and DOC outcome remains speculative, although several studies support the potential prognostic value of sleep spindles in comatose and vegetative patients [96, 107]. For instance, several authors have reported the occurrence of spindles in 11 out of 20 traumatic and 3 out of 10 hypoxic VS/UWS patients, relating their density increase in the follow-up to the clinical recovery of traumatic patients [108]. In conclusion, several prognostic markers have been identified in DOC patients, such as sleep spindles and preservation of REM stages. This would justify the use of neurophysiologic assessment in the clinical routine, although

adapted and validated standardized behavioural scales are rarely used in sleep research in DOC.

Concerning imaging techniques, several similarities have been detected between normal sleep and DOC patients. PET imaging has demonstrated a significant reduction in cerebral blood flow during NREM stage, to 60 % of normal waking values [10, 109, 110]. Similar findings have been mainly reported for VS/UWS patients with values reduced to 40–50 % of normal ones [27, 74, 111, 112]. Cerebral metabolism in comatose patients is reduced to approximately 55 % of normal values [10], whereas in patients with a LIS, overall supratentorial cerebral metabolism has been shown to be partially [111] or fully [10] preserved. As far as regional variations, precuneus region is less active than the rest of the brain during both slow-wave sleep (SWS) [113] and REM sleep [114, 115]. This region has been suggested as a crucial actor in conscious processes, and identified as a principal node in the DMN by fMRI [42]. Of note, connectivity in this region was shown to be indistinguishable between controls and LIS patients, relatively preserved in MCS, significantly reduced in VS/UWS patients [48] and could not be identified in brain death [41].

Resting-state investigations have also been attempted using other modalities, such as EEG [81] and arterial spin labelling techniques [116].

Conclusions

In the last decades, the development of life-saving medical techniques resulted in a major interest in patients surviving severe brain injury. Ever since, the scientific advances have changed neuroscientists' and clinicians' view of severely brain-injured patients, promoting both a deeper understanding of brain functions in impaired consciousness and a better diagnostic and prognostic assessment in patients with DOC. We here provided an updated overview of the contribution of functional neuroimaging and EEG techniques in the assessment of patients with DOC, by further highlighting the parallels and gaps between impaired consciousness in sleep and in DOC. The use of this technology-based assessment appears to be imperative when assessing this challenging patient population, especially when one considers that bedside behavioural assessment is not always accurate [60]. However, despite the progresses of these techniques and the deeper understanding we have achieved over these conditions, much still needs to be done. The neuroimaging and electrophysiological tools that permit most of the recent discoveries cannot yet be routinely included in the clinical setting until they can be reliably used at the single-subject level, hence allowing us to translate the results of such studies into clinical decisions relevant to the individual patient under our care.

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Sleep and Epilepsy

44

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Introduction

The relationship between sleep and epilepsy has intrigued researchers and thinkers since antiquity. Passouant [1] mentioned Hippocrates' description of "fears, rages, deliria, leaps out of bed, and seizures during the night." Aristotle observed that in many cases, epilepsy began during sleep. Despite these early observations, the intriguing relationship between seizure and sleep was neglected by the medical profession until the end of the nineteenth century. Echeverria [2], Fere [3], and Gowers [4] gave clear descriptions of the relationship of epilepsy to the sleep-wake cycle. In a study of hospitalized epileptics, Fere [3] noted that in more than two-thirds of 1985 patients, the attacks occurred between 8:00 PM and 8:00 AM. It is interesting to note that even in those days, Fere mentioned the effect of epilepsy on sleep—he noted apparently associated difficulties with falling asleep and impairment of sleep efficiency, suggesting the facilitation of seizures by sleep deprivation. In the beginning of the twentieth century, Turner [5], Gallus [6], and Amann [7] emphasized that many seizures were nocturnal and occurred at certain times of the night. These reports were followed by those of Langdon-Down and Brain [8], Patry [9], Busciano [10], and Magnussen [11].

All of these early observations were made on the basis of clinical features alone and without the benefit of electroencephalography (EEG), which was not described until 1929. The observation of Gibbs and Gibbs [12] in 1947 of the occurrence of paroxysmal discharges in the EEG twice as often during sleep as during the waking state marks the beginning of the modern era in the study of the relationship between epilepsy and sleep. Combining clinical with EEG observations, those authors showed that indeed, a distinct relationship between epilepsy and sleep exists. This report was followed by many original observations, notably those of Janz [13], Passouant [14], Gastaut et al. [15], Cadilhac [16], Niedermeyer [17], Montplaisir [18], Broughton [19], Billiard [20], Kellaway [21], and other researchers.

This chapter provides an overview of the effect of sleep on epilepsy as well as the effect of epilepsy on sleep. The usefulness of sleep in the diagnosis of epilepsy and the practical relevance to understanding the relationship between sleep and epilepsy are also discussed.

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Interrelationship Between Sleep and Epilepsy: Physiologic Mechanisms

There is a reciprocal relationship between sleep and epilepsy: Sleep affects epilepsy, and epilepsy in turn affects sleep. To understand this relationship, it is important to review briefly the mechanism that generates paroxysmal EEG discharges and clinical seizures as well as the mechanism of initiation of sleep.

Basic Mechanism of Epilepsy

An understanding of the basic mechanism of epilepsy is derived primarily from studies of animal models and human clinical epilepsy [22, 23]. Experimental animal models of focal

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epilepsy are produced by topical application of agents or focal electrical stimulation to the neocortex and limbic cortex to provoke partial seizures, whereas electric shock or systemic injection of convulsants and penicillin have been used for generalized epilepsy models [23]. Over the years, these models have been used to study the basic mechanisms of epilepsy and seizure generation as well as to test potential disease-modifying or antiepileptogenic therapies [22]. More recently, a number of genetic animal models have also been developed such as the genetic absence epilepsy rat from Strasbourg (GAERS) [24], the Wistar Albino Glaxo/Rijswijk rat (WAG/Rij) [25] and the *Stargazer* mice [26] models for human absence epilepsy and the Nav1.1 [27] and Kv7.2/7.3 [28] mouse models that reproduce many of the phenotypic and pharmacologic features of human severe myoclonic epilepsy of infancy (SMEI) and benign familial neonatal convulsions (BFNCs) [28], respectively. These models have contributed to the molecular and genetic knowledge of epilepsy and will aid in identifying and validating novel targets for the treatment and prevention of epilepsy [22, 29]. Finally, this translational approach to studying human epilepsy can also be used to study the relationship between sleep and epilepsy [30].

Neuronal synchronization and interactions between neurons and neuronal populations are the basic features of brain function [31]. Alteration of synchronization and neuronal hyperexcitability are also central factors in epilepsy that may transform an interictal to an ictal state [23]. Factors enhancing synchronization are conducive to active ictal precipitation in susceptible individuals. These factors include nonspecific influences, such as sleep, sleep deprivation, and others. In addition, seizure itself may produce sleep disturbance.

Neuronal mechanisms of focal and primary generalized epilepsies differ. An understanding of the basic mechanism of human focal epilepsy is derived from studying patients with mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE) [23, 32] and from patients with focal cortical dysplasia (FCD), a malformation of cortical development [33–35]. A fundamental mechanism in generating focal epileptiform discharges (spikes or sharp waves) is a paroxysmal depolarization shift (PDS) in the epileptic neurons [36], originally described by Matsumoto and Ajmone-Marsan [37], followed by post-hyperpolarization [38]. PDS can be considered a giant excitatory postsynaptic potential (EPSP) caused by an abnormally prolonged depolarization of millions of neurons with positivity inside and negativity on the surface (spikes or sharp waves). The oscillation of a PDS involving a large area of cerebral cortex causes an alteration of behavior, manifesting as focal or secondarily generalized jerking movements.

In generalized epilepsy, nonspecific thalamic reticular nuclei are responsible for recruiting, and specific thalamic nuclei are responsible for augmenting responses; both are also responsible for triggering generalized seizures by synchronizing afferent inputs to the cortex from these nuclei [39, 40]. This thalamocortical interaction is responsible for changing the name of centrencephalic epilepsy to corticoreticular epilepsy for petit mal absence seizure [41]. According to the corticoreticular hypothesis, spike-and-wake discharges are linked to the thalamocortical mechanisms that generate spindles. A synchronous burst-pause firing pattern of the thalamocortical volleys of alternating EPSPs and inhibitory postsynaptic potentials (IPSPs) generates sleep spindles [42, 43]. It is believed that these thalamic rhythmic oscillations are transformed into generalized epileptic spike-and-wave discharges when the cortex is hyperexcitable [44], with enhancement of the discharges from the potentially epileptic neurons in the cerebral cortex generating spikes or multiple spikes followed by a prolonged γ-aminobutyric acid (GABA)-mediated inhibitory mechanism causing slow waves. Currently, the corticoreticular hypothesis on the origin of generalized absence epilepsy seems to be the most widely accepted [45]. However, contrary to the long-established principle that absence seizures are generalized from the onset, recent clinical and animal data suggest a cortical "initiation site" of spike-and-wave discharges (SWDs) [46, 47]. Indeed, high-density EEG, magnetoencephalography, and functional magnetic resonance imaging studies in patients with different idiopathic generalized epilepsy have shown the appearance of spike-and-wave discharges in discrete, mainly frontal and parietal cortical regions, immediately before their diffusion over the rest of the cortical mantle [48–50]. The immediate bilateral spread of generalized epileptiform discharges depends on a genetically determined diffuse cortical hyperexcitability [51, 52]. Furthermore, although considerable attention has been given to the complex bidirectional interactions between sleep spindles and SWDs, it remains unclear whether the temporal association between these events implies a causal relationship between these two EEG oscillations [46]. Current evidence suggests that although the corticothalamocortical circuit is the main network responsible for generating pathological SWDs and the naturally occurring sleep spindles, their initiation site is different: SWDs initiate in the cortex, and sleep spindles are of thalamic origin [46].

Epileptogenesis of the neurons is dependent on several factors, both genetic and acquired, that maintain increased neuronal hyperexcitability and increased neuronal synchronization as well as factors encouraging failure of inhibitory mechanisms [23]. Examples of some of these factors are decreased dendritic spines and branches, cortical sprouting of surviving axons to cause increased synchronization, altered ionic microenvironment in and around the epileptic neurons, attenuation of inhibitory influences causing enhanced synchronization, and alteration of calcium and chloride ion channel distribution [23].

It is important to understand the interictal and ictal states as well as the mechanism of ictal termination and postictal state. The hallmark of an interictal state from the physiologic

point of view is the focal or diffuse interictal EEG spike-and-wave discharge (SWD) [23]. These patterns are diverse and variable. Highly reproducible interictal spikes are typical of cryptogenic and benign forms of epilepsy such as childhood absence epilepsies or benign epilepsy with centrotemporal seizures (BECTSs) [53]. On the contrary, focal epilepsies secondary to brain lesions, especially FCD, have more irregular features that include sharp waves, fast oscillations, and bursts of repetitive spike-and-wave and polyspike-and-wave, frequently associated with short bursts of fusiform micro polyspikes, defined as brushes [54]. This electrographic pattern is enhanced during non-REM sleep and also associated with well-localized, brief, low-voltage activity [55, 56]. The epileptic neuronal aggregates producing interictal spikes show increased synchronization but with a decrease in firing rates, which may explain hypometabolism of the interictal focus as noted on positron-emission tomography using [18] F-fluorodeoxyglucose scans [23]. Prevention of ictal spread and maintenance of the interictal state are determined by strong inhibitory influences that also keep the neurons in an excessively synchronous state [23].

The ictal onset is determined by a combination of a failure of inhibitory interictal mechanisms and enhancement of excitatory synaptic activities, which may be initiated by an excess of subcortical synchronizing afferent input, as in generalized seizures or focal hypersynchronous discharge [23]. The true ictus in a generalized seizure, initiated in the cortex, may depend on a failure of inhibitory mechanism coupled with synchronizing thalamocortical input, as well as the influence of the reticular formation of the brain stem, particularly in the pontine region for the tonic phase [23]. A combination of diminution of synaptic inhibition, nonspecific excitation, propagation along the efferent projection pathways, and trans-synaptic alteration in excitation determines the appearance of partial ictus [23]. Investigations into both human and animal studies have revealed the presence of abnormal high-frequency (200- to 600-Hz) oscillations, named "fast ripples," which are seen in interictal spikes and are capable of precipitating ictal onset [57–59]. Electrical synapses (gap junctions) seem to play a crucial role in the propagation of abnormal high-frequency oscillations [60]. For the ictal termination, the two most important mechanisms are active inhibition and the failure of synchronization [23]. If these mechanisms fail, the patient may develop status epilepticus. Postictal phenomena (neuronal depression, neuronal deficit, EEG slowing, etc.) are sequelae to events that cause termination of the ictus. In the postictal state, there is neuronal hyperpolarization and neuronal depression causing termination of seizure and postictal EEG slowing.

Mechanism of Sleep

In humans, there are two sleep states: desynchronized or rapid eye movement (REM) sleep and synchronized or non-REM (NREM) sleep. These sleep states are determined by two different mechanisms [61]. NREM or synchronized sleep seems to act as a convulsant because this state is characterized physiologically by an excessive diffuse cortical synchronization mediated by the thalamocortical input [62, 63]. This predisposes to activation of seizure in an already hyperexcitable cortex. In REM or desynchronized sleep, there is inhibition of thalamocortical synchronizing influence as evidenced by depression of recruiting rhythms generated by low-frequency electrical stimulation of the nonspecific thalamic nuclei [62]. Thus, there is attenuation of bilaterally synchronous epileptiform discharges at this stage of sleep. During REM sleep, there is also a tonic reduction in the interhemispheric impulse traffic through the corpus callosum [64]. This also contributes to the limitation of propagation of the generalized epileptiform discharges.

Cortical excitability for epileptogenesis is higher during sleep than during wakefulness [62]. This observation was based on the finding of a significant drop in the threshold for electroconvulsive shock in the sleep deprivation (specifically desynchronized sleep deprivation) experiments in rats, suggesting heightened neural excitability. The increase of cortical excitability during NREM sleep seems to depend on the peculiar pattern of activity of neurons during this vigilance state [65, 66]. In fact, in the transitions from wakefulness to NREM sleep, neurons enter in a so-called state of "bistability," changing their activity from a tonic- to a burst-pause firing mode. In particular, during NREM, slow-wave sleep neuronal activity alternates between two distinct states: one characterized by depolarized membrane potential with burst of action potentials (upstate, on period) and the other associated with hyperpolarized membrane potential and neuronal silence (downstate, off period) [67, 68]. Recent experimental studies have shown that during sleep deprivation, cortical neurons of awake rats may become transiently bistable, with local populations of neurons undergoing brief off periods similar to those observed in NREM sleep [69]. These changes are accompanied by stronger and more synchronous responses to cortical electrical microstimulation reflecting an increased neuronal excitability during sleep deprivation [65]. Studies in human epilepsy [70, 71] utilizing a paired-pulse technique during transcranial magnetic stimulation, showing an increased cortical excitability following sleep deprivation, support the previous observations in rats [62, 65]. This factor of cortical excitability coupled with the fact that the inhibitory mechanism (e.g., postspike hyperpolarization and afferent inhibition) may be less effective during sleep favors activation of focal cortical epileptiform discharge.

Physiologic synchronization can be defined as a state during which there is appearance of the same frequency in two or more oscillators due to coactivation of a large number of neurons [43]. In NREM sleep, spindles and slow waves result from synchronization. As stated earlier, a synchronous burst-pause firing pattern of the thalamocortical volleys of alternating EPSPs and IPSPs generates sleep spindles [42]. Extensive study by Steriade and colleagues [43, 72–81] has shown the importance of thalamocortical participation in the genesis of sleep spindles, delta waves, and very slow (infraslow) oscillations. Sleep spindles are generated in the thalamic reticular nucleus, resulting from synaptic interactions in a network involving the GABAergic reticular thalamic nucleus, glutamatergic thalamocortical neurons, and cortical pyramidal neurons [82]. Cortical pyramidal neurons project to the thalamic reticular nucleus, which in turn has two-way connections with thalamocortical neurons of the dorsal thalamus, which in turn projects to the cerebral cortex. Sleep spindles are abolished after isolation of the reticular nucleus from the rest of the thalamus and cerebral cortex [83]; however, spindle oscillations persist in the reticular thalamic nucleus disconnected from dorsal thalamic and cortical inputs [84]. Delta waves are generated at both cortical and thalamic levels. Hyperpolarization of thalamocortical pathways causing functional deafferentation from the sensory input is responsible for generation of delta waves [79]. Very slow oscillations (<1 Hz) are generated in the cortex (see also Chap. 5). The very slow oscillations must be generated in cortical networks because these are present in athalamic preparations [76, 77] and absent from the thalamus of decorticate animals [75, 85]. It has been proposed that the vast majority of K complexes appearing during sleep are generated by the very slow (<1 Hz) cortical oscillations.

Lesions and stimulation experiments have shown the existence of structures responsible for cortical synchrony in the forebrain as well as in the hindbrain [43, 86]. More than 70 years ago, Morison [87] observed recruiting synchronizing cortical responses after low-frequency electrical stimulation of the midline thalamic nuclei, evidence of an intimate thalamocortical relationship. In 1944, Hess [88] even suggested the existence of a thalamic sleep center. Later studies, however, have shown that the thalamus is responsible for the genesis of spindles and not for sleep slow waves or the behavioral aspect of sleep [43, 86].

The theory about REM or desynchronized sleep suggests that there are anatomically distributed and neurochemically interpenetrated "REM-on" and "REM-off" cells in the brain stem [89] (see also Chaps. 5 and 41). REM sleep is dependent on an interaction between REM-on cells and REM-off cells in the brain stem. Thus, the interaction and oscillation between the REM-promoting and REM-inhibiting neurons generate the REM-NREM cycle. The various chemical mechanisms (e.g., cholinergic, aminergic, GABAergic, and glutamatergic) participating in NREM and REM sleep may also be responsible for activation or inhibition of epileptiform discharges during sleep [90].

An understanding of the basic mechanism of epilepsy and sleep helps us understand the mechanism of activation and suppression of seizure discharges during sleep and in particular during different stages of sleep. Sleep-induced seizures result from an altered interaction among sleep-generating neuronal networks, arousal systems, and the generators for epileptogenesis. In other words, there is a complex interaction between cortical and subcortical mechanisms. The activation of ictal and interictal seizures during NREM sleep seems to be related to the existence of a thalamocortical synchronizing mechanism, whereas suppression during REM sleep is due to depression of the thalamic synchronizing mechanism and a tonic reduction of interhemispheric transmission during REM sleep [62, 64]. The role played by the arousal mechanisms in facilitation of seizures remains somewhat controversial. According to some investigators [91, 92], arousal mechanisms are important in facilitating the seizures, whereas other investigators [93] postulate that arousal mechanisms, particularly the posterior hypothalamic histaminergic system, exert an antiepileptic effect. In support of the arousal mechanism, facilitating seizures is the suggestion [91] that sudden bursts of excitatory inputs from the wake-promoting neurons in the histaminergic posterior hypothalamic neurons and basal forebrain cholinergic neurons to the already hyperexcitable neocortical neurons might exacerbate the cortical hyperexcitability precipitating seizures [51]. Seizures occurring shortly after awakening in juvenile myoclonic epilepsy (JME) and generalized tonic-clonic seizures on awakening may be cited as clinical examples in support of the role of the arousal mechanisms facilitating sleep-related seizures [94].

Frontal lobe epilepsy is predominantly nocturnal, and the presence of strong thalamocortical projections to the frontal lobes might be a straightforward anatomical explanation to the preferential occurrences of nocturnal seizures in frontal lobe epilepsy. Because infraslow oscillations such as slow oscillations, delta waves, and spindles are mainly evident in the frontal lobe region, we can hypothesize that an epileptogenic focus (either secondary to an anatomic lesion or by a functional alteration) localized in the frontal lobe could be more prone to be activated by these oscillatory mechanisms. Furthermore, the strong presence of nACh receptors in both cortical and subcortical structures, known to modulate sleep and arousal oscillations at the cortical and subcortical levels [95], could facilitate the occurrence of an unbalanced excitation/inhibition circuitry within the GABAergic reticular thalamic neurons [96] and, subsequently, facilitate nocturnal seizures through the synchronizing effect of spontaneous oscillations in the frontal thalamocortical connections.

Interrelationship Between Epilepsy and Sleep

The activation of 3-Hz SWDs during NREM sleep is supported by the hypothesis of corticoreticular epilepsy of Kostopoulos and Gloor [97] and Gloor [41]. Kostopoulos and Gloor [97] argued that the 3-Hz spike-and-wave discharges of primary generalized corticoreticular or petit mal epilepsy are the result of an excessive response of cortical neurons to those thalamocortical volleys that are responsible for production of normal sleep spindles. In 1942, Morison [87] produced recruiting responses after intralaminar thalamic stimulation. In 1947, Jasper and Droogleever-Fortuyn [98] succeeded in producing 3-Hz spike-and-wave discharges after similar stimulation in the presence of cortical hyperexcitability. Spencer and Brookhart [99] and Spencer and Kandel [100] showed similarities between recruiting responses and cortical sleep spindles in the cat. Both of these waves resulted from summated postsynaptic potentials of cortical neurons due to low-frequency thalamocortical volleys. Gloor [101] confirmed and extended these observations with the feline model of generalized epilepsy induced by intramuscular penicillin and concluded that spike-and-wave discharges resulted from summated postsynaptic potentials of the cortical neurons as a result of the thalamocortical volleys that would normally produce sleep spindles and recruiting responses. Penicillin obviously caused cortical hyperexcitability.

In this connection, it is important to note that Niedermeyer [102] was the first to suggest that generalized synchronous spike-and-wave discharges originated from the physiologic K complex. It was previously suggested that the delta waves are enhanced after deafferentation of the cortex, suggesting that subcortical white matter participates in the production of EEG slow waves [103, 104]. The initial observation of Niedermeyer [17] in 1965 was followed by other reports from the same author and his collaborators and subsequently other authors [105, 106]. Elegant studies by Steriade and colleagues clearly showed the propensity of spike-and-wave discharges to occur during sleep as a result of transformation of the very slow sleep oscillations into paroxysmal discharges [73, 75, 78, 79]. It has been suggested that the depolarizing phase of the very slow oscillations progressively increases in amplitude and decreases in duration, resembling a PDS. The actual mechanism converting the very slow sleep oscillations into rhythmic spike-and-wave discharges is not clearly understood, however, but involves an interaction between neurons, glia, and ions [75]. A good neurophysiologic explanation has been given by Steriade and McCarley for seizures being triggered by K complexes [66]. A synchronous burst-pause firing pattern of the thalamocortical volleys will cause enhancement of the discharges from the potentially epileptogenic neurons, generating spikes or multiple spikes. The interictal spike-and-wave discharges may be triggered by arousal mechanism generating epileptic K complexes and terminating in ictal discharges accompanied by clinical seizures. Thus, all these studies show a close interrelationship among spike-and-wave discharges, K complexes, and sleep spindles, confirming common mechanisms and circuits for transmission shared by the epileptic neurons and normal phasic events of sleep [17, 63, 107, 108]. The spike-and-wave discharges are triggered by the very slow cortical oscillations, which disappear after decortication but survive after thalamectomy [73].

Wyler [109] studied epileptic neurons during sleep and wakefulness in 14 normal and 17 abnormal neurons recorded from alumina gel-induced chronic neocortical epileptic foci in four male *Macaca mulatta* monkeys during transition between sleep and wakefulness. During sleep, the neurons that were mildly epileptic during wakefulness changed their firing pattern drastically and behaved like neurons that were grossly epileptic during wakefulness; normal neurons and those neurons that were grossly epileptic during wakefulness did not change the firing pattern significantly. The author concluded that the neurons may represent the "critical mass" for initiation of seizure activity during synchronized sleep, which is characterized by burst-synchronizing events such as sleep spindles.

Shouse et al. [110] studied the mechanism of seizure suppression during REM sleep in cats. They created two seizure models in 20 cats, systemic penicillin epilepsy and electroconvulsive shock, and produced two types of lesions: bilateral electrolytic lesions in the mediolateral pontine tegmentum producing a syndrome of REM sleep without atonia, and systemic atropine injection producing REM sleep without thalamocortical EEG desynchronization. These authors made the following conclusions based on these experiments:

1. REM sleep retarded the spread of epileptiform discharges in the EEG.
2. The descending brain stem pathways responsible for lower motor neuron inhibition during REM sleep also protected against generalized motor seizure during REM sleep.
3. The mechanism to prevent spread of seizure discharge used a separate pathway in the ascending brain stem structures that caused thalamocortical EEG desynchronization during REM sleep.
4. The data thus suggest a cholinergic mechanism for thalamocortical EEG desynchronization and for retardation of EEG discharges during wakefulness and REM sleep.

They further concluded that for generalized epilepsy, REM sleep was the most potent antiepileptic state in the sleep-wake cycle. It is important to note that Cohen et al. [111] found a lowered convulsive threshold during REM deprivation in cats. REM deprivation thus may exacerbate epilepsy.

It is worth to mention that besides sleep spindles, K complexes, and slow oscillations, another EEG sleep pattern characterized by ultraslow EEG oscillations (with a period of about 20–40 s) also become evident during the build up and consolidation of NREM sleep, both during visual and quantified EEG analysis [112–114]. Ultraslow oscillations are mainly manifested over the frontal regions and are thought to express cyclic changes in cortical and/or subcortical excitability [115, 116]. They often appear as transitional or intermediate states between sleep and wakefulness especially at sleep onset and during the transition toward REM sleep. These features are visually scored and included in the framework of the cyclic alternating pattern (CAP) [112], which is composed of a repetitive, biphasic pattern in which sequences of K complexes, delta bursts, and/or faster activities (phase A) periodically interrupt the tonic theta/delta background activity of sleep (phase B). CAP phases A and B are considered to reflect, respectively, a condition of transient activation and inhibition [112, 115]. These transitional and intermediate states, mainly expressed by the phase A of CAP, act as a gate, facilitating the occurrence of both ictal and interictal epileptic manifestations [112, 117].

Effect of Sleep on Epilepsy

Because of the awareness of an intimate relationship between sleep and epilepsy, various authors have classified seizures according to the time of occurrence of the seizures (clinical and electrical) during certain times in the sleep-wake cycle. Thus, seizures have been classified as waking, sleep, diffuse (both diurnal and nocturnal), circadian, ultradian, and infradian epilepsies. Box 44.1 lists biorhythmic (according to timing) classification of seizures [91]. Diurnal (waking) seizures are mostly primary generalized epilepsies that are mainly genetically determined. Nocturnal (sleep-related) seizures are most often localization-related seizures. Diffuse epilepsies (those occurring randomly during the night and day) show both ictal and interictal discharges during sleep and waking states. These are often associated with diffuse central nervous system dysfunction and are symptomatic generalized seizures. They are often medically refractory.

Box 44.1 Biorhythmic Classification of Seizures

Diurnal (Waking) Epilepsies

- Absence seizures,
- Juvenile myoclonic epilepsy,
- Generalized tonic-clonic seizure on awakening.

Nocturnal (Sleep-Related) Epilepsies

- Nocturnal frontal lobe epilepsy,
- Autosomal dominant nocturnal frontal lobe epilepsy,
- Benign epilepsy of childhood with centrotemporal spikes with or without occipital paroxysms,
- Continuous spike-and-wave discharges during slow-wave sleep,
- Landau–Kleffner syndrome.

Diffuse Epilepsies (Randomly Occurring During Night and Day)

- Lennox–Gastaut syndrome,
- West's syndrome (hypsarrhythmia),
- Progressive myoclonus epilepsies.

As early as 1885, Gowers [4] analyzed 840 institutionalized patients with a variety of seizure disorders and observed that 21 % of seizures occurred exclusively at night; 42 % exclusively in the daytime; and 37 % at random, both during the day and during the night. According to Gowers, the two most susceptible periods were the onset of sleep and the end of sleep. Langdon-Down and Brain [8] and Patry [9] made similar observations. In all three series, the analysis was based on institutionalized patients. Langdon-Down and Brain [8] observed that in a series of 66 patients, 24 % had sleep, 43 % had diurnal, and 33 % had diffuse epilepsies. In a sample size of 31, Patry [9] found 19 % sleep, 45 % diurnal, and 36 % diffuse epilepsies. Using the average of these three groups of institutionalized epileptics, the incidence of each of these three types of seizures in relation to the sleep-wake cycle is 22 % sleep, 44 % diurnal, and 34 % diffuse epilepsies. Thus, the incidence is similar in these three series. Langdon-Down and Brain [8] found the peak incidence of waking epilepsies to be 1–2 h after awakening, approximately 7:00–8:00 AM; smaller peaks were found at approximately 3:00 PM and 6:00–8:00 PM. Sleep epilepsies had two peaks, 10:00–11:00 PM and 4:00–5:00 AM (i.e., early and late at night, similar to that noted by Gowers [4]).

Among the contemporary epileptologists, Janz [13, 118] has contributed most toward classification of seizures based

on the sleep-wake cycle. He analyzed two large series of outpatients with tonic-clonic generalized seizures. In the first series of 2110 patients [13], Janz [118] found 45 % sleep, 34 % diurnal, and 21 % diffuse epilepsies. In the second series of 2825 similar patients, the incidence was 44 % sleep, 33 % diurnal, and 23 % diffuse epilepsies. Therefore, the two series were similar. Janz [13] called diurnal seizures *awakening epilepsies* because of the high prevalence of seizure during awakening from sleep. In a sample size of 314 outpatient seizure patients, Billiard [20] found 15 % sleep, 53 % diurnal, and 32 % diffuse epilepsies. It should be noted that Billiard included a variety of types of epilepsies in his analysis. Earlier, Hopkins [119] analyzed a series of outpatient tonic-clonic generalized seizures and found 51 % sleep, 30 % diurnal, and 19 % diffuse epilepsies. Janz [13, 118] also noted increased frequency at the beginning and end of the night in sleep epilepsies, similar to that observed by Gowers [4]. It is important to note that the earlier classification was based only on clinical studies and no nighttime EEGs were obtained. The contemporary epileptologists and neurologists had the benefit of obtaining the EEG and all-night polysomnographic (PSG) studies using standard sleep scoring criteria. As regards stability of type, Janz [13] reported that 10 % of awakening epilepsies later became sleep epilepsies, whereas only 6 % became diffuse epilepsies. According to Janz [13, 118] and Hopkins [119], sleep and diffuse epilepsies lasting for 2 years rarely become awakening epilepsies. The differences in the incidence of the three types of seizures may be due to the selection of patients (i.e., outpatient, institutionalized, generalized, or partial seizures).

The importance of classification based on sleep-wake cycle is that this classification may shed light on the prognosis and etiology. Patients with diffuse epilepsies often have intractable seizures and structural neurologic deficits, with poor prognosis as compared to patients with awakening or sleep epilepsies [120]. Analyzing the various data, Shouse [120] stated that idiopathic type is generally awakening type, those associated with organic structural lesions are of the diffuse type, and the sleep epilepsies are intermediate in terms of organicity. D'Alessandro et al. [121] analyzed 1200 patients visiting the epilepsy center during a 5-year period (1974–1979). They found that 90 of the 1200 (7.5 %) had sleep epilepsy (i.e., had one or more seizures exclusively during sleep). This frequency is lower than that found by Janz [13] and Kajtor [122] but similar to that noted by Gibberd and Bateson [123]. The authors concluded that pure sleep epilepsies have a good prognosis. They rarely have waking seizures during the first few years after the onset of epilepsy.

A number of investigators have studied the question of whether epilepsy manifests biorhythmicity—specifically, whether there are circadian, ultradian, or infradian epilepsies. Kellaway et al. [21, 124] cited the specific relationship of epileptic phenomena to the sleep-wake cycle as an example of a circadian rhythm. It should be noted, however, that Autret et al. [125] noted an increase in focal discharges during NREM stages 1 and 2 and in generalized discharges during NREM stages 3 and 4, and a reduction or disappearance of the discharges in REM sleep during any time of the day and night. This evidence argues against a circadian rhythmicity. Kellaway et al. [21, 124, 126] suggested that epileptiform activity is linked to two rhythms: circadian and ultradian, related to NREM-REM cycle at 90–100 min. Stevens et al. [127] suggested that focal EEG discharges in adults may at times show an ultradian 90- to 100-min periodicity in phase with prior NREM-REM sleep cycles throughout the day and night. Binnie [128] and Martins da Silva and Binnie [129] also noted periodicities of interictal discharges, both during diurnal waking and during nocturnal sleep EEG recordings. In most of their patients, periodicities were longer or shorter than the typical 90- to 100-minute REM-NREM cycle. However, Kellaway et al. [124] failed to document waking ultradian rhythmicity in petit mal spike-and-wave discharges. In one case of petit mal absence, Broughton et al. [130] provided strong evidence for ultradian daytime variations of spike-and-wave discharges, mainly at the REM cycle rate. However, these observations have been made based only on one case study.

There are clear methodological problems in studying biorhythmicity in epilepsy [128]. The classic methods include temporal isolation to observe the free-running rhythms (entrainment) and shifting the time zone. Such studies in epilepsy, however, have not been performed in detail [128]. Circadian rhythm, sleep, and epilepsy have been studied by Quigg [131] and others [90, 132, 133]. These authors have reported transient dysfunction of normal circadian function during seizures. Transient disruption of hormones under circadian modulation (e.g., an increase in prolactin secretion within 15 min of onset of seizures, particularly generalized seizures) is well known. There is a suggestion that there may be possible damage to suprachiasmatic nuclei as a result of repeated seizures. Quigg [131] noted subtle functional defects in primary circadian regulation in rats, but no gross abnormalities were noted. Quigg et al. [134] demonstrated that electrically induced seizures in rats isolated from time cues and light for 3-week trials induced advances and delays in circadian rhythm of temperature. Based on these findings, the authors suggested that circadian dysregulation might contribute to some of the altered endogenous cycles associated with epilepsy. In a recent prospective pilot study, Hoftsra et al. [133] evaluated seizure timing with respect to the individual's circadian phase as measured by the dim light melatonin onset (DLMO). The authors found that temporal lobe seizures occurred most frequently in the 6 h before DLMO and

frontal lobe seizures mainly in 6–12 h after the DLMO. Quigg [131] suggested that melatonin might have an anticonvulsant effect and may be responsible for limbic seizures not occurring predominantly during sleep. However, the relation between melatonin and seizures remains controversial [135–137]

Several studies show circadian influence on the occurrence and timing of seizures. Of all the epilepsy syndromes, mesial temporal lobe epilepsy (MTLE) appears to be particularly vulnerable to circadian effects, but there is no conclusive evidence for this, as seizure distribution among different syndromes remains confusing because of the complex interrelationship between the circadian effects, the vigilance state, antiepileptic drugs, and possibly unknown pathophysiologic effects of the epilepsy itself. Both animal studies [138, 139] and human studies [137] have provided evidence for circadian influence in MTLE. By comparing the circadian timing of seizures in patients with MTLE with seizures occurring in an animal model of focal limbic epilepsy, Quigg et al. demonstrated that both groups had more seizures between 0700 and 1900 with a nadir of temporal lobe seizure occurrence between 0200 and 0600. Because humans and rats have sleep-wake patterns that are 180° out of phase with each other, Quigg et al. [138] argued that the circadian modulation of limbic seizure occurrence is not likely to be secondary to the vigilance state but influenced by the primary circadian pacemaker or secondary circadian rhythms other than sleep. Using a forced desynchronization protocol in a small group of patients with juvenile myoclonic epilepsy, Pavlova et al. [140] showed that most interictal epileptiform discharges occurred during NREM sleep (ratio of 14:1) and in the two patients who had slept during all circadian phases, there was suggestion of a circadian variation in discharges, independent of any vigilance state. Further studies are needed to confirm these findings in JME and also in other epilepsy syndromes.

Contrary to biorhythmicity, seizure occurrence in relation to the vigilance state has been more extensively documented by recent studies employing scalp or intracranial electrocorticography monitoring to record seizures. These studies have confirmed past clinical observations that seizures from different brain regions have a strong tendency to occur in different diurnal patterns [141, 142]. Using intracranial electrocorticographic monitoring, Hofstra et al. [141] found a prevalence late in the morning and early afternoon for seizures originating from the mesial temporal lobe; frontal seizures occurred preferentially during the night (between 2300 and 0500 h) and parietal seizures between 1700 and 2300 h. In the awake state, larger proportions of clinical seizures were seen from 0500 to 1100 h and from 1700 to 2300 h. During sleep, larger proportions occurred from 1100 to 1700 h and from 2300 to 0500 h [141]. Durrazo et al. [142] analyzed 669 seizures from 131 consecutive adult patients with localized partial epilepsy of different lobar onset. They found that frontal and parietal seizures occurred more frequently at night and had similar unimodal distribution that was 180° out of phase relative to the occipital lobe. Occipital and mesial temporal lobe (MTL) seizures were more frequent in daytime. Finally, it has recently been shown that the clinical evolution of a seizure (from an aura to a clonic, tonic, or generalized attack) also clusters at specific times of day and at specific phases of the sleep-wakefulness cycle [143].

Frontal lobe seizures most commonly arise from NREM sleep [144–147]. In an analysis of 613 seizures in 133 patients, Herman et al. [146] noted that 57 % of frontal lobe seizures occurred during NREM sleep, particularly stage 2, compared with 40 % of mesial temporal lobe, 24 % of neocortical temporal lobe, and about 13 % of occipitoparietal lobe seizures. A study aimed at evaluating the topography of the epileptogenic zone and the etiologic substrate as risk factors for sleep-related focal epilepsy has shown that regardless of its anatomical localization (frontal or extrafrontal), the presence of a type II focal cortical dysplasia (Taylor-type) increases considerably the risk of sleep-related epilepsy [34]. This finding further highlights the complexity of studying seizure occurrence in relation to biorhythmicity or vigilance state in humans as many intrinsic and extrinsic factors, known and possibly unknown, have to be taken into account.

Finally, the question of infradian rhythmicity in epilepsy, as exemplified by catamenial epilepsy (i.e., menstrual related epilepsy), remains controversial. Almqvist [148] found a periodicity in 47 of 146 long-stay patients with epilepsy. The author noted that in some of the patients, the interval of the attacks was equal to the period of the menstrual cycle. However, the concept of catamenial epilepsy, although generally accepted [149], remains questionable and difficult to define as seizure clustering is a common occurrence in many types of epilepsy [150, 151]. Many animal studies have shown a seizure threshold-lowering effect of estrogen and mild antiseizure effect of progesterone [152]. However, a recent transcranial magnetic stimulation study has shown altered variations in cortical excitability during the menstrual cycle in women with epilepsy that cannot be solely explained by hormonal fluctuations across the menstrual cycle [153].

In conclusion, epilepsy in some patients may show a circadian temporal periodicity and an association with sleep periodicity, but it is not known whether this periodicity is "state" linked (sleep vs. wakefulness) or "time" linked (nocturnal vs. diurnal) [154]. Webb [154] considered epileptic events to be "state dependent," whereas Martins da Silva and Binnie [129] considered them to be "time dependent." This understanding may be important for effective control of epilepsy by optimization of the drug regimen. It should also be recognized that there are circadian variations of drug absorption, interaction, and metabolism (e.g.,

valproate absorption is reduced at night because of gastrointestinal physiologic changes at night, and carbamazepine shows circadian variation in autoinduction) complicating management of seizures [155]. In 1985, Binnie [128] raised the question: Can we improve patient care if we learn about biorhythms in epilepsy? Unfortunately, 30 years later, we are still looking for a definite answer [132].

Effect of Sleep on Specific Seizure Types

In this section, we briefly describe the effect of sleep on clinical seizures as well as on the interictal EEG epileptiform discharges in both generalized and partial seizures.

Clinical Seizures

Generalized Epilepsies

Generalized epilepsies commonly include generalized tonic-clonic (grand mal) epilepsy, petit mal (absence epilepsy), juvenile myoclonic epilepsy, infantile spasms (West's syndrome), and Lennox–Gastaut syndrome. Diurnal or *awakening epilepsy*, a term introduced by Janz [156] to differentiate from sleep and diffuse epilepsies, also belongs to the category of generalized epilepsies, which include generalized tonic-clonic, absence, and benign juvenile myoclonic seizure. Some varieties of diffuse epilepsies (e.g., Lennox–Gastaut and West's syndromes and progressive myoclonic epilepsies) also belong to generalized seizures.

Primary Generalized Grand Mal Seizure

Primary generalized grand mal seizure occurs almost exclusively in NREM sleep [157] and is most frequently seen 1–2 h after sleep onset and at 5:00–6:00 AM, as noted originally in 1885 by Gowers [4] and later by others [8, 9, 13]. Grand mal seizure may occur only during sleep or only during the daytime, or be randomly distributed. In a study of 171 patients, Billiard et al. [158] found exclusively nocturnal seizures in only 8 %. This study also confirmed the observations of Passouant et al. [159] and Bessett [157] that primary generalized seizure occurs exclusively in NREM sleep. Passouant et al. [160] called the seizure occurring exclusively during sleep *l'epilepsie morpheique*; this is considered a benign form of epilepsy. These patients rarely go on to develop waking epilepsies, and when they do, it is after the first 2 years from onset [121].

Petit Mal (Absence) Epilepsy

Absence seizures occurring during sleep are difficult to diagnose, and clinical absence seizures are observed in the waking state. According to Niedermeyer [17], there may be fluttering of the eyelids during the spike-and-wave discharges in sleep. Gastaut et al. [161], Gastaut and Broughton [162], and Patry et al. [163] described occasional cases of petit mal status in REM sleep.

Juvenile Myoclonic Epilepsy

Meier-Ewert and Broughton [164] noted increased myoclonic seizures shortly after awakening in the morning, and the duration of the attack is longer on awakening from NREM than from REM sleep. Occasionally, these attacks occur on awakening in the middle of the night or later in the afternoon [9, 13, 165]. Myoclonic seizures can be subtle and misinterpreted as simple clumsiness for many years until the arrival of a generalized seizure. These patients may also have daytime absence seizures with staring spells that can mimic daytime sleep attacks. Patients may be exceedingly sensitive to sleep deprivation and alcohol consumption. Using transcranial magnetic stimulation, Manganotti et al. [71] have shown that cortical excitability is increased early in the morning in patients with JME; this finding may explain the increased seizure susceptibility in these patients at this time of the day.

Lennox–Gastaut Syndrome

In Lennox–Gastaut syndrome, the clinical seizures consist of tonic, myoclonic, generalized tonic-clonic, atonic, and atypical absence [166]. Information regarding the effect of sleep on the clinical seizures in this syndrome is lacking in the literature [167]. Tonic seizures, typically activated by sleep [168], are much more frequent during NREM sleep than during wakefulness and are never seen during REM sleep [169]. They may only be characterized by subtle and frequently undetected brief apneas.

West's Syndrome (Infantile Spasms)

Maximum clinical seizures, often spasms in series, are seen on arousal from sleep or before going to sleep [170]. Less than 3 % of spasms are obtained in sleep.

Partial Epilepsies

Clinical seizures in simple partial seizures and complex partial seizures (CPSs) are more frequent during the day [20, 121]. In Billiard's [20] study of 156 patients, 61.5 % had daytime and 11.5 % had nocturnal seizures only. According to Montplaisir et al. [171–173], Laverdiere and Montplaisir [174], and Rossi et al. [175], REM sleep did not facilitate temporal lobe seizure. However, other authors [159, 176, 177, 178] observed ictal phenomena during both stages of sleep. In fact, Epstein and Hill [178] described a case of temporal lobe seizure with unpleasant dreams during REM sleep associated with increased epileptiform activities in the EEG in the temporal region. Frontal lobe epilepsies occur

more commonly during sleep than during the waking state [146].

Pure sleep epilepsies mostly present as focal seizures with or without secondary generalization [13, 20]. Benign epilepsy of childhood with centrotemporal spikes (BECTSs) and continuous spike-and-wave discharges during slow-wave sleep (CSWS) are also typical examples of sleep epilepsies and are described in the next section.

Interictal Epileptiform Discharges

Primary Generalized Grand Mal Tonic-Clonic Seizures

Interictal EEG discharges (Fig. 44.1) generally increase in NREM sleep and disappear in REM sleep [18, 20, 103, 125, 162, 179–181]. Mostly, the discharges are prominent at sleep onset and during the first part of the night. Sometimes

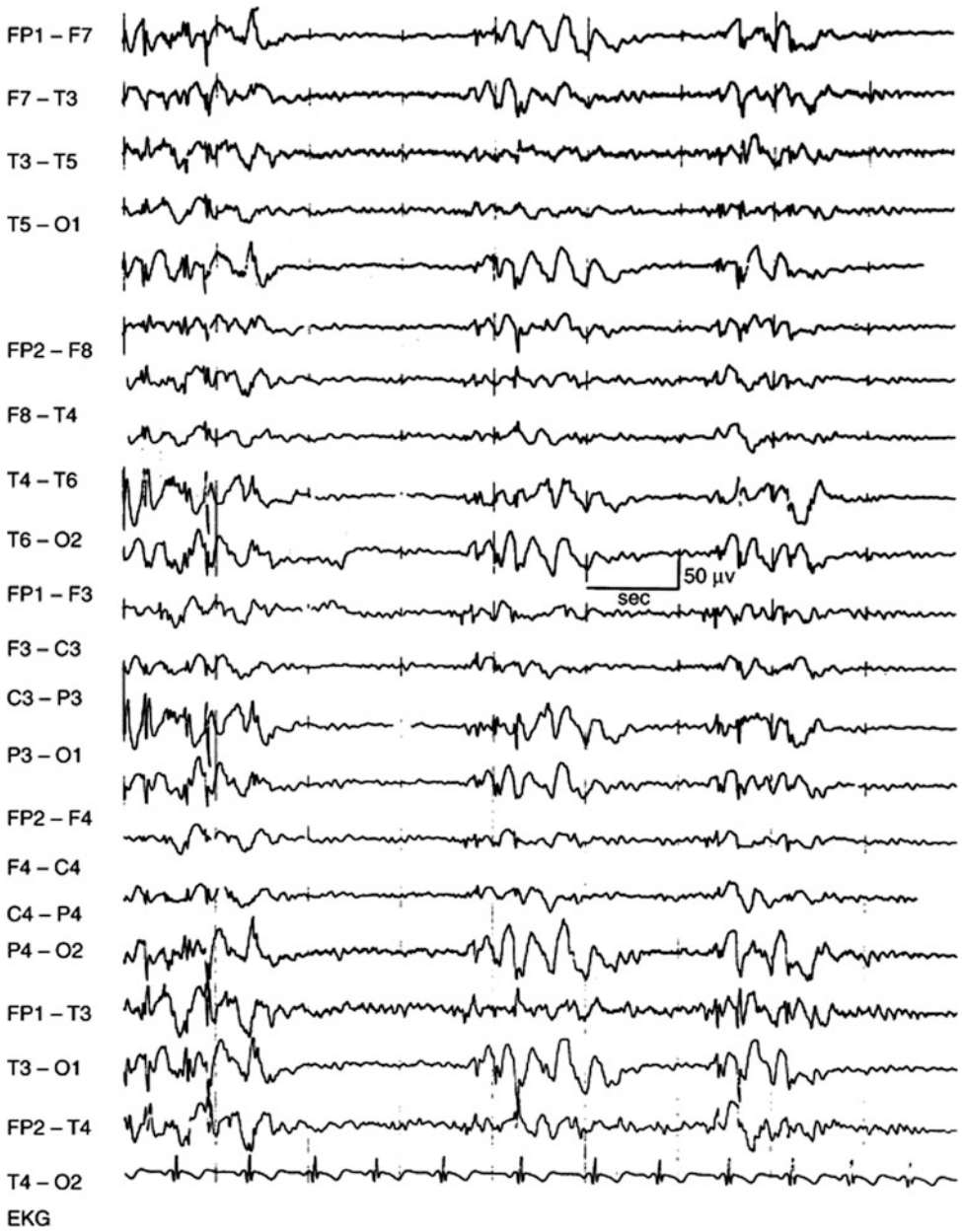

Fig. 44.1 Interictal, primarily generalized epileptiform discharges (4- to 5-Hz spike-and-wave and multiple spike-and-wave discharges) seen synchronously and symmetrically with frontal dominance of amplitude in a patient with generalized tonic-clonic seizures. (EKG, electrocardiography)

the discharges are activated during NREM sleep in the late part of the night, possibly resulting from reduced serum levels of antiepileptic medications [18]. Interictal discharges may be fragmented or may appear as polyspikes or focal spikes during NREM sleep. According to Billiard [20], interictal discharges are more frequent during NREM than during REM sleep (41 % vs. 9 %) in pure sleep epilepsy, but in waking or random epilepsy, interictal discharges are seen throughout the day and night. With nocturnal epilepsies, the daytime EEG remains normal in a high percentage of patients [182].

Petit Mal (Absence Epilepsy)

According to Sato et al. [183], Tassinari et al. [184], and Billiard et al. [158], interictal EEG discharges (Fig. 44.2) in absence attacks are present during all stages of NREM sleep. These are more marked during the first sleep cycle [183] but generally absent in REM sleep. The pattern during REM sleep is similar to that during wakefulness with reduced duration [183, 184]. Sato et al. [183] described alterations of spike-and-wave discharge morphology during different sleep stages: regular or irregular spike-and-wave discharges in NREM stages 1 and 2, and irregular polyspikes

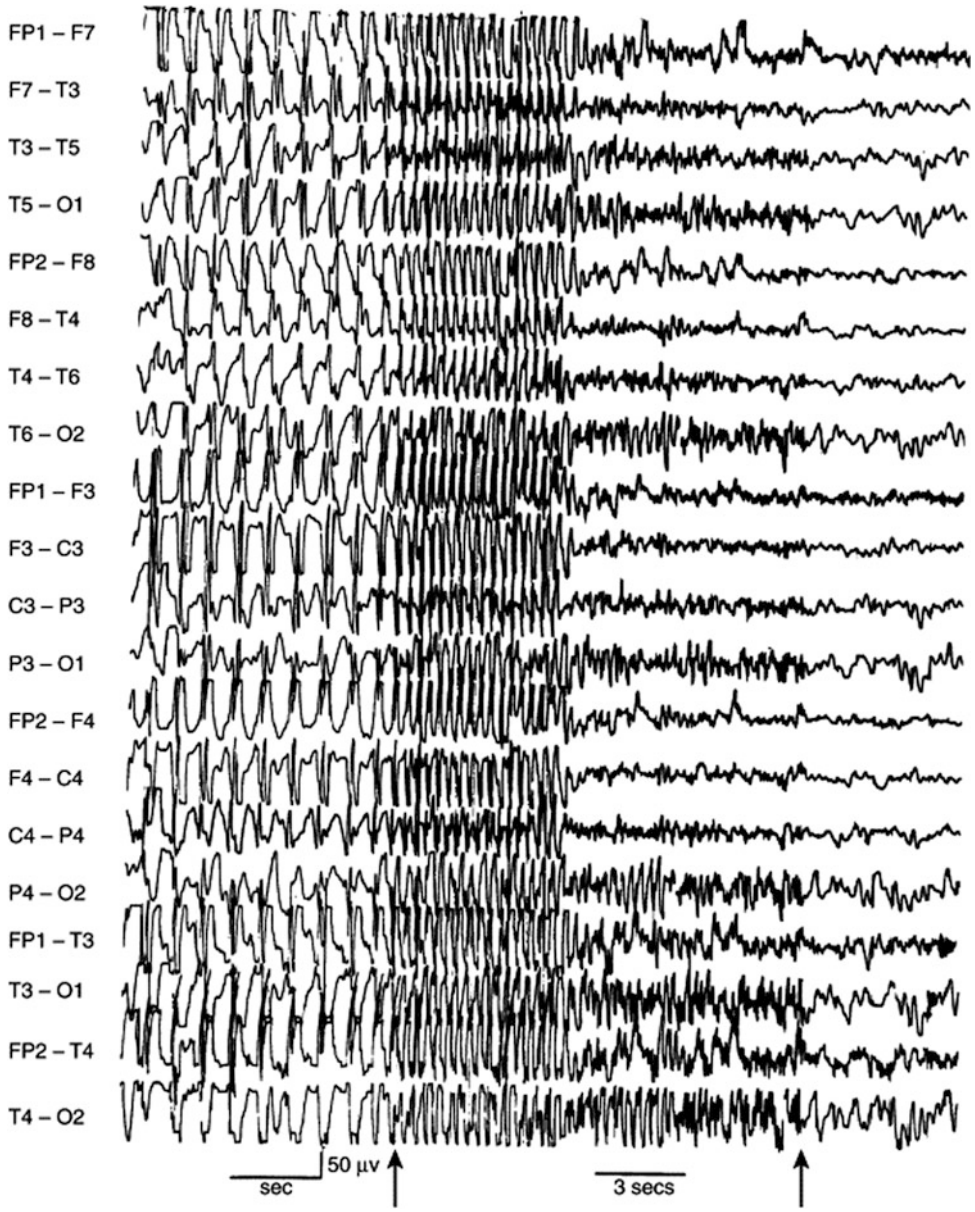

Fig. 44.2 Three-hertz spike-and-wave discharges noted synchronously and symmetrically with dominance of the amplitude anteriorly in a patient with absence spells (petit mal). Note the paper speed on the panel to the *left* at 30 mm/s (*sec*) and to the *right* at 10 mm/s (*3 secs*; between the *arrows*)

and slow waves during NREM stage 3. In addition, fragmentation or focalization of spikes can be seen over the frontal regions during NREM sleep.

Juvenile Myoclonic Epilepsy

Interictal discharges (Fig. 44.3) in these patients are prominent at sleep onset and on awakening [18, 185]. During NREM sleep, IEDs are facilitated by arousal fluctuations, and conversely, they may promote sleep instability and further foster epileptic activity and conceivably seizures [186, 187]. According to Touchon [165], induced awakening is a better facilitator than spontaneous awakening in these patients.

Lennox–Gastaut Syndrome

The typical EEG finding (Fig. 44.4) in Lennox–Gastaut syndrome is slow spike-and-wave discharges (1.5–2.5 Hz). In sleep, these may be intermixed with trains of fast spikes of 10–25 Hz lasting 2–10 s (the so-called grand mal discharges) as interictal abnormalities. The spike-and-wave discharges characteristically increase in NREM sleep [167]. Sometimes bursts of electrodecremental activity alternate

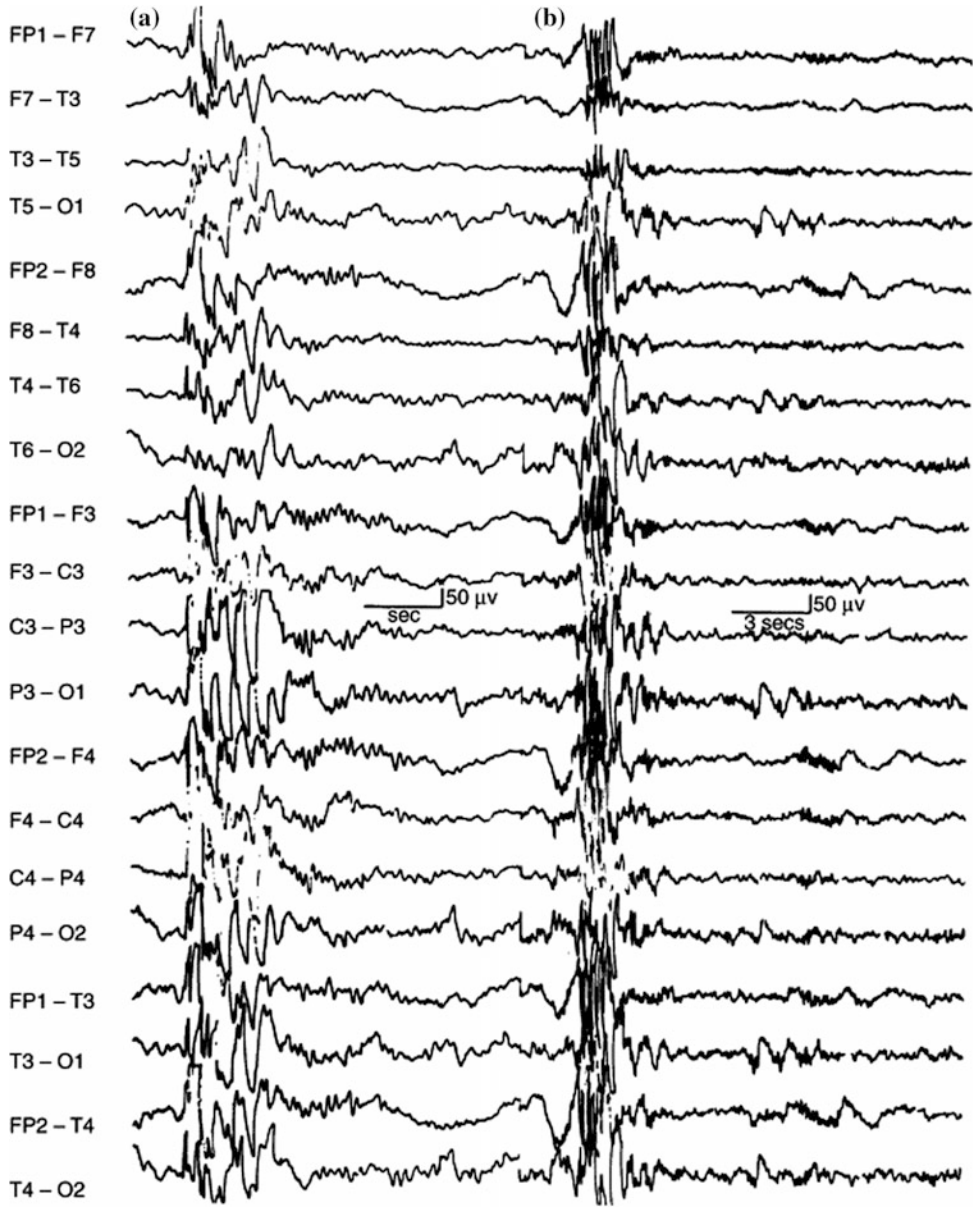

Fig. 44.3 Interictal generalized multiple spike-and-wave discharges in the EEG of a patient with juvenile myoclonic epilepsy. Note the recording at 30 mm/s (*sec*) on the *left* (**a**) and at 10 mm/s (*3 secs*) on the *right* (**b**)

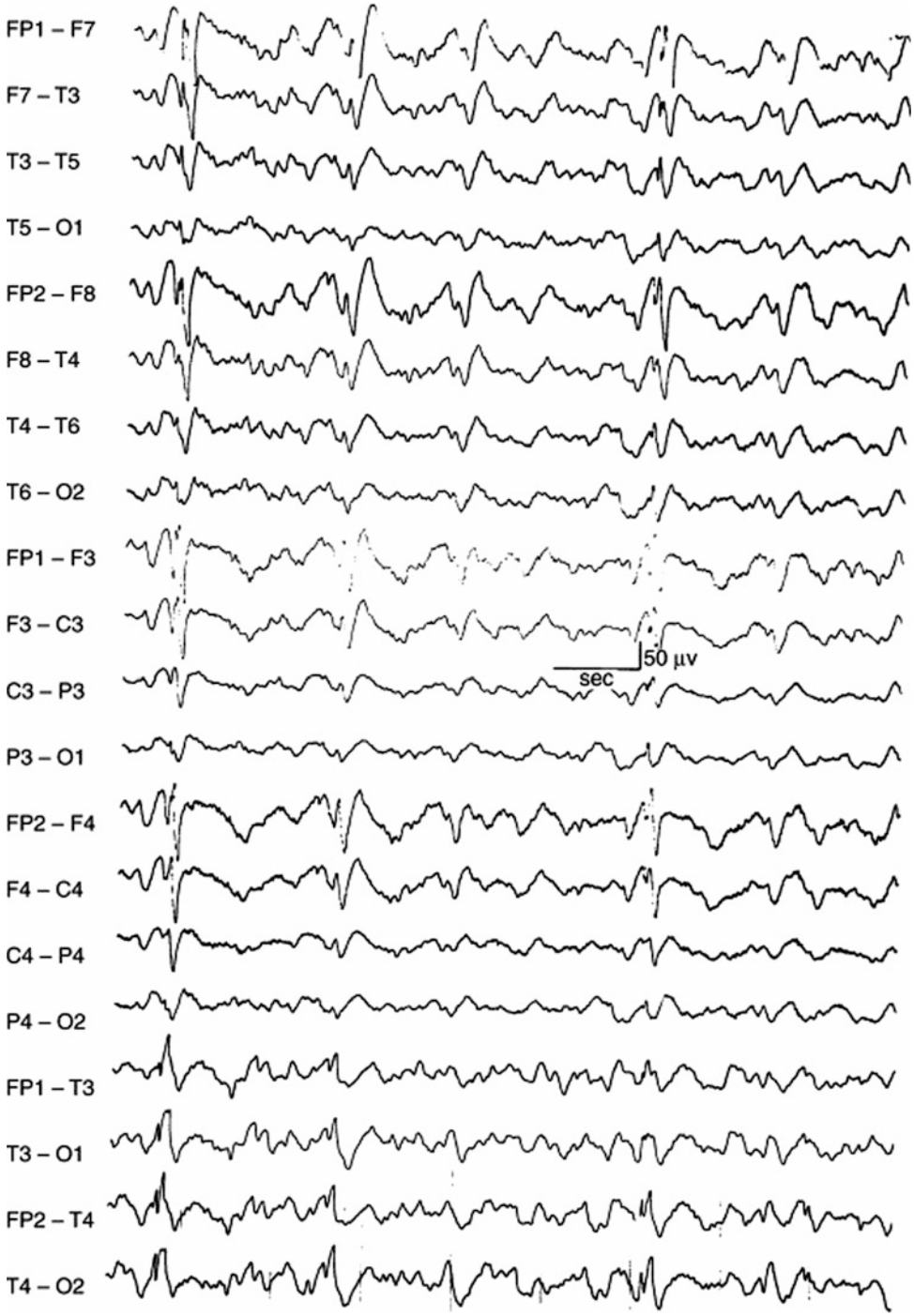

Fig. 44.4 Generalized slow spike-and-wave (2.0- to 2.5-Hz) bursts in a patient with Lennox–Gastaut syndrome

with bursts of polyspikes, giving rise to a burst suppression-like pattern [167]. According to Markand [188], prognosis is better in those patients with significant increase of interictal EEG abnormalities during sleep.

West's Syndrome (Infantile Spasm)

The characteristic EEG finding of West's syndrome (Fig. 44.5) is hypsarrhythmia (high-amplitude slow waves and spikes or sharp waves occurring irregularly), which may show progressive changes during sleep. The characteristic pattern seen during wakefulness may increase in NREM sleep. The hypsarrhythmic EEG of wakefulness may change during NREM sleep into a periodic bilaterally synchronous diffuse pattern interspersed with flattening, resembling "burst suppression," [159] and may even normalize during REM sleep. Occasionally, the waking EEG may be normal, but the NREM sleep EEG may show the irregular high-voltage slow waves and spikes [189].

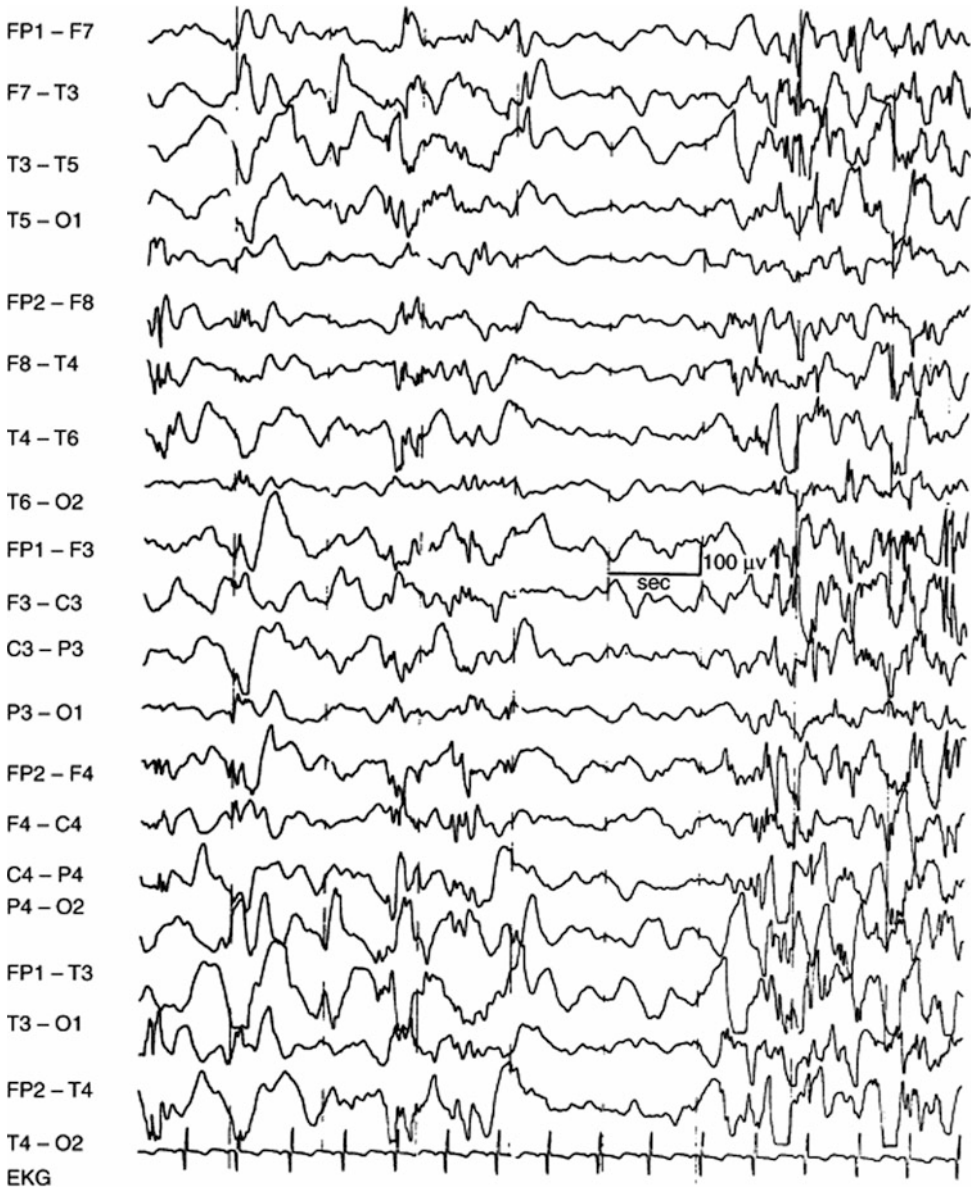

Fig. 44.5 Electroencephalogram showing hypsarrhythmic pattern in a 9-month-old girl with infantile spasms

Partial Epilepsies

An increase of interictal EEG discharges (Fig. 44.6) during NREM and diminution or disappearance during REM sleep have been found both in surface and depth electrode studies and in animal studies [177, 190–195]. Interictal epileptiform discharges increase generally at sleep onset, peak in slow-wave sleep, but then decrease in REM sleep [173, 193, 196, 197]. Malow et al. [197, 198] studied the relationship of spikes to absolute log delta power, a continuous measure of sleep depth, and found that interictal discharge spiking was maximum during slow-wave sleep, particularly on the ascending slope of increasing log delta power. In another study, Malow et al. [199] concluded that temporal interictal epileptiform discharges observed during continuous overnight EEG studies provided important lateralizing information for the presurgical evaluation of temporal lobe epilepsy patients. Although generally observed during NREM sleep, an increase in interictal epileptiform discharges can rarely be observed during REM sleep [165, 178, 200–202]. An important point to note is that during NREM sleep, the discharges spread ipsilaterally and contralaterally from the primary focus, whereas during REM sleep, the discharges seem to focalize maximally [172, 180, 203]. Localizing value of REM sleep in temporal lobe epilepsy has also been shown in other studies [195, 204]. Depth electrode studies in humans by Montplaisir et al. [173] and Lieb et al. [203] showed increased spike discharges during NREM sleep and a reduction of the discharges during REM

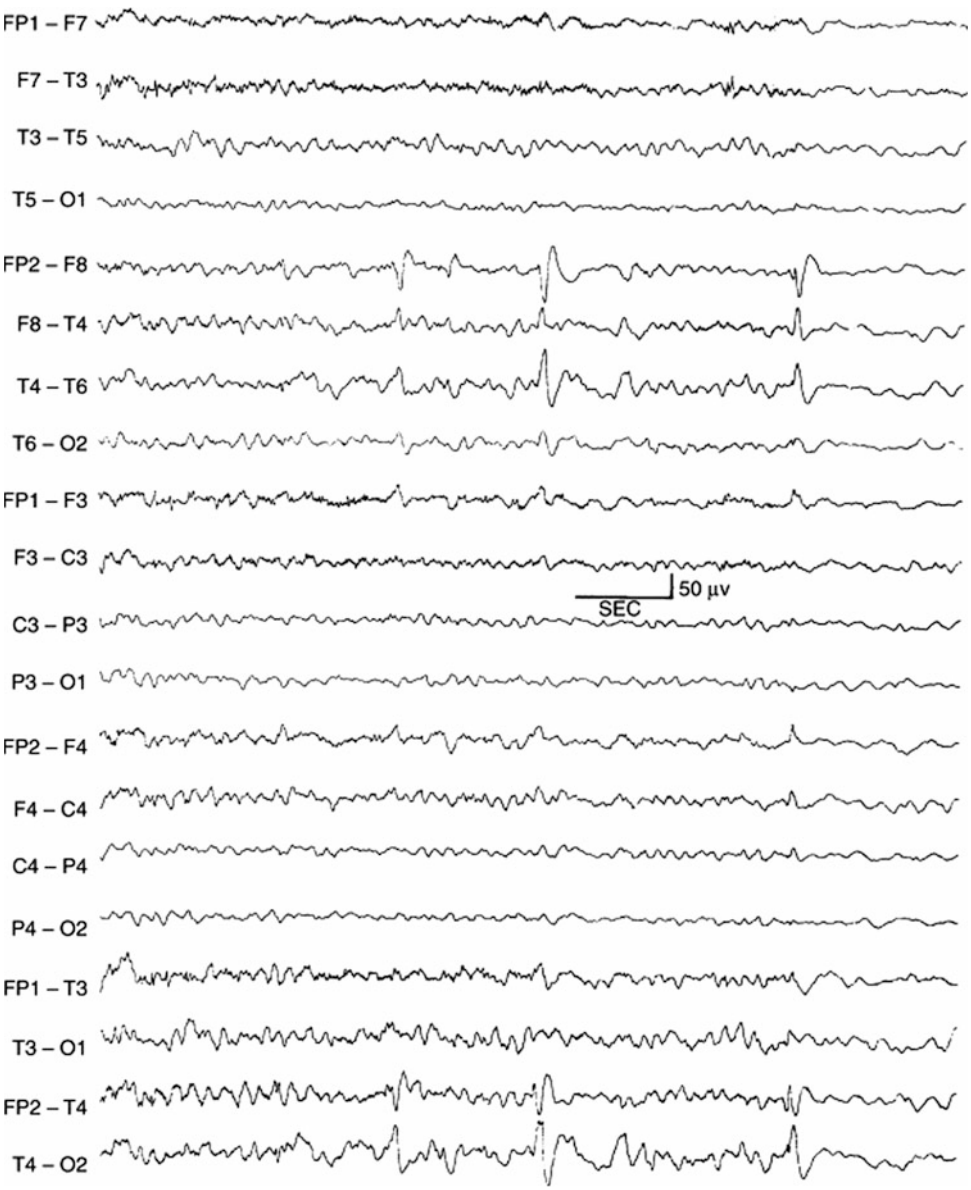

Fig. 44.6 Focal right anterior and mid-temporal sharp and slow waves showing phase reversal at F8-T4 electrodes in a patient with complex partial seizure

sleep. Depth electrode studies also showed that during REM sleep, the spike discharges became maximally focalized [174, 175, 203].

Autret et al. [181] reviewed 236 adult epileptics attending outpatient clinics and classified the seizures in two ways: (1) according to the time of onset of seizures by history (e.g., diurnal, nocturnal, and diffuse epilepsies) and (2) according to the interictal activation during all-night PSG study. They found more frequent myoclonic attacks and increased seizure frequency in patients with diurnal epilepsy. Patients with increased incidence of interictal activities during sleep have less generalized motor seizure, more frequent complex partial seizure (CPS), a higher seizure frequency, and the appearance of new interictal activities during sleep. These authors did not find a significant relationship between the two classifications. It should be noted that these data are at variance with the results of Janz [118].

Lieb et al. [203] performed all-night depth electrode recordings in 10 patients with medically refractory CPS and used a computer spike recognition technique for depth spike activities arising from medial temporal lobe sites. They found the most frequent depth spike activity during deep sleep in six patients and during light sleep in three patients and an equal number during deep and light sleep in one patient. They did not find a strong relationship between temporal lobe epilepsy and sleep pattern. Their findings that the discharge rates are greatest during NREM sleep and are suppressed during REM sleep are in agreement with the previous reports of temporal lobe epileptics. Similar depth electrode findings in temporal lobe epilepsies have been

reported by Montplaisir and coworkers [171, 174, 205] and Passouant [206]. In some previous studies, however [177, 207], maximal spike activity was seen during light sleep. In the study by Lieb et al. [203], the site showing maximal spike activity did not necessarily correspond to the site chosen for temporal lobectomy. This suggests that the interictal spikes and seizure-generating capacity may not bear a close relationship to underlying pathology.

Rossi et al. [175] obtained direct cerebral recordings (stereo-EEG) by stereotactic implantation of stainless steel electrodes on preselected brain sites in 19 patients with medically refractory partial epilepsy who were potential candidates for surgery. They found that interictal spiking increased at the onset of sleep, reaching a maximum level during deep NREM sleep and returning to a lower level during REM sleep. The level in REM sleep was slightly lower as compared with that during wakefulness. They further noted that the spike rate was not influenced by spike location but was affected by the local level of epileptogenicity (i.e., the higher the epileptogenicity, the lower the variation) and that the interictal spiking across sleep and wakefulness showed wide variation in different patients and in the different regions of the same patients.

In conclusion, NREM sleep is the stage of augmentation of interictal focal and generalized EEG discharges. In REM sleep, generalized discharges are usually suppressed, but focal discharges may persist.

To explain the variation in spiking during sleep and wakefulness, three factors may be cited [175]: (1) subcortical-cortical interplay of the mechanisms for sleep and wakefulness as well as EEG synchronization [208], (2) alteration in the cortical excitability during sleep and wakefulness [70, 71, 209], and (3) location of the epileptic lesion [56, 146]. The first factor may play a role in generalized seizures, and the second and the third factors may play a role in the genesis of partial seizures.

Status Epilepticus

The information regarding effect of sleep on status epilepticus is limited, as this is a neurologic emergency and the first priority is treatment of the patient rather than spending time on prolonged recording. Therefore, limited information is available in certain types of status epilepticus. Gastaut [210] defined *status epilepticus* as a condition in which seizure persists for a sufficient length of time or is repeated frequently enough to produce a fixed and enduring epileptic condition. Current guidelines propose a definition of 5 min or more of (1) continuous clinical and/or electrographic seizure activity or (2) recurrent seizure activity without recovery (returning to baseline) between seizures as most seizures lasting longer often do not stop spontaneously [211]. Gastaut [210] classified status epilepticus into three types: (1) generalized status epilepticus consisting of convulsive and nonconvulsive types, (2) simple and complex partial status epilepticus, and (3) unilateral status epilepticus.

Generalized tonic-clonic (grand mal) status epilepticus occurs during the early part of the night [212]. Tonic status as may be seen in patients with Lennox–Gastaut syndrome, in whom it occurs almost exclusively during sleep and is seen mostly during NREM sleep [155]. Myoclonic status epilepticus can arise in two forms [210]: (1) as part of the primary generalized status epilepticus and (2) as the type associated with acute or subacute encephalopathies. In both these conditions, the myoclonic status epilepticus is markedly attenuated during sleep [213]. Petit mal status or absence status epilepticus may be terminated during sleep [213]. Gastaut and Tassinari [214] demonstrated that NREM sleep disrupts the EEG discharges, which are replaced by polyspikes or polyspike-and-wave complexes or even isolated bursts of spikes. According to several authors [14, 215], there may be recurrence of absence status on awakening during the night or in the morning. Occasionally, the spike-and-wave discharges of petit mal status epilepticus may persist during NREM and REM sleep throughout the night [14]. In simple partial status epilepticus, both improvement and activation during sleep have been noted [213]. According to Froscher [213], the role of nocturnal sleep in complex partial status epilepticus remains unknown. Continuous spike and wave discharges during slow wave sleep (CSWS) is discussed in the next section.

Special Seizure Types Related to Sleep-Wake Cycle

In 2010, the International League Against Epilepsy published its revised terminology and concepts for organization of seizures and epilepsies. Generalized and focal are redefined for seizures as occurring in and rapidly engaging bilaterally distributed networks (generalized) and within networks limited to one hemisphere and either discretely localized or more widely distributed (focal). Classification of electroclinical syndromes is now more flexible and can be organized according to a specific purpose, for example age at onset, specific underlying cause or, as in this chapter according to vigilance state (sleep-related epileptic syndrome, Box 43.2) [216]. The second edition of the International Classification of Sleep Disorders [217] listed certain diagnostic criteria for sleep-related epilepsy (Box 44.3).

Box 44.2 Sleep-Related Epilepsies

Generalized Epilepsies and Syndromes

- Juvenile myoclonic epilepsy,
- Generalized tonic-clonic seizures on awakening,

- Tonic seizures (as component of Lennox–Gastaut syndrome).

Focal Epileptic Syndromes

- Benign epilepsy of childhood with centrotemporal spikes with or without occipital paroxysms,
- Nocturnal frontal lobe epilepsy,
- Autosomal dominant nocturnal frontal lobe epilepsy,
- Nocturnal temporal lobe epilepsy.

Undetermined (Focal or Generalized) Epileptic Syndromes

- Epilepsy with continuous spike-and-wave discharges during slow-wave sleep, or electrical status epilepticus,
- Landau–Kleffner syndrome or acquired epileptic aphasia.

Box 44.3 Diagnostic Criteria for Sleep Seizures

- More than 70 % of the episodes occur in sleep.
- Patient complains of one or more of the following:
- Sudden awakening,
- Abnormal sleep-related motor activities,
- Urinary incontinence,
- Tongue biting.
- Patient has two of the following features:
- Generalized tonic-clonic limb movements,
- Focal limb movement,
- Twitching of the face,
- Automatism,
- Postictal confusion and lethargy,
- PSG: ictal or interictal epileptiform discharge in any stage of sleep (an initial EEG may remain normal in many true cases of epilepsy),
- The symptoms do not meet the diagnostic criteria for another primary sleep disorder (e.g., RBD and partial arousal disorder).
- No medical, mental, or substance use disorder or medication use

PSG, polysomnography; RBD, rapid eye movement sleep behavior disorder.

Benign Epilepsy of Childhood with Centrotemporal Spikes

A clear description of BECTS, or benign focal epilepsy of childhood with rolandic spikes, was given by Nayrac and Beaussart in 1958 [218]. Later, Beaussart [219] drew attention to the benign nature of the condition. This is a childhood seizure occurring between 3 and 13 years of age, at an average age of onset of 7, seen mostly during drowsiness and sleep. The clinical seizures are characterized by focal clonic facial seizures often preceded by perioral numbness. In many cases, the patients have generalized tonic-clonic seizures that appear to be secondary generalization. On occasion, there is speech arrest. Consciousness is preserved. The EEG shows centrotemporal or rolandic spikes or sharp waves (Fig. 44.7) with a typical morphology of a triphasic sharp wave of high amplitude localized to the centrotemporal region but sometimes spreading to the contralateral hemisphere. Epileptiform discharges sometimes may occur outside the centrotemporal region and show occipital paroxysms in children exhibiting symptoms similar to those noted in BECTS [53]. The activation of interictal epileptic discharges (IEDs) by NREM sleep is a well-known feature of benign epilepsy of childhood with rolandic spikes. Authors agree in reporting a marked increase of IEDs during NREM sleep and a substantial reduction during REM sleep [220–224]. IEDs tend to be present throughout the night in each consecutive NREM cycles, showing a higher correlation with spindle frequency activity with respect to slow-wave activity time course [224]. The same correlation with spindle frequency activity was found also in other epileptic syndromes of childhood characterized by a marked activation of interictal spikes during sleep as the benign epilepsy with occipital paroxysms, the Landau–Kleffner syndrome, and the continuous spike-and-wave discharges during slow-wave sleep syndrome [225–227]. These findings suggest that the thalamocortical network that plays an important role in pacing sleep spindles in the generalized 3-Hz spike-and-wave discharges may also modulate focal discharges [82].

Indeed, it has been observed that local recurrent oscillatory activity and localized spike-and-wave discharges can be confined within a regional thalamocortical circuitry involving a circumscribed pool of neurons within the cortex [228, 229]. The above data suggest that subtle age-dependent dysfunctions of the thalamocortical system may play an important role in the pathophysiology of epileptic syndromes of childhood characterized by a marked activation of interictal spikes during sleep.

The prognosis of BECTS is generally excellent, with cessation of seizures by the age of approximately 16 years, without any neurologic sequelae and satisfactory response to anticonvulsant therapy. However, in some patients, the marked activation of IEDs during sleep may induce neuropsychological disorders [230]. For these reasons, as proposed in the 2010 Report of the ILAE Commission on Classification and Terminology, it would be better to replace the term “benign” with the term “self-limited” [216].

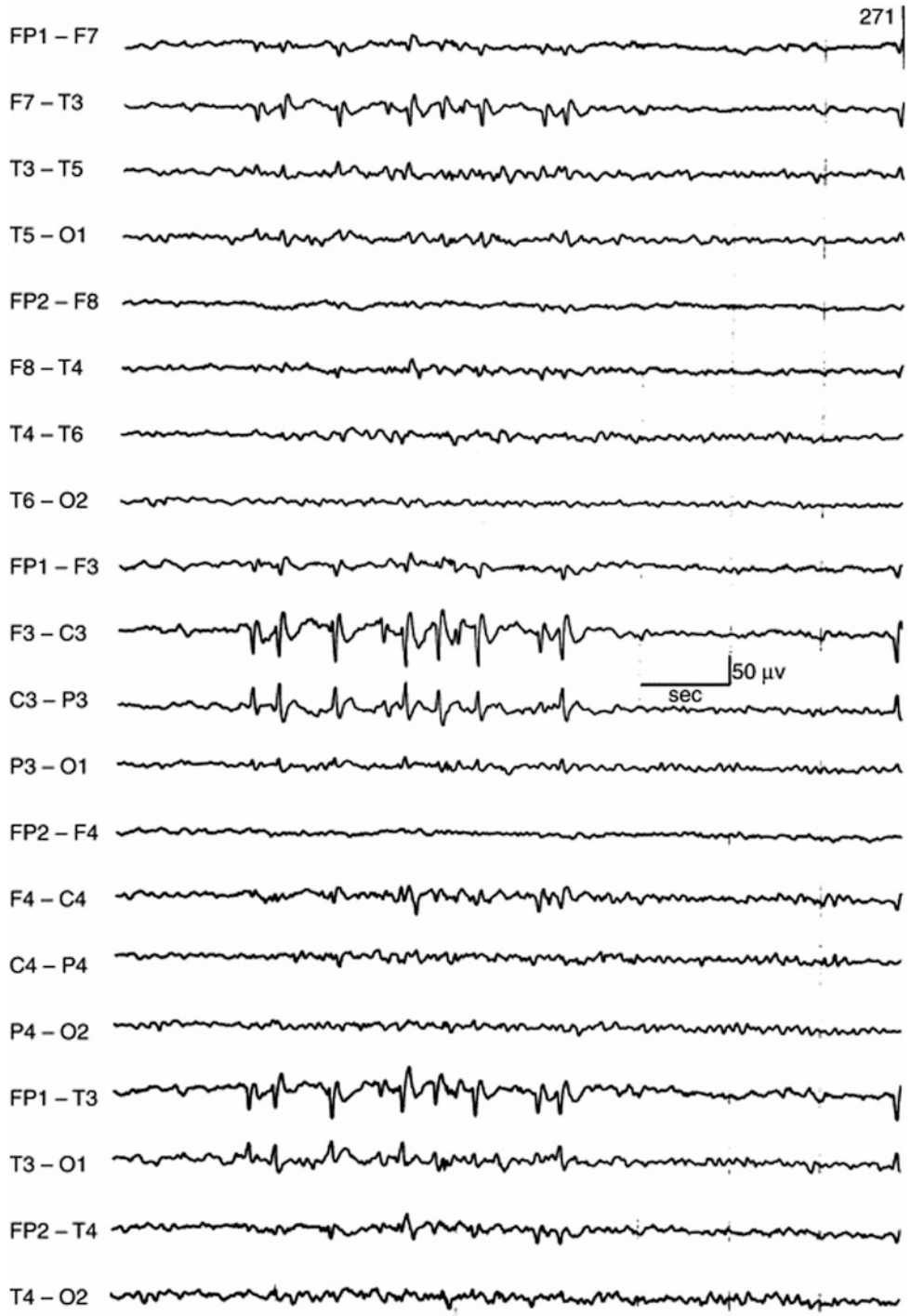

Fig. 44.7 Left centrotemporal spikes and sharp waves in patient with benign focal epilepsy of childhood with rolandic spikes

Juvenile Myoclonic Epilepsy of Janz

JME, an electroclinical syndrome, was described by Janz and Mathes [231] and later published in detail by Janz and Christian [232]. The onset of the syndrome is usually between 13 and 19 years and is manifested by massive bilaterally synchronous myoclonic jerks, which are most commonly seen in the morning shortly after awakening [232, 233]. The EEG is characterized by generalized spike-and-wave and typically multiple spike-and-wave discharges (see Fig. 44.3), seen in a synchronous and symmetric manner. Photosensitivity [234] and the phenomenon

of perioral myoclonia [235] of the lips, tongue, jaw, or throat (precipitated predominantly by talking) may occur in a large number of patients with JME. The excellent response to anticonvulsants makes this condition relatively benign, although not "self-limited" and easily distinguishable from the malignant syndrome of progressive myoclonus epilepsies.

Epileptic Syndrome with Generalized Tonic-Clonic Seizure on Awakening

Epileptic syndrome with generalized tonic-clonic seizure on awakening [233, 236] is manifested by the occurrence in the second decade of generalized tonic-clonic seizures on awakening from sleep. This is a rare syndrome, and clinically, there may be occasional absence or myoclonic manifestations and photosensitivity resembling JME. There is considerable overlap between generalized tonic-clonic seizures on awakening and JME. Patients with generalized tonic-clonic seizures on awakening should have had at least six generalized tonic-clonic seizures, and in JME patients, there are relatively frequent myoclonic jerks and infrequent generalized tonic-clonic seizures [94].

Continuous Spike-and-Wave Discharges During Slow-Wave Sleep

CSWS, formerly known as electrical status epilepticus during sleep (ESES), is a disease of childhood characterized by generalized continuous spike-and-wave EEG discharges during slow-wave sleep. All-night PSG study is necessary for diagnosis. The patients display progressive behavioral disturbances, although the seizures disappear within months or years. This entity is rare and found in children between 5 and 15 years of age. ESES was first described by Patry et al. [163] in 1971 in six children. Later, Tassinari and coworkers reviewed the literature and gave a comprehensive description of the entity [237–239]

Most of the patients had a prior history of epilepsy. The characteristic EEG finding consists of 2.0 to 2.5 cycles/sec generalized spike-and-wave discharges seen during at least 85 % of NREM sleep and suppressed during REM sleep (see Fig. 18.22a–c). Occasional bursts of spike-and-wave discharges or focal frontal spikes were noted during REM sleep. There were a few bursts of generalized spike-and-wave discharges seen in the EEG during wakefulness. These EEG discharges disrupted the stages of NREM sleep. In particular, the vertex sharp waves, K complexes, and spindles could not be well recognized. However, the cyclic pattern of REM-NREM persisted normally. Generally, there were no sleep disturbances, but some children had difficulty awakening in the morning. CSWS is now considered an epileptic encephalopathy of childhood characterized by cognitive and motor impairment and epilepsy [238, 239]. The etiologic heterogeneity of CSWS has been emphasized by Veggiotti et al. [240] and supported by a recent report of its presence in Rett syndrome [241]. The EEG findings of continuous epileptic discharges generally disappear within 3 years of appearance [237–239]. Focal abnormalities, in the EEG, may persist, however. It is not clear whether CSWS is a focal epilepsy or a generalized epilepsy with heterogeneous presentation, and hence, it is classified under the category of undetermined epileptic syndromes. Seizures show a benign course and respond well to antiepileptic medications, with disappearance of seizures by the mid-teens. The psychological impairment, however, persists.

Landau–Kleffner Syndrome

Landau–Kleffner syndrome (LKS) is an acquired aphasic syndrome occurring in a previously normal child and probably is a variant of CSWS [242]. The characteristic language dysfunction in LKS is an apparent "word deafness" or auditory verbal agnosia. There are many similarities between CSWS and LKS, and the type of neuropsychological dysfunction may depend on the location of the discharge (e.g., frontal in CSWS and temporal in LKS). Most CSWS patients have no evidence of language dysfunction. Approximately 70–80 % of children have seizures that are characterized by eyeblinking, head dropping, or minor automatisms with secondary generalization. These patients respond to antiepileptic medications and remain seizure-free by the mid-teens. The EEG pattern is similar to that noted in CSWS.

Nocturnal Temporal Lobe Epilepsy

Nocturnal temporal lobe epilepsy (NTLE) has not been well characterized. It has been described by Bernasconi and coinvestigators [243] in a subgroup of 26 patients with refractory temporal lobe epilepsy without structural lesion, with more than 90 % of seizures occurring during sleep. Focal seizures with transient impairment of consciousness, staring, automatism, and experiential or other sensory components occurring predominantly during sleep characterize the clinical syndrome. These simple partial staring seizures are frequently followed by secondary generalization. The following features differentiate patients with NTLE from the typical nonlesional temporal lobe epilepsy patients with diurnal seizures: a rare family history of epilepsy, low prevalence of childhood febrile seizures, infrequent and nonclustered seizures, and favorable surgical outcome [94, 243].

Nocturnal Frontal Lobe Epilepsy

In the early 1980s, Lugaresi and Cirignotta [244] and Lugaresi et al. [245] reported cases of paroxysmal attacks occurring during NREM sleep characterized by prominent motor behaviors in the form of dystonic posturing, tremors, and ballistic movements of the limbs, lasting 15 s to 2 min and not associated with epileptic abnormalities on the scalp EEG (Box 43.4). The attacks could respond to low doses of carbamazepine, posing the question of whether they represented epileptic seizures or sleep-related movement disorders. These attacks, termed *nocturnal paroxysmal dystonia*, were later demonstrated to represent a form of nocturnal frontal lobe epilepsy (NFLE) [245–248]. Nocturnal frontal lobe epilepsy (NFLE) is a syndrome of heterogeneous etiology as genetic, lesional, and cryptogenetic forms have been described. Although generally considered a benign clinical entity, severe, drug-resistant forms do exist [249].

Box 44.4 Nocturnal Frontal Lobe Epilepsy: Salient Features

- Movements: tonic, clonic, bipedal, bimanual, bicycling, choreoathetoid, ballismic,
- Retropelvic thrust,
- Motor and sexual automatisms,
- Contralateral dystonic posturing,
- Contralateral arm abduction with or without eye deviation,
- Oftentimes exclusively nocturnal,
- Sudden onset and termination in NREM sleep,
- Duration: usually less than a minute,
- Short postictal confusion,
- Often in clusters,
- Mistaken for nonepileptic seizures,
- Ictal EEG may be normal,
- Interictal EEG may or may not show spikes.

The spectrum of frontal lobe epilepsy manifestations include the so-called paroxysmal arousals, characterized by abrupt arousals from NREM sleep often accompanied by asymmetric tonic or dystonic posturing or complex movements such as pelvic thrusting, pedaling, choreoathetoid and ballistic movements of the limbs (Videos 1, 2, 3), lasting less than 20 s [250–252] and the so-called epileptic nocturnal wanderings (Video 4) [253, 254], more complex events lasting 2–4 min and associated with agitated ambulation and jumping about. Notably, paroxysmal arousals, often recurring quasi-periodically every 20–40 s for long stretches during NREM sleep, are often associated with attacks of nocturnal paroxysmal dystonia and epileptic nocturnal wanderings in the same patient and can represent the initial manifestations of the more prolonged attacks [255]. The increasing complexity of NFLE ictal motor behaviors, from minor to major events, reflects a different duration and propagation of the discharge within the frontal lobe [255, 256].

The peculiar features of NFLE thus consist of its nocturnal recurrence, related to NREM sleep stages in over 80 % of the seizures [257], and of the characteristic motor pattern with truncal and bipedal gross and often violent movements with dyskinetic features; the latter have led to the definition of hypermotor or hyperkinetic seizures.

Functional brain imaging in frontal lobe seizures (nocturnal paroxysmal dystonia and paroxysmal arousals) indeed confirms that the peculiar motor patterns are related to involvement of mesial, especially cingulate, motor areas [258, 259]. Studies with intracerebral electrodes (stereo-EEG) conducted in drug-resistant patients with NFLE have shown that the seizure onset in patients with asymmetric tonic or dystonic posturing is generally localized in the posterior portion of the frontal cingulate gyrus and in the posterior mesial frontal cortex with a primary involvement of the supplementary motor area [56, 260]. In patients with seizures characterized by hyperkinetic automatisms and complex motor behaviors, the region of seizure onset may involve the dorsolateral and anterior frontal regions (frontopolar and frontal anteromesial regions) [56, 261, 262]. Seizure characterized by the association between fear and nocturnal wandering seem to involve a cerebral network including the anterior cingulate, orbitopolar, and temporal regions [260, 263–265]. Moreover, it has been shown that "hypermotor seizures" may also be found in seizures originating from the temporal lobe and the insula [263, 266–269]. In such cases, the hyperkinetic features appeared 8–40 s after the beginning of the discharge in the temporal or insular regions, when the discharge spreads to other cortical structures such as the cingulate, frontal, and parietal cortices (Video 5) [266, 269]. Such a possibility of an extra-frontal origin of seizures renders the term NFLE somewhat misleading. Recently, in order to improve the definition of the disorder and establish well-defined diagnostic criteria, a consensus conference was held. It was recommended to change the name into "Sleep related Hypermotor Epilepsy (SHE)," considering that seizures are associated with sleep rather than time of day, seizures may arise outside the frontal lobe and the hypermotor aspects if the attacks are characteristic [270]. The etiology of SHE may be genetics, due to a cortical abnormality or unknown. Diagnostic criteria were developed with three levels of certainty: witnessed (possible) SHE, video-documented (clinical) SHE, and video-EEG-documented (confirmed) SHE. Due to the recurrence of nocturnal motor events, several NFLE patients may complain of non-restorative sleep and of daytime sleepiness [249, 257, 261].

Autosomal Dominant Nocturnal Frontal Lobe Epilepsy

Scheffer et al. [271] described an autosomal dominant form of frontal lobe epilepsy in six families. Brief motor seizures usually occurred in clusters during sleep. The disorder usually started in childhood and persisted through adult life. Patients were of normal intellect and had normal neurologic examination and neuroimaging. Response to carbamazepine was excellent. In most cases, interictal EEGs were normal, although one family with daytime attacks had epileptiform discharges. Video telemetry during the attacks confirmed their epileptic nature. They called this condition autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). The clinical features of ADNFLE were later confirmed by Thomas et al. [272] in one family with very frequent seizures during infancy, in which carbamazepine therapy again was dramatically effective, and by Oldani et al. [273], who studied 33 patients and found similar results. In 1995, Phillips et al. [274] mapped a gene responsible for ADNFLE in a large Australian kindred to chromosome 20q13.2, and Steinlein et al. [275] demonstrated that epileptic nocturnal frontal lobe (ENFL) type 1 was due to mutations in *CHRNA4*, the gene encoding the A4 subunit of the acetylcholine (ACh) neural receptor. Another linkage site was later reported to chromosome 15q24 accounting for ENFL type [2, 276] and mutations in *CHRNB2*, the gene encoding for the B2 subunit of the ACh neural receptor localized on chromosome 1 as accounting for ENFL type 3 [277]. Another linkage locus to chromosome 8p12.3-8q12.3 and a missense mutation in the gene *CHRNA2* encoding for the neural ACh receptor A2 subunit have been reported in familial seizures characterized by complex and finalized ictal behavior resembling epileptic nocturnal wanderings [264], as well as mutations in the corticotropin-releasing hormone gene [278].

Genetic findings thus implicate the nicotinic ACh receptors in ADNFLE. Mutations responsible for ADNFLE work by increasing the receptor sensitivity to ACh [279], indicating that a gain of function of the mutant receptors underlies the neuronal dysfunction responsible for the epileptic seizures. Mutated nicotinic receptors responsible for ADNFLE were also found to be more sensitive to carbamazepine, which works as a noncompetitive inhibitor of the nicotinic ACh receptors [280]. On the basis of the genetic findings and functional imaging data [281], the pathogenesis of ADNFLE has been attributed to dysfunction in the dorsal cholinergic ascending arousal system, and a common background with the arousal parasomnias has been hypothesized based on epidemiologic and clinical data [282, 283]. In animal models, it has been shown that a mutation of the nicotinic receptors may provoke an unbalanced excitation/inhibition circuitry within the GABAergic reticular thalamic neurons, thus favouring seizures through the synchronizing effect of spontaneous thalamocortical oscillations [96]. On the other hand, other experimental studies have reported an involvement of nAChR in the regulation of arousals, sleep stability, and the activity-rest pattern [95]. The observed genetic alterations in NFLE could create the conditions for both arousal instability and seizure generation [284].

However, ADNFLE is not only related to mutations in the cholinergic system. Since 2005, other genes, not belonging to the nACh receptor subunit family, have been identified. In particular, Combi et al. [278, 285] found mutations of the corticotropin-releasing hormone gene in sporadic and ADNFLE cases. The in vitro functional analysis of both variations demonstrated an altered level of protein expression suggesting an interrelation between CRH concentration and neuronal excitability with a possible effect on thalamocortical loop dysfunctions [278]. Very recently, a further CRH mutation has been found in the protein pro-sequence region of the CRH of two affected siblings of an Italian ADNFLE family [286]. In 2012, a further gene on chromosome 9 encoding the sodium-activated potassium channel subunit 1 (KCNT1) was associated with ADNFLE [287]. In particular, four variants in KCNT1 were identified in three families and in a sporadic ADNFLE case, all showing a severe ADNFLE phenotype with early onset, high prevalence of intellectual disabilities, and psychiatric or behavioral problems, including psychosis, catatonia, and aggression. Very recently, mutations in the DEPDC5 gene were reported as responsible for different types of focal epilepsies, including ADNFLE [288]. However, the prevalence of mutations in this gene remains to be assessed.

In summary, ADNFLE is a heterogeneous genetic syndrome that can be incidental to mutations in different genes. Mutations in these genes, however, account only for a minority of cases [289], and their mean penetrance ranges from 60 to 80 %. Hence, further studies are needed to better characterize this heterogeneous syndrome. Given the high intrafamilial variability and the overlapping features of the clinical manifestations, ADNFLE patients do not show a clear distinction from sporadic NFLE cases, except for certain ADNFLE mutations frequently associated with specific additional neurologic or psychiatric symptoms.

Effect of Sleep Deprivation on Epilepsy

The diagnostic value of sleep-deprived EEG has been well documented [190, 290–293]. What is the mechanism of activation during sleep deprivation? This is probably not a sampling effect and not related to sleep alone [290, 291, 293]. In a study using paired-pulse transcranial magnetic stimulation in 30 patients with untreated newly diagnosed epilepsy (15 idiopathic generalized and 15 focal epilepsies) and 13 healthy control subjects before and after sleep deprivation, Badawy et al. [70] noted an increase in cortical excitability following sleep deprivation at short interstimulus intervals. This change was most

prominent in the patients with idiopathic generalized epilepsy. Manganotti et al. [71] observed similar cortical hyperexcitability following sleep deprivation in a cohort of patients with juvenile myoclonic epilepsy. These findings confirmed the hypothesis that sleep deprivation increases cortical excitability in epilepsy. Sleep deprivation increases the epileptiform discharges mostly in the transition period between waking and light sleep and also has a localizing value [291, 293]. Although the original study by Rodin et al. [294] in 1962 found epileptiform discharges in healthy subjects after sleep deprivation, later studies [293, 295] failed to confirm these observations.

Rowan et al. [291] studied 43 consecutive patients using two types of activation: sleep deprivation (24 h in adults and partial deprivation in children) and sedated sleep (after oral secobarbital). They obtained useful information in 44 % of sleep-deprived as opposed to 14 % of sedated sleep records. The patients were referred because of doubtful diagnosis of epilepsy or because seizure types could not be determined. They also found sleep deprivation superior to sedated sleep for differentiating those with a final diagnosis of seizure. It should be noted that sleep alone does not explain the activating effect of sleep deprivation. The mechanism remains largely unknown. Experimental [65] and human studies [70, 71, 291] suggest an increased cerebral excitability after sleep deprivation. Degen [292] studied 127 waking and sleep EEGs after sleep deprivation in 120 epileptic patients on anticonvulsant medication. He found seizure activity in 63 % of the patients, although in the previous EEG records of these patients, only 19 % had shown seizure activity; thus, sleep deprivation increased the incidence of seizure activity. Approximately 48 % of discharges occurred during slow-wave and 25 % during REM sleep.

It is notable that in 1896, Patrick and Gilbert [296] apparently performed sleep deprivation studies in human beings. The studies by Bennett [297] in 1963 and Mattson et al. [298] in 1965 established the value of sleep deprivation as a diagnostic tool in patients with seizure disorders. Rodin [299] compiled the incidence of activation after sleep deprivation from an analysis of the literature and came up with a figure of approximately 45 %. Later studies by Frucht et al. [300], Roupakiotis et al. [301], and Teraita-Adrados et al. [302] confirmed the value of sleep deprivation in activating EEG epileptiform discharges. Recent studies [303] also supported that sleep deprivation activates ictal and interictal epileptiform discharges. There is, however, a contrasting observation by Malow et al. [304], who failed to note increasing seizure frequency after partial sleep deprivation in inpatient video-EEG monitoring in a group of 84 patients with medically refractory epilepsy.

Phenomena During Sleep that Can Be Mistaken for Epilepsy (Nonepileptiform Disorders)

Certain paroxysmal arousal disorders in NREM sleep may be mistaken for seizures, particularly for CPS. Some examples of these disorders are night terrors (pavor nocturnus), somnambulism (sleepwalking), confusional arousals, tooth grinding (bruxism), rhythmic movement disorder, benign sleep myoclonus of infancy, hypnagogic foot tremor, and nonepileptic seizure (nocturnal pseudo-seizure). Two other parasomnias usually associated with REM sleep, REM sleep behavior disorder (RBD), and nightmares (dream-anxiety attacks) may be mistaken for seizures. These conditions are listed in Box 43.5. Box 43.6 lists some salient features of nonepileptic seizures that may help differentiate this condition from a true seizure [305].

Box 44.5 Conditions That May Mimic Nocturnal Seizures

- Confusional arousals,
- Sleepwalking,
- Sleep terror,
- REM sleep behavior disorder,
- Rhythmic movement disorder,
- Tooth grinding (bruxism),
- Benign sleep myoclonus of infancy,
- Hypnagogic foot tremor,
- Nonepileptic seizure (nocturnal pseudo-seizure).

Box 44.6 Features of Nonepileptic Seizure (Pseudo-Seizure)

- Predominantly diurnal; sometimes nocturnal,
- Gradual onset and gradual termination,
- Prominent pelvic thrusting, mainly forward,
- Asynchronous (out-of-phase) clonic limb movements,
- Eyes usually closed,
- Prominent head movements (horizontal—"no-no"—or rotary),
- Lack of concern about symptoms (*la belle indifference*),
- Urinary incontinence and self-injury: extremely rare[308],
- Video-EEG: normal awake EEG.

Considering the similarities and the possible coexistence of parasomnias in people with NFLE [282], the diagnostic process may be challenging, especially if it is only based on anamnestic investigations. A reliable semeiological description of motor events occurring during the night is often difficult to collect

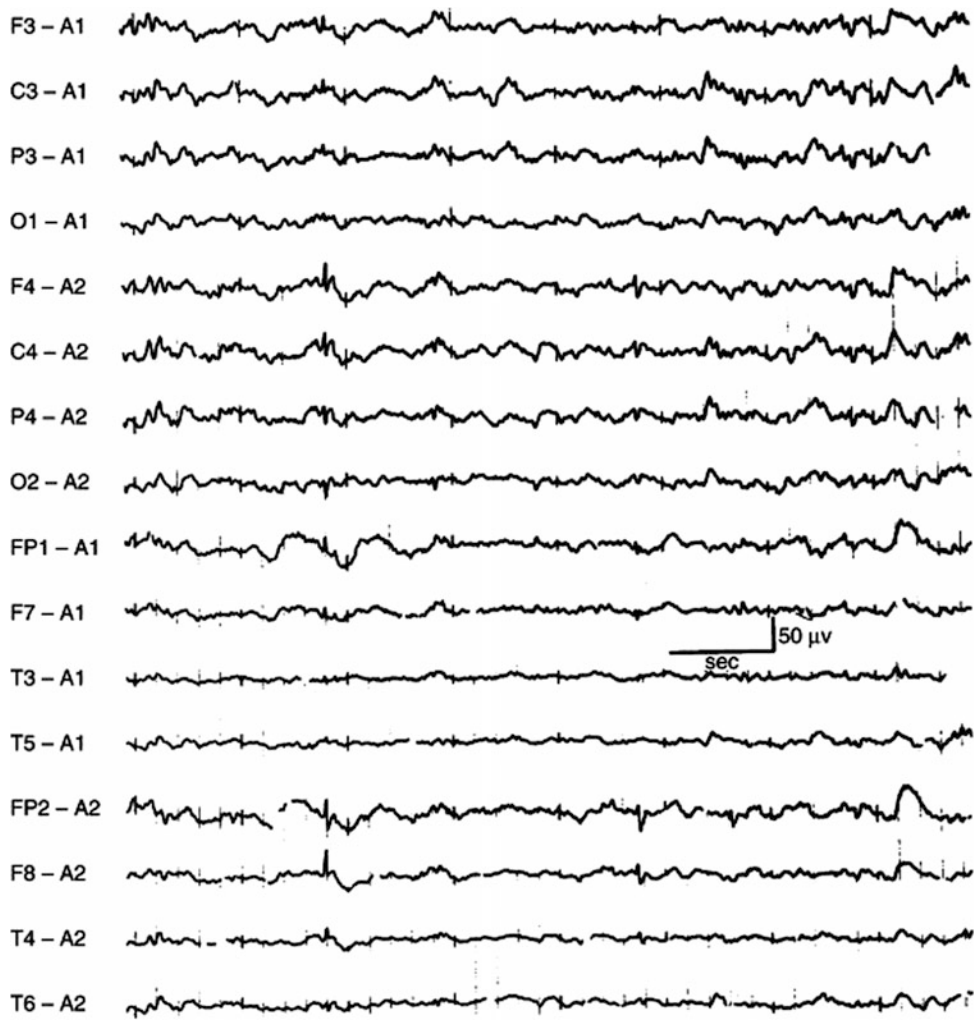

Fig. 44.8 Small sharp spikes (benign epileptiform transients of sleep) seen in channels 5–8 and 13–16 from the *top*

from a witness or sleep partner because observers may be lacking or, if present, not fully reliable or awake when attacks occur. Recent efforts to obtain a systematic assessment of the diagnostic reliability of clinical history have devised two instruments: the Frontal Lobe Epilepsy and Parasomnias Scale [306] and the Structured Interview for NFLE [307]. Albeit clinically useful, these tools are limited by contradictory diagnostic accuracy [249, 308]. Interictal EEGs fail to disclose epileptiform abnormalities in a substantial percentage of NFLE patients [257]. Moreover, small sharp spikes or benign epileptiform transients of sleep, as noted in the EEG (Fig. 44.8) in stages 1 and 2 NREM sleep, may resemble true epileptiform spikes even though the distribution, morphology, and occurrence during particular stages of sleep without any clinical accompaniments differentiate these from true epileptiform spikes [309]. On the other hand, the presence of EEG epileptiform discharges independent of nocturnal attacks may not be proof sine qua non that the attacks are of an epileptic nature [19]. Practical suggestions for differential diagnosis between the arousal parasomnias and NFLE seizures have been proposed [257, 306]: NFLE should be suspected if attacks recur several times during the same night; if they occur in a stereotyped fashion; if tremor, dystonia, or ballism are noted during the attack; if the attacks arise in or persist into adulthood; and if there is a good response to low doses of carbamazepine [310]. Unfortunately, however, these suggestions rely on expert opinion and are not validated against any "gold standard."

Sleep video-polysomnography is considered the "gold standard" diagnostic test; however, it does not always capture the event in a single-night recording. Moreover, even when the nocturnal episode has been recorded, the diagnosis remains doubtful because ictal scalp EEG fails to disclose epileptiform abnormalities, or because the episode captured is a minor motor event, like the so-called paroxysmal arousal (PA), for which the diagnosis is not reliable even among experts [311].

Recently, Derry et al. [312] conducted an accurate and systematic evaluation of parasomnias and NFLE seizures recorded on video-EEG monitoring in order to identify features

that could be used to reliably distinguish parasomnias from nocturnal frontal lobe epilepsy. They noticed that the discrepancy between historical account and recorded events were more prominent in NREM parasomnias than in NFLE; moreover, the clinical features of the initial arousal behaviors (abrupt or slow movements) were often indistinguishable between the two conditions. In contrast, the clinical features of the evolution and the offset of the events could better differentiate NFLE from parasomnias. Indeed, the presence of a coherent speech and a verbal interaction with the neighboring individuals during the episode, the possibility to modify the event by the actions of individuals present, and the absence of a clear and distinct offset of the attack were highly indicative of a NREM parasomnia. Despite the limits of V-PSG, the possibility of analyzing the video of the nocturnal attack remains an important diagnostic tool, making home video recording a useful adjunct when episodes are infrequent, even if the onset of the episode is missed [310, 313].

Effect of Epilepsy on Sleep

An objective evaluation of the states of sleep in epileptic patients reveals that they are altered in a large percentage of patients studied. Although the utility of sleep in the diagnosis of epilepsy is well established, the altered sleep characteristics in epileptics are not well known. One of the difficulties has been that most of the studies have been conducted in patients who have been on anticonvulsants, thus adding the confounding factors of the effect of anticonvulsants on sleep architecture. Furthermore, there have not been good longitudinal studies to determine the effect of epilepsy on sleep in the early versus late stages of the illness. Despite these limitations, there have been several studies from which a general consensus has been reached regarding the effect of epilepsy on sleep and sleep structure. A variety of sleep disturbances have been observed in epileptics and can be summarized as follows [177, 179, 201, 314]: a reduction in REM sleep; an increase in wake after sleep onset (WASO); increased instability of sleep states, such as unclassifiable sleep epochs; an increase in NREM stages 1 and 2; a decrease in NREM sleep stages 3 and 4; a reduction in the density of sleep spindles; and an increase of sleep-onset latency. A recent study conducted in drug-resistant epileptic patients has shown that surgery can improve subjective and objective (PSG-documented) sleep parameters during the early postoperative period with resultant reduction in excessive daytime sleepiness [315].

Box 44.7 lists effects of epilepsy on sleep architecture (macrostructure and microstructure). In patients with absence spells, sleep macrostructure may be normal, but microstructural alterations showing increased cyclic alternating patterns may have relevance to the postulated physiologic mechanism of spike-and-wave generation utilizing the same thalamocorticothalamic pathways that are used for sleep spindles and K complexes. Sleep structural alterations are related to frequency of nocturnal seizures and increased interictal epileptiform discharges during sleep. Severe sleep disruption related to spike-and-wave discharges may be partly responsible for cognitive impairment in epileptics, including patients with CSWS and LKS.

Box 44.7 Effect of Epilepsy on Sleep Architecture

- Increased sleep-onset latency,
- Increased number and duration of awakenings after sleep onset,
- Increased cyclic alternating pattern,
- Reduced sleep efficiency,
- Reduced sleep spindles and K complexes,
- Reduced REM sleep,
- Increased stage shifts,
- Abnormal sleep cycling,
- Sleep state instability (unclassifiable sleep epochs).

Nocturnal seizures may alter sleep architecture by five mechanisms: (1) effects of seizures (ictal discharges); (2) effects of interictal discharges; (3) effects of antiepileptic medications; (4) associated organic brain disorders; and (5) comorbid primary sleep disorders (e.g., sleep apnea, insomnia, and restless legs syndrome/periodic limb movements in sleep). Three questions may be asked regarding the effect of epilepsy on sleep:

1. Is sleep quality related to the duration and type of seizures?
2. Is sleep quality related to repeated episodes of seizures or poorly controlled seizures?
3. Can epilepsy lead to a sleep disorder?

These questions are discussed in the next sections.

Sleep Complaints in Patients with Epilepsy

Patients with epilepsy may complain of excessive daytime sleepiness (EDS), insomnia (inability to fall or maintain sleep and early morning awakening), and adverse daytime consequences related to insomnia and EDS, as well as unusual movements and behaviors intruding into sleep. EDS in epileptics may result from clinical seizures, particularly nocturnal seizures and ictal or interictal EEG epileptiform discharges; comorbid conditions such as obstructive sleep apnea syndrome (OSAS; see later) and polycystic ovary syndrome (PCOS); and effects of antiepileptic medications (see later). Box 44.8 lists causes of EDS in epileptic patients. Maganti et al. [316] reported that EDS and sleep complaints are common among adults with epilepsy, and in some patients, these

may be due to underlying sleep disorders such as sleep apnea. Khatami et al. [317] assessed sleep-wake habits and EDS using a standardized questionnaire in 100 consecutive outpatients with epilepsy and 90 controls. Sleep complaints were more common in epilepsy patients than in controls, and sleep maintenance insomnia and EDS were found frequently; they noted that loud snoring and restless legs symptoms are the only independent predictors of EDS in epilepsy patients. Jenssen et al. [318], based on a questionnaire and chart review of a tertiary referral center, noted subjective somnolence to be related mainly to depression rather than to obstructive sleep apnea (OSA) and other variables. A recent case–control study from Brazil [319] found that patients with epilepsy had more EDS, daytime dysfunction, and sleep disorders compared with a control group. In a systematic review of PubMed-cited articles from 2002 to 2012 (most studies were cross-sectional and questionnaire-based), Giorelli et al. [320] concluded that EDS was related more frequently to undiagnosed sleep disorders than to epilepsy-related factors.

Box 44.8 Causes of Excessive Daytime Sleepiness in Epileptics

- Clinical seizures, particularly nocturnal seizures,
- Frequent ictal and interictal epileptiform EEG discharges,
- Coexisting disorders (e.g., sleep apnea and polycystic ovary syndrome),
- Depression.

Manni and Terzaghi [321] described two elderly men with late-onset sleep-related tonic-clonic seizures and RBD. The authors hypothesized that RBD may facilitate seizure occurrence. In a later study, Manni et al. [322] reported co-occurrence of epileptic seizures and RBD in six cases. The authors cautioned that further investigations of the occurrence of RBD episodes and epilepsy are needed to understand the neurobiological significance of this comorbidity.

Relationship Between Seizure Type, Severity of Seizure, and Extent of Sleep Deficits

The relationship between seizure type, severity of seizure, and extent of sleep deficits remains somewhat controversial, and the reports are contradictory. WASO, sleep stage shifts, and sleep fragmentation are found in all seizure types [157, 314, 323–326]. Reduction of REM sleep and an increase in NREM stages 1 and 2 are in part dependent on the type of epilepsy. Declerck et al. [314] found an increase of NREM stages 1 and 2 and a reduction of REM sleep in 258 patients with primary generalized or partial seizures with secondary generalization as compared with 223 nonepileptic subjects. Seizure occurrence during sleep accentuates sleep deficits, which are more marked in primary generalized and partial seizures with secondary generalization than in other types. In 25 % of epileptics, Declerck et al. [314] could not evaluate PSG recordings because of severe encephalopathies associated with seizures. Similar findings were obtained by Bessett [157]. Baldy-Moulinier [323] noted a decrease of REM sleep in patients with CPS occurring during sleep. However, Baldy-Moulinier found markedly reduced REM sleep in patients having only one attack of secondary generalized seizure during the night. It is interesting to note that Bessett [157] in human epileptics and Baldy-Moulinier [323] in temporal lobe epilepsy models found no rebound REM sleep in subsequent recordings after REM sleep loss, which is contrary to the usual findings of REM rebound after REM deprivation. In summary, WASO and sleep fragmentation are found in all types of epilepsy, and generalized seizures are associated with an increase of NREM stages 1 and 2 and a reduction of REM sleep. In CPS, there is often REM reduction only. Besset [157] could not discriminate NREM stages or REM sleep in the EEG because of disrupted sleep architecture due to the seizures (ictal and interictal).

Hoeppner et al. [327] studied self-reported sleep disorder symptoms in epilepsy. They gave a questionnaire relating to six aspects of sleep: delayed sleep onset, night awakenings, dreams, night terrors, sleepwalking, and fatigue on awakening. They evaluated four groups of subjects: (1) Four patients with simple partial seizures, (2) 18 patients with CPS, (3) Eight patients with generalized seizures, and (4) 23 controls (14 women and 9 men aged 16–53 years). They found significantly more sleep disorder symptoms (particularly frequent awakenings at night) in patients with simple partial seizures and CPS. The generalized group behaved like the control group. Patients with the most frequent seizures, irrespective of type, had the most sleep disturbances.

Roder-Wanner et al. [328] obtained polygraphic sleep recordings in 43 patients with different types of epilepsies. They found that patients with generalized epilepsy had a higher percentage of deeper stages of sleep (NREM 3 and 4) than patients with focal epilepsy. These observations are correlated with the factor of photosensitivity, which was noted in a subgroup of these patients. The authors concluded that there was no real relationship between sleep structure and the type of epilepsy. Thus, there is some controversy regarding the relationship between seizure type and sleep. It can be concluded, however, that the severity of sleep deficits is in part correlated with severity of the seizure disorder. Animal studies support such a conclusion [329, 330]. In

previous studies, sleep structure abnormalities may have been related to clinical or subclinical seizure activity preceding the PSG investigation or to the medication received during the study.

There are contradictory reports regarding REM sleep disturbance [179]. On seizure-free nights, REM sleep is usually normal, but REM decrement is noted when there are primary or secondary generalized seizures during the night. There is no REM suppression during partial seizure without secondary generalization [157, 323]. Bowersox and Drucker-Colin [331] stated that increased cortical neuronal excitability and reduced seizure threshold may result from chronic REM sleep deprivation secondary to repeated and frequent nocturnal generalized seizures. In a recent review, Ng and Pavlova [332] hypothesized that desynchronized EEG with altered connectivity is responsible for seizure suppression in REM sleep. In fact, after reviewing several studies, Jaseja and Jaseja [333] observed a linear relationship between reduction of REM sleep and intractable or refractory epilepsy and postulated REM sleep duration as a biomarker for predicting intractability of seizure. The authors even made a novel suggestion of deep brain stimulation (specifically of pedunculopontine nucleus) as a novel therapeutic approach in intractable epilepsy to increase REM sleep percentage.

In a series of 15 patients with temporal lobe seizure disorders, Touchon et al. [334] found increased WASO, shifting of the sleep stages, and increases in NREM sleep stages 1 and 2. In a study of 23 patients with temporal lobe epilepsy, Kohsaka [335] found significantly decreased sleep efficiency and increased awakenings in both treated and untreated patients. He also noted increased NREM stage 4 in untreated patients compared to healthy controls. The site of the primary focus may determine the type of the sleep disturbances [18]. Foci in the amygdalohippocampal region may lead to increased WASO and decreased sleep efficiency. Frontal lobe epileptics, however, may show a specific reduction in stages 3 and 4 NREM sleep.

In a questionnaire-based study of 40 children with tuberous sclerosis, Hunt and Stores [336] found that concurrent epilepsy was significantly associated with sleep disturbances in these children. This observation was corroborated by Bruni et al. [337], who found a more disrupted sleep architecture in patients with tuberous sclerosis and epilepsy compared with seizure-free children. In large series of children with epilepsy, there was a correlation among seizure frequency, incidence of interictal epileptiform discharges, duration of seizure disorders, behavior problems, poor quality of sleep, and disturbed breathing during sleep [338, 339]. Becker et al. [340] noted that 80 % of 30 children complaining of sleep disturbance had PSG documentation of OSA, abnormal sleep architecture, and fragmentation.

de Weerd et al. [341] reported poor quality of life and sleep disturbances that were more common in adults with focal seizures with or without secondary generalization compared with controls. A variety of PSG-documented sleep abnormalities have been described in patients with JME [136, 342, 343] and focal temporal lobe epilepsy. Bazil et al. [136] documented reduction of REM sleep by seizures in temporal lobe epilepsy. Sleep abnormalities in absence seizures gave conflicting results [180]. In BECTS, no sleep architectural abnormalities are noted [42, 344].

Several authors have noted that sleep abnormalities are more common in patients with primary or secondary generalized seizures than in those with partial focal epilepsies [42, 344, 345], but other studies have shown that patients with severe or medically refractory temporal lobe seizures may have equally severe sleep structural abnormalities [343, 344]. Several investigators have reported severe sleep abnormalities in symptomatic epilepsies associated with neurologic deficits [166, 346–351]. In all of these patients, both sleep dysfunction and seizure disorders must be treated simultaneously to obtain best results.

In several reports, PSG findings and sleep abnormalities have been described in partial seizures, especially frontal lobe [352, 353] and temporal lobe [136, 353] seizures. Tachibana et al. [352] showed an improvement in sleep structure after treatment with appropriate antiepileptic drugs (AEDs) (Fig. 44.9).

Can Epilepsy Lead to a Sleep Disorder?

It is generally thought that sleep deficits in seizure disorders are secondary to the severity of the seizure disorder and are a direct result of seizures during sleep. However, studies by Tanaka and Naquet [354] demonstrated progressive sleep deficits in amygdala kindling models. In addition, the sleep deficits persisted one month after discontinuation of kindling procedures.

Shouse and Sterman [329] produced amygdala kindling in 10 adult cats and studied their sleep and waking patterns chronically. They found a progressive sleep disturbance and retention of the deficit over a prolonged period after termination of amygdala stimulation. These findings suggest the "kindling" of a sleep disturbance in addition to a seizure disorder. The authors further stated that sleep abnormalities cannot be viewed as a simple or temporary side effect of epileptiform activity. It appears that a permanent change in sleep physiology occurs in epilepsy. These observations of Shouse and Sterman [329] partially answer the question posed by Passouant [1]: "Can epilepsy lead to a sleep disorder?" Effective treatment of epilepsy with anticonvulsant

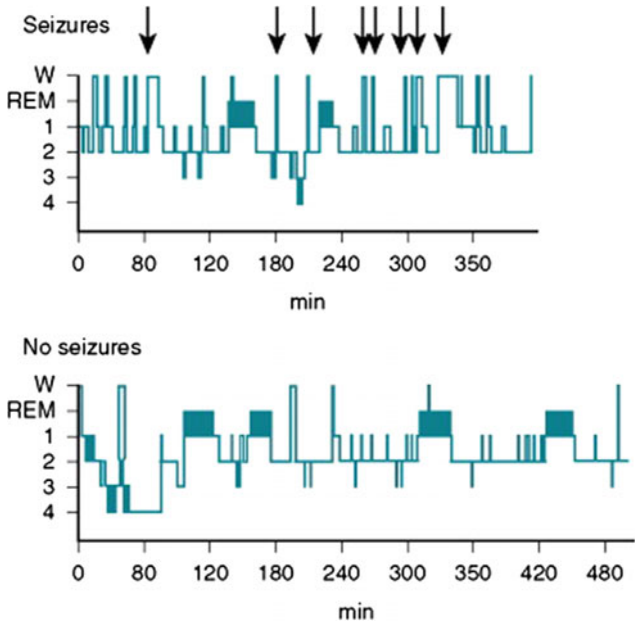

Fig. 44.9 *Top* Polysomnogram showing increased slow-wave and REM sleep along with frequent awakenings during the night with eight nocturnal seizures. *Bottom* Sleep architecture showing remarkable improvement in the same patient following treatment with carbamazepine. Modified from Tachibana et al. [352]

medications or surgical methods normalizes sleep disturbances in human epilepsy [325].

Can a Sleep Disorder Lead to Epilepsy?

In 1995, Silvestri et al. [355] reported six patients who were diagnosed in childhood as having disorders of arousal and later developed epileptic seizures. The sleep disorders consisted of sleepwalking and night terrors, all confirmed by PSG studies. The seizures noted were complex partial in five and generalized tonic-clonic in one. Nocturnal monitoring confirmed the epileptic nature of these events. The authors hypothesized that because both disorders of arousal and epilepsy are related to sleep and share other common factors such as age of onset and precipitating factors, these disorders share common functional substrates, and it is possible that disorders of arousal may later turn into epileptic seizures. It should be noted, however, that sleepwalking and sleep terrors are frequently noted in children, and seizures may simply coexist with these NREM parasomnias. Most sleep specialists and epileptologists simply do not believe that such parasomnias can later turn into epileptic seizures. It should also be remembered that cases of typical disorders of arousal not associated with epileptic discharges in epileptic children have been described [14, 162, 356].

Effect of Anticonvulsants on Sleep and Sleep Architecture in Epileptics

Malow et al. [357] noted increased Epworth Sleepiness Scale scores in 28 % of 158 adult epilepsy patients. Peled and Lavie [250] described bursts of generalized spike-and-wave complexes during stages 2 and 3 of NREM sleep, preceded by K complexes and associated with arousals causing sleep disruption and daytime sleepiness. Some patients with epilepsy may have EDS as a result of sleep apnea (see later) and PCOS, which is more common in women with epilepsy, especially those patients taking valproic acid, than those without epilepsy [358]. Betts et al. [359] reported 30 % of women treated with valproic acid, 6 % with lamotrigine or carbamazepine, and 14 % of age-matched controls with clinical and biochemical evidence of PCOS. PCOS is associated with increased prevalence of OSAS [196, 360].

Some patients with epilepsy may complain of insomnia, which may be difficulty falling asleep or maintaining sleep, or early morning awakening associated with adverse daytime consequences of sleepiness, inability to concentrate and pay attention, and impairment of the quality of life. Insomnia in epileptics may be related to sleep fragmentation and repeated arousal as a result of nocturnal seizures and interictal EEG epileptiform discharges, some AEDs, depression and anxiety, or withdrawal or tapering of AEDs during video-EEG monitoring for presurgical evaluation of refractory seizures or may be due to an associated primary sleep disorder (Box 43.9). Some AEDs (lamotrigine and felbamate) may cause insomnia. Sadler [361] reported a 6.4 % incidence of dose-dependent insomnia among patients taking lamotrigine. In contrast, Foldvary et al. [362] failed to observe any effect of lamotrigine in a PSG study in seven subjects with epilepsy on sleep efficiency, sleep latency, or total sleep time. The other antiepileptic medication that was found to have stimulant-like effects in patients with epilepsy is felbamate [363, 364]; however, because of serious toxicity, felbamate has largely been withdrawn from the market and is rarely used nowadays to treat epilepsy.

Box 44.9 Causes of Insomnia in Epileptics

- Nocturnal seizures and interictal epileptiform discharges causing repeated arousals,
- Some antiepileptic drugs (AEDs; e.g., lamotrigine and felbamate),
- Withdrawal or tapering of AEDs during video-EEG monitoring,
- Depression and anxiety,
- Associated primary sleep disorder.

There is a dearth of well-controlled, careful studies documenting the effects of anticonvulsant medications on sleep architecture that properly take into account the effects of seizures on sleep. Only limited data are available. It is somewhat daunting to study the effects of AEDs in epileptics taking into consideration all the confounding factors. Objectively, the sleep architecture should be studied by PSG recordings before starting the patient on medication—that is, in the drug-free state—and then restudied with the patient on chronic therapy with one rather than multiple drugs. From a practical point of view, this is somewhat difficult because when the patient presents to the physician, he or she must be treated before performing these investigations. Furthermore, the pharmacokinetic and pharmacodynamic effects of AEDs show considerable variation depending on the age and genetic predisposition. There may be a circadian effect of the drugs, and comorbid conditions may also affect sleep. Furthermore, AEDs may have residual effect on sleep architecture even after withdrawal of the medication [365]. Johnson [325] reviewed the literature up to about 1981 showing the effects of acute and chronic exposure to anticonvulsant drugs in relation to the sleep pattern. Acute exposure to anticonvulsants may reduce REM and NREM stages 3 and 4 and increase stage 2 NREM sleep. Acute and chronic drug trials in epileptics suggest that the main effects of anticonvulsants consist of sleep stabilization, however, which includes a reduction in WASO and an increase in NREM stages 2, 3, and 4, along with sleep spindle density. These improvements are concomitant with the reduction of seizures. The bulk of the evidence in the literature points to the fact that effective anticonvulsant treatment and seizure control result in reduction of sleep disturbance. Thus, the effects may be due to the reduction of seizures and not to any specific effect of the anticonvulsants on sleep architecture.

In a survey of experimental epilepsy in animals, Wauquier et al. [366] observed that sleep fragmentation as obtained in epileptic animals and in humans may be the consequence of microarousals. Anticonvulsants may suppress microarousals because of their sedative properties and hence lead to stabilization of sleep fragmentation and normalization of sleep. Anticonvulsants may normalize sleep, however, because of a specific action on particular abnormal EEG patterns. Thus, despite the suggestion that anticonvulsants themselves may be responsible in part for the fragmentation and disruption of sleep architecture, the general consensus is that anticonvulsant medications normalize sleep architecture, most probably by reduction of the seizures.

AEDs have both detrimental and beneficial effects [367]. Most AEDs, however, normalize and stabilize sleep [118, 325, 343, 368] due to the suppression of clinical seizures and interictal discharges or a direct consequence of AEDs. In addition, the AEDs may also have neuromodulatory effects causing sleep disruption [369–371]. Most of the first-generation AEDs may delay REM sleep onset or suppress REM sleep percentages [42, 326, 368]. Some AEDs cause weight gain [372] (e.g., valproic acid, vigabatrin, pregabalin, gabapentin, and probably also carbamazepine) and decrease upper airway muscle tone (e.g., benzodiazepines and phenobarbital), which may have deleterious effects on the upper airway muscles causing sleep apnea in some patients [42] (see later). The effects of AEDs in sleep can be divided into general effects consisting of reduction of REM and slow-wave sleep, reduction of sleep latency, increased percentage of NREM stages 1 and 2, and specific effects depending on the individual AEDs (Table 44.1). In the following paragraphs, effects of the traditional or first generation and some of the newer AEDs are briefly discussed.

Older Antiepileptic Drugs

In most of the studies, phenobarbital is found to increase stage 2 NREM sleep and decrease sleep-onset latency, REM sleep, and WASO without any significant effect on slow-wave sleep [346, 373, 374]. Wolf et al. [373] reviewed the literature to assess the effect of barbiturates, phenytoin, carbamazepine, and valproic acid treatment on sleep. They noted significant reduction of REM sleep, a reduction in total awake time, and an increase in NREM stage 2 sleep as the short-term effects of barbiturates. The long-term effects of barbiturates are similar in general, but in some cases, the sleep pattern returned to the premedication level. Wolf et al. [373] performed a prospective polygraphic study of sleep in epileptic patients before and after medications using a crossover design. They studied phenobarbital, phenytoin, ethosuximide, valproic acid, and carbamazepine. The authors included 40 unmedicated patients to study the effect of phenobarbital and phenytoin. The short-term effects of phenobarbital included reduction of WASO and REM sleep and increase of stage 2 NREM sleep. There was no relationship with the serum drug levels.

Manni et al. [375] performed an objective and subjective assessment of daytime sleepiness using the multiple sleep latency test (MSLT), clinical, and psychometric data on 10 patients with generalized epilepsy treated chronically with phenobarbital, 10 patients with cryptogenic partial epilepsy treated with carbamazepine, and 10 healthy controls. These authors found that patients on phenobarbital had a greater daytime sleep tendency and performed worse on the digit symbol substitution test compared to the other two groups. In a similarly designed study [376], they noted a shorter mean sleep latency in patients on phenobarbital compared with patients on sodium valproate and controls. Psychomotor functioning was also poor in patients on phenobarbital compared to controls, whereas patients on valproate had

Table 44.1 Effects of antiepileptic drugs (AEDs) on sleep architecture*

AEDs	SE	SI. LAT	Stage 1	Stage 2	SWS	REM	WASO
Phenobarbital	D	D	I	I	–	D	D
Phenytoin	D	D	I	I	D	–	D
Primidone	?	D	?	?	I	D	?
Carbamazepine	I	D	–	–	I	D (*Tr*)	D
Valproic acid	–	–	?	–	I	?	I
Ethosuximide	D	I	I	–	D	I	I
Benzodiazepines	D	D	D	I	D	?	D
Felbamate	D	?	?	?	?	?	?
Gabapentin	I	D	D	–	I	I	D
Lamotrigine	–	–	–	–	D	I	–
Levetiracetam	–	–	–	I	D	–	–
Oxcarbazepine	?	?	?	?	?	?	?
Pregabalin	I	D	–	–	I	–	D
Tiagabine	I	–	–	–	I	–	–
Topiramate	–	–	–	–	–	–	–
Zonisamide	?	?	?	?	?	?	?
Vigabatrin	?	–	?	?	?	?	?

D decreased; *I* increased; – no change; *?* unknown; *SE* sleep efficiency; *SI Lat* sleep latency; *SWS* slow-wave sleep; *WASO* wake after sleep onset; *D* (*Tr*) transiently decreased

some attentional impairment and a tendency toward longer motor movement time. However, they did not find a correlation between the assessed parameters and serum drug concentrations.

Phenytoin generally causes a reduction of sleep-onset latency, REM sleep, and slow-wave sleep as well as sleep efficiency, but causes increased stages 1 and 2 NREM sleep [351, 371]. Phenytoin also increases daytime sleepiness. The short-term effects of phenytoin included no change in the percentage of WASO, a decrease in NREM sleep stages 1 and 2, and an increase in sleep stages 3 and 4; there was no change in REM sleep and no relationship with the serum drug levels. Wolf et al. [373] studied the long-term effects of phenytoin in 12 patients. The long-term effects were in general a reversal of the short-term effects and consisted of an increase of NREM sleep stages 1 and 2 with a decrease of slow-wave sleep. REM sleep, however, remained unaltered.

Carbamazepine has been studied fairly extensively in various studies. This AED is found to increase sleep efficiency and slow-wave sleep but decrease REM sleep in healthy subjects [374] and transiently decrease REM in epileptics. Baldy-Moulinier [323] reported normalization of disturbed sleep pattern in temporal lobe epileptics after carbamazepine treatment. After acute carbamazepine administration in cats, Gigli et al. [377] reported an increase of NREM stage 1 sleep and total sleep time, a decrease of REM sleep, and reduced duration of awakenings. Some studies examined the effects of carbamazepine in treated versus untreated epileptic patients [334, 342, 343]. Studies in healthy normal subjects showed that carbamazepine can increase slow-wave sleep, decrease REM sleep, and consolidate sleep [378–380]. In some studies, the EEG effects in epileptics have been contradictory. For example, Legros and Bazil [371] failed to find any EEG effects during sleep in 10 epileptics treated with long-term carbamazepine, but Bell et al. [369] found increased slow-wave sleep and decreased stage 2 NREM sleep with carbamazepine monotherapy.

There have been very limited studies to describe effects of primidone on the sleep EEG. In one study using 30 healthy subjects, a single dose of primidone (250 mg) resulted in an increase of slow-wave sleep and a reduction in REM sleep [381]. Treating epileptic patients with 750 mg primidone daily for 3 months resulted in reduced sleep-onset latency and REM density but not percentage [382].

The effects of ethosuximide included disrupted sleep, increased sleep latency, increased stage 1 sleep, decreased slow-wave sleep, and increased REM sleep and awakenings [373, 383].

Valproic acid in general has minimal effects on sleep architecture in patients with epilepsy [368, 373–375, 384]. Findji and Catani [384] reported an improvement of sleep organization and increase of slow-wave sleep in epileptic children after treatment with valproic acid. At higher doses, however, Harding et al. [385] observed a decrease of delta and REM sleep.

The benzodiazepine group of drugs is generally used for status epilepticus (e.g., lorazepam, diazepam, and midazolam), but sometimes clonazepam is used in some

drug-resistant seizures and certain types of seizures (e.g., myoclonic seizures and Lennox–Gastaut syndrome). These drugs generally cause decreased sleep efficiency, sleep-onset latency, stage 1 NREM and slow-wave sleep, and arousals [325, 368, 386].

Newer Antiepileptic Drugs (AEDs)

Most of the traditional AEDs adversely affect nocturnal sleep, sleep architecture, and daytime vigilance, but newer AEDs in limited studies have shown minor and even positive effects [387].

Several newer AEDs have come onto the market to treat patients with seizure disorders; most of them have been indicated to use as add-on drugs, but some are being used as primary AEDs. These drugs have not been studied extensively to determine their effects on sleep architecture.

Felbamate is one of the earlier drugs in the newer generation but has largely been discontinued because of severe hepatotoxicity. This drug has been reported to cause insomnia in epileptic patients [363, 388].

Gabapentin was originally developed to treat seizure disorder, but later was found to be useful in many other conditions, such as neuropathic pain and restless legs syndrome/periodic limb movements in sleep. In healthy subjects, gabapentin increases slow-wave sleep [382, 389, 390]. Placidi et al. [391] studied the effects of long-term gabapentin treatment on nocturnal sleep in drug-resistant epileptics and observed an increase in slow-wave and REM sleep, and a reduction of arousals and stage 1 NREM sleep.

Lamotrigine has minimal effects on sleep in general [351, 371]. Lamotrigine may cause increased REM sleep and decreased slow-wave sleep [374]. Sadler [361] reported insomnia (difficulty initiating and maintaining sleep shortly after administration of the drug) requiring reduction in dosage or discontinuation of the drug in over 6 % of 109 patients treated with lamotrigine. This finding, however, was contradicted by Foldvary et al. [362], who did not find any insomnia in any of 10 adult patients with focal epilepsy on lamotrigine treatment.

Levetiracetam in general has minimal effect on sleep architecture in normal volunteers. Bell et al. [369] studied levetiracetam in normal volunteers and patients with epilepsy in a double-blind, placebo-controlled study. They found increased stage 2 NREM sleep in both epileptics and controls, and increased REM sleep latency only in the healthy subjects and decreased slow-wave sleep in patients. In a double-blind, crossover, placebo-controlled study in 14 healthy volunteers using PSG and the MSLT after oral administration of levetiracetam up to 2000 mg/day or placebo for 3 weeks, Cicolin et al. [392] found increased total sleep time and sleep efficiency and decreased WASO. MSLT findings did not differ between the two groups. The authors concluded that levetiracetam in healthy volunteers consolidated sleep without causing any daytime sleepiness.

Oxcarbazepine has not been adequately studied but has been noted to cause excessive sleepiness [346].

Pregabalin is a more recent AED and has been studied in a limited manner. Hindmarch et al. [393] studied 24 healthy volunteers and measured sleep objectively using PSG and subjectively using a questionnaire. Compared with the placebo, pregabalin significantly increased slow-wave sleep and reduced sleep-onset latency and REM sleep percentage. Subjective evaluation showed significant improvement in sleep quality, but ratings of behavior following awakening were impaired.

Tiagabine, a selective GABA reuptake inhibitor, has been used for partial and secondary generalized seizures. In healthy elderly subjects, tiagabine significantly increased slow-wave sleep and sleep efficiency [394, 395]. In patients with primary insomnia, tiagabine increased slow-wave sleep and reduced WASO in a dose-dependent manner [396, 397].

Topiramate, tiagabine, zonisamide, and vigabatrin, which are used in some partial secondary generalized seizures, especially in those not responding to other AEDs, have not been adequately tested to study the effects of these drugs on sleep architecture in epileptic patients. Bonanni et al. [370], following topiramate monotherapy in an open-label trial with 14 epileptics, found no difference in sleep architecture and daytime sleepiness as measured objectively by multiple sleep latency testing. Bonanni et al. [398] studied the effects of carbamazepine and vigabatrin on daytime sleepiness in patients with partial epilepsy by measuring with MSLT and overnight PSG. The results suggested that vigabatrin did not significantly affect sleep architecture in their patients with epilepsy. Vigabatrin treatment in medically refractory epilepsy, however, causes weight gain, making these patients susceptible to developing OSAS [399].

Lacosamide, a later generation novel AED used as an add-on therapy, has been shown in a small group of drug-resistant epileptics to have no detrimental effects on sleep quality and quantitative EEG characteristics [387]. The other more recently approved AEDs have not been studied to see the effects on sleep architecture.

Nonpharmacologic Treatment

Vagus nerve stimulation has been used with some success in patients with refractory or intractable seizure disorder. However, in addition to improving the seizure state and daytime alertness, vagus nerve stimulation caused sleep disordered breathing in some patients [400–403].

Summary

A survey of the literature thus reveals that we need more studies to understand the interactions among anticonvulsants, sleep, and epilepsy. Based on the literature and their own investigations, Declerck and Wauquier [368] emphasized the importance of the use and development of automatic methods to assess antiepileptic-induced sleep changes in patients with epilepsy. It may be that the anticonvulsants disrupt the circadian distribution of interictal discharges during the night, and this may have practical relevance in terms of treatment.

Sleep, Epilepsy, and Autonomic Dysfunction

There are a number of autonomic nervous system (ANS) changes, particularly involving the respiratory and cardiovascular systems, during sleep [404] (see also Chap. 11). Furthermore, epilepsy itself may cause changes in the ANS, and thus, there is a close interrelationship between sleep, epilepsy, and the ANS.

ANS changes involving the cardiovascular system during sleep consist of reduction of blood pressure and heart rate during NREM sleep and wide fluctuation of these during REM sleep [404]. Respiration shows considerable changes during NREM and in particular during REM sleep (see Chap. 11). Sleep adversely affects breathing, even in normal individuals, and often triggers seizures in epileptic patients. Knowledge of the central autonomic network makes it easy to understand why this relationship between ANS, sleep, circulation, and respiration exists [405, 406]. The nucleus tractus solitarius, a structure in the region of the medulla important for sleep and for cardiovascular and respiratory regulation, is reciprocally connected with the limbic-hypothalamic and other forebrain structures [405, 406] (see also Chap. 11). This connection explains why epileptic seizures triggered by the limbic-hypothalamic or other forebrain structures may interact with the cardiovascular and respiratory regulation during sleep. Respiratory dysrhythmia during generalized seizures, after seizure discharges in the limbic system, and after experimental stimulation of the limbic areas is documented [407]. The coexistence of sleep apnea and epilepsy, once thought to be rare, is increasingly recognized (see later).

It is well known that in generalized tonic-clonic seizures and CPS, transient abnormalities of ANS functions may occur and may consist of alterations in cardiac rhythm, blood pressure, and respiration [408]. In addition, it is well known that epileptiform discharges without any clinical accompaniments may produce a variety of autonomic abnormalities. In patients after electroconvulsive [409] treatment and in animal models after pentylenetetrazol injection [410], there are intense changes in blood pressure and cardiac rhythms. Similar changes have been observed in patients with focal temporal lobe discharges. Furthermore, the phenomenon of unexpected sudden death in patients with epilepsy [411, 412] may account for up to 15 % of deaths in epileptic patients and may be the result of some unexplained autonomic dysfunction affecting the cardiac rhythm (see further on).

Epilepsy and Sleep Apnea

The association between epilepsy and sleep apnea was once thought to be a rare combination; however, in 1981, Wyler and Weymuller [413] described a 26-year-old man with medically intractable CPS and upper airway OSA, whose seizure control improved after treatment of sleep apnea with tracheostomy. Since then, sleep apnea has been increasingly recognized as a comorbid condition of patients with epilepsy. Sleep, epilepsy, and breathing are all interrelated. Both sleep and seizures may adversely affect breathing, and disordered breathing during sleep may in turn adversely affect seizures. Also, while the cause of sudden unexpected death in epilepsy is not definitely known, it has been suggested that the combination of postictal central apnea and neurogenic pulmonary edema may be responsible [414]. There is sufficient theoretical justification for why epilepsy and sleep apnea may coexist. Sleep adversely affects breathing even in normal individuals; for example, sleep is associated with increased upper airway resistance, mild alveolar hypoventilation, mild hypoxemia and hypercapnia, impaired central chemosensitivity with decreased hypoxic and hypercapnic ventilatory responses, and decreased number of functioning medullary respiratory neurons (see Chap. 11). These adverse effects may cause sleep apnea or sleep-disordered breathing (SDB) in susceptible individuals such as patients with seizures. It is well known that sleep and sleep deprivation may trigger seizures in patients at risk.

There is clinical and experimental evidence to suggest that generalized seizures as well as seizure discharges in the limbic-hypothalamic system may cause SDB [405, 407]. Reciprocal connections between central respiratory neurons in the medulla (in the region of nucleus tractus solitarius) and the limbic-hypothalamic and other forebrain structures may explain why epileptic seizures triggered during sleep by the discharges in the limbic-hypothalamic and orbitofrontal regions may interfere with respiratory regulation, causing SDB [405]. Experimental stimulation in animals in the limbic area, including the orbitofrontal cortex, may cause respiratory dysrhythmia [407]. Stimulation of the limbic areas in humans, including that during depth recording, may cause SDB [407]. Furthermore, severe hypoxemia during prolonged seizure or status epilepticus may cause SDB. It

should also be remembered that apnea causing severe hypoxemia may trigger seizures in susceptible individuals during prolonged apnea. Sleep apnea, in most cases, however, does not trigger seizures in those who do not have a propensity toward epilepsy. Recurrent apneas during the night in patients with sleep apnea syndrome cause sleep fragmentation and sleep deprivation, which may trigger seizures in susceptible individuals. Other factors that may trigger seizures associated with sleep apnea include decreased cerebral blood flow in epileptics due to cardiac arrhythmias and decreased cardiac output. Some other factors contributing to sleep apnea in seizure patients include weight gain related to AEDs (e.g., valproate, carbamazepine, gabapentin, pregabalin, and vigabatrin) [374, 399, 415], alteration of upper airway muscle tone by AEDs, or endocrine disorders caused by AEDs.

The frequently quoted figure for the prevalence of sleep apnea from the Wisconsin Cohort Study by Young et al. [416] is 4 % in men and 2 % in women. However, the more recent study from the Wisconsin cohort data listed prevalence figures of moderate-to-severe OSAS (defining by an apnea-hypopnea index of >15 events per hour, all accompanied by excessive daytime sleepiness) at 10 % in men and 3 % in women among 30–49 years but 17 % in men and 9 % in women among 50–70 years [417]. An estimated prevalence of epilepsy in the general population is approximately 1 % [418]. Therefore, by chance association, some patients may have both sleep apnea and epilepsy. A perusal of the literature reveals a few scattered case reports and letters to the editor to document the coexistence of sleep apnea and epilepsy. Wyler and Weymuller [413] were the first to document improvement of both sleep apnea and seizures after tracheostomy treatment for OSAS. Daytime PSG recordings by Chokroverty et al. [419] documented obstructive, mixed, and central apneas in eight patients with partial complex seizures with secondary generalization. In a retrospective survey from a tertiary care sleep medicine division, we reported a prevalence of approximately 6 % of sleep apnea in epileptics [420]. This survey almost certainly underestimated the prevalence of seizure in sleep apnea patients, because the diagnosis was made on the basis of questionnaire only and not by direct interview. Many patients did not answer all relevant questions. Our survey, however, is somewhat similar to the retrospective survey by Sonka et al. [421] that included 480 adult patients with sleep apnea syndrome, 19 of whom (4 %) had a history of seizures. Devinsky et al. [422] reported an improvement in seizure frequency and severity in six of seven patients with refractory partial epilepsy and sleep apnea after treatment. Vaughn et al. [423] identified 10 patients with recurrent seizures and OSA. Following continuous positive airway pressure (CPAP) and positional therapy, there was considerable reduction of seizure frequency. Koh et al. [424] reported improvement of seizure control after treatment of sleep apnea in children with neurodevelopmental disorders and intractable epilepsy. Malow et al. [425] documented OSA in one-third of 39 patients with medically refractory epilepsy undergoing PSG prior to epilepsy surgery. They concluded that sleep apnea is common among men, older subjects, and those with nocturnal seizures.

In a retrospective review of 63 adult epilepsy patients who had PSGs, Malow et al. [426] identified 45 (71 %) with obstructive sleep apnea. Twenty-eight patients with OSA were treated with CPAP, and most reported improvement in seizure control. Subsequent studies by Malow et al. [415, 427] confirmed this improvement of OSA in epileptics after CPAP therapy. Chihorek et al. [415] provided evidence that OSA is a risk factor for epilepsy in older adults and its treatment by CPAP may improve seizure control in this population. The limitation of this study is the small number of patients in each group (11 with late-onset or worsening seizures and 10 seizure-free individuals over the age of 50 years), but this is an important study that should encourage larger prospective studies in the future documenting increasing association of OSA with epilepsy and the effect of treating OSA. In a more recent study, Malow et al. [427] randomized 22 adult subjects with medically refractory epilepsy and coexisting OSA to therapeutic CPAP therapy and 13 similar subjects to sham CPAP. Based on their observations of a significant reduction of the apnea-hypopnea index in the therapeutic group as compared to the sham group, the authors concluded that this pilot study provided valuable information for designing a comprehensive trial to test the hypothesis that treating OSA in epileptics would improve seizure control. Recent results from Cleveland Clinic Group of treating OSA in epileptics with CPAP titration reinforced this conclusion [428]. These authors studied 76 patients with epilepsy and OSA, 43 of which had CPAP titration but 33 were not on CPAP treatment (declined or could not tolerate). The percentage with 50 % or more seizure reduction and the mean percentage of seizure reduction were greater in those on CPAP than in those not on therapy. The literature survey thus gives a high prevalence of sleep apnea in epilepsy and documented improvement of seizure control following effective treatment of sleep apnea [357, 415, 427–433].

SUDEP and Sleep

In epileptic patients, especially in those with pharmacoresistant epilepsy, the risk of sudden unexpected death (SUDEP) is 24–40 times higher with respect to the general population [434, 435]. SUDEP is considered to be the result of a peri-ictal concurrence of a number of predisposing and

precipitating factors [436]; nevertheless, SUDEP is primarily a sleep-related phenomenon, and sleep-related seizures seem to be an independent risk factor for SUDEP [437]. Autonomic factors such as cardiac or respiratory dysfunctions, or both, have been implicated in SUDEP; however, conclusive evidence on their role is still lacking and how they might be related to one another or to an epileptic seizure, eventually leading to sudden death, has not been elucidated yet [438].

Different factors could explain the higher susceptibility to death during sleep-related seizures [436–440]: (a) Seizure-related increase in heart rate is especially evident when seizures occur during sleep and in clusters [439], (b) seizures during sleep could create an extreme autonomic imbalance with a sudden switch from a predominant vagal tone to an extreme sympathetic tone [438], (c) the sympathetic overstimulation due to an abrupt withdrawal of AEDs is especially evident during sleep [440], (d) a comorbidity with obstructive sleep apneas could further increase seizure-related arrhythmias and respiratory complications [439, 441], and (e) the prone position might increase the risk of a mechanical obstruction of the nose and mouth [442].

Utility of Sleep in the Diagnosis of Epilepsy

Utility of sleep in the diagnosis of epilepsy was well established after the landmark paper by Gibbs and Gibbs [12] in 1947 showing activation of epileptiform discharges in the sleep EEG. For the diagnosis of epilepsy, the following sleep recordings are recommended: (1) a standard sleep EEG recording, (2) an EEG recording after sleep deprivation, (3) an all-night PSG study, (4) a video-PSG study, (5) an MSLT, and (6) a 24-h ambulatory EEG and sleep recording. Box 44.10 outlines a suggested protocol for EEG recording in patients suspected to have epilepsy.

Box 44.10 Suggested Protocol for Electroencephalography Recording in Patients Suspected of Epilepsy

1. Routine EEG recording with hyperventilation and photic stimulation.
2. If negative for interictal epileptiform activity (IEA), EEG with sleep (natural or induced) recording.
3. If negative for IEA, EEG study with partial (at least 4 h) or total (24 h) sleep deprivation.
4. If negative for IEA after three to four EEGs, prolonged (4- to 6-h) daytime EEG with sleep recording.
5. If negative for IEA, overnight polysomnographic (PSG) study, preferably video-PSG study for electroclinical correlation. Change the monitor speed to 30 mm/s instead of the usual sleep recording speed of 10 mm/s during interpretation of the recording. Use appropriately devised seizure montage with full complement of electrodes (see Chaps. 17 and 18) or special electrode placements (e.g., T1 and T2 electrodes).
6. If still negative for IEA, ambulatory 24-h EEG recording.
7. If still negative for IEA, long-term video-EEG monitoring for 24–72 h or longer if necessary.
8. Finally, in some patients, invasive intracranial EEG monitoring using subdural grids, strips, or depth electrodes may be necessary for localizing and lateralizing a focus.

Sleep EEG Recording and Sleep Deprivation Study

The usefulness of sleep EEG recording and sleep deprivation is discussed in detail in the previous paragraphs. For such recordings, a full complement of electrodes should be used and various montages have been suggested (see Chap. 18). Broughton [19] listed some of the main indications and objectives of sleep EEG recording as follows: (1) normal EEGs in patients suspected of epilepsy to establish the diagnosis of true epilepsy; (2) normal waking EEGs in patients with known epilepsy to clarify the type of epilepsy; (3) patients with febrile convulsions showing normal waking EEGs; (4) assessment of the familial predisposition to epilepsy in family members; and (5) assessment of the degree of drug control, for example, in patients with hypsarrhythmia.

Interictal EEG findings can help in the confirmation of the diagnosis of epilepsy, in the classification of seizures, and in the identification of specific epileptic syndromes. Epilepsy is a clinical diagnosis, and a single normal EEG in a patient with suspected epilepsy does not exclude the diagnosis of true epilepsy. The reason for a normal EEG in such a patient may be a sampling problem or the fact that the epileptic foci are located in a deeper brain region (e.g., orbitofrontal and medial interhemispheric region). Surface electrodes may not pick up these discharges located in a deeper site. A third reason may be that the EEG recording was obtained without the benefit of sleep or sleep deprivation. In such patients, the protocol suggested in Box 43.10 should be followed. The EEG findings may help in the classification of seizures. Bilateral synchronous spikes or spike-and-wave complexes in the interictal EEGs suggest primary generalized epilepsy. Particular characteristics of generalized epileptiform discharges may help in diagnosing certain epileptic syndromes (e.g., slow spike-and-wave discharges seen synchronously and symmetrically in the Lennox–Gastaut syndrome;

multiple transient spike-and-wave discharges in JME); focal spikes present consistently in one location may correlate with partial epilepsy.

All-Night Polysomnographic Recording

Broughton [19] listed the following important indications to perform all-night PSG study:

1. To differentiate between epileptic and nonepileptic nocturnal events (e.g., pseudo-seizures, syncope due to cardiac arrhythmias, and parasomnias),
2. To clarify the classification in patients with known sleep epilepsies,
3. To diagnose CSWS,
4. To diagnose benign epilepsy of childhood with rolandic spikes,
5. To lateralize or localize the principal focus during REM sleep by the use of stereo-EEG (this may be important before surgical treatment is considered),
6. To unmask the primary focus in a patient with secondary bilateral synchrony during REM sleep by causing suppression of the generalized discharges,
7. To reveal abnormalities in patients with hypsarrhythmia, for whom waking EEGs rarely may be normal but sleep EEGs may, and to clarify focal abnormalities in such patients,
8. To diagnose tonic seizures in patients with Lennox–Gastaut syndrome,
9. To diagnose sleep apnea or other primary sleep disorders, which may be mistaken for or associated with epilepsy,
10. To investigate patients complaining of excessive daytime somnolence that cannot be explained by their anticonvulsant medication.

Two additional indications are (1) to document cardiac arrhythmias that may arise during sleep and may be confused with, or even give rise to, seizures and (2) to document sleep disturbances and sleep architecture in epileptics so that these disturbances may be treated to prevent chronic sleep deprivation, which may in turn have deleterious effects on epilepsy itself. In suspected seizure disorders, all-night PSG recording should include multiple EEG leads and special montages. Figure 44.10 is a representative sample showing upper airway OSA in a patient with CPS and sleep apnea.

Video-Polysomnographic Study

The value of video-PSG for the diagnosis of parasomnias and seizure disorders has been well documented by Aldrich and Jahnke [443] (see also Chap. 26). Figure 44.11 is a PSG showing the onset of a partial seizure recorded at 10 and 30 mm/s paper speed.

Multiple Sleep Latency Test

The MSLT [444, 445] is indicated in patients complaining of EDS that is not explained on the basis of anticonvulsant medication. Seizure during sleep may lead to repeated arousals, causing EDS with further increase of seizure frequency, thus creating a vicious cycle. Sometimes, narcolepsy may be mistaken for epilepsy, and an important diagnostic test for narcolepsy is the MSLT. Finally, as discussed earlier, patients with epilepsy may have sleep apnea, which can be diagnosed by showing reduced sleep-onset latency on the MSLT that is causing EDS.

Ambulatory 24-h EEG Recording and Sleep Scoring

Ambulatory 24-h EEG recording and sleep scoring allow for recording of the EEG discharges throughout the day to understand the circadian and ultradian rhythmicity and the effects of sleep on the interictal discharges. The question of whether epilepsy manifests biorhythmicity was discussed earlier. Technical problems associated with unattended recordings, however, are serious limitations. Ambulatory EEG recording permits 24 h of continuous recording in patient's normal day-to-day environment. This type of recording is valuable in documenting interictal epileptiform discharges in the presence of normal routine EEGs. The presence of movement and muscle artifacts and lack of video documentation of the behavior are distinct disadvantages of ambulatory recording.

Long-Term Video-EEG Monitoring

In some patients, simultaneous video and EEG monitoring in the inpatient unit for several days is necessary to document an ictal epileptiform discharge and its characteristic behavioral correlate, thus providing indisputable evidence of a true

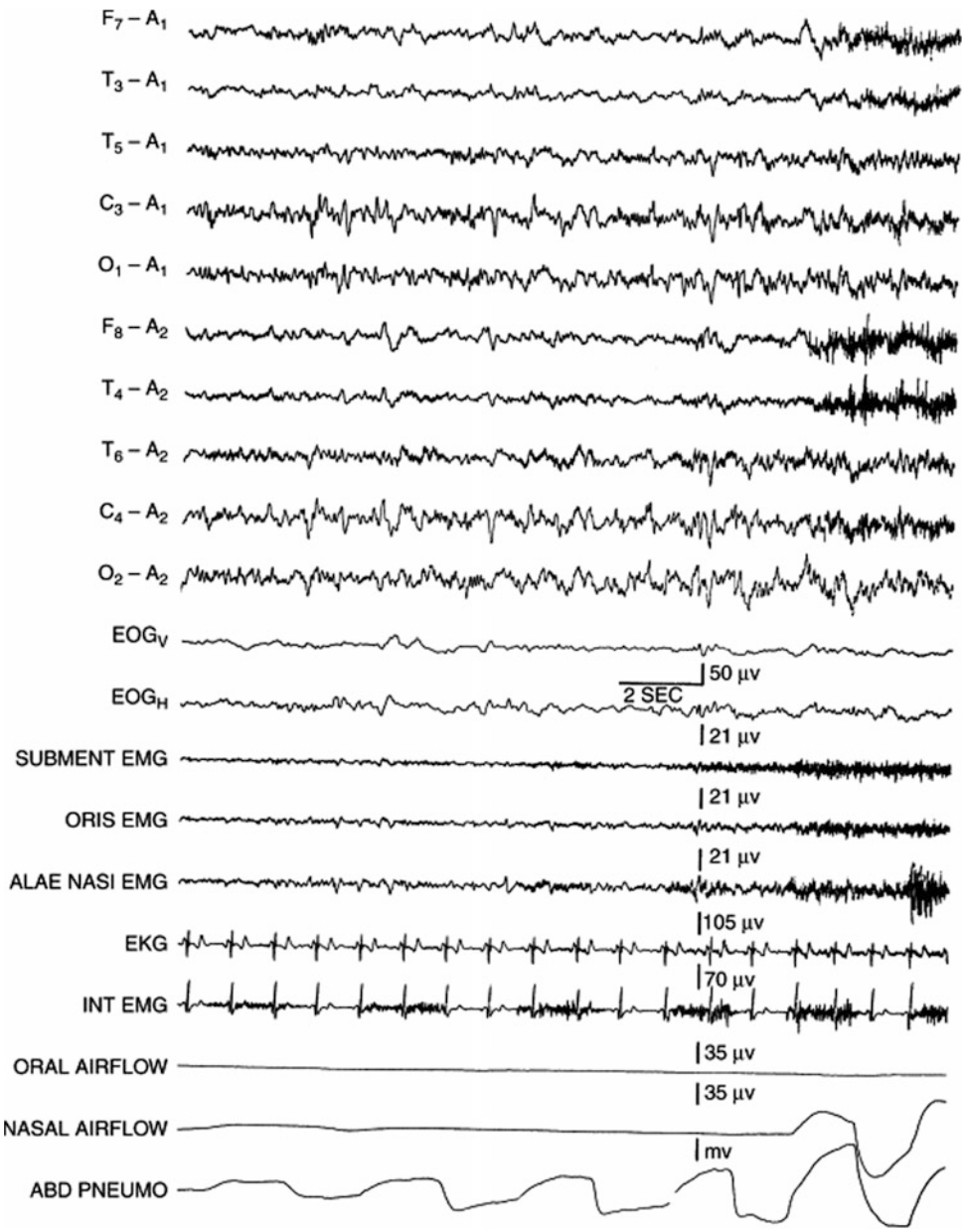

Fig. 44.10 Polysomnographic recording in a patient with partial complex seizure and sleep apnea showing EEG (top 10 channels); vertical (EOG_V) and horizontal (EOG_H) electrooculograms; submental (*SUBMENT*), orbicularis oris (*ORIS*), alae nasi, and intercostal (*INT*) electromyograms (*EMG*); electrocardiogram (*EKG*); oral and nasal airflow; and abdominal pneumogram (*ABD PNEUMO*). Note upper airway obstructive apnea during NREM stage 2 sleep. No epileptiform discharges are seen in the EEG during the episodes. Paper speed is 15 mm/s

seizure episode. Documentation of an ictal epileptiform discharge during long-term video-EEG monitoring permits unambiguous evidence of the presence of true seizure. Persistent normal background EEG activity (alpha rhythm in an adult) and absence of postictal slowing after an apparent seizure episode are inconsistent with a diagnosis of true seizure.

Intracranial Recordings

When the results of EEG, including long-term monitoring and neuroimaging (see later), are discordant in localizing the focus, drug-resistant patients with focal epilepsy should be referred to a specialized epilepsy surgery center for evaluating the possibility of an intracerebral electrophysiologic investigation. Different tools are used to record results of intracranial EEG procedures, depending on a given center's philosophy. The most widely used devices are subdural electrodes arranged in strips or grids according to each patient's needs [446]. They allow an extensive coverage of the cortical surface, but sampling of deep-seated structures is prevented. Intracerebral electrodes are used to record from lesions in deep structures (amygdala, hippocampus, cortex within sulci, and on the mesial portion of the hemispheres) [447], and they provide information from a limited volume of tissue. Other less invasive techniques involve epidural [448] and foramen ovale electrodes [449].

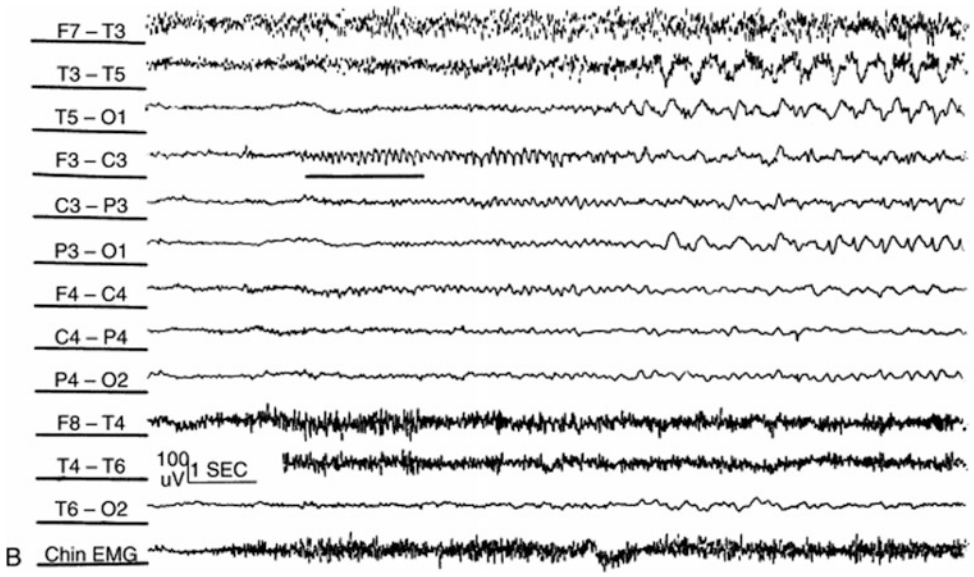

Fig. 44.11 A portion of a PSG recording using 12 channels of EEG showing the onset of a partial seizure recorded at 10 mm/s paper speed. The *underlined* activity represents rhythmic ictal discharges beginning over the left hemisphere (F3-C3) and spreading rapidly to the right hemisphere and is accompanied by clinical seizure. Although at 10 mm/s paper speed (**a**), the *underlined* activity superficially resembles muscle artifacts, at 30 mm/s paper speed (**b**), it becomes obvious that this activity is the beginning of the rhythmic epileptiform discharges in the EEG. Reproduced with the permission from Aldrich and Jahnke [443]

Neuroimaging

Neuroimaging studies are indispensable in investigating the presence of structural lesions that may serve as epileptogenic foci. Anatomic studies (computed tomography and magnetic resonance imaging of the brain) are usually performed in all adults with new-onset seizures and in children without any characteristic epileptic syndromes to identify any structural brain disorders. Specialty magnetic resonance imaging of the brain is more sensitive than computed tomography, and that is the preferred procedure.

Functional or physiologic studies (single-photon-emission computed tomography and positron-emission tomography) may be able to identify seizure foci by revealing areas of cerebral hypermetabolism or hyperperfusion during an ictal episode and areas of hypometabolism during the interictal period.

Practical Relevance to Understanding the Relationship Between Sleep and Epilepsy

An understanding of the relationship between sleep and epilepsy is important for three main purposes:

1. Such an understanding can aid in the diagnosis of seizure and in differential diagnosis between epileptic and nonepileptic events and among different types of seizures.
2. An understanding of this relationship can increase the understanding of the pathogenesis of triggering mechanisms of seizures during sleep and the mechanism and nature of sleep disturbances induced by epilepsy.
3. Therapeutic manipulation can be guided by the knowledge obtained through an understanding of the relationship between epilepsy and sleep. It may be possible to adjust the timing of the drug dose, but this really has not been useful from a practical point of view. An understanding of the biorhythmicity and the relationship between sleep and epilepsy may be important to choosing the type of anticonvulsant, so that one may avoid those with marked hypnotic effects in nocturnal seizure patients and use drugs with less sedative effects (e.g., carbamazepine, valproic acid, and lamotrigine). Finally, one may manipulate sleep stages—that is, give anticonvulsants that may increase REM or NREM stages 3 and 4—to reduce the ictal or interictal discharges.

Finally, as Broughton [19] stated, it may be necessary to put some patients on a strict program of sleep hygiene (see Box 26.17 in Chap. 26) or to treat the sleep disorders with pharmacologic agents because of the deleterious effects the epilepsy has on sleep and sleep on epilepsy. Such patients may be advised to avoid sleep deprivation, alcohol in the evening, and late evening exercise and to maintain regular sleep and waking hours. Broughton [19] suggested that the improvement of nocturnal sleep after such a regimen may be

associated with definite reduction of seizure frequency and overall improvement in general well-being.

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Dreaming in Neurological Disorders

45

Mark Solms, Susan Malcolm-Smith, and Danyal Wainstein

Background

Historically, there has been little systematic investigation of changes in dreaming due to neurological damage, despite numerous clinical reports of marked abnormalities. Accordingly, the subject remains poorly understood. This reflects the lack of development in the field of dream research itself: an understanding of the brain mechanisms of dreaming has lagged behind that of other mental functions. There are two main reasons for this. First, unlike most mental functions that were the focus of nineteenth and twentieth century behavioural neuroscience, dreaming is almost entirely subjective. The observable data are retrospective, single-witness qualitative descriptions, only indirectly related to the phenomenon of dreaming itself. This poses special methodological problems.

The second reason for the undeveloped state of this field is closely related to the first. Researchers seeking an objective approach to dreaming eagerly alighted on a physiological state that correlates closely with it—namely rapid-eye-movement (REM) sleep [1–4]. This physiological state was then conflated with dreaming itself, resulting in the development of neuropsychological models of dreaming which were in fact models of REM sleep [5]. This conflation was compounded by the fact that the models were empirically grounded in animal studies (where dream reports are of course precluded) rather than human lesion studies of the kind that informed models of most other mental functions. When the conventional human lesion studies were belatedly performed, it became apparent that dreaming and REM sleep are in fact doubly dissociable states [6].

A traditional neuropsychology or behavioural neurology grounded in the systematic application of clinico-anatomical correlation—which was widely applied to other mental functions since the mid-nineteenth century—is little more than 20 years old in the case of dreaming. Incidental reports of changes in dreaming associated with focal cerebral damage did nevertheless accumulate in the literature over a long period, albeit without any attempt to synthesise the scattered observations into a coherent picture. Systematic clinico-anatomical group studies were first published in the 1980s [7–9]. The available evidence was not comprehensively reviewed before the 1990s [10–12]. The clinico-anatomical studies have since been complemented by a slew of functional brain imaging studies, with strongly convergent findings [13]. Rigorous pharmacological probes of the neurochemistry of dreaming (as opposed to REM sleep) have not yet been conducted [14].

An understanding of the brain mechanisms of dreaming is now beginning to emerge. Systematic observation of abnormalities of dreaming in neurological disease has contributed fundamentally to this emerging picture. The bewildering array of abnormalities may perhaps best be grouped under two headings: (1) deficits of dreaming and (2) excesses of dreaming.

Deficits of Dreaming

The earliest clinical observations of changes in dreaming with neurological disease concerned *cessation* of dreaming (or cessation of aspects of dreaming). The terms 'Charcot–Wilbrand syndrome' and 'anoneira' have been used to describe this abnormality, which is typically (but not exclusively) seen in the acute phase of posterior cortical pathology.

Charcot–Wilbrand Syndrome

The concept of this syndrome, based on two case reports by Charcot [15, 16] and Wilbrand [17, 18] was first articulated by Pötzl [19]. He defined the syndrome as 'mind-blindness with disturbance of optic imagination' (p. 306). Nielsen [20]

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defined it as 'visual agnosia plus loss of the ability to revisualise' (p. 74). Critchley's [21] widely cited definition was:

> a patient loses the power to conjure up visual images or memories, and furthermore, ceases to dream during his sleeping hours. (p. 311)

Critchley described prosopagnosia and topographical agnosia or topographical amnesia as associated features. The localisation of the lesion producing this syndrome was never precisely defined, but the occipital cortex was implicated by most early authors (especially area 19)—usually bilaterally. The Charcot–Wilbrand syndrome remained in late twentieth century nosographical usage, although the condition was (until recently) considered rare. A reasonably modern definition of the syndrome reads:

> the association of loss of the ability to conjure up visual images or memories and the loss of dreaming … [indicating] a lesion in an acute phase affecting the posterior regions. (Murri et al. 1984, p. 185) [8]

Deficient revisualisation (called 'irreminiscence' in the nomenclature of Nielsen [20]) was the fundamental deficit in almost all definitions of the syndrome. Cessation of dreaming ('or at least, an alteration in the vivid visual component of the dreaming state'; Critchley [21], p. 311) was seen as a secondary consequence of the visual imagery deficit. The associated visual agnosias, too, were originally considered to be caused by defective revisualisation, since visual agnosia was classically understood as a loss of 'visual memory images' [21, 22].

Subsequent advances in the agnosia concept, and a misreading of the original case reports, have resulted in considerable nosological confusion regarding this syndrome [12, 23]. It is widely assumed that Wilbrand's case—an elderly female patient with bilateral posterior cerebral artery thrombosis—could not *visualise* familiar places [20, 21, 24, 25]. However the original report stated only that she was unable to *recognise* familiar places. This symptom (which we would today call topographical *agnosia*) was conceptualised, in accordance with classical theory, as a disorder of 'topographical *memory*' [17] (Wilbrand 1887, p. 52, emphasis added). This conceptualisation was then misconstrued by secondary authors as a disorder of topographical *revisualisation*. The original report reveals that Wilbrand's case actually lacked the cardinal feature of the so-called Charcot–Wilbrand syndrome. As the patient herself clearly stated: 'With my eyes shut I see my old Hamburg in front of me again' [15, 16] (Wilbrand 1887, p. 56). Charcot's case [15, 16]—also a probable PCA thrombosis (autopsy findings were lacking)—was quite different. He described a striking absence of visual mental imagery. The Charcot–Wilbrand syndrome is therefore misnamed.

It is also misconceived. Charcot's [15, 16] patient ceased to dream in visual images, but he continued to dream in words. Wilbrand's [17, 18] patient, on the other hand, dreamed 'almost not at all anymore' (p. 54). The original report is ambiguous as to whether Wilbrand's patient merely dreamed infrequently or actually lost the capacity to dream completely (and then gradually recovered it), but either way, there is no question of an isolated loss of *visual* dream imagery, which is what Charcot's patient unequivocally described. The 'Charcot–Wilbrand syndrome' therefore appears to be two different (but related) syndromes, one characterised by loss of *visual* dream imagery and the other by *global* cessation or suppression of dreaming. This distinction is supported by a review of the world literature [12].

Charcot's Variant: Isolated Loss of Visual Dream Imagery

At least 10 case reports of isolated loss of visual dream imagery have been published, together with five further reports of patients who experienced deficits of specific *aspects* of visual dream imagery (e.g., colour, movement, faces). Cessation of visual imagery or aspects thereof results from various pathologies, usually of acute onset (thrombosis, haemorrhage, trauma, CO poisoning) but it has also been described in cases of neoplasm, probable Alzheimer's disease, calossal dysgenesis, and Turner's syndrome). The lesion is typically localized to the mesial occipito-temporal or lateral occipito-parietal regions, and is usually bilateral, but precise localising information is often lacking [12, 15, 25–40].

Defective revisualisation (irreminiscence) is a constant feature in these cases, although it is typically restricted to the disordered aspect of vision (e.g. colour, movement, faces) in cases where the loss of visual dream imagery is partial. This strongly suggests a common underlying image-generation deficit causing the same disorder in both waking and dreaming cognition. Various forms of visual agnosia are commonly associated features, but agnosia is definitely absent in some cases and therefore cannot be considered integral to the syndrome [12].

Most published reports of deficits in visual dream imagery derive from retrospective accounts in a clinical setting. However, the reports have been confirmed directly upon REM awakening in at least three cases [21, 32, 34].

Negative Findings

Notably, modality-specific deficits of dream imagery outside the higher visual sphere have never been demonstrated. Thus, although achromatopsic, akinetopsic, prosopagnosic and hemineglect disorders are duplicated in dreams, cortically blind and hemianopic patients invariably report normal vision (full fields) in their dreams. Moreover, hemiplegic patients experience normal somatomotor and somatosensory functions in their dream imagery (as do acute-phase paraplegic and quadriplegic patients). The same applies to the extrapyramidal movement disorders. Similarly, nonfluent aphasics claim to speak normally in their dreams [12].

Of related interest, perhaps, is the fact that the dreams of patients with substantial impairments of executive function due to dorsolateral prefrontal lesions are indistinguishable from the dreams of controls (Badenhorst and Solms, unpublished observation). These findings point to a differentiated network of forebrain structures involved in dream cognition.

Wilbrand's Variant: Global Loss or Suppression of Dreaming

At least 106 cases of global loss or suppression of dreaming have been reported, excluding leucotomy cases which will be discussed separately (see Solms [12] for a full listing of these cases). A larger number of cases in group studies, for which individual case data were lacking, and where 'not dreaming' was defined in variable ways [7–9] have also been reported.

As with Charcot's variant, global anoneira is typically—but not invariably—associated with acute onset, focal cerebral lesions (thrombosis, haemorrhage and trauma are the most commonly reported pathologies). The first systematic attempt to identify the lesion site responsible for global cessation of dreaming pointed to the inferior parietal lobule [12]. Unilateral lesions of either hemisphere were shown to be commonplace, with no lateralising bias. However, at least two cases have since been reported in which the parietal lobe was apparently spared [41, 42], as indeed it appears to have been in Wilbrand's original case [18]. A re-analysis of Solms' data by Yu [43] revealed that the lesions in his 'parietal' cases almost always extended into adjacent occipito-temporal tissues (especially Brodmann areas 22, 19 and 37). It is therefore still not possible to make a more precise localising statement than the one offered by Murri et al. ([8], p. 185): 'a lesion in an acute phase affecting the posterior regions'.

The reference to an *acute phase* is not superfluous. Solms [12] observed that almost all cases of global anoneira recover the capacity to dream within 12 months. This fact, which suggests diaschetic effects, may help explain the imprecise localisation of the causal lesion.

Of particular clinical interest is Solms' [12] observation that hydrocephalus is associated with cessation of dreaming, which recovers after successful VP shunting. Cessation of dreaming might therefore be used as an indicator of shunt malfunction.

Defective revisualisation (irreminiscence) is a relatively common but by no means invariable feature of these cases. It was over-represented in the earlier case reports for the probable reason that patients were only asked about their dreams once irreminiscence had been established. The more recent cases reported by Solms [12] were part of an unselected clinical series and are therefore more likely to be representative. Global cessation of dreaming (unlike visually deficient dreaming) therefore cannot be reduced to irreminiscence.

Not surprisingly, considering the lesion site, global anoneira is frequently associated with disorders of spatial cognition, including visuospatial short term memory [12]. The lack of association between cessation of dreaming and *long term* memory disorder of any kind excludes the possibility that cessation of dreaming is really a memory disorder—failure to remember dreams as opposed to cessation of dreaming per se [44–46]. This applies also to the various language disorders that were previously thought to explain loss of dreaming [10, 47–50]. In his systematic survey, Solms [12] found no relationship between language disorder of any kind and reported cessation of dreaming.

Retrospective reports of absence of dreaming on morning awakening have repeatedly been confirmed by the REM awakening method [41, 42, 51, 52]. This further supports the assumption that this disorder concerns cessation of dreaming per se, as opposed to loss of *memory* for dreams. Even severe amnesiacs with bilateral hippocampal lesions report dreams on awakening from REM sleep and at sleep onset (Ramachandran 2004 [personal communication]) [53, 54].

Cessation or Suppression of Dreaming Following Prefrontal Leucotomy

In a survey of 200 cases of prefrontal leucotomy, Frank [55] observed that a common result of the procedure was 'a poverty or entire lack of dreams' (p. 508). In a later report on the same series of cases, then comprising more than 300 patients, he confirmed this finding [57]. Replication of Frank's observations findings was forthcoming from other authors [24, 57–60] (Slater cited in Humphreys and Zangwill [61]). Moreover, Jus et al. [57] confirmed the absence of dream reports following prefrontal leucotomy by the REM awakening method.

In apparent contradiction to these reports, however, Humphrey and Zangwill [61], Cathala et al. [7], Murri et al. [8, 9] and Doricchi and Violani [10] all observed a relatively *low* incidence of cessation of dreaming with anterior versus posterior cerebral lesions. The same applies to the observation reported above to the effect that the dreams of frontal patients are indistinguishable from those of controls (Badenhorst and Solms, unpublished observations). This apparent contradiction was resolved when Solms [12] reviewed the lesions in the previously reported cases and described nine new cases with cessation of dreaming following naturally occurring bifrontal lesions. His conclusion was that dreaming was entirely spared with *dorsolateral* prefrontal cortical lesions, and affected only with deep *white matter* lesions in the ventromesial quadrant of the frontal lobes (see Figs. 45.1 and 45.2). The lesion site in his nine cases coincided exactly with the area that was targeted by prefrontal leucotomy: 'a circumscribed lesion just anterior to the frontal horns of the ventricle, in the lower medial quadrant of the frontal lobes' [62] (Walsh 1994, p. 177). A re-analysis of the original data in 35 cases from Solms' [12] series with global cessation of dreaming associated with subcortical lesions revealed that the lesion was located in either the deep frontal white matter (areas F09 and F14 in the classification of Damasio and Damasio [63]; see Fig. 45.3), or the head of the caudate nucleus, or both [64]. The lesion is typically bilateral. Of theoretical importance is the fact that the region defined as 'head of the caudate nucleus' in this study included the nucleus accumbens (which is situated immediately beneath it).

It is noteworthy that the psychotropic medications that replaced prefrontal leucotomy as the treatment of choice for psychotic disorders, block dopamine (DA) transmission in a mesial forebrain pathway that projects primarily to the nucleus accumbens. Probably related to this is the observation that both prefrontal leucotomy in general and cessation of dreaming in particular, due to lesions in this general area, are associated with reduced motivational incentive [12] as indeed are most antipsychotic medications [65]. Also of interest in this connection is the observation by Piehler [59] and Schindler [60] to the effect that early recovery of dreaming after prefrontal leucotomy typically coincided with psychiatric relapse, suggesting that absence of dreaming could serve as an index of the clinical success of the operation. Dreaming is, after all, a psychotic state.

Effects of Pontine Brainstem Lesions

Cessation of dreaming following circumscribed pontine lesions—with or without cessation of REM sleep—has never been demonstrated (see Solms [6, 12] for reviews), despite the longstanding assumption that dreaming is caused by—if not identical with—the cyclical, spontaneous activation of cholinergic (ACh) cells in the mesopontine tegmentum during the REM state, together with reciprocal inhibition of serotonergic (5HT) and noradrenergic (NA) cells in the dorsal raphe and locus coeruleus complex [66, 67]. Consciousness in general is of course frequently compromised by pontine lesions, but at least eight cases with cessation or near-cessation of REM sleep have been reported in which patients were capable of communicating meaningfully about their dreams [68–71]. Indeed, one such patient did actually report loss of dreaming [68], but the lesion—caused by ruptured traumatic aneurysm of the basilar artery—almost certainly extended beyond the pontine brainstem and included the visual–spatial cortical areas discussed above. Even this isolated case therefore does not support the old equation of pontine brainstem mechanisms with dream generation. (The relationship between dreaming and REM sleep is discussed further below.)

Neuroimaging and Transcranial Magnetic Stimulation Studies Related to Dreaming

Neuroimaging studies have determined patterns of regional brain activation and deactivation during REM sleep, the stage of sleep during which dream reports are most frequently obtained [72]. These patterns of activity are highly consistent with those areas of the brain linked with dreaming by the clinical lesions studies reviewed above. Significant increases in regional brain activity have been observed in the basal forebrain and other limbic and paralimbic structures, including the hippocampal complex, the anterior cingulate cortex and the pontine tegmentum, during REM sleep [73–75].

Furthermore, Braun et al. [76] reported a dissociated pattern of activity between visual association areas (extrastriate cortices—fusiform, inferotemporal, and ventral lateral occipital) and primary visual areas (striate cortices) during REM sleep compared with slow-wave sleep. Activation within the visual association cortices was also shown to correlate positively with activity within parahippocampal gyri and contiguous portions of the hippocampus, and with deactivation of dorsolateral and orbital prefrontal association areas. Based on these findings, the authors concluded that 'during REM sleep, the extrastriate cortices and paralimbic areas to which they project may be operating as a closed system, functionally disconnected from frontal regions in which the highest order integration of visual information takes place. Such a dissociation could explain many of the experiential features of dreams' (p. 94). This notion of a closed loop between certain medial forebrain and limbic regions and higher order visual association areas is consistent with Solms's [6, 12] suggestion that dreaming is a

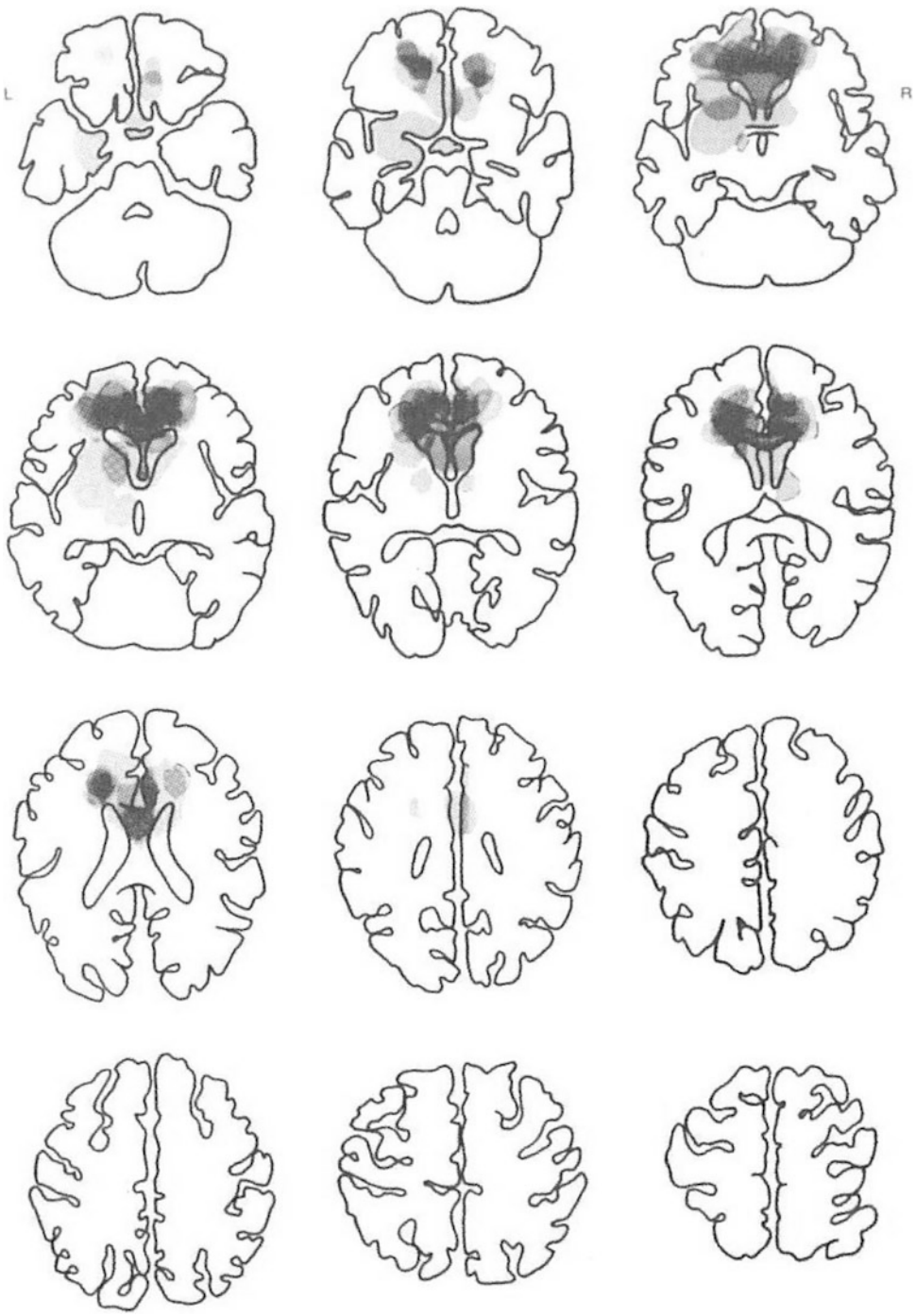

Fig. 45.1 Combined facsimile of scans in nine cases with global cessation of dreaming caused by deep frontal lesions, illustrating the strong involvement of the white matter surrounding the frontal horns of the lateral ventricles [12]

product of deep frontal structures activating higher visual association areas during sleep, instead of the executive and motor areas they activate during waking, thereby generating imaginary (versus real) action.

A recent study, using [15O]H_2O PET in healthy subjects with habitually high and low dream recall frequencies, also showed that high dream recallers—compared with low dream recallers—had greater regional cerebral blood flow in the temporal–parietal junction during slow wave sleep, REM sleep, and waking, as well as greater regional cerebral blood flow in the medial prefrontal cortex during REM sleep and waking [77]. These brain regions are highly consistent with those identified by lesion studies as being critically related to the dream process. As the temporal–parietal junction may facilitate the orientation of attention during sleep to external stimuli, it has been argued that the increase in activation of this region may be responsible for the observed increase in intrasleep wakefulness in high dream recallers. According to

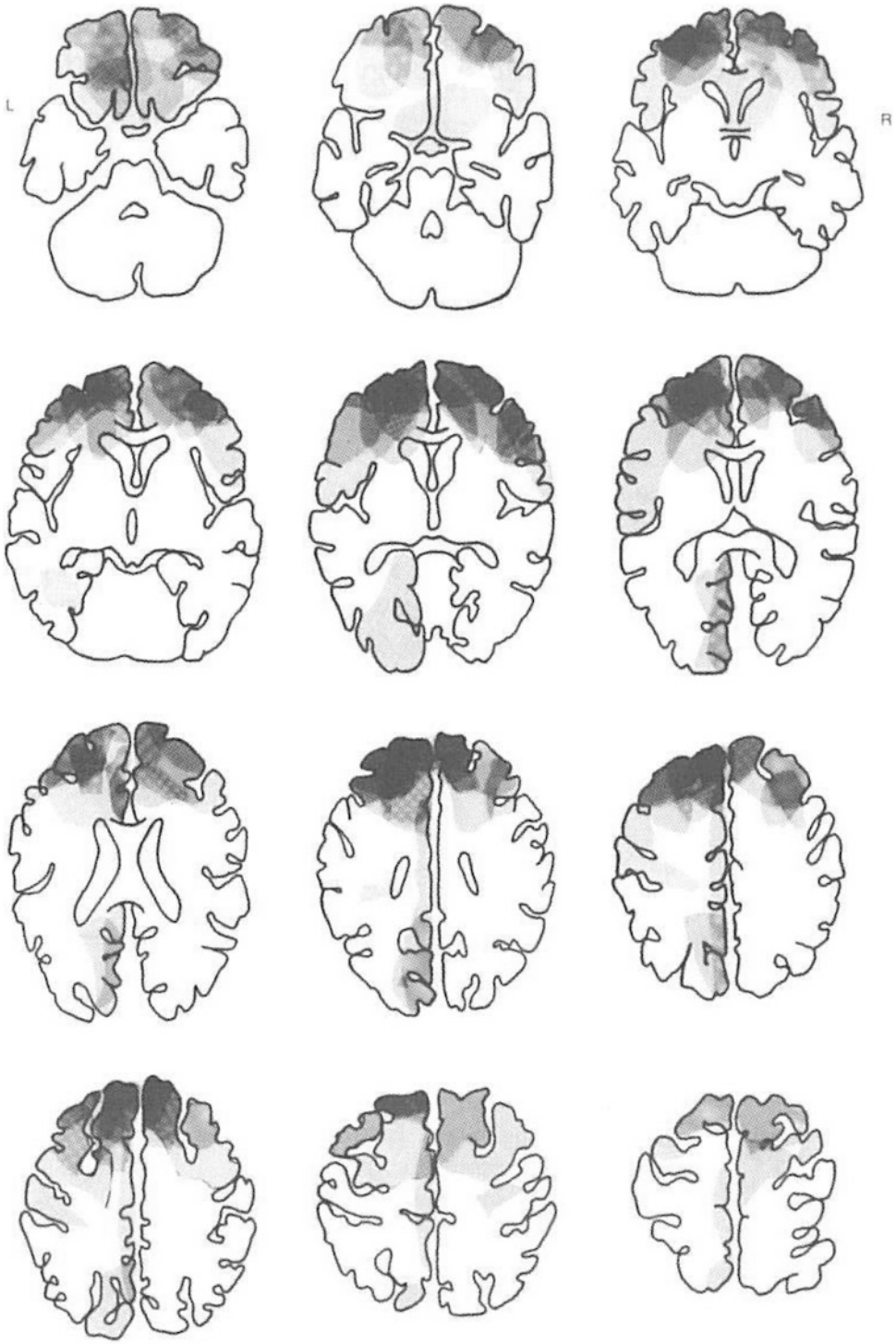

Fig. 45.2 Combined facsimile of scans in 14 cases with preserved dreaming with bifrontal lesions, illustrating the relative preponderance of cortical convexity involvement [12]

the *arousal–retrieval model* of dreaming [78], intrasleep wakefulness may facilitate the encoding of the dream content into long-term memory, consequently facilitating dream recall upon awakening in high dream recallers.

Consistent with this explanation, high dream recallers are more reactive to their external environments during all stages of sleep, as well as during wakefulness, when compared with low dream recallers [79]. (Using a novelty oddball paradigm, high dream recallers were shown to have enhanced P3a and late latency event-related potentials (ERPs) to novel and unexpected auditory stimuli. The P3a and late latency potentials are associated with complex cognitive processes such as familiarity, episodic memory and emotional processing [80–82]. Eichenlaub et al. [79]

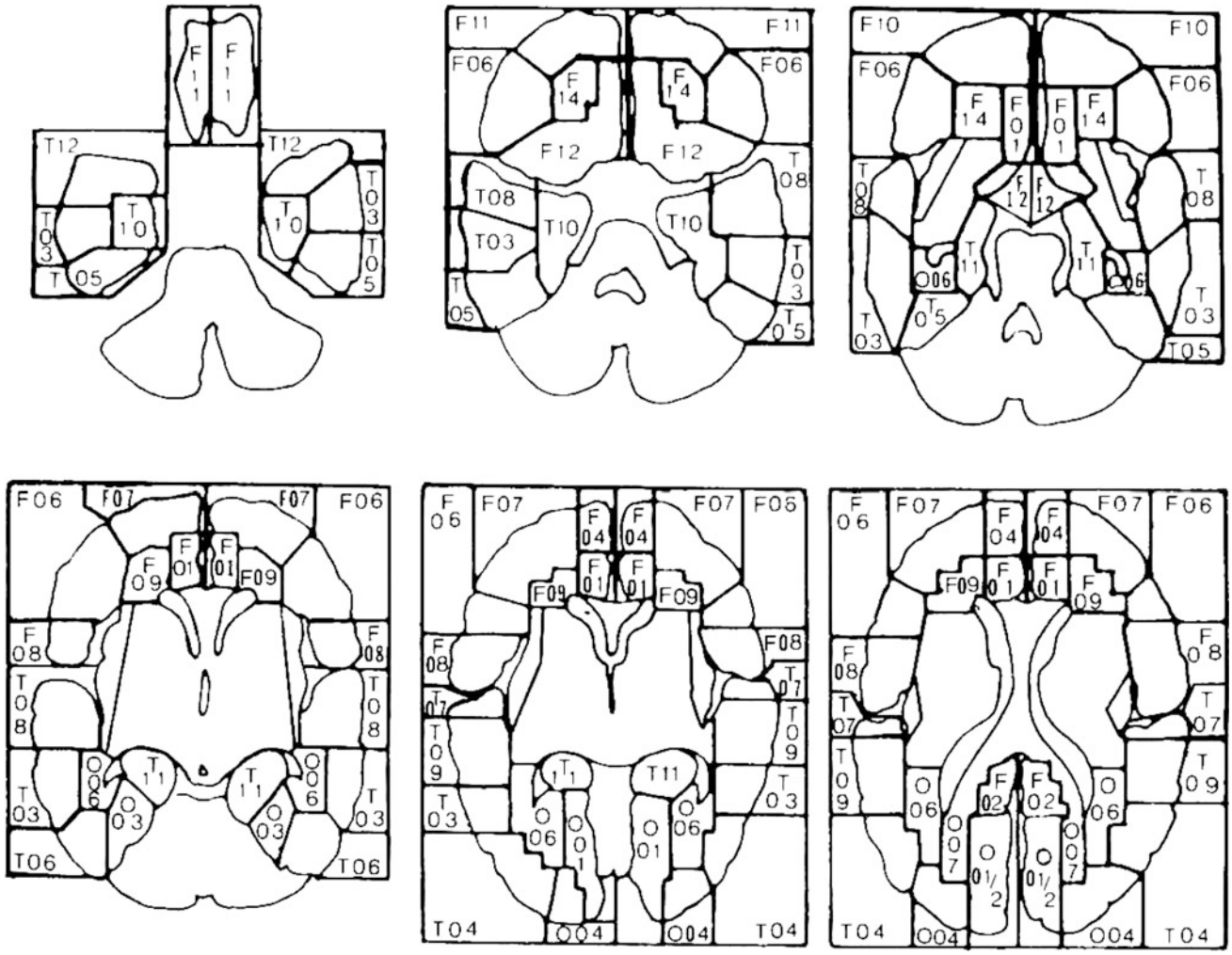

Fig. 45.3 Global cessation of dreaming is associated with subcortical lesions located in the deep frontal white matter (areas F09 and F14 in the classification of Damasio and Damasio [63], shown here)

have argued that these robust differences in brain responsivity show that the cerebral organisation of high recallers is intrinsically different to that of low recallers and that this difference may potentially facilitate either production or encoding of the dream.

This propensity to be more reactive to the external environment is consistent with enhanced activation of the posterior attentional networks in high dream recallers. Whether increased dream recall in habitually high dream recallers is due to more efficient encoding of the memory trace of the dream into long-term memory, or whether activity within these regions indicates a genuine increase in dream activity, remains inconclusive.

However, the latter possibility is supported by a recent set of transcranial magnetic stimulation (TMS) studies which found that visual dream imagery could be enhanced by inhibiting certain frontal regions while stimulating the right posterior parietal cortex, during stage 2 sleep but not during slow-wave sleep [83, 84]. This finding must be understood in relation to the fact that TMS is unable to propagate through connected networks during slow-wave sleep as efficiently as during lighter NREM sleep (Massimini et al. 2005) [85]. It nevertheless corroborates the notion that activity in posterior association cortex is responsible for the perceptual construction of dreams and moreover that activity in these regions during sleep represents an increase in dream activity.

Despite strong evidence that higher visual association cortices are responsible for the perceptual construction of dreams, it has recently been shown that primary visual areas may also be involved. In an innovative combined EEG/*f*MRI study, participants' dream imagery (as verbally reported) was decoded from neural activity measured during sleep onset, by software trained to correlate discrete visual stimuli (i.e. pictures) with brain activity during waking [86]. Horikawa et al. [86] concluded that the 'principle of perceptual

equivalence, which postulates a common neural substrate for perception and imagery, generalizes to spontaneously generated visual experience during sleep' (p. 642). As lesions to primary visual regions do not result in dream loss, or any visual disturbances in dreams [12], the exact contribution of the primary visual regions to dream imagery remains unclear.

Excesses of Dreaming

Dream/Reality Confusion

Solms [12] loosely grouped together 12 case reports in the literature and 10 of his own cases under the heading of dream/reality confusion (or 'anoneirognosis'). These patients reported excesses of dreaming, ranging from increased frequency and/or vivacity of dreams to intrusions of dreaming and dream-like thinking into waking cognition. The principle justification for collecting these cases under a unitary nosological heading was that the focal lesions (representing a wide variety of pathologies) that cause 'anoneirognosis' were typically located in the transitional zone between the anterior diencephalon and basal forebrain. Kindred phenomena are, however, also observed with visual de-afferentation, peduncular hallucinosis, delirium, parkinsonian syndromes, Guillain–Barre syndrome and a variety of toxic and metabolic conditions. The common denominator in these cases may therefore simply be degradation of constraints on consciousness. Certainly, any suggestion at this stage that dream–reality confusion may be considered to be a focal symptom is unjustified.

Dream/reality confusion in parkinsonian syndromes is difficult to interpret. Increased dreaming and hallucinations are frequently seen with Parkinson's disease (PD) but this may be iatrogenic. It is well established that hallucinations and excessive dreaming can be provoked by the administration of L-dopa, both in PD [87] (and in normal subjects, independently of any concomitant changes in REM sleep [88]. Accordingly, it has been shown that reduction of dopaminergic medication, and administration of dopamine blockers, reduces hallucinations and excessive dreaming in PD [89]. However, visual hallucinations in PD may also be an indication of the presence of Lewy body pathology, with involvement of parieto-occipital and limbic regions [90–92]. Excessive dreaming in parkinsonian syndromes may, therefore, have a different mechanism in cases with and without cortical Lewy bodies. In PD, hallucinations occur late in the course of the disorder, whereas they are an early feature of dementia with Lewy bodies (DLB).

Hallucinations and dream/reality confusion are also common in narcolepsy [92]. In these cases, hallucinations may accompany or follow attacks of cataplexy and sleep paralysis. Hallucinations of a presence of someone nearby ('sensed presence') or a pressure on the chest with breathing difficulties ('incubus/succubus'), and floating/flying and 'out of body' experiences, are typical in these cases. Dreams can occur at sleep onset (at night or during daytime naps) as well as on awakening (Rosenthal's syndrome). The retention of elements of normal waking mentation, such as volitional control or environmental awareness, is characteristic of narcoleptic dreams.

Various other rare disorders are associated with dream/reality confusion. Idiopathic hypersomnia manifests in excessive daytime sleepiness, prolonged unrefreshing sleep and 'sleep drunkenness' on attempting to wake up. Habitual dreaming, hypnagogic hallucinations and sleep paralysis are common in these cases [91]. Kleine–Levin syndrome is a rare disorder characterised by recurrent episodes of hypersomnia, compulsive eating behaviour and various psychopathological changes like hypersexuality, irritability or apathy. Hallucinations, delusions and 'dreamy states' are reported in 14–24 % of patients with KLS [93]. In fatal familial insomnia, a variant of Creutzfeldt–Jakob disease (CJD), progressive insomnia is coupled with an oneiric stuporous state in which patients perform complex, jerky movements that correspond to dream content which patients are later able to report [94]. Dream/reality confusion with hallucinations also occurs in sporadic CJD [95].

In populations without neurological disorders, excessive dreaming has been reported as a primary complaint in certain sleep clinics [96]. A study comparing these patients to controls revealed that complaints of excessive dreaming were related to significant microstructural changes, including increased arousals, intrasleep awakenings, period leg movements, alpha–delta sleep and REM density; however, no macrostructural changes were noted, and no differences in REM sleep and sleep onset latencies were apparent. Excessive dreamers were also found to be significantly more stressed, fatigued and anxious than controls, and to have more headaches.

Nightmares

Nocturnal seizures (and complex partial seizures in particular) sometimes present as recurring nightmares [97, 98]. Solms [12] identified 24 cases of this type in the literature and nine in his own series. Of theoretical interest is the fact that such nightmares typically occur during non-REM sleep. The content of the nightmares frequently coincides with that of the patient's typical aura or 'dreamy state' seizures [12, 98, 99]. Penfield was able to artificially generate a waking aura resembling the recurring nightmare in one case by stimulating exposed cortex in the region of the epileptogenic focus [100–102]. Successful pharmacological or

surgical treatment of the seizure disorder invariably results in disappearance of the recurring nightmares. These facts further support the interpretation of the nightmares in these cases as seizure equivalents (and indeed as non-REM phenomena).

As with dream/reality confusion (which frequently co-occurs with nightmares), increased frequency of nightmares is associated with a wide range of toxic and withdrawal states and metabolic abnormalities. The grounds for detaching these two 'excesses of dreaming' from each other are not entirely clear. The common denominator here may therefore, once again, simply be general degradation of constraints on consciousness.

It is important to note that nocturnal panic attacks and sleep terrors are not instances of nightmares. Detailed dream recall is often lacking in such attacks [103, 104], although in certain studies dream content has been reported [105].

REM Behaviour Disorder (RBD)

In this disorder, dreamed behaviours are physically acted out. This is due to disruption of pontomedullary mechanisms that induce REM atonia [106]. The enacted behaviours may be dramatic or even violent, and usually relate to vivid, frightening dreams. A fair proportion of cases injure their bed partners [107]. The disorder is most common in males, and onset is often in the sixth or seventh decade. RBD manifests mainly in the second-half of the sleep cycle (where REM is predominant). Increased slow-wave sleep, and increased periodic limb movements across all sleep stages are also seen [107–111].

Of special interest is the association of RBD with the parkinsonian syndromes. The presence of RBD in PD patients is associated with cognitive deficits and appears to predict dementia [112, 113]. Disorders with Lewy body pathology often involve RBD. The incidence of RBD in PD is 25–50 % and more than 50 % in DLB and MSA. In contrast, disorders without Lewy bodies rarely involve RBD. Notably, idiopathic RBD may present many years prior to the other symptoms of an incipient parkinsonian syndrome [107, 113–118]. The prognostic significance of RBD as a precursor to PD, DLB and MSA is now well established, resulting in the suggestion that the term 'cryptogenic' RBD should replace 'idiopathic' RBD [109, 111, 119, 120].

Pharmacological Findings

The chemical and pharmacological evidence is extremely difficult to interpret. This is due partly to the dynamic interactions that characterise neurotransmitter systems, and the paucity of rigorous pharmacological studies [14]. Mention will only be made here of recent findings which seem particularly relevant to understanding dream generation, and the distinction between dreaming and REM sleep.

The neurochemical signature of the REM state is well established: namely, autochthonous activation of ascending pontine ACh cells—which is thought to produce characteristic pontine–geniculate–occipital (PGO) waves—and reciprocal inhibition of pontine aminergic (5HT and NA) cells—which is thought to demodulate the dreaming forebrain [121]. Equally well established is the fact that non-REM sleep has the opposite pattern. Less widely known is the fact that, unlike other aminergic brainstem cells, the source cells in the ventral tegmental area (VTA) of the mesocortical DA pathway described above in connection with prefrontal leucotomy continue to fire at equal rates during sleeping and waking [121, 122]. These cells also fire with greater interspike variability during REM than non-REM sleep [121]. This has recently been shown to indicate prominent burst activity in the REM state [123], resulting in greater terminal DA release. DA delivery to the nucleus accumbens is in fact maximal during REM sleep when compared with NREM sleep and waking [124].

The REM state is also characterised by minimal prefrontal glutamate release [124], which presumably coincides with the observation reported above to the effect that dorsolateral prefrontal lesions have no obvious effect on dream content (and with the observation that this region is strongly deactivated in PET imaging studies of REM sleep [72]). The chemical signature of the REM state, as regards the neurotransmitter interactions underlying the observed regional patterns of forebrain activation and deactivation, is certainly more complex than was previously assumed [125].

This complexity is underscored by the impenetrable thicket of psychopharmacological evidence. Of particular value is any evidence that could clarify the pathophysiology of dream cessation following deep ventromesial frontal lesions. Since the sleep cycle is unaffected by such lesions [56], it is reasonable to assume that they impair a mechanism which is specific to dream generation (as opposed to REM generation). Two competing hypotheses have been advanced to account for dream cessation following deep ventromesial frontal lesions (and the commensurate hyperactivation of this region in *f*MRI and PET imaging of dreaming sleep and schizophrenic hallucinations [72, 125, 126]). The first hypothesis is that it reflects the activation of ACh cells in the basal forebrain; the second is that it reflects the activation of DA cells in the VTA.

Against the former hypothesis is the observation that ACh antagonists (like scopolamine), rather than suppressing dreaming and dream-like thinking, have the opposite effect: they produce dream/reality confusion [127, 128]. In fact, in this respect, anticholinergic drugs mirror the effects of lesions in cholinergic basal forebrain nuclei [129]. These and

other considerations led Braun [130] to observe that activation of these nuclei during REM sleep may actually reflect *inhibition* of forebrain ACh in dreaming sleep.

In favour of the latter hypothesis is the observation that DA agonists (like L-dopa) increase dream bizarreness, vivacity, complexity and emotionality without having any commensurate effects on REM sleep [87]. DA agonists, of course, also provoke other symptoms of psychotic cognition. Systematic studies of the effects on dreaming of DA antagonists have not yet been performed. However, a preliminary study by Yu (unpublished observation) of the effects on dreaming of antipsychotic medications recently found significant dream-suppressing effects.

Particularly incompatible with the view that dreaming and REM sleep are generated by the same pontine mechanisms is the accumulating evidence to the effect that 5HT agonists (SSRIs), like anticholinergics, have the opposite effect to what the REM-dreaming hypothesis would have predicted. SSRIs suppress REM sleep but produce excesses of dreaming, of both types described above [131–137].

The available pharmacological evidence therefore supports the view that dreaming—like other forms of psychosis—is primarily generated by (demodulated) DA mechanisms rather than ACh ones [138]. It is likely that interactions between the DA system and other neurotransmitter systems also affect dreaming, as enhanced dreaming has been shown in populations receiving noradrenergic beta blockers. However, the neurochemical basis of dreaming is likely to be far more complex than this, the only conclusion that the limited current evidence reasonably allows. Nevertheless, the roles of reward processing and addiction, as they relate to DA activity in the brain, have more recently been used to try and elucidate the dream process.

Reward and Motivational Processes During Sleep and Dreaming

DA circuitry is also central to reward processing. The mesocortical–mesolimbic (MC-ML) DA system is defined as the 'system [that] is formed by dopamine neurons located in the ventral tegmental area … which project to the nucleus accumbens, prefrontal cortex, septum, amygdala, and hippocampus' [123]. This system has been termed the SEEKING system by Panksepp [139] and it is thought to 'drive and energize many mental complexities that humans experience as persistent feelings of interest, curiosity, sensation seeking' (p. 145). It is also involved in reward processing, which refers to 'an instinctual affective and exploratory drive to seek biologically-important stimuli in the external or internal ('intrapsychic') environment' (Perogamvros and Schwartz, p. 1936) [140].

Perogamvros and Schwartz [140] have proposed the *reward activation model* (RAM) of dreaming, which postulates that reward processing during sleep may contribute to the consolidation of memories with a high motivational/emotional relevance, as well as aid in the modulation of REM sleep through projections to REM generating brainstem structures. Due to the strong interconnections between the hippocampus and the ventral tegmental area—which drives DA activity in the MC-ML circuits—RAM proposes that activation of the hippocampus during sleep may stimulate the VTA and lead to reward activation during sleep; in turn, VTA activity can lead to the reactivation of certain memories in the hippocampus. It is thought that during SWS in particular, the reactivation of the ventral striatum and the hippocampal complex allows for the consolidation of 'memory-reward associations' [141]. Therefore—and as originally proposed by Freud [142]—'the fabric of the dream-thoughts is respolved into its raw material' (p. 543).

In support of motivational theories of dreaming are studies of addiction, which has been associated with activity in the MC-ML dopamine system [143]. It is common for abstinent drug addicts to have increased dream content related to finding and taking drugs, a phenomenon that Johnson [144] first termed 'drug dreams'. As many as 80 % of acutely abstinent drug addicts experience drug dreams [145], which is related to drug craving in addicts and previous drug users [146–149]. Drug craving can be triggered by cues related to drug taking, both conscious and unconscious [150]. These types of drug-related cues have also been shown to be associated with the subsequent occurrence of drug dreams [151, 152]. In the absence of these drug-related cues, drug dreams tend to dissipate [145]. Drug dreams persist in drug addicts undergoing pharmacological treatment during abstinence, such as methadone treatment in heroin addicts and nicotine gum in smokers [153], (indicating that drug dreams do not merely result from physical withdrawal, but rather are a type of psychological withdrawal [145]. Furthermore, up-regulation of the MC-ML dopamine system—as measured indirectly by the Limbic System Activity Scale—has been associated with drug dreams [154]. The association between this up-regulation of the MC-ML dopamine system and the presence of drug dreams provides further evidence for this system's role in the motivational aspects of dream genesis [145]. This line of research has been used to argue that not only is the DA system involved in dream genesis, but that the content of drug dreams favours a motivational impetus for dream genesis [144, 155].

Conclusion

Despite the minimal attention that neurologists typically pay to dreams, their assessment can be of diagnostic interest, and have prognostic and management implications. They can also be a major source of distress to patients. There is every reason to expect that systematic studies of clinical dream phenomena will continue to provide valuable new insights into the functions and malfunctions of the human brain and mind. The extension of our understanding of dreams to healthy populations by means of more contemporary research methods has been extremely valuable in furthering our knowledge of the dream process. Consistencies in certain neurophysiological models of dreaming in these two populations are providing the field with sound theoretical departures from which the dream process can be better understood.

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Sleep in Psychiatric Disorders

46

Peter L. Franzen and Daniel J. Buysse

Introduction

Numerous studies support a bidirectional relationship between poor sleep and psychiatric symptoms and disorders. The incidence of psychiatric symptoms and disorders is elevated among sleep-disordered patient populations, and sleep disorders are likewise overrepresented in psychiatric patients. This overlap can complicate both the diagnosis and treatment of sleep and psychiatric disorders.

Sleep disturbance has long been considered a manifestation of an underlying psychiatric condition; however, other conditions, including chronic pain [1], medical illnesses, and other sleep disorders, can also lead to insomnia complaints. As an example, Forsell and Winblad [2] investigated the prevalence of psychiatric symptoms in the oldest old. Sleep disturbances were named as the most common psychiatric symptom observed. There are many other plausible reasons, however, that sleep disturbances would be frequently observed in an over-90 population, including age-related neurologic changes and increases in sleep apnea prevalence.

The automatic attribution of insomnia or "sleep difficulties" to psychiatric disorders is problematic for several reasons: (1) Sleep is a physiologically driven process, not simply a state of mind, with mounting evidence that sleep is biologically linked to mood disorders; (2) sleep disturbances can exist independent of psychiatric symptoms or remain after a psychiatric disorder remits; and (3) sleep disturbances have been identified as an important underlying risk factor for psychiatric disorders, as well as in their severity and recurrence. While insomnia may be a frequent consequence of some medical and psychiatric disorders (secondary insomnia), it is now clear that insomnia can be an independent problem that precedes or co-occurs with another condition (comorbid insomnia). In support of this, both ICSD-3 and DSM-5 no longer have separate categories for "primary" or "secondary" insomnia associated with psychiatric and medical conditions. Rather, the clinician is asked to note whether significant comorbidities are present. Thus, it is important to consider other factors in addition to psychopathology that can affect sleep. Such distinctions are important for understanding the pathophysiology of sleep disturbances and may impact treatment.

This chapter reviews the various relationships between sleep and psychiatric disorders, focusing on sleep disturbances and psychiatric symptoms in a broad sense; on psychopathology in individuals with sleep disorders; and on sleep findings in various psychiatric disorders. The chapter concludes with some considerations for approaching sleep disturbances in the treatment of patients with psychiatric disorders.

Sleep Disturbances, Sleep Loss, and Psychiatric Disorders

Insufficient sleep, as a result of sleep loss (e.g., short sleep duration) and/or sleep disturbances (e.g., poor sleep quality, difficulty falling asleep, or staying asleep) can significantly impact mood and psychopathology. Sleep disturbances are frequently observed in psychiatric disorders: 50–80 % of individuals with a primary psychiatric disorder report sleep disturbances at some point during the course of their disorder [3]. Epidemiologic evidence from different countries shows that self-reported habitual sleep duration is associated with increased risk for psychopathology. For instance, large epidemiologic studies from Germany and Korea show that short (≤ 5) and long (>9) sleep times are associated with increased cross-sectional risk for depressive, anxiety, and substance use disorders [4, 5]. Shorter sleep duration (<8 h) and frequent nightmares were significantly associated with increased risk for suicidal ideation and suicide attempts in an epidemiologic sample of 1362 adolescents ages 12–18 from China [6]; the risk for suicide attempts remained significant

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after controlling for depressive symptoms. Similar findings for increased suicide risk in adults experiencing frequent nightmares have also been reported [7].

Longitudinal studies further demonstrate that sleep problems in childhood increase the risk for psychiatric problems in adulthood. In a longitudinal sample, 943 children with parent-reported sleep and psychiatric symptoms at ages 5, 7, and 9 were assessed for current anxiety and depression using standardized structured interviews at ages 21 and 26 [8]. Persistent sleep problems in early childhood predicted adulthood anxiety disorders but not adulthood depression in this sample.

Both insomnia and hypersomnia symptoms are associated with increased incidence and severity of psychiatric disorders. A survey of 7954 people in scattered major US cities between 1981 and 1985 as part of the National Institute of Mental Health Epidemiological Catchment Area study [9] revealed that 40 % of those with insomnia and 46.5 % of those with hypersomnia met the criteria for mental illness using criteria from the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised.* Ten percent of the sample complained of insomnia and 3.2 % of hypersomnia [10]. Fourteen percent of the patients with insomnia met criteria for major depression, compared to 9.9 % of those with hypersomnolence. The rate of new psychiatric disorders at one-year follow-up was greater among respondents with persistent sleep complaints. The numbers in this study were thought to be low due to strict criteria for defining insomnia and the omission of generalized anxiety disorder (GAD) and personality disorders from the survey. In a study by Mosko et al. [11], 66.5 % of 206 patients presenting to one sleep disorder center reported one episode of major depression in the previous 5 years, and 25.7 % described themselves as depressed on presentation. Additional studies have established substantial risk of developing major depression and generalized anxiety in patients with sleep disorders [12–14]. Both insomnia and hypersomnia are associated with worsening course of depression [15] and increased suicidal behavior [16].

Sleep loss/deprivation also leads to mood dysregulation. Experimental studies manipulating sleep duration consistently demonstrate a negative impact on self-reported mood [17], although mood can become dysregulated in the opposite direction as well (e.g., mood elevation, giddy laughter). Sleep deprivation has also been shown to increase physiological reactivity to negative emotional images as measured by pupil dilation [18], as well as amygdala activation in response to both negative [19] and positive [20] images. Negative consequences from sleep deprivation are in general more common and can impact functioning. For example, sleep deprivation can impair interpersonal transactions. Average nightly sleep duration was assessed in a sample of medical residents [21]. Reports of treating others badly or feeling belittled/humiliated by colleagues increased as average nightly sleep decreased. Although reported by a smaller percentage of respondents, the incidence of violent behavior (i.e., hitting, kicking, and punching) showed the same inverse relationship with sleep duration.

Sleep deprivation can lead to negative consequences for psychiatric disorders, particularly bipolar disorder. Irregular social rhythms and sleep deprivation can elicit mania in some patients with bipolar disorder [22–25]. Sleep deprivation may also induce bipolar disorder in vulnerable individuals. Lack of sleep has also been associated with the *development* of bipolar disorder [26], as well as pre- and postpartum psychosis [27–29], and greater rates of depression in both new mothers and new fathers have been attributed in part to the sleep disruption that occurs with the arrival of a newborn [30]. A sleep deficit has been found to prospectively predict the development of depressive symptoms in patients with bipolar disorder [31].

Although sleep loss is generally considered to have negative effects with regard to mental health, sleep deprivation can have rapid, albeit usually transient, antidepressant effects. Among patients with major depressive disorder, symptoms can improve following total sleep or selective rapid eye movement (REM) sleep deprivation. The improvement is transient and occurs in 40–60 % of patients with endogenous depression [32–34]. Sleep deprivation can lead to an antidepressant response in patients with bipolar disorder as well [35]. One study [36] in 141 hospitalized, currently depressed, bipolar patients used three total sleep deprivation nights (each separated by one night of recovery sleep) combined with lithium and bright light therapy for two weeks; 70 % had >50 % reductions in Hamilton Rating Scale for Depression, which persisted at one month in 55 %.

Associations Between Sleep Disorders and Psychiatric Symptoms/Disorders

Insomnia

Although insomnia commonly co-occurs with other medical or psychiatric illnesses, insomnia independently places an individual at risk for future medical and psychiatric complications [37]. Not only is psychopathology more severe in people who complain of sleep disturbances, insomnia itself specifically confers an increased risk for the *future* development of a mood or anxiety disorder, even when controlling for baseline mood symptoms [10, 38]. A recent meta-analysis of 21 studies found that insomnia doubles the risk for depression (i.e., odds ratio of 2.10; 95 % CI: 1.86–2.38) [39]. Breslau et al. [13], in a three-year longitudinal study of 979 young adults, found a lifetime prevalence of

16 % for insomnia. Patients with insomnia had a fourfold increase in risk for developing major depression compared to patients without insomnia; notably, sleep disturbance was a stronger predictor of the subsequent development of depression than any other factor.

The timing of chronic insomnia and psychiatric illness was assessed by telephone interview in a population-based sample of 14,915 Western European participants [40]. Of the 19.1 % of the sample with insomnia, about one-quarter had a current psychiatric diagnosis and another quarter had a psychiatric history. For those with mood disorders, insomnia either preceded (40 %) or appeared at the same time (22 %) as mood symptoms. In contrast, insomnia tended to appear at the same time (38 %) or after (34 %) as the development of an anxiety disorder. The strongest predictors of having a psychiatric history were severe insomnia, primary insomnia, or insomnia related to a medical condition, and insomnia persisting more than one year. Studies have shown a relationship between suicide and insomnia in depression [22] and panic disorder [41], as well as higher rates of insomnia [42] and poor sleep quality [16] among suicidal individuals, again illustrating the bidirectional relationship between sleep and psychopathology.

Circadian Rhythm Disorders

Circadian rhythm disorders, such as delayed or advanced sleep phase syndrome, are characterized by abnormal timing of sleep. Difficulty in sleeping at desired, typically socially appropriate times can significantly impact functioning. For example, a severely delayed sleep schedule can significantly impede academic or occupational functioning; such stresses can easily lead to depression, which may in turn hamper the behavioral self-control needed to try to "normalize" the individual's schedule (e.g., taking melatonin at the appropriate time, engaging in a consistent sleep-wake schedule, chronotherapy). As many as three-quarters of individuals with delayed sleep phase syndrome have a past or current history of depression [43], and depression severity correlates with circadian misalignment [44, 45]. Evening circadian chronotype without delayed sleep phase syndrome is also associated with elevated rates of psychopathology, including depression and substance use disorders [46, 47].

Sleep Apnea

Sleep fragmentation and chronic intermittent hypoxemia induced by sleep-disordered breathing (SDB) lead to impairments in cognitive and affective domains (see El Ad and Lavie [48] for review). Patients diagnosed with obstructive sleep apnea often present to sleep disorders centers with concomitant symptoms of depression and other psychopathology. Affective consequences of SDB include elevated rates of depression, anxiety, and hostility symptoms based on self-report questionnaires [49, 50], although inconsistencies have been reported [51]. In a large cohort of Veterans Administration healthcare beneficiaries, those with sleep apnea had significantly greater prevalence of mood disorders, anxiety, post-traumatic stress disorder (PTSD), psychosis, and dementia compared to patients without sleep apnea [52].

The association between SDB and depression has been consistently found, with reports ranging from 24 to 58 % of SDB patients meeting diagnostic criteria for depression [11, 53–55]. In a recent general population study consisting of nearly 19,000 Western Europeans responding to a telephone survey, 0.8 % were found to have both SDB and depression [56]. They found that 17.6 % of individuals with SDB also were diagnosed with depression and 18 % of depressed individuals were diagnosed with SDB. After controlling for obesity and hypertension, an individual with major depression is still at increased risk of also having SDB. Because depression and SDB are both prevalent conditions in the general population, these findings are of particular relevance to both psychiatrists and sleep specialists. That nearly one-fifth of individuals with one of these disorders may have the other underscores the importance of screening for SDB in people diagnosed with depression, and vice versa. By accurately identifying both disorders when present, treatment outcomes for both disorders may be improved (see Schroder and O'Hara [57] for further discussion). Successful treatment of SDB, usually with positive airway pressure therapy but also with surgery, leads to improvements in quality-of-life measures and in anxiety and depression symptoms, although some studies have not found such improvements [50, 58–61]. These inconsistencies may be partly due to overlapping symptoms of depression and OSA, and the possibility that depressive symptoms may be slower to resolve. Long-term use of positive airway pressure therapy (one year or longer) in 300 patients was associated with decreasing depression symptoms; however, depression symptoms remained persistently elevated in 42 % of the sample [62]. Excessive daytime sleepiness was a significant predictor for persistent depression.

Studies in children have tended to not clearly differentiate primary snoring from obstructive sleep apnea; however, cross-sectional evidence suggests a strong increase in behavior problems and neurocognitive abnormalities in children with SDB (see Schechter [63]). Surgical interventions seem to help. Many children who received adenotonsillectomy to treat their SDB have improved academic and behavioral functioning (e.g., aggression, inattention, hyperactivity, alertness) [64–66], although positive results have not always been reported [67].

Restless Legs Syndrome/Periodic Limb Movements

Restless legs syndrome (RLS) is another prevalent sleep disorder that is associated with depression and anxiety [68–70], as well as attention-deficit/hyperactivity disorder (ADHD). An increased association between RLS and depression, and RLS and ADHD, has been reported (see Cortese et al. [71]; Picchietti and Winkelman [69] for reviews). Winkelmann et al. [72] found an increased risk of having 12-month depressive and anxiety disorders based in 130 adult RLS patients who were compared to over 2000 community respondents with other types of physical disorders. Not all studies have found increased depression; one retrospective review of 100 consecutive idiopathic RLS patients failed to find an association between RLS severity and Beck Depression Inventory scores [73]. Whether the increased incidence of psychiatric disorders in RLS patients is due to sleep disruption, or to some shared pathophysiologic process, or is spurious cannot be determined by the epidemiologic associations found to date. Such findings, however, do support assessing psychiatric symptomatology in the diagnosis and treatment of RLS patients.

Narcolepsy

Patients with narcolepsy are at increased risk for psychopathology [74, 75]. In comparison with a general population comparison sample, most depressive and anxiety disorders were more prevalent in a sample of 320 individuals with narcolepsy, especially depression (OR, 2.67) and social anxiety (OR, 2.43) which impacted nearly 20 % [76]. Narcolepsy patients were found to exhibit greater psychosocial impairments than two matched comparison groups (epilepsy patients and normal controls) [77]. Hypnagogic hallucinations, part of the symptom tetrad of narcolepsy, do not occur in all cases of narcolepsy, nor do they typically indicate psychotic symptomatology. There are reports of an increased association between narcolepsy and psychotic disorders, although this association has been disputed [78].

Sleep in Psychiatric Disorders

Studies of REM sleep architecture in various psychopathologic states have been conducted since Dement first evaluated REM sleep in schizophrenic patients in 1955. Subsequently, REM sleep changes were most often examined in relation to affective disorders [79]. Subsequently, numerous studies used measures have examined REM outcomes (i.e., REM sleep latency, REM density, and REM sleep distribution) in various other psychiatric disorders such as schizophrenia, eating disorders, personality disorders, and substance abuse disorders. Others studies examined these same measures as diagnostic measures to distinguish various psychopathologic states from major depression. Unfortunately, a great deal of confusion has resulted from various methodologic issues and diagnostic uncertainties in psychiatric patients. Examples of methodologic differences in studies include the number of consecutive nights patients are studied, determination of the time between sleep onset and REM sleep onset (REM sleep latency), the definition of increased REM density, concurrent use of psychotropic drugs, period of withdrawal from psychotropic medications, sleep schedule, and the severity of the illness [80]. Just as important is the overlap of symptoms among various disorders found in the Research Diagnostic Criteria, the DSM-V, and other classifications for mental disorders. Although in theory, psychiatric diagnoses are categorically distinct from one another, in clinical practice, such distinctions are more difficult to make, and comorbid psychiatric diagnoses are common. All of these factors weaken the ability of sleep measures to serve as sensitive or specific diagnostic markers.

Mood Disorders

Major Depression

Major depression is the psychiatric disorder most studied by sleep researchers, and several theories of the mechanisms involved have been published [81]. In approximately 90 % of cases, major depression results in insomnia. A smaller percentage of patients with major depression complain of excessive sleepiness: Most are adolescents and young adults [82]. Whereas depressed adolescents and young adults may be more prone to be "long sleepers," studies of older depressed patients with the complaint of hypersomnolence have failed to show evidence of pathologic sleepiness [83]. Sleep disturbances can interfere with treatment response in depression. In a sample of depressed women treated with interpersonal psychotherapy, those with higher pretreatment subjective sleep quality ratings showed significant post-treatment improvement in mood symptoms compared to treatment nonresponders [84]. Similar findings of worse subjective sleep quality being associated with worse treatment response have also been reported in patients with depression receiving combined pharmacologic and psychological treatments [85]. Conversely, improvement in subjective sleep quality following depression treatment is associated with lower recurrence rates of depression [86]. Treating insomnia in addition to depression may speed recovery from depression. In a double-blind study, adults with comorbid depression and insomnia who were assigned to fluoxetine and eszopiclone coadministration had improved

sleep and higher rates of responders and remitters compared to those assigned to fluoxetine and placebo [87]. Nonpharmacological interventions for insomnia may also speed recovery from depression. A small randomized control trial of individuals with comorbid insomnia and depression compared patients taking escitalopram and receiving either cognitive behavioral therapy for insomnia (CBT-I) or a control insomnia therapy [88]. Depression remission and insomnia remission rates were higher in those who received CBT-I (61.5 and 50 %, respectively) versus those randomized to a control therapy (33.3 and 7.7 %, respectively). In another study, CBT-I similarly improved insomnia severity index scores (by almost half) in those with low and high levels of depression and both depression symptoms and suicidal ideation significantly improved following treatment [89].

Efforts have been made to distinguish major depression from other psychopathologic states by use of sleep electroencephalography (EEG) and other biological markers. The primary well-documented changes in sleep architecture include shortened REM sleep-onset latency, increased REM density, reduced total sleep time, reduced sleep efficiency, increased awakenings, decreased slow-wave sleep (SWS), and a shift of SWS from the first non-REM (NREM) cycle to the second (Fig. 46.1). More recently, high-amplitude fast-frequency EEG activity has been suggested as a marker for depression [90]. Sleep architecture changes found in depression may serve as a marker for the development of depression in those individuals genetically predisposed to depression.

Changes in sleep architecture, particularly in REM sleep and deep NREM sleep, are more pronounced with age in major depression. Prepubertal depressed children are less likely to show changes in sleep architecture than postpubertal depressives [91, 92]. There has been some conflict in the literature about whether REM sleep latency in depressed children is normal or shortened [93]. Changes in sleep architecture in adolescents appear to depend on the severity of the illness. Inpatient, psychotic, or suicidal adolescents may exhibit the typical adult changes of major depression, whereas the sleep of adolescents who are not as severely depressed may show no changes [93–96].

Aging has a marked influence on sleep, such as REM sleep latency, in depression; elderly depressed patients often have a REM sleep onset of less than 10 min. Older patients with a history of suicide attempts have longer sleep-onset latency, reduced sleep efficiency, and increased REM density than nonattempters [97]. Depressed men have less SWS than depressed women [98], but women may have more and higher amplitude beta activity [99]. Women with past depressive episodes appear to experience more sleep disruption and reduced REM sleep latency [100] in the immediate postpartum months.

Studies of the effects of antidepressant medication on REM sleep measures in patients with major depression have suggested that improved treatment response is associated with immediate and persistent antidepressant-induced prolongation of the REM sleep latency, reduction of total REM sleep time, and REM density [101, 102]. The occurrence of sleep-onset REM sleep episodes and shorter REM sleep duration during maintenance treatment with antidepressants has been associated with increased risk of relapse during treatment [103]. Studies of the effects of electroconvulsive therapy (ECT) on REM sleep architecture suggest that they are not as pronounced as those observed with most antidepressants [104]. As with pharmacotherapy, patients with post-ECT EEG signs of depression are more likely to have recurrence of the illness [105].

Bipolar Disorder

Sleep disturbances are quite common in bipolar disorder and can include insomnia and/or more typically hypersomnia during a depressive episode and reduced need to sleep during a manic episode (for review, see [106]). Sleep disturbances, especially insomnia, are also common during inter-episode periods when individuals are euthymic [107] and are associated with risk for the recurrence of a mood episode [108]. As sleep loss can trigger mania, using behavioral interventions for insomnia (stimulus control instructions and sleep restriction) could be a concern, as they involve some degree of sleep restriction. A case series of 15 individuals with bipolar disorder demonstrated that modified behavioral insomnia interventions can be useful without greatly increased risk of mania [109].

Patients in the manic phase of bipolar disorder have been shown to have reduced total sleep time, which gradually extends as the manic phase passes [110]. There is also a reduction in stages 3 and 4 sleep. No consistent change in REM sleep has been found, probably due to excitability and subsequent reduction of total sleep in these patients, but most studies show the same changes as seen in major depression [111]. It has been suggested that the switch from euthymia or depression into the manic phase occurs during sleep [112]. Lithium, which is the primary drug used to treat the manic phase of bipolar disorder, has been found to increase SWS and reduce REM sleep. Greater REM density during the inter-episode period in bipolar disorder has also been observed [113]. Further, manic symptoms and impairment three months later were associated with increased duration of the first REM period and the amount of SWS, and depressive symptoms and impairment were associated with REM density.

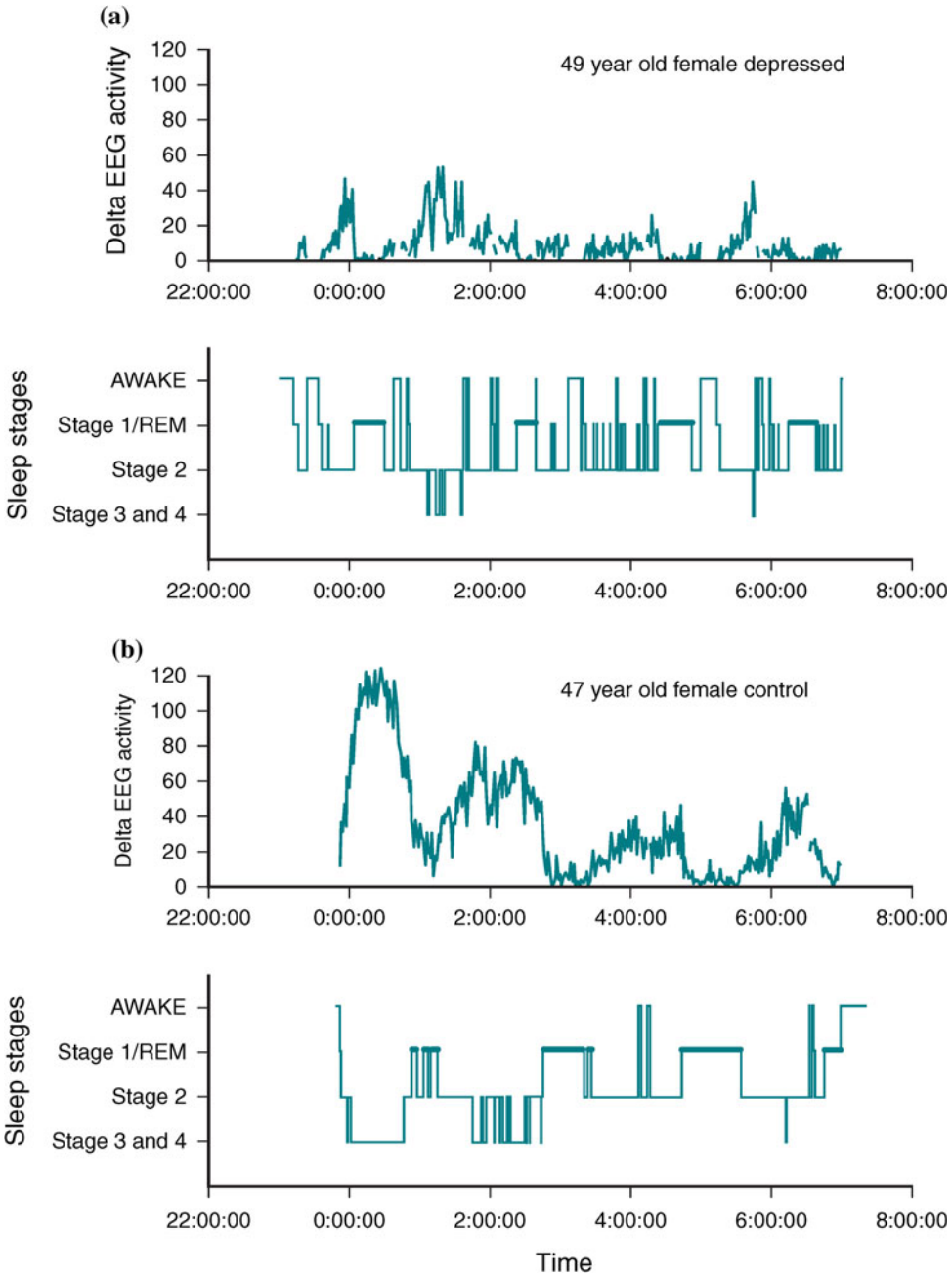

Fig. 46.1 Representative sleep histograms for a patient with major depressive disorder (**a**) and an age- and sex-matched healthy subject (**b**). In each figure, the *top panel* shows EEG delta activity during NREM sleep identified by computer algorithm, and the *bottom panel* shows the sleep histogram from visual sleep stage scoring. Relative to the control subject, the depressed patient has a longer sleep latency, more wakefulness during sleep, less visually scored stage 3/4 sleep and EEG delta activity, and shorter REM sleep latency

Anxiety Disorders

Anxiety disorders are the most prevalent group of psychiatric disorders. Anxiety symptoms and disorders co-occur with many sleep disorders. Anxiety has also long been associated with sleep disturbances, especially insomnia, as a quiet mind is a prerequisite to fall asleep, and anxiety is characterized by heightened worry and rumination. While less research has been done in this area compared to mood disorders, strong cross-sectional associations between sleep and anxiety [114], and significant risk relationships between sleep disturbance and the prospective development of anxiety disorders, have been reported (i.e., panic disorder and GAD [115]. Treating insomnia may reduce anxiety symptoms. A meta-analysis of the impact of CBT-I on anxiety found small to moderate effects on anxiety in individuals with and without a comorbid anxiety disorder [116].

Generalized Anxiety Disorder

While anxiety symptoms are most often associated with sleep initiation difficulties, Belanger et al. [117] found a more varied pattern of sleep difficulties in GAD. They examined self-reported insomnia symptoms both before and after a cognitive behavioral intervention targeting excessive

worry in 44 primary GAD patients. Insomnia subtypes included difficulty initiating sleep (48 %), difficulty maintaining sleep (64 %), and early morning awakenings (57 %); 77 % experienced at least one symptom, 41 % two symptoms, and 26 % all three. Comorbid depression, an important confounding variable, was not discussed and may have influenced study results. In polysomnographic studies, patients with GAD typically have prolonged sleep-onset latency, increased stages 1 and 2 sleep, less SWS, lower REM sleep percentage, and, with the exception of isolated reports, increased or normal REM sleep latency [118, 119]. No difference has been found between patients with GAD alone and those with GAD and depression [120].

Panic Disorder

Panic disorder can present with multiple somatic and emotional symptoms that can resemble symptoms of medical conditions such as mitral valve prolapse syndrome, cardiovascular dysautonomia, and sleep choking syndrome. The diagnosis may depend on the presentation of psychiatric symptoms, as opposed to autonomic and respiratory symptoms. Controversy exists over the roles of increased brain stem carbon dioxide receptor sensitivity and dysautonomia in panic [121–127]. It has been suggested that a number of substances and situations provoke panic attacks, such as caffeine, nicotine, over-the-counter cold remedies, cannabis, cocaine, sleep deprivation, excessive sugar intake, exercise, relaxation, hyperventilation, stress, and even fluorescent lighting [128].

As many as 70 % of patients with panic disorder have difficulty with sleep-onset and maintenance insomnia [129, 130], and often report sleep paralysis [131] and hypnagogic hallucinations [132]. Overbeek et al. [130] compared 70 panic patients and 70 controls on six types of sleep complaints. Panic disorder patients had more sleep complaints, including insomnia and daytime sleepiness, and those panic patients with comorbid depression and panic patients who also had nocturnal panic attacks had the highest frequency of sleep complaints.

Panic attacks can occur in any stage of sleep, but most occur during NREM sleep just before the onset of SWS. Symptoms similar to those associated with nocturnal panic attacks may be observed in patients with arrhythmias, gastroesophageal reflux, sleep apnea [133], sleep terrors, REM sleep behavior disorder, and paroxysmal hypnogenic dystonia [134]. More rarely, panic attacks can occur solely at night. It has been suggested that patients with sleep-only panic attacks experience depression more frequently than panic disorder patients who do not experience sleep-related panic attacks [135]. Of people diagnosed with panic disorder, 44–71 % have a history of nocturnal panic [136], and 30–45 % experience episodes of recurrent episodes of nocturnal panic [137]. Nocturnal panic is typically experienced as more intense than daytime panic. Fear of sleep can develop and lead to restricted sleep, which in turn might facilitate nocturnal panic events [137]. Patients with nocturnal panic attacks tend to experience worse daytime panic attacks, more somatic symptoms [138], and more comorbid psychiatric disorders [139] than daytime-only panic disorder patients.

Polysomnographic studies in nondepressed patients with panic disorder have reported normal sleep-onset latency and modestly reduced total sleep time and delta sleep [140]. However, studies in patients with panic and comorbid major depression have reported features typical of major depression, with substantially prolonged sleep-onset latency, reduced total sleep time, sleep disruption, reduced SWS, and early REM sleep onset [141–144].

Post-traumatic Stress Disorder

PTSD is caused by exposure to events in which a person witnesses or hears of a threat to the integrity (life) of themselves or a loved one, often in natural disasters, combat, torture, physical/sexual assault, or other situations involving physical and psychological abuse. Sleep complaints are nearly universal in individuals diagnosed with PTSD and include nightmares [145], difficulties initiating and/or maintaining sleep (in 70–90 % of individuals with PTSD) [146–148], and sleep paralysis [149]. REM sleep behavior disorder has also been associated with PTSD [150, 151], as has sleep paralysis [149]. Sleep disturbances shortly after trauma exposure predict the development of PTSD at follow-up assessment [152–154]. PTSD patients who report more severe sleep symptoms also report more depression severity, suicidality, anxiety, and substance use [155–157].

Current first-line interventions for PTSD do not directly target the nighttime symptoms in either pharmacotherapeutic (e.g., selective serotonin reuptake inhibitors [SSRIs]) or cognitive behavioral therapy (CBT) approaches; the former has minimal benefits on nightmares and insomnia [158–160], and the latter had minimal benefits for 48 % of PTSD patients who had a reduction in daytime symptoms in one study [148]. Fortunately, behavioral sleep interventions are effective in reducing nighttime symptoms in PTSD. For chronic nightmares, imagery rehearsal therapy has been found to reduce nightmare frequency and severity in both individuals with PTSD and those who have nightmares as a primary sleep disorder [161]. Nightmare reductions have lasted up to 30 months in follow-up studies [162] and are associated with significant reductions in daytime PTSD symptoms, depression, anxiety, and quality of life [163–166]. Effective behavioral interventions for primary insomnia (i.e., stimulus control instructions, sleep restriction) can also effectively reduce PTSD-related insomnia [164, 167, 168]. Prazosin, an α_1-adrenergic receptor antagonist, has emerged as promising treatment of PTSD-related sleep

Table 46.1 Drugs that affect sleep

Drug		Effects on Sleep	Comments
Barbiturates	Acute:	↑TST	Rapid development of tolerance
		↓WASO	Withdrawal insomnia
		↓REM	Daytime sedation
		↑Stage II, ↑spindles	
		↑ or ↓Delta	
	Withdrawal:	↓TST	
Benzodiazepines	Acute:	↓SL (most agents)	Agents vary in onset and duration of action
		↑TST	Daytime sedation (with long-acting agents)
		↓WASO	Tolerance develops (with short-acting agents)
		↓REM	Withdrawal insomnia (with short-acting agents)
		↑Stage II, ↑spindles	
		↓Delta (most agents; some ↑delta)	
	Withdrawal:	↓TST	
Benzodiazepine receptor agents (e.g., zolpidem)	Acute:	↓SL ↑TST	Sleep architecture not typically altered Withdrawal effects inconsistently seen
		→REM	
		→Delta	
	Withdrawal:	or ↑WASO	
Chloral hydrate		↑TST	Little information on tolerance or withdrawal
		→REM	
		→Stage II	
		→Delta	
L-Tryptophan		→ or ↑TST → or ↑REM	Effects are mild and inconsistent and may be delayed
		↑Delta	
Alcohol	Acute:	↑TST 2nd half of night	Acute effects variable
		↑WASO 2nd half of night	
		↓REM 1st half of night	
		↑Delta	
	Chronic:	→TST	
		→REM	
		↓Delta	
	Withdrawal:	↓TST ↑WASO	Degree of REM rebound may correlate with likelihood of withdrawal delirium
		↑REM	
		↓Delta	
Narcotics	Acute:	↑WASO	Effects vary with specific agents
		↓REM	
		↓Delta (total), with ↑delta "bursts"	

(continued)

Table 46.1 (continued)

Drug		Effects on Sleep	Comments
	Chronic:	→WASO →Delta	
	Withdrawal:	↓WASO	Hypersomnolence may occur during withdrawal
Aspirin	Acute:	↓Delta	May act via prostaglandin inhibition and temperature effects
Amphetamines	Acute:	↓TST ↑WASO, ↑movements	Sleep-wake cycle may be severely disrupted during acute use and withdrawal
		↓REM	
		↓Delta	
	Withdrawal:	↑TST	
		↑REM	
Caffeine		↑SL ↓TST	May have effects on sleep EEG even when no subjective disturbance occurs
		↑WASO	
		↓REM	
		↓Delta (1st half of night)	
Miscellaneous stimulants (e.g., nico tine, cocaine, pemoline, methyl-phenidate)		↑SL ↓TST ↓REM	
Antidepressants (e.g., tricyclic and monoamine oxidase inhibitors, except trimipra mine)	Acute:	↓WASO ↓REM ↑Stage II ↑Delta	Sleep effects vary with sedative potential of specific agent; MAOIs may cause ↑WASO
	Withdrawal:	↑WASO	
		↑REM	
Selective serotonin reuptake inhibitors	Acute:	→ or ↑WASO →TST ↓REM →Delta	May cause insomnia or hypersomnia May produce eye movements in non-REM sleep
Trazodone	Acute:	↓WASO → or ↓REM	Less suppression of REM sleep than tricyclics and MAOIs
		→ or ↑Delta	
Lithium		↓REM	
		↑Delta	
Phenothiazine		↑TST ↑Delta	Effects mild and variable, according to specific agent REM effects inconsistent
Reserpine		↑WASO	Can cause insomnia, nightmares
		↑REM	
		↑Delta	
Yohimbine		↑REM	
		↓Delta	
Clonidine		→TST	Can cause insomnia, daytime sedation
		↑WASO	
		↑Stage shifts	
		↓REM	

(continued)

Table 46.1 (continued)

Drug		Effects on Sleep	Comments
α-Methyldopa		↑REM (1 st half of night) ↓Delta	Can cause nightmares
Diuretics		↑WASO	Probably acts via nocturia, hemodynamic effects
Cimetidine		↑Delta	Can cause daytime sedation
Baclofen		↑TST	
L-Dopa		→TST	In toxic doses, causes insomnia, delirium
		→ or ↓REM	
		→Delta	
Methysergide		→TST	
		→ or ↓REM	
		↑Delta	
γ-Hydroxybutyrate		↑TST	
Steroids		↑WASO	

SL = sleep latency; WASO = wakefulness after sleep onset; TST = total sleep time; MAOIs = monoamine oxidase inhibitors; ↑ = increased; ↓ = decreased; → = unchanged.
Source Adapted from Buysse and Reynolds [249]

disturbance, including both nightmares and insomnia symptoms [169]. Both prazosin and a behavioral sleep intervention that included insomnia and nightmare-related components were found to have similar treatment response rates (~60 % compared to ~25 % in a placebo), which were further associated with improvements in both sleep and daytime PTSD symptoms in a placebo-controlled trial [170].

Much like polysomnographic studies of insomnia, in which sleep variables do not significantly differ from those of controls, reports of polysomnographic abnormalities in PTSD have been inconsistent (see Germain [171]; Kobayashi et al. [172] for meta-analytic review). This disorder has been associated with increased sleep-onset latency, decreased sleep efficiency, increased wakefulness after sleep onset, decreased total sleep time, reduction in stage 2 sleep, and increased stage 1 sleep [173]. There is controversy over the effects on REM sleep: Some authors report normal REM sleep parameters [173], whereas others report reduced REM sleep latency and increased REM density [174–176]. Nightmares have been found to occur during both NREM and REM sleep [177, 178]. Authors have speculated that PTSD may be a disorder of REM sleep mechanisms [179].

Obsessive–Compulsive and Social Phobia Disorders

Less work has been done in obsessive–compulsive disorder or social phobia, although these disorders too are common. Patients with social phobia show increased sleep-onset latency, awakening after sleep onset, and reduced total sleep time [180]. In obsessive–compulsive disorder, sleep can become restricted by repeatedly engaging in compulsive behaviors. Sleep studies in obsessive–compulsive disorder show decreased total sleep time, increased number of awakenings, shortened REM sleep latency, reduced stage 4 sleep, and reduced sleep efficiency [181].

Eating Disorders

Most studies of patients with bulimia show very little change in REM sleep measures compared with controls. REM sleep architecture studies of patients with anorexia nervosa have been more contradictory: Some report no change in REM sleep parameters [182], whereas others suggest that there are changes similar to those seen in major depression [183]. These findings may be due to high rates of comorbidity with affective disorders and frequent family history of affective disorders in anorexia patients. Patients with severe untreated anorexia nervosa often show reduced total sleep time, decreased sleep efficiency, increased wakefulness after sleep onset, increased stage 1 sleep, and decreased SWS. Sleep normalizes after weight is gained [184, 185]. One study suggests that there is initial shortening of the REM sleep latency with severe weight loss but that, with recovery of weight, the REM sleep latency returns to normal [186].

Schizophrenia

Patients with schizophrenia often sleep worse than healthy individuals, with sleep continuity disturbance, reduced SWS, decreased REM latency, and increased REM sleep, although there are contrasting studies showing relatively little change in sleep. Variability in documented sleep architecture changes and sleep quality are most likely due to differences in the age of patients, medications, study techniques, and other variables. In one report, sleep quality was disturbed in all 20 schizophrenia participants, and half showed either marked delayed or free-running circadian rhythms as indicated by urinary melatonin [187]. In comparison with unemployed controls, all the patients had longer sleep onsets and sleep durations based on 6 weeks of actigraphy. Sleep efficiency, stage 2 sleep, sleep continuity, total sleep time, and total REM sleep decrease on withdrawal of neuroleptics [188–190]. In one study [188], patients with tardive dyskinesia had an earlier onset of REM suppression after withdrawal of medication. Mean REM sleep latency was shorter, and total REM sleep time was greater, in patients with tardive dyskinesia than in those without tardive dyskinesia. NREM sleep parameters improved more on withdrawal of medication than REM sleep parameters. All patients had prolonged sleep-onset latencies. SWS was more abundant in patients without tardive dyskinesia. Studies have suggested an inverse relationship between SWS and sleep maintenance and brain ventricle size [191–193]. It has been suggested that reductions in SWS and increases in negative symptoms may be related to reduced anabolism and accelerated aging or atrophy of the brain [194]. SWS also does not rebound after sleep deprivation in patients with schizophrenia [195]. In several more recent and larger studies, reduced sleep spindle activity and EEG power has been observed in individuals with schizophrenia [196–198], suggesting thalamocortical dysfunction. In a further study, reduced density and number of sleep spindles in schizophrenia predicted less overnight improvement in sleep dependent memory consolidation on a finger-tapping motor sequence task [199]. Thus, sleep dysregulation may be a marker or mechanism for the neurocognitive dysfunction central to schizophrenia.

Borderline Personality Disorder

Borderline personality disorder as defined by the DSM-5 encompasses a number of symptoms of other psychiatric disorders, including major depression. In numerous studies of borderline personality disorder, sleep architecture changes are very similar to those observed in patients with major depression [200–203]. Borderline personality disorder patients have less total sleep time, less sleep efficiency, reduced SWS, increased stage 2 sleep, reduced REM sleep latency, and increased REM density. Subjects with borderline personality disorder frequently have symptoms of depression and have been shown to have abnormalities of other biological markers associated with depression [204].

Childhood Psychiatric Disorders

Sleep disturbances are associated with a variety of behavioral and emotional problems in childhood and adolescence: anxiety and depression [205, 206], attention/hyperactivity symptoms [207, 208], and behavioral problems such as acting out [209]. As reported in the adult literature, a number of studies have suggested a bidirectional association between sleep and behavioral/emotional problems in childhood [210, 211].

Sleep and behavioral/emotional problems were longitudinally assessed in 490 children between the ages of 4 and 15 [206]. Sleep problems at age 4 were associated with an increase in behavioral/emotional symptoms in mid-adolescence, although evidence for a reciprocal relationship was inconsistent. Early childhood sleep problems (mother-reported overtiredness and trouble sleeping at age 3–5) were similarly found to predict the early-onset use of alcohol and other drugs during mid-adolescence (age 12–14) in a longitudinal sample of 257 high-risk Caucasian Americans families [212]; sleep problems also predicted elevated attention and anxiety/depression symptoms during adolescence, although these problems did not mediate the relationship between early childhood sleep problems and substance use.

Childhood sleep problems are also associated with increased risk for adult psychopathology. Parent-reported sleep and psychiatric symptoms at ages 5, 7, and 9 were compared with current anxiety and depression using standardized structured interviews at age 21 and 26 in a longitudinal sample of 943 individuals [8]. Persistent sleep problems in early childhood predicted adulthood anxiety disorders (46 %:33 % ratio of adolescents with anxiety who did and did not have persistent childhood sleep problems, respectively), but not adulthood depression, in this sample. Although similar connections between sleep and depression are found in both pediatric and adult populations, polysomnographic differences in clinical populations with depression have been less consistent in the child and adolescent literature (see Ivanenko et al. [213]).

Tourette's syndrome often results in sleep disruption. Increased SWS and decreased REM percentages, and

increased awakenings and motor tics, were observed in a sample of 14 Tourette's syndrome patients less than 23 years old compared to 11 matched controls [214]. Motor tics may disturb sleep, and patients with comorbid ADHD experience the most sleep disturbance [215, 216].

ADHD may be associated with childhood insomnia [215], sleep deprivation, and snoring and obstructive sleep apnea [63], and sleep problems are much more likely to be reported by adults with ADHD. Several polysomnographic studies in children with ADHD have reported relatively normal sleep parameters [217–219]; however, an investigation of 38 school-age boys with ADHD and 64 control school-age boys using sleep diaries and actigraphy found increased instability in sleep onset and sleep duration in the patient group [208]. Objective and subjective sleep was measured in 20 adults with primary ADHD [220]. Compared to matched controls, patients had an increase in polysomnographically measured total sleep time and periodic limb movements in sleep; the latter were inversely related to subjective total sleep time. Subjective sleep quality was lower in patients than the controls. Sleep complaints were also more likely to be reported in a sample of 120 adults with ADHD compared to a control sample, including RLS symptoms and not feeling refreshed in the morning, although complaints of insomnia were related to comorbidity with depression [221].

Rates of sleep disturbances in >75 % in children with autism have been reported [222, 223]. One study compared individuals with autism to their nonaffected siblings [224]. With the autism group, sleep problems such as bedtime resistance, insomnia, and daytime sleepiness were more likely than in the sibling group (respective odds ratios: 2.7, 4.1, and 7.6). Sleep problems were also associated with more behavioral problems such as greater withdrawal, aggression, and total behavioral problems.

Alcohol and Substance Abuse Disorders

Dependence on alcohol or other drugs of abuse almost invariably leads to sleep problems both while on and when trying to get off the substance. Withdrawal effects can often lead to insomnia or hypersomnia symptoms. The impact on sleep can last for years into abstinence, as has been documented in alcohol abuse. Long-term chronic problem drinkers have markedly fragmented and shortened sleep that contains more light and less deep sleep, as well as elevated percentages of REM sleep, after 1–2 years of abstinence [225–227]. Sleep disturbances have been suggested as a pathway for the development of alcohol and substance abuse and are associated with increased risk for relapse following substance abuse treatment. For example, the adolescent who finds she cannot fall asleep unless first smoking marijuana may shift from being an occasional to a habitual user. Alcohol is an oft-used self-medication for difficulty falling asleep; unfortunately, while alcohol is quite effective in hastening sleep onset, the effect wears off after a few hours, leading to sleep fragmentation [228]. Alcohol also has the unexpected effect of interacting with sleep loss, leading to marked daytime sleepiness [229, 230]. Likewise, sleep disruption can be highly frustrating and may be one of the motivating factors driving some back to substance use if disrupted sleep suddenly becomes very prominent during the initial withdrawal and subsequent abstinent period.

Both daytime sleepiness and insomnia symptoms can lead to self-medication with stimulants and to alcohol and marijuana use, which, given the negative effects these substances have on sleep, can lead to an escalating pattern of use and worsening sleep disturbance. Subjective sleep complaints consistently predict relapse in individuals with alcohol dependence, as do objective, polysomnographic markers of sleep disturbance. In the first few weeks of abstinence, elevated REM density was the best predictor of relapse 3 months postdischarge from a 1-month treatment program [231, 232]. At 5 months, REM measures no longer predicted relapse at 1 year; however, objective sleep disturbances consistent with insomnia symptoms, including long sleep latency and poor sleep efficiency, were predictive. Sleep latency measured about 1 month into abstinence was the best predictor of patients who relapsed by the fifth month [233].

Johnson and Breslau [234] reported a positive association between trouble sleeping and nicotine, alcohol, and other drugs of abuse in a large cross-sectional survey of 13,381 adolescents 12–17 years old, suggesting that sleep difficulty, psychiatric symptomatology, and substance use may co-occur within the same individuals. Thus, specific attention to sleep and psychiatric symptoms in people undergoing alcohol and other drug abuse treatment programs may well improve outcomes and decrease relapse rates in these populations.

Medication Effects and Substance Abuse

The reader is referred to Table 46.1 for a review of the acute, chronic, and withdrawal effects on sleep parameters of various medications and substances of abuse.

Treatment of Sleep Problems in Patients with Psychiatric Illness

Patients who present to sleep disorders centers frequently exhibit symptoms of psychopathology, which may or may not be due to psychiatric illness. Because many sleep practitioners do not have extensive psychiatric training, it is often necessary to engage the assistance of a psychiatrist or psychologist to evaluate a patient with suspected or known psychiatric illness. Psychological tests such as the Inventory of Depressive Symptoms, Beck Depression Inventory, and State Trait Anxiety Inventory are useful for screening patients with sleep disorders for psychopathology. These tests alone, however, are somewhat limited. Many patients with untreated organic sleep disorders such as sleep apnea show changes in psychological tests that are suggestive of psychopathology, but the changes may resolve following effective treatment of the disorder; continued assessment is warranted, however, as symptoms may not resolve.

Likewise, may patients with psychiatric illness often have sleep symptoms. The sleep disorder specialist may be called upon to help determine whether there is an underlying organic disorder such as sleep apnea, RLS, or periodic limb movements that may cause or contribute to the symptoms. In addition, the sleep specialist can be especially helpful in assessing and correcting behaviors that contribute to sleep impairment. The sleep disorder specialist may also be in a position to recommend sleep-specific pharmacotherapy, typically involving sedatives and stimulants (i.e., onset of action, duration of action, relative toxicity, drug interactions, drug withdrawal effects, and relative effects on alertness and sleep parameters).

There is mounting objective evidence to support the claim that behavioral/CBT-I interventions are useful in improving insomnia in patients with psychiatric illness (see Smith et al. [235]. for a thorough review of relevant issues and outcome data for CBT-I interventions in the context of other psychiatric and medical disorders). Behavioral interventions include stimulus control instructions [236] and sleep restriction [237]. CBT-I interventions usually include an additional cognitive component, such as correcting dysfunctional beliefs about sleep (e.g., "If I don't get enough sleep tonight, I'll fall apart tomorrow"), although no evidence shows that CBT-I interventions are superior to behavioral interventions alone. In addition, there are data to support the argument that patients with chronic insomnia have sustained benefit with and without adjunctive sedative administration [238, 239]. Most evidence supporting the use of behavioral intervention in psychiatric populations comes from studies in depression and PTSD. Given the links between sleep and psychopathology described earlier, however, such behavioral interventions may prove quite valuable for other disorders such as other anxiety disorders, dementia, or within pediatric populations. Indeed, a pilot study of CBT-I in 15 individuals with persistent persecutory delusions reported large reductions in both insomnia and persecutory delusions (in two-thirds and half the sample, respectively) that persisted at one month [240].

The severity of the insomnia of a psychiatric patient often parallels the severity of the illness. Therefore, the aggressiveness of medication and behavioral management of insomnia in psychiatric patients should parallel the severity of psychiatric symptoms. Patients with severe sleep disturbance due to schizophrenia or affective psychosis often require sedating neuroleptics as well as adjunctive sedative-hypnotics. Patients with schizophrenia and affective disorders with nocturnal hallucinations may need additional neuroleptic medication for better control of their illness to reduce nighttime hallucinations. Chronic psychiatric illnesses with associated insomnia are much more difficult to manage and may require long-term insomnia treatment with medications such as benzodiazepine receptor agonists. Psychiatric illnesses that are intermittent (e.g., major depression) may require hypnotics only during the active phase of the illness.

In some instances, medications used in psychiatric patients aggravate an existing organic sleep problem or insomnia. Antidepressants, antipsychotics, and antihistamines may aggravate RLS. Sometimes, nocturnal akathisia, which has symptoms very similar to RLS, is caused by neuroleptic compounds. Medications such as selective serotonin and serotonin–norepinephrine reuptake inhibitors (SSRI, SNRI), monoamine oxidase inhibitors, bupropion, buspirone, and some tricyclic drugs (protriptyline, desipramine) can have stimulating properties, may aggravate insomnia. Despite studies showing sleep disruption with stimulating antidepressants, however, patients placed on these compounds often report subjective improvement in their sleep, particularly with the SSRIs.

There is little evidence that treatment of insomnia due to depression without other interventions such as psychotherapy, antidepressant therapy, or ECT relieves depression [241]. Combinations of antidepressants and sedatives can improve insomnia without interfering with the antidepressant effectiveness or onset of action [242, 243]. Pharmacotherapy for insomnia in patients with affective disorders can be addressed in one of several ways: The patient can be given an antidepressant alone, a combination of two antidepressants (e.g., SSRI plus low-dose trazodone, doxepin, or mitazapine), or a combination of a benzodiazepine receptor agonist hypnotic plus an antidepressant. Some antidepressants, such as most of the tricyclic antidepressants and trazodone, have the advantage of causing sedation without the addition of another drug but are limited by side effects (e.g., dry mouth, constipation, myoclonus), toxicity, and daytime cognitive and alertness impairment. SSRIs are

sometimes combined with other sedating antidepressants such as trazodone to improve sleep. The potential for drug interaction between some antidepressants [244] and development of the "serotonin syndrome" exists in this scenario. Additionally, there is little empirical evidence to support the use of trazodone in primary insomnia, despite its widespread use to treat insomnia in the USA. There are no studies of long-term use of trazodone for treating insomnia [245], and unfortunately, little treatment outcomes research for secondary insomnia (due to psychiatric or other conditions) exists despite its widespread prevalence.

While there are case reports that tricyclic antidepressant and SSRIs can lead to or exacerbate RLS symptoms, this has not always been supported. Brown et al. [246] did not find an association between antidepressant use and RLS using a retrospective chart review sample of 200 consecutive patients presenting with sleep-onset insomnia. Leutgeb and Martus [247] compared RLS symptoms before and after 6 months of tricyclic or SSRI pharmacotherapy in a sample of 243 mood or anxiety disorders patients. Antidepressant pharmacotherapy was not found to be a significant risk factor for RLS symptoms, although nonopioid analgesics, usually with caffeine, were associated with increased risk of RLS.

The appropriate selection of a sedative-hypnotic for patients with psychiatric illness is often more difficult than for the general population. There is greater potential for adverse drug interactions with multiple psychotropic medications than between most sedatives prescribed along with medications used for other conditions. Particular attention must be paid to the duration of action of sedatives in patients with anxiety. There may be a tendency for increased daytime anxiety in patients taking short- and intermediate-acting sedative-hypnotics [248]. Alternative approaches include using multiple doses of intermediate-acting benzodiazepines (e.g., lorazepam, alprazolam, oxazepam) during the day and using the same medication at bedtime as a hypnotic. Another approach is to use a long-acting antianxiety agent such as diazepam, clonazepam, or chlordiazepoxide less frequently during the day and also as a hypnotic. As some of the intermediate- and long-acting benzodiazepine antianxiety agents have slower absorption, they may need to be given approximately an hour before bedtime for the sedative properties to have enough time to take effect. Patients with nocturnal panic attacks may benefit from benzodiazepines such as alprazolam, estazolam, or clonazepam. In addition, various antidepressants, β-blockers, calcium channel blockers, and α agonists may be useful.

As with all patients, those with chronic psychiatric illness with associated chronic insomnia require careful follow-up to ensure that no long-term adverse effects result from psychotropic drugs and, in cases in which medications with abuse potential are necessary, that the patients do not increase their dose. When any patient presents to the sleep disorders center taking an excessive amount of a sedative with abuse potential, or taking a normal dose of a sedative for a prolonged period, it is very important to determine whether there is a psychiatric illness or any underlying tendency to abuse drugs. Some patients with sleep disorders such as persistent psychophysiologic insomnia and periodic limb movements may not have had the underlying causes of their insomnia identified and therefore resort to long-term use of sleeping medication. These individuals may increase the dose of the sedative to quite large amounts to achieve sleep, yet do not experience the craving or euphoria often associated with substance abuse. For them, it is quite important to identify the underlying causes of the sleep problem. After long-term use of large doses of sedatives, it is very important that the patient be tapered gradually. After treatment of underlying organic sleep disorders and training in sleep hygiene and relaxation skills, these patients may be able to sleep without the help of habituating medication.

Conclusion

Although sleep quality and duration impact affective function, the pathophysiologic processes by which sleep is linked to daytime mood and functioning are poorly understood. Continued research efforts to expand our knowledge of sleep and its functions will improve our understanding of the pathophysiology of disordered sleep generally and its role in the development and maintenance of psychopathology, and pave the way for continued improvements in behavioral and pharmacologic interventions to improve outcome and functioning in individuals with sleep and/or psychiatric disorders.

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Sleep Disturbances in General Medical Disorders

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Sudhansu Chokroverty

Introduction

General medical disorders through metabolic, toxic, or anoxic disturbances may cause a disruption of neuroanatomic substrates for sleep/wakefulness by indirectly affecting the sleep-/wake-promoting neurons. It is therefore incumbent upon the sleep specialist, general internist, and primary care physician to have a high index of suspicion for the presence of sleep disorders so that appropriate steps for assessment and management of these patients can be instituted. This chapter deals with medical disorders—excluding neurologic diseases—associated with sleep dysfunction, which may cause added distress to the existing complaints related to the medical disorders and which may need special attention. For example, if a patient suffering from bronchial asthma or coronary artery disease, complaining of difficulty initiating or maintaining sleep, unrefreshing sleep, and excessive daytime sleepiness, seeks the attention of a physician, these complaints are obviously causing additional distress and need special attention. The latest edition of the International Classification of Sleep Disorders (ICSD-3) [1] does not list a separate category of sleep disturbances associated with medical disorders, in contrast to the first edition. These medical disorders are mentioned within the seven major categories of sleep disorders as well as in Appendix A of the ICSD-3 [1].

Gislason and Almqvist [2] did an epidemiologic study in a random sample of 3201 Swedish men ages 30–69 years. Difficulty initiating or maintaining sleep and too little sleep were the major complaints, followed by excessive daytime somnolence or too much sleep. Sleep maintenance problems became more frequent with increasing age. The following conditions were associated with the sleep complaints: systemic hypertension, bronchitis and bronchial asthma, musculoskeletal disorders, obesity, and diabetes mellitus. The authors suggested that the reported increased mortality among patients with sleep complaints might be related to the intercurrent somatic diseases.

In a questionnaire of 100 adult male medical and surgical patients in a teaching hospital in Melbourne, Australia, Johns and coworkers [3] found that increasing age and ischemic heart disease were mostly associated with long-term sleep disturbances. In a three-year longitudinal study comprising 6800 men and women aged 65 and older, risk factors associated with insomnia included several medical conditions such as heart disease, cancer, diabetes, and stroke as well as hip fractures and use of sedatives [4]. Several other epidemiologic studies [5–8] attest to the frequent association of sleep disturbances with medical disorders. Stroe et al. [7] studied 2612 individuals drawn from an unselected adult population-based sample (18–65 years) to characterize excess daytime sleepiness (EDS) associated with a variety of chronic medical disorders (MD) using Epworth Sleepiness Scale (ESS) as a standardized measure. Sixty-seven percent of the sample reported a MD and the prevalence of 31.4 % in individuals with MD. Among general medical disorders the highest degree of sleepiness associated with significant sleep difficulties (e.g., sleep onset and maintenance problems with frequent awakenings) was found in patients with peptic ulcer diseases. They also noted significant sleep disturbance in those with colitis and that clinically significant EDS increased directly with the number of MD. Using self-reported measures of sleep habits and polysomnographic study (obtained in a subset) in a community-based sample of 3282 men and women aged 18–65 years, Budhiraja et al. [8] documented a prevalence of insomnia of 21.4 % with 2.2 times higher odds ratio for those with any medical disorders than in those without medical disorders. They also noted that prevalence of insomnia increased with increasing number of medical conditions. However, PSG evidence of disturbed sleep was noted in only a small subset of comorbid insomnia population.

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When a patient presents to a sleep specialist with sleep disturbance, with the complaint of either insomnia or hypersomnia, the first important step is to obtain a detailed medical history and other histories, followed by physical examination to uncover a cause for the sleep disturbance. Often, the patient presents to an internist or a family practice physician, who may then refer for a consultation to a sleep specialist if there are sleep complaints. Therefore, a comprehensive knowledge of major medical disorders that may present with sleep disturbance is essential. In this chapter, a review of the salient clinical diagnostic points of some important medical disorders presenting with sleep disturbance is offered, along with information on key laboratory investigations.

Medical Disorders that Cause Sleep Disturbances

Several medical disorders are associated with sleep disturbances, as listed here. The mechanisms and general features of sleep disturbances in medical disorders are also briefly described. For further details, readers should consult general textbooks of internal medicine.

- Cardiovascular diseases: cardiac arrhythmia, congestive cardiac failure, ischemic heart disease, and nocturnal angina
- Intrinsic respiratory disorders: chronic obstructive pulmonary disease, asthma (including nocturnal asthma), and restrictive lung disease
- Gastrointestinal diseases: peptic ulcer disease, reflux esophagitis, celiac disease, Whipple's disease, and functional bowel disorder
- Endocrine diseases: hyperthyroidism, hypothyroidism, diabetes mellitus, and growth hormone deficiency and excess
- Renal disorders: chronic renal failure and sleep disturbances associated with renal dialysis
- Hematologic disorders
- Rheumatic disorders, including fibromyalgia syndrome and systemic lupus erythromatosis
- Dermatologic disorders
- Acquired immunodeficiency syndrome
- Lyme disease
- Chronic fatigue syndrome
- Medical and surgical disorders of patients in medical and surgical intensive care units
- African sleeping sickness (trypanosomiasis)
- Cancer
- Medication-related sleep–wake disturbances.

Mechanism of Sleep Disturbances in Medical Disorders

Sleep disturbance may have an adverse effect on the course of a medical illness. Thus, a vicious cycle may result from the effect of sleep disturbance on the medical disease and the effect of the medical illness on sleep architecture.

Sleep may be disturbed in medical disorders by a variety of mechanisms, including

- Indirect effects on the hypnogenic neurons in the diencephalon and brain stem, and respiratory neurons in the brain stem, by metabolic disturbances (e.g., renal, hepatic, or respiratory failure; electrolyte disturbances; hypoglycemia or hyperglycemia; ketosis; and toxic states)
- Adverse effects on sleep organization and sleep structure by drugs used to treat medical illness
- Disturbances of circadian rhythm (i.e., sleep–wake schedule)
- Effects on the peripheral respiratory mechanism (including respiratory muscles) causing respiratory sleep-disordered breathing
- Esophageal reflux, which may be due to prolongation of acid clearance of the lower esophagus, aspiration, and reflex mechanism (see Chap. 11)
- Adverse effect on sleep structure after prolonged immobilization resulting from medical disorders
- Dysfunction of the autonomic nervous system caused by medical disorder (e.g., diabetes mellitus, and amyloidosis).

General Features of Sleep Disturbances in Medical Illness

Sleep architecture, sleep continuity, and sleep organization may be affected in a variety of medical illnesses. Patients may present with either insomnia or hypersomnolence, but the most medical disorders present with insomnia. Some patients may have a mixture of insomnia and hypersomnolence (e.g., those with chronic obstructive pulmonary disease or nocturnal asthma). Other sleep complaints include abnormal motor activity and behavior intruding into sleep (parasomnias), sleep-related breathing problems with sleep fragmentation and snoring during sleep, and disturbances of normal sleep–wake rhythm (circadian rhythm disorders). Table 47.1 lists the medical causes of insomnia. For medical causes of hypersomnolence, see Table 3.1 in Chap. 3.

Patients with insomnia may complain of lack of initiation of sleep, inability to maintain sleep, repeated arousals at

Table 47.1 Medical causes of insomnia

Congestive heart failure
• Ischemic heart disease
• Nocturnal angina
• Chronic obstructive pulmonary disease
• Bronchial asthma, including nocturnal asthma
• Peptic ulcer disease
• Reflux esophagitis
• Rheumatic disorders, including fibromyalgia syndrome
• Lyme disease
• Acquired immunodeficiency syndrome
• Chronic fatigue syndrome

night, and early morning awakening. Daytime symptoms of fatigue, inability to concentrate, irritability, anxiety, and sometimes depression may be related to the sleep deprivation. Polysomnographic (PSG) findings include prolonged sleep latency, reduction of rapid eye movement (REM) sleep and slow-wave sleep (SWS), more than 10 awakenings per night, frequent stage shifts, early morning awakening, increased waking after sleep onset (WASO), and increased percentage of wakefulness and stage 1 non-REM (NREM) sleep.

Patients with hypersomnolence may present with repeated daytime somnolence, fatigue, depression, headache, and intellectual deterioration related to repeated sleep-disordered breathing (SDB) and hypoxemia [9]. PSG findings consist of SDB, repeated arousals with oxygen desaturation at night, sleep fragmentation, sleep stage shifts, reduced SWS, shortened sleep-onset latency on the multiple sleep latency test, and sometimes REM sleep abnormalities [9].

Systemic medical disorders may cause neurologic disturbances, which in turn may cause sleep disturbances either directly by affecting sleep–wake systems in the central nervous system (CNS) or indirectly by affecting breathing. Sleep-related breathing dysfunction and other sleep disturbances which may be seen in neurologic illness are described in Chap. 41.

Specific Medical Disorders and Related Sleep Disturbances

Cardiovascular Disease

It is generally well known that sleep disturbances may occur in cardiovascular diseases, particularly in patients with ischemic heart disease, myocardial infarction, or congestive cardiac failure (CCF). Cardiac arrhythmias and sudden cardiac death at night are also known to occur, although adequate objective tests, including PSG study to document such disturbances, are lacking.

Ischemic Heart Disease

A careful inquiry into history is most important in making the diagnosis. The patient complains of a sense of tightness in the middle of the chest and a band-like feeling around the chest. The pain is often induced by exertion and relieved by rest. Generally, it lasts only a few minutes. When the patient complains of pain on lying supine, it is known as *angina decubitus,* whereas pain that awakens the patient at night is known as *nocturnal angina.* Infrequently, the pain results in coronary artery spasm accompanied by transient ST-segment elevation in the electrocardiogram (ECG), and the entity is then known as *Prinzmetal's* or *variant angina.* The condition is most common in middle-aged men but may affect postmenopausal women. Complications include cardiac arrhythmias; left ventricular failure; acute myocardial infarction; and sudden cardiac, often nocturnal, death.

Sleep disturbances are very common in patients with ischemic heart disease. Pain may awaken the patient, causing frequent awakenings and reduced sleep efficiency. Obstructive sleep apnea syndrome (OSAS) is associated with arterial hypoxemia causing cardiac ischemia. Simultaneous recording of an ECG may show ST-segment depression at least 1 mm below the horizontal, whereas ST-segment elevation occurs in Prinzmetal's or variant angina. Often, the patient complains of discomfort in the arms during the retrosternal pain. Pain may sometimes radiate to the epigastrium or to the neck and the jaw. It may be accompanied by shortness of breath. An ECG is essential for the diagnosis of ischemic heart disease or myocardial infarction. Coronary angiography provides information about the site of coronary artery occlusion.

Treatment consists of avoiding exertion for patients susceptible to angina attacks and administration of drugs such as nitrates, β-blockers, and calcium channel antagonists.

Patients with severe symptoms that persist despite medical treatment may need surgical treatment in the form of coronary artery bypass grafting or stenting.

Factors contributing to myocardial ischemia, infarction, or arrhythmia include increased sympathetic surge during REM sleep, increased platelet aggregability, hypotension associated with SWS and altered balance between fibrinolytic and thrombotic factors, oxygen desaturation, and increased ventricular diastolic pressure and volume associated with supine posture. There is also increased risk of CCF among patients with the onset of myocardial infarction at night [10]. Patients with diabetes, advancing age, and impaired ventricular function are at an increased risk for developing nocturnal myocardial infarction [11, 12].

"Nondippers" (those hypertensive patients whose blood pressure during sleep does not decline or declines less than 10 % from daytime to nighttime readings) have significant risk for developing cardiac arrhythmias, stroke, and death from cardiovascular disease [13]. Newman et al. [14] have shown that daytime sleepiness associated with sleep disturbances in elderly patients, especially women, is a predictor of cardiovascular morbidity and mortality and CCF.

Nocturnal Angina, Myocardial Infarction, and Sleep Disturbance

Nocturnal angina or myocardial infarction may cause frequent arousal, sleep maintenance insomnia, and impaired sleep efficiency. Nocturnal angina is known to occur during both REM and NREM sleep stages. Karacan et al. [15] found increased sleep-onset latency, reduced SWS, decreased sleep efficiency, and very little change in REM sleep on PSG study in 10 patients with a history of nocturnal angina. In several reports, circadian susceptibility to myocardial infarction (attacks are most likely between midnight and 6:00 AM) has been described [16, 17]. Broughton and Baron [18] in an early report found decreased sleep efficiency, increased sleep stage shifts, increased awakenings, and decreased REM sleep in 12 patients with acute myocardial infarction studied in the ICU. Sleep patterns became normal by the ninth day of the illness.

Coronary artery disease (CAD) is one of the most frequent causes of morbidity and mortality [19]. Sleep-disordered breathing (SDB) and CAD have a bidirectional relationship [20]. Impairment of cardiac function by CAD determines the severity of SDB [21]. Fifty percent of patients with CAD have SDB and if the cardiac function is impaired most apneas are of obstructive nature. In contrast, in patients with acute myocardial infarction (MI) causing impaired cardiac function, half of the SDB patients will have obstructive and the other half will have predominantly central apneas [22]. Cross-sectional and case-control studies have documented increased prevalence of calcified and noncalcified coronary artery plaques (subclinical coronary atherosclerosis) in SDB [21, 23, 24].

In several epidemiologic studies, there is a clear relationship between increased cardiovascular morbidity and mortality and sleep disturbances associated with SDB. Patients with CAD and obstructive sleep apnea (OSA) may have an increased cardiac risk due to nocturnal myocardial ischemia triggered by apnea-associated oxygen desaturation. In many case-control studies in the past, an association between sleep apnea and increased risk of myocardial infarction was noted [25–27]. Epidemiologic data from the Sleep Heart Health Study demonstrated a linear relationship between the apnea–hypopnea index (AHI) and risk of CAD, including myocardial infarction [28]. In a population-based prospective study including a postal questionnaire regarding sleep complaints in a random sample of 1870 subjects, Mallon et al. [29] provided evidence at the 12-year follow-up that there was an association between difficulty falling asleep and CAD mortality in men. In a more recent population-based prospective Sleep Heart Health Study, Gottlieb et al. [30] noted that OSA was a significant predictor of incident CAD in men 70 years or less but not in older men or women of any age.

A high prevalence of OSA in patients with CAD has been noted in several other studies [31–43]. An important early observational study was done by Marin et al. [35] recruiting men with OSA or simple snorers from a sleep clinic and a population-based sample of healthy men matched for age and body mass index with untreated severe OSA patients (total $N = 1651$). All had PSGs and were followed up at least once per year for a mean of 10.1 years; compliance with treatment of OSA with continuous positive airway pressure (CPAP) was checked with a built-in meter. Multivariate analysis adjusted for confounders showed that untreated severe OSA increased the risk of fatal and nonfatal myocardial infarction and stroke compared with healthy participants; CPAP treatments reduced this risk. The authors also noted that mild-to-moderate untreated OSA patients had an intermediate risk for these events, indicating a dose–effect relationship. The survival benefit to CPAP therapy in these patients as shown by Marin et al. [35] is also supported by other studies [32, 44, 45]. Prior to the study by Marin et al. [35], long-term beneficial effects of CPAP treatment in patients with OSA and CAD were shown by Milleron et al. [46]. These authors treated 25 of 54 patients with OSA and CAD (29 declined treatment). At a mean follow-up of 87 months, the treatment significantly reduced the risk of occurrence of cardiovascular death, acute coronary syndrome, hospitalization for heart failure, or need for coronary revascularization. Similar results were observed by Doherty et al. [47], who reported that deaths from cardiovascular disease were more common in an untreated group (61 patients who were intolerant to CPAP) than in a CPAP group (107 patients) after follow-up of 7.5 years [47].

There are some more recent studies showing adverse short-term and long-term outcomes in patients with acute MI and SDB. There is evidence that patients with acute MI and SDB have more severe CAD predisposing them to the development of heart failure [21, 37–41]. Recent long-term outcome studies in patients with acute MI and SDB are all observational in nature, precluding from making any definite conclusions [21]. The study by Lee et al. [48] enrolling 120 patients with an acute MI showed that those with comorbid severe OSA had higher incidence of adverse events than those with less severe or no OSA after a follow-up period of 18 months. In another case-control study [40], including MI patients with and without OSA, those who received CPAP treatment for OSA had a lower risk of recurrent MI than untreated OSA patients and similar to those without OSA after a follow-up period of six years. However, long-term effects of CPAP treatment in patients with acute coronary syndrome and OSA in terms of preventing development of heart failure and recurrent MI and mortality cannot be determined definitely without further randomized control studies using larger number of patients and a longer follow-up [21].

In an important study, Kripke et al. [49] noted increased mortality rates among patients with ischemic heart disease, stroke, and cancer who slept 4 h or less, or more than 10 h. Wingard and Berkman [50], in their study of approximately 7000 adults over a period of 9 years, also found excessive mortality from ischemic heart disease in short sleepers (less than 7 h) and long sleepers (more than 9 h). Poor sleep was thus associated with increased risk of future cardiovascular morbidity or mortality. These results, however, were contradicted by a later study by Mallon et al. [29] observing that short or long sleep duration did not influence the risk of CAD mortality or total mortality for either gender. In a later study, Meisinger et al. [51] reported a modest association between short sleep duration and difficulty maintaining sleep, and risk of occurrence of myocardial infarction in middle-aged women, but not men, from a general population sample in Germany. In a more recent study [52], a positive association was noted between short sleep duration and poor sleep quality, and CAD in a selected sample of Indian adults. Therefore, short sleep duration and poor sleep quality can be considered modifiable CAD risk factors, at least in this population.

Heart Failure

Heart failure is the preferred term instead of congestive heart failure as pulmonary congestion, although common, is not a universal feature [53]. There is a strong association between advancing age and HF, and 10 % of the population over the age of 80 has HF. Furthermore, in the USA, HF is the leading cause of hospitalization for those older than 65 years. Chronic HF is a growing public health problem affecting more than 2 % of the adult population, and HF is a leading cause of morbidity and mortality [53, 54]. SDB is the most common comorbidity in HF and newly diagnosed CSA and OSA are independently associated with increased mortality in HF [55–60]. There are two phenotypes: HF with reduced (<50 %) ejection fraction (EF) [HFrEF] or what is known as systolic HF; and HF with preserved (exceeding 50 %) EF (HFpEF) and this is now the preferred term instead of what was known as diastolic HF [60]. About 40–50 % of patients with HF belong to HFpEF. HFpEF is often associated with comorbidities (e.g., hypertension, type 2 diabetes mellitus, and atrial fibrillation) and is commonly seen in older individuals [53, 60, 61]. SDB occurs in 70 % or more of the HF patients (OSA and CSA–CSB, each in about half of these patients). Rostral fluid shift from the lower extremities in the recumbent position at night in HF patients worsens OSA [62, 63]. CSA–CSB relates in part to the instability of the central respiratory controllers in the brain stem [53, 59, 64–67].

Mechanism of Central Apnea and Cheyne–Stokes Breathing in Heart Failure

CSB (see Fig. 41.6b in Chap. 41) is characteristic of heart failure.

The following factors play a role in the complex mechanism of CSA–CSB during sleep in HF [52–66, 68–79].

1. Increased loop gain;
2. Increased arterial circulation time;
3. Decreased functional residual capacity (FRC);
4. Altered apnea threshold;
5. Decreased reactivity of cerebral blood flow; and
6. Physiologic instability of the respiratory control system during transition to sleep, sleep stage shifts, and arousals.

Loop Gain (see also Chap. 25)

This is an engineering term implying a ratio of the ventilatory response to internal or external stimuli (e.g., a disturbance in ventilations such as apnea–hypopnea). In HF, there is an augmented chemosensitivity (i.e., increased loop gain) caused by both a pulmonary congestion and an unstable respiratory controller [59, 60, 64, 78, 79] causing increased ventilation in response to increased partial pressure of arterial carbon dioxide ($PaCO_2$) and also to an extent decreased partial pressure of oxygen (PaO_2) resulting in further instability in the central controller. Recent work has shown that CO_2 plays a key role in the pathophysiology of CSR (see further on) [59, 66, 78]. The increased loop gain in HF results from three major components [59]:

1. Increased chemosensitivity (increased central controller gain);
2. Decreased FRC (i.e., increased plant gain causing a large change in $PaCO_2$ for a given change in ventilation); and
3. Increased circulation time (mixing gain).

Increased Arterial Circulation Time These results from a combination of cardiomegaly, decreased cardiac output, and increased pulmonary blood volume. This delayed circulation time prolongs the time it takes for pulmonary blood $Paco_2$ and Pao_2 to reach the central and peripheral chemoreceptor sites. The longer the delay is, the longer is the cycle of CSB. The circulation delay is very common in HFrEF but the circulation time may be normal in HFpEF.

Decreased Functional Residual Capacity (FRC) It is due to a combination of pleural effusion, enlarged heart, and pulmonary congestion causing decreased pulmonary compliance in patients with heart failure. FRC decreases further in the supine position, promoting CSB. Decreased FRC causes underdamping—that is, for a given change in ventilation (e.g., transient cessation of breathing), there is an increased response to changes in Pao_2 and $Paco_2$ [4, 59, 65].

Altered Apnea Threshold Respiration during NREM sleep depends entirely on the metabolic control system (mainly $Paco_2$ levels) and so a small change in $Paco_2$ level will have intense effect on ventilation [58–60, 80, 81]. The apnea threshold (defined as the level of $Paco_2$ below which breathing stops) is close to the actual level of $Paco_2$ during sleep. This proximity of the two $Paco_2$ levels is called $Paco_2$ reserve which is further narrowed in some HF patients promoting development of CSA in HF. Furthermore, HF patients chronically hyperventilate due to pulmonary congestion resulting from rostral fluid shift in the supine position stimulating pulmonary irritant receptors to stimulate ventilation [59, 64, 66] which lowers the CO_2 crossing the apnea threshold [81]. The resultant apnea promotes increase in CO_2 causing hyperventilation. Thus, a vicious cycle of crescendo–decrescendo (CSR) pattern of breathing is perpetuated.

Decreased Reactivity of Cerebral Blood Flow A change in $Paco_2$ causes alteration in cerebral blood flow (CBF) which is called cerebrovascular reactivity [59, 66]. The physiologic homeostatic regulation of CBF in response to changes in $Paco_2$ protects brain including central chemoreceptors. Patients with HF have decreased cerebrovascular response to $Paco_2$ causing breathing instability during sleep [59, 66, 82].

CSB occurs during sleep and wakefulness, although it is pronounced during sleep. It has been shown that HF patients with CSB during daytime wakefulness have almost a four-fold increased mortality [78]. In many patients with heart failure, there is low $Paco_2$ and a failure of rise of $Paco_2$ during sleep, unlike that which occurs in normal individuals as a result of increased venous return in the supine position, increased respiratory rate, and increased ventilation. Heart failure patients with $Paco_2$ less than 35 mm Hg have a high probability for developing central apnea because the low $Paco_2$ is close to the apnea threshold (i.e., the level of $Paco_2$ at which breathing ceases due to a lack of chemoreceptor stimulation).

Mechanism of Obstructive Apnea in Heart Failure CSB itself may predispose to obstructive apnea by decreasing the tone of the upper airway dilator muscles at the end of the ventilatory cycle (the lowest point or nadir). Other factors for obstructive apnea in heart failure include venous congestion in the oropharyngeal region in right heart failure, especially in the supine position, and comorbid obesity [59, 64]. The presence of periodic breathing (e.g., CSB) in heart failure may increase the morbidity and mortality and so it is important to be aware of this. Treatment with CPAP/bilevel positive airway pressure (BIPAP) with or without low-flow (1–2 L/min) supplemental oxygen inhalation and assisted servo-ventilation (ASV) in selective cases may improve the pattern of breathing (see further on).

Clinical-Pathologic Consequences of Heart Failure and Sleep Apnea

The common symptoms of heart failure in obstructive sleep apnea patients include paroxysmal nocturnal dyspnea, orthopnea, daytime sleepiness and fatigue, and sleep onset and maintenance insomnia. Recurrent episodes of apnea and hypopneas accompanied by repeated arousals, hypoxemia, hypercapnia, and sympathetic activation adversely affect cardiovascular function, particularly in patients with CAD and incipient cardiac dysfunction. Indications for overnight PSG in these patients include witnessed apneas, habitual snoring, nocturnal angina, and unrefreshing restless sleep; overnight PSG is also indicated in patients requiring cardioverters or defibrillators: those requiring cardiac transplantation and those with cardiac arrhythmias. It should be noted that many patients with HF may not present with the classic symptoms of sleep apnea such as snoring, daytime sleepiness, and obesity explaining an underdiagnosis of CSA in HF [58, 59, 78, 83]. Many of these patients may actually have unexplained insomnia and have reduced quality of life and increased mortality [59, 78, 83]. Therefore, a high index of suspicion for possible SRBD in HF patients is needed and many even recommend routine screening for SRBD in these

patients to improve outcome and prevent adverse consequences. The pathophysiological consequences resulting from repeated episodes of apnea, hypoxemia, reoxygenation, and arousals throughout the night consist of increased sympathetic nervous system activation, oxidative stress, systemic inflammation, and endothelial dysfunction. CSA–CSB is associated with malignant nocturnal cardiac arrhythmias (e.g., ventricular tachycardia and premature ventricular contractions) in part due to increased sympathetic activation [59, 66]. Atrial fibrillation is also common in HF patients with CSA. Patients with severe CSB may show reduced heart rate variability suggesting autonomic dysfunction [78, 84, 85] which may be associated with increased mortality in HF patients [86]. Treatment of CSA improves nocturnal cardiac arrhythmias and the associated increased mortality [66, 78, 79, 83].

There is an increased mortality associated with sleep apnea and heart failure [87–89]. He et al. [88] reported for the first time that, among 385 men with OSA, those with an apnea index of more than 20 per hour had an increased mortality when compared to those who had been treated with either CPAP or tracheotomy. This was a retrospective study, but later studies confirmed these earlier observations [32, 34]. In a more recent study, Gami et al. [90] reported occurrence of sudden death from cardiac causes in 46 % of patients with OSA as compared to 21 % without OSA from midnight to 6:00 AM. It should be noted that several factors have been associated with the development and progression of CCF and increased mortality in OSA. The following factors are thought to be responsible for vascular endothelial dysfunction causing CAD, hypertension, and stroke: increased sympathetic activity, repeated hypoxemias, re-oxygenation, hypercapnia, hypercoagulopathy, release of endothelin, abnormal endothelial-dependent vasodilation and vascular growth factor and apoptosis, increased levels of inflammatory mediators, increased concentration of adhesion molecules, and oxidative stress [65, 67, 91–94]. Randomized controlled trials with CPAP in patients with OSA have shown improved cardiac function, sympathetic nervous system activity, quality of life, reduction of blood pressure, and reversal of the various neural, hormonal, and biochemical abnormalities, suggesting a cause-and-effect relationship [95–97].

Most of the more recent studies confirmed an increased mortality with a hazard ratio of 2.1–5.7 for CSB [75, 78, 98–101] excepting two studies [102, 103]. Khayat et al. [55] reported the results of the largest prospective study evaluating the effect of SRBD on post-discharge mortality in 1117 hospitalized inpatients with acute heart failure (AHF) with a median follow-up of three years. They concluded that newly diagnosed CSA and OSA are both independently associated with post-discharge mortality in patients with AHF and reduced EF. An independent relationship between SRBD and mortality in untreated patients with stable chronic HF has been reported in several studies [56, 101, 104]. The effect of treatment, however, of CSA or OSA on survival in HF remains unknown.

Principles of Treatment of Heart Failure and Sleep Apnea
The principles of treatment of HF with sleep apnea (both OSA and CSA–CSB) are outlined in the following five steps:

1. The initial step is optimizing medical therapy for HF;
2. General measures;
3. Treatment of OSA;
4. Treatment of CSA–CSB; and
5. Miscellaneous other measures.

I. **Medical therapy for HF**. It is beyond the scope of this chapter to describe in detail medical therapy and the readers are referred to standard texts for this [54]. Briefly, diuretics (both thiazide and loop diuretics) are used to relieve pulmonary congestion, beta-blockers are used to reduce sympathetic activation, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) a combination of ARBs and neprilysin inhibitor and aldosterone antagonist are used to reduce ventricular afterload and improve cardiac output [59, 60, 64, 66, 78, 105, 106]. It is notable that digitalis glycosides which were a mainstay of treatment for decades had no beneficial effect on mortality in HF in a major clinical trial, and these cardiac glycosides are no longer first-line therapy for HF [105].

II. **General measures**. These include weight loss, avoidance of supine sleep, smoking, alcohol ingestion, and sedative-hypnotic use before bedtime (see Table 47.2).

III. **Treatment of obstructive sleep apnea**. The gold standard for treatment of OSA in heart failure is treatment with CPAP or BIPAP (see Chap. 34). Adequate treatment of OSA in heart failure utilizing the measures outlined in Table 47.2 eliminates excessive daytime somnolence (EDS) and improves sleep of these patients. Such treatment may also decrease blood pressure in hypertensive patients and may help reduce the dose of antihypertensive medications. The treatment of OSA with CPAP increases ventricular ejection fraction significantly even within one month after therapy [58, 59, 107–109]. In a meta-analysis of studies involving both OSA and HF, CPAP treatment improved left ventricular ejection fraction [110]. The most recent addition to OSA treatment is hypoglossal nerve stimulation by an implanted device trial in an observational study in 126

Table 47.2 Principles of treatment of obstructive sleep apnea and heart failure

Adequate treatment of heart failure
General Measures
• Weight reduction if needed
• Follow general sleep hygiene measures
• Avoid alcohol and sedative-hypnotics
• Cessation of smoking
• Avoid supine position in subset of patients with positional OSA
Treatment of OSA
• Treat any nasal abnormalities (e.g., septal deviation)
• Nocturnal CPAP/BIPAP
• Supplemental oxygen through CPAP if needed
• Dental appliances
• Upper airway surgery
• Hypoglossal nerve stimulation
• Tracheostomy

BIPAP Bilevel positive airway pressure; *CPAP* Continuous positive airway pressure; *OSA* Obstructive sleep apnea

individuals (OSA without HF) who could not tolerate or accept CPAP [111]. The data on HFpEF are limited. Arias et al. [112] reported that 15 of 27 consecutive patients with OSA had impaired left ventricular relaxation. The authors performed a double-blind sham-controlled crossover trial of CPAP for 12 weeks and noted an improvement in diastolic function.

IV. **Treatment of CSA–CSF**. Treatment of central sleep apnea in heart failure is more difficult than treating OSA. The general measures for treating central apnea/CSB are listed in Table 47.3. Adequate treatment of heart failure may improve or eliminate periodic breathing and decrease circulation time due to increased stroke volume, decreased pulmonary congestion, increased FRC, and decreased sympathetic activity. Javaheri et al. [75, 79, 113, 114] have clearly shown improvement after aggressive treatment of heart failure with diuretics, ACE inhibitors, ARBs, β-blockers, and positive airway pressure devices. CPAP treatment for central apnea has not produced as dramatic results as in OSA. Javaheri has shown that, in mild-to-moderate central apnea patients, overnight use of CPAP improved central apnea in 43 % of patients with systolic heart failure (HFrEF) [115, 116]. The number of premature ventricular contractions, bigemini, and episodes of ventricular tachycardia also decreased. However, severe central apnea patients with heart failure did not respond to short-term CPAP treatment. Treatment lasting from one-to-three months with nasal CPAP in patients with heart failure showed a reduction in the AHI with desaturation and decrease in plasma and urinary norepinephrine, in addition to an increase in ventricular ejection fraction. There are other reports of quality of life [117] improvement and reduction of mortality in such patients after CPAP treatment [35, 118–121], although a large Canadian CPAP trial for congestive heart failure (CANPAP) contradicted this [113]. However, a later study by Arzt et al. [122] showed suppression of central sleep apnea by CPAP and transplant-free survival in heart failure. Cardiac transplantation will virtually eliminate central apnea, but a large number of such patients develop OSA due to weight gain [123]. Cardiac pacing and cardiac resynchronization therapy have been shown to improve some patients with central apnea in heart failure [124–128]. Atrial pacing was thought to improve patients with obstructive apnea [124, 128], but other studies [129–132] did not support such an improvement. Nocturnal nasal supplemental oxygen therapy improves central apnea in heart failure patients [133–140]. Such treatment decreases muscle sympathetic nerve activity and improves left ventricular ejection fraction and quality of life. Additional studies, however, are needed to determine whether such treatment decreases the morbidity and mortality in patients with HFrEF [65, 140]. Bordier et al. [140] in a recent review analyzed 17 studies to determine the effects of nocturnal oxygen therapy (NOT) as an alternative treatment for sleep apnea in HF patients. They concluded that NOT was effective in approximately 50 % of cases with a 50 % reduction of AHI in CSA–CSB but had no effect on obstructive respiratory events. Furthermore, there were no reports of NOT-related death or other harmful effects on the myocardium.

Since its introduction in 2001, adaptive servo-ventilation (ASV) has been shown to reduce CSA events and improve

Table 47.3 Principles of treatment of central apnea and Cheyne–Stokes breathing in heart failure

Aggressive treatment of heart failure
• CPAP/BIPAP
• Adaptive pressure support servo-ventilation
• Atrial overdrive pacing or biventricular pacing
• Supplemental oxygen
• Cardiac transplantation
Pharmacologic treatment (e.g., acetazolamide, theophylline, and diazepam) in selective cases

BIPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure

cardiac function in patients with CSB and HF [104, 141–148]. In contrast to these findings, the results of the recently published servo-ventilation heart failure (SERVE-HF) trial put the sleep community in turmoil [149]. Cowie et al. [149] included 1325 patients with symptomatic chronic HF (NYHA grades II–IV) with reduced ejection fraction (≤ 45 %) and predominant central apnea (AHI ≥ 15) who were randomized to treatment with a specific ASV device (ResMed Autoset CS) or conventional medical therapy (control group). ASV had no significant benefit on the primary outcomes and no beneficial effect on a broad spectrum of functional measures. In contrast, there was a significant increase in both all-cause and cardiovascular mortality with the ASV group. The increased mortality in this study is unexplained. In an editorial in Sleep Medicine Journal by Randerath [142] and in another editorial in New England Journal of Medicine by Magalang and Pack [140], several questions were raised and possible mechanism (some of which were also suggested by Cowie et al. [149]) were discussed. Until the issue is further clarified, the current recommendation [150] is not to use ASV in HF patients with predominantly CSA.

Miscellaneous Other Measures

1. Nocturnal supplemental carbon dioxide (or added dead space) has been used to increase $PaCO_2$ above the apnea threshold but is currently not recommended to treat CSA–CSB in HF [64, 66, 78].
2. Pharmacotherapy with theophylline (a respiratory and cardiac stimulant) and acetazolamide (a carbonic anhydrase inhibitor causing metabolic acidosis) has been used in small trials to treat CSA–CSB in HF with limited success. These agents are not commonly used in HF patients [55, 66, 78, 151].
3. Device-based therapy and cardiac transplantation. These measures have been described above briefly. The latest addition to device-based therapeutic armamentarium is phrenic nerve stimulation [152]. This is an implantable device-based therapy inserted intravenously into a thoracic vein. The phrenic nerve can be stimulated at a set frequency to prevent central apnea [59]. A multicenter randomized control trial (RCT) is ongoing [153].

Hypertension

A high prevalence (22–48 %) of sleep apnea and related symptoms (e.g., EDS) has been noted in patients with systemic hypertension [154–157]. In contrast, studies by Escourrour et al. [158] found no significant difference between 21 hypertensive and 29 normotensive patients in sleep stage distribution and disorganization, AHI and duration, and arterial oxygen saturation (Sao_2). The prevalence of hypertension in sleep apnea patients is approximately 50–90 % [5, 159–167]. In the Wisconsin Sleep Cohort study, a dose–response relationship between hypertension and the AHI as well as snoring has been described [168, 169]. Furthermore, studies have confirmed that treatment of sleep apnea by nasal CPAP reduces blood pressure [6, 170].

Previously Stradling and Davies and others [7, 171–175] made a persuasive argument based on a critical analysis of the literature, and taking into consideration the confounding variables (e.g., age, sex, smoking, obesity, and alcohol consumption), that there is no convincing evidence yet supporting the contention that OSA is a significant independent risk factor for sustained hypertension in humans. Silverberg and Oksenberg [176, 177], however, contended that, even when the confounding factors are taken into consideration, OSA is an independent risk factor for hypertension and that treatment of OSA reduces daytime as well as nighttime blood pressure.

There is now convincing evidence of an association between hypertension and sleep apnea [178–183]. Epidemiologic studies suggest that approximately 50 % of patients with OSA have hypertension and about 30 % of patients with hypertension develop OSA. Compelling evidence on the association between OSA and hypertension in

humans has been provided by epidemiologic studies [164, 179, 181, 184]. In drug-resistant hypertension, the prevalence of OSA is even higher; one study quoted a figure of 83 % [185]. The Sleep Heart Health Study, in a prospective cross-sectional analysis of more than 6000 subjects, showed an independent association between hypertension and OSA [179]. A subgroup analysis by Bixler et al. [180] failed to show this association in subjects older than 65 years. The Wisconsin Sleep Cohort Study [181] was able to show that OSA is an independent risk factor for high blood pressure during a 4-year follow-up study that also showed a dose–response relationship between OSA and blood pressure independent of confounding factors. A population-based case-control study failed to show an association between OSA and high blood pressure in postmenopausal woman [186]. OSA has been considered to be an important risk factor for hypertension [187]. Several reports including randomized, placebo-controlled studies revealed very significant reduction in mean blood pressure during sleep in the CPAP-treated group [188–193] (see Chap. 34 for a detailed discussion). Several recent studies [194, 195] supported these results. Oral appliances also have shown to improve hypertension. A number of well-designed studies [196–199], however, have failed to show significant improvement in blood pressure after CPAP treatment. In a prospective long-term follow-up study [200] of 83 patients with uncontrolled hypertension, coronary heart disease (CHD), and OSA randomized to control or CPAP groups, 73 patients completed the study. CPAP was used for 4.5 ± 1.1 h/night and the median follow-up period was 36 months (interquartile range = 24–54 months). Systolic blood pressure (SBP) decreased by 8 mm Hg ($P = 0.01$) but diastolic blood pressure (DBP) did not reach statistical significance (81 ± 10 mm Hg vs. 79 ± 8 mm Hg; $P = 0.49$). ESS was significantly reduced ($P < 0.001$) and hypertension control improved in the CPAP group. The same group of authors in another study sought to determine predictors of blood pressure fall with CPAP treatment in hypertensive patients with CHD and OSA [201]. Sixty-six patients with moderate-to-severe OSA had used CPAP for a mean of 4.3 h/night with a mean follow-up of 36 months (range 24–60). There was a reduction in both SBP and DBP as well as improvement of daytime somnolence as measured by ESS. These authors noted that baseline BMI, mean blood pressure, and CPAP compliance are independent predictors of a decrease of BP in these patients.

Thus, OSA is a risk factor for hypertension [202–204] but some studies found a lack of such relationship [205–207]. However, as stated above, several randomized control trials (RCTs) have shown a decrement of BP in OSA patients following CPPA treatment [204, 208–210]. In a meta-analysis covering six studies (observational and randomized control trials), the pooled estimate showed a favorable reduction of BP after CPAP treatment in patients with resistant hypertension and OSA [211]. A recent large meta-analysis including 1000 CPAP-treated patients with OSA from 16 RCTS showed significant but small reduction in BP [212]. Several recent RCTs also showed that the average fall of BP is small [207, 213, 214]. Daytime hypersomnolence [assessed by Epworth Sleepiness Scale (ESS)] has been cited as an important predictive factor for BP reduction after CPAP [201]. It should, however, be noted that CPAP does not cause significant reduction of BP on nonsleepy hypertensive patients with OSA [215, 216]. Huang et al. [201] cited the following factors contributing to hypertension in OSA patients: 1. increased sympathetic activation; 2. systemic inflammation; 3. oxidative stress; 4. endogenous vasoactive factors; 5. endothelial dysfunction; and 6. metabolic regulation.

It has been estimated that a fall of BP of 3.3 mm Hg is associated with a reduction of 20 % risk of stroke and a 15 % risk of coronary arterial disease [201].

Although the results have so far been promising, further studies are needed to confirm the beneficial effect of CPAP therapy on high blood pressure in OSA patients [211, 217, 218].

"Nondippers," those hypertensive patients whose blood pressure during sleep does not decline or declines less than 10 % from daytime to nighttime readings have significant risk for developing cardiac arrhythmias, stroke, and death from cardiovascular disease [13, 219, 220]. In addition, extreme dippers (whose BP during high time sleep falls excessively by 20 % or more) and reverse dippers (those in whom the BP instead of declining increases during sleep above the waking values) are similarly also at increased risk.

In addition to systemic hypertension, OSA may also cause severe pulmonary arterial hypertension, particularly in patients with preexisting cardiopulmonary diseases [65, 187]. Factors for developing pulmonary hypertension include several mechanisms such as repeated hypoxemia causing pulmonary vasoconstriction, left ventricular diastolic dysfunction resulting in increased left ventricular end-diastolic pressure, and possible pulmonary vascular remodeling [65]. It is important to remember that several long-term studies have shown improvement of pulmonary arterial hypertension following treatment of OSA with CPAP.

The recognition of the association of metabolic syndrome with OSA should direct attention to an early diagnosis and treatment with a view to preventing serious consequences such as stroke or myocardial infarction. The metabolic syndrome is a serious risk factor for cardiovascular disease and includes hypertension, hypertriglyceridemia (dyslipidemia), central obesity, glucose intolerance and insulin resistance (syndrome X) or hyperinsulinemia, and low levels of high-density lipoprotein cholesterol [51, 65, 221]. Kaplan

[221] spoke about a deadly quartet: upper body obesity, glucose intolerance, hypertriglyceridemia, and hypertension.

Cardiac Arrhythmias and Sleep

An understanding of the interaction between the autonomic nervous system (ANS), cardiac innervation, and sleep is important to appreciate the effects of sleep on cardiac rhythms. Readers are referred to Chaps. 11 and 41 for such review. It is known that there is an imbalance between sympathetic and parasympathetic tone during REM and NREM sleep. During REM sleep, there is an intermittent increase in sympathetic nerve activity, reaching even higher levels than in wakefulness. This surge causes intermittent increase in the heart rate and blood pressure, although at the same time, vagal tone (parasympathetic activity) is suppressed, causing irregular breathing, oxygen desaturation, and a few periods of apneas. These alterations in the sympathetic and parasympathetic balance can be clinically measured by recording heart rate variability (see also Chap. 11). The high-frequency (HF: 0.15–0.4 Hz) heart rate spectrum reflects parasympathetic tone, the low-frequency (LF: 0.01–0.05 Hz) spectrum reflects sympathetic tone, and the intermediate frequency (0.06–0.14 Hz) spectrum reflects a mixture of both activities. The LF/HF ratio is used in clinical practice to indicate overall sympathetic tone. Sudden cardiac death after myocardial infarction is associated with a decrease of heart rate variability. Based on heart rate variability studies, Bonnet and Arand [222] have clearly shown an increase in HF heart rate spectrum with a decrease of LF in NREM and an increase in LF and a decrease in HF in REM sleep and wakefulness.

A relationship between sleep and atrioventricular arrhythmias has been noted, but reports in the literature are somewhat contradictory. Atrial arrhythmias, such as atrial flutter, atrial fibrillation, paroxysmal atrial tachycardia [223], and first- and second-degree atrioventricular block [224], have been described in normal subjects during REM sleep, but no clear relationship between different sleep stages and atrial arrhythmias has emerged. A prominent sinus arrhythmia has been noted in several studies in normal subjects using Holter monitoring [225]. Brodsky and colleagues [226] monitored 24-h continuous ECGs in 50 male medical students with no apparent heart disease and observed sinus pauses of 1.8–2.0 s' duration in 30 % of them, as well as episodes of second-degree heart block (Mobitz type I) in another 6 %. Guilleminault and associates [227] noted 42 episodes of sinus arrest in four young, healthy adults that lasted 2–9 s during REM sleep. No associated apneas or significant oxygen desaturation was observed. Osuna and Patino [228] observed REM-related sinus arrest in a subject without any associated OSA or oxygen desaturation. The incidence of nocturnal bradyarrhythmias decreases with advancing age [229].

Contradictory results have been noted in human studies of the effects of sleep on ventricular arrhythmia, but the majority shows an antiarrhythmic effect of sleep on ventricular premature beats (VPBs) [230]. This seems to be due to enhanced parasympathetic tone during sleep, conferring protection against ventricular arrhythmia, and sudden cardiac death. Pitzalis et al. [231] evaluated 45 patients with frequent premature ventricular contractions to find out whether the phenomenon of sleep suppression may be a sensitive and specific parameter for predicting the antiarrhythmic effect of β-blockers and premature ventricular contractions. Based on Holter recordings, these authors concluded that sleep suppression of the premature ventricular contractions was a sensitive characteristic for identifying those patients with premature ventricular contractions who are likely to benefit from administration of β-blockers. Ventricular arrhythmias are also noted to occur during arousal from sleep [230]. A classic example was provided by Wellens and colleagues [232], who described a 14-year-old girl awakened from sleep by a loud auditory stimulus who had ventricular tachyarrhythmia. The authors postulated that increased sympathetic activity triggered these episodes, because they could be prevented by the β-blocker propranolol.

Lown's group [233] noted reduction of VPBs by at least 50 % in 22 subjects and 25–35 % in 13 others during sleep. De Silva [234] noted reduction in VPBs in all stages except REM sleep, with stages 3 and 4 NREM sleep showing the most effect. Pickering and colleagues [235] described 12 untreated patients with frequent ventricular extrasystoles who showed a significant decrease in both the heart rate and extrasystoles during sleep. Intravenous propranolol, and to a lesser extent intravenous phenylephrine, produced a similar decrease in the heart rate and ventricular arrhythmias during wakefulness. These changes appear to be mediated by the ANS, the sympathetic system dominating the parasympathetic system. They found that the frequency of ventricular arrhythmias was similar in both REM and NREM sleep. Their findings are similar to those of Lown and colleagues [233].

The observations of Pickering's group [235] also contrast with those of Smith et al. [236], who studied 18 patients in a coronary care unit to document frequency of cardiac arrhythmias in wakefulness and sleep. They found no significant difference in the occurrence of ventricular or atrial premature contractions during sleep and wakefulness. Similarly, Richards et al. [237], in a pilot overnight sleep study on nine patients with cardiovascular disease in the medical ICU, did not find any increase in incidence of dysrhythmias during any sleep stages or during sleep state in these critical

care unit patients. Disturbed sleep in coronary care patients [23] may explain the discrepancies in these data.

Cardiac Arrhythmias, Autonomic Deficits, and Obstructive Sleep Apnea Syndrome

Several investigators [94, 225, 238–242] reported a variety of cardiac arrhythmias in patients with OSAS (Fig. 47.1). These arrhythmias are determined by the changes in the ANS. The most common is bradytachyarrhythmia alternating during apnea and immediately after termination of apnea. The other dysrhythmias consist of the following: sinus bradycardia with less than 30 beats/min; sinus pauses lasting from 2 to 13 s; second-degree heart block; and ventricular ectopic beats, including complex and multifocal ectopic beats, and ventricular tachycardia. There is a clear relationship between the level of Sa_{O_2} and premature ventricular contractions and sleep apnea syndrome. Patients with Sa_{O_2} below 60 % are the most vulnerable. Hoffstein and Mateik [243], using nocturnal PSG, prospectively studied 458 patients with OSAS. They found a prevalence rate of 58 % of cardiac arrhythmias in these patients, and those with arrhythmias had more severe apnea and nocturnal hypoxemia than those without arrhythmias. Earlier studies showed a higher prevalence than more recent epidemiologic studies suggested. Roche et al. [244] performed a prospective study in 147 consecutive patients referred for assessment of OSAS. The authors found OSAS in over 45 % with AHI 10. They found significantly more nocturnal paroxysmal asystole in OSAS patients than in controls (10.6 % vs. 1.2 %). They further noted that the number of episodes of bradycardia and pauses increased with the severity of OSAS. CPAP treatment followed for one year showed amelioration of arrhythmic events in OSAS patients, indicating the usefulness of CPAP treatment. The Sleep Heart Health Study [242] investigated 228 patients with severe sleep apnea (AHI >30/h) and 338 individuals without sleep apnea, and found a significant relationship between nonsustained ventricular tachycardia, bigeminy, trigeminy, or quadrigeminy and severe OSA.

ANS dysfunction was implicated in cardiovascular morbidity and mortality in OSAS (e.g., hypertension, left ventricular failure, increased risk of coronary or cerebral events) [245]. CPAP treatment can prevent the cardiovascular risks associated with ANS dysfunction.

Gami et al. [90], after reviewing the PSGs and death certificates of 112 Minnesota residents who have died suddenly from cardiac causes during the period from July 1987 to July 2003, concluded that OSAS patients had a peak sudden death from cardiac causes during sleeping hours, contrasting with the nadir of sudden death in those without OSAS and in the general population. Peltier et al. [246] recruited 32 patients complaining of EDS and snoring and performed PSG studies and 2-h oral glucose tolerance tests as well as autonomic testing consisting of heart rate response to deep breathing, Valsalva maneuver, head-up tilt, and quantitative sudomotor axon reflex testing (QSART). These authors found that 19 of 24 patients with OSAS had abnormal glucose tolerance, and cardiac autonomic dysfunction was more strongly associated with impaired glucose regulation than OSAS. They concluded that cardiovagal and adrenergic dysfunction are responsible for cardiovascular adverse effects in OSAS, but the question remains whether impaired glucose regulation in such patients may have been responsible for such ANS dysfunction. Further studies using

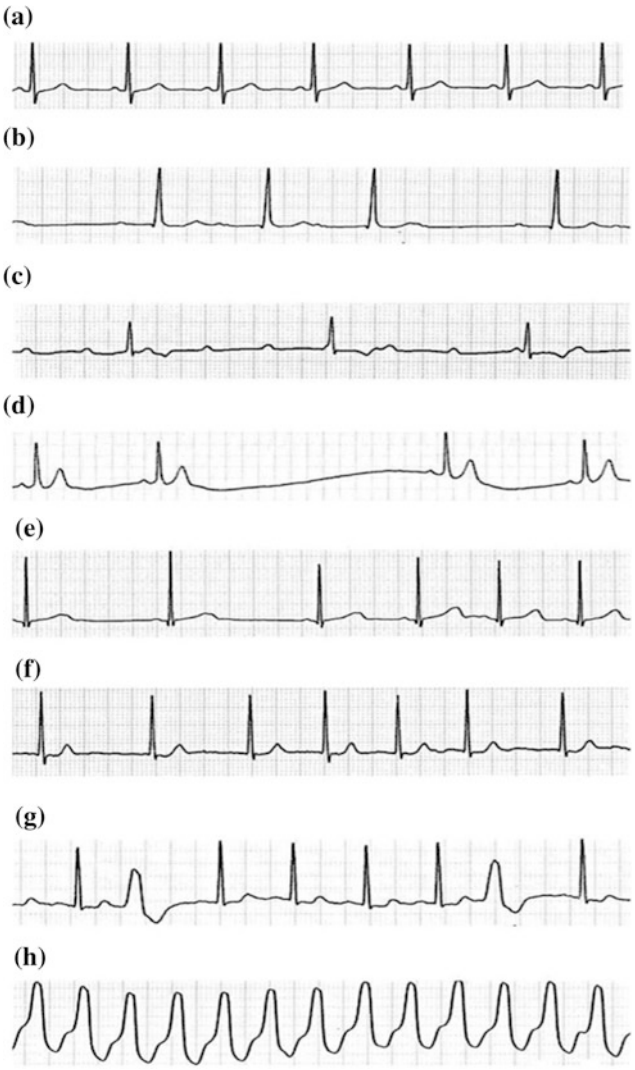

Fig. 47.1 Examples of various ECG rhythms that might be seen during sleep. **a** Normal sinus rhythm. **b**, **c** Atrioventricular conduction block: P wave is not followed by the QRS complex. **d** Sinus pause. **e** Atrial fibrillation: No P waves are visible. **f** Sinus arrhythmia. **g** Isolated extrasystoles. **h** Ventricular tachycardia. Note that the QRS complex is narrow in the supraventricular arrhythmias differentiating them from ventricular arrhythmias (in the absence of preexisting bundle branch block). (Reprinted from Ref. [94]) (Reproduced with permission [94])

larger numbers of patients are needed to resolve this complex relationship between OSAS, autonomic function, and glucose regulation.

Cardiac Arrhythmias and OSA

Recent studies have confirmed a high prevalence of cardiac arrhythmias in OSA patients [247–253] with improvement after effective CPAP therapy [247, 248, 250, 251]. Linz et al. [251] in a systematic literature search noted that the prevalence of OSA in atrial fibrillation (AF) patients is high (about 40–50 %). Effective CPAP therapy of OSA improves catheter ablation success rates in AF patients. Dediu et al. [248] found a favorable response after successful positive pressure therapy in patients with cardiac arrhythmias. Vizzardi et al. [250] conducted a meta-analysis including 1298 articles and observed that arrhythmias are frequent in OSA. Based on this analysis, the authors suggested that treatment with an implantable cardioverter/defibrillator and CPAP should be considered in some of these patients who may show improvement. Figueiras-Rama et al. [251] in a review article concluded that tachy-bradyarrhythmics including AF are highly prevalent in OSA (moderate–severe) which is an indifferent risk factor for such atrial arrhythmias. CPAP therapy has shown a significant effect in preventing or abolishing atrial arrhythmias. Some of the suggested mechanisms in the literature include hypoxia, hypercapnia, autonomic dysfunction, inflammation, negative intrathoracic pressure, and acute atrial stretch. Namveldt et al. [253] in a population-based study from Norway recruited 486 subjects (mean age of 49 with 55 % men) who underwent an overnight PSG study for suspected OSA. They found that 271 out of 486 (55.8 %) had OSA. The prevalence of ventricular premature complexes is increased in middle-aged patients with mild–moderate OSA suggesting an association between OSA and ventricular arrhythmias even in mild OSA patients.

Sudden Cardiac Death

An analysis of the time of sudden cardiac death in 2203 individuals by Muller et al. [254] revealed a low incidence during the night and a high incidence from 7:00 to 11:00 AM. Similarly, nonfatal myocardial infarction and myocardial ischemic episodes are more likely to occur in the morning. It is known that sympathetic activity increases in the morning, causing increased myocardial electrical instability; thus, sudden cardiac death (SCD) may result from a primary fatal arrhythmia.

LaRovere et al. [255] correlated increased cardiovascular mortality among patients with a first myocardial infarction with reduced baroreflex sensitivity. *Reduced baroreflex sensitivity* is defined as less slowing in heart rate for a given rise in arterial blood pressure, which indicates reduced vagal tone.

McWilliams [256] first suggested that ventricular fibrillation is the cause of sudden death and that sympathetic discharges play an important role in causing this fatal arrhythmia. During sleep, cardiovascular hemodynamic activity is decreased, as are heart rate and blood pressure, owing to withdrawal of sympathetic tone and increased vagal tone (see Chap. 11).

Reduced vagal tone, as measured by decreased heart rate variability in 24-h Holter monitoring, was found by Kleiger et al. [257] to be a powerful predictor of increased mortality and SCD after myocardial infarction. Autonomic imbalance (either sympathetic overactivity or parasympathetic underactivity) may trigger ventricular arrhythmias [258].

Besides myocardial infarction, another clinical entity known as *long QT syndrome* may cause syncope or sudden death [259–264]. Based on an evaluation of 54 patients with congenital long QT syndrome (LQTS) and 67 controls, Shamsuzzaman et al. [265] concluded that the presence and severity of OSA in patients with LQTS are associated with increased QT prolongation which is an important biomarker of sudden death. Treatment of OSA may reduce QT prolongation, thus reducing the risk of LQTS-triggered SCD. In long QT syndrome, the ECG shows a prolonged QT interval with abnormal U waves and torsades de pointes (polymorphic ventricular tachycardia). Gami et al. [266] included 10,701 consecutive adults who had PSG study between July 1987 and July 2003 to assess incident resuscitated or fatal SCD. During an average follow-up of 5.3 years, 142 patients had resuscitated or fatal SCD (annual rate of 0.27 %). The authors concluded that in 10,701 adults referred for PSG, OSA predicted incident SCD. The degree of nocturnal hypoxemia strongly predicted SCD. OSA is thus a novel risk factor for SCD. Another cause of sudden death in young adults in the Western literature is the Brugada syndrome, described in 1992 [267–270]. Patients with this syndrome present with life-threatening ventricular tachyarrhythmias without any structural cardiac lesions, and the ECG shows characteristic abnormalities of atypical right bundle branch block and ST-segment elevation over the right precordial leads. An involvement of the ANS is suggested, and abnormal I-MIBG single-photon emission computed tomography (SPECT) uptake in Brugada syndrome indicating presynaptic sympathetic dysfunction of the heart has been reported by Wichter et al. [271]. The Brugada syndrome has a genetic basis and links to mutation in *SCN5A,* the gene encoding the alpha subunit of the sodium channel. The ideal treatment suggested for this syndrome is implantation of a cardioverter/defibrillator. Sudden unexpected nocturnal death syndrome (SUNDS) is another disorder found in Southeast Asia with abnormal ECG findings similar to those noted in Brugada syndrome [272, 273]. It has been

suggested that both SUNDS and Brugada syndrome may have a common genetic and biophysical basis [274].

Intrinsic Respiratory Disorders

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD), the third leading cause of death in the USA and worldwide, is caused largely by cigarette smoking and also combined with a genetic α_1-antitrypsin deficiency. Patil et al. [275] in a retrospective review reported a 2.5 % in-hospital mortality following acute exacerbation of COPD in 70,000 patients. The COPD is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as an irreversible progressive airflow limitation causing an inflammatory response in the lung parenchyma giving rise to the clinical features of chronic bronchitis and emphysema [276].

The salient clinical features include chronic cough, exertional dyspnea, tightness in the chest, and sometimes wheeze. Physical examination reveals inspiratory and expiratory sonorous wheeze (rhonchi) and crackles (crepitations or rales). Patients with resting hypoxemia and hypercapnia may exhibit cyanosis. Investigations should include radiographic examination of the chest and pulmonary function tests. Complications include polycythemia, pulmonary hypertension, cor pulmonale, and cardiac arrhythmias.

To understand sleep disturbances, it is important to have some knowledge of gas exchange during sleep [277]. In COPD patients, Sao_2 and Pao_2 fall and $Paco_2$ rises during sleep; these values worsen during REM sleep [278–280]. In some patients, SDB (e.g., apnea, hypopnea, or periodic breathing) is associated with reduced Sao_2 saturation, which is generally short lived (less than 1 min) and mild to moderate in intensity [281–283]. Episodes of Sao_2 desaturation during REM sleep last more than 5 min and are more severe than in NREM sleep [281, 284, 285]. Physiologic changes in respiration, respiratory muscles, and control of breathing (see Chap. 11) during sleep adversely affect breathing in these patients. In COPD patients, two basic mechanisms worsen hypoxemia during sleep: alveolar hypoventilation, which is worse during REM sleep, and ventilation–perfusion mismatch [286–289].

Other groups at risk for hypoxemia include the middle-aged and elderly (particularly men), postmenopausal women, and obese individuals [277]. Diminished ventilatory response to hypoxia and hypercapnia in some COPD patients contributes to increasing nocturnal oxygen desaturation [277]. Nocturnal hypoxemia causes repeated disruption and fragmentation of sleep architecture [277].

COPD patients are traditionally divided into two phenotypes, "pink puffers" and "blue bloaters" [290–292]. Pink puffers generally have normal blood gases, hyperinflated lungs, no hypoxemia or hypercapnia, no cardiomegaly, or cor pulmonale, and are cachectic and short of breath [277]. In contrast, blue bloaters are generally hypoxemic and hypercapnic, have cor pulmonale, polycythemia, an enlarged heart, reduced ventilatory response to hypoxemia and hypercapnia, have a stout body habit, and have less dyspnea [277]. In general, blue bloaters have more severe hypoxemia of longer duration than pink puffers [293, 294]. It should be noted that oxygen saturation for both groups is somewhat similar during wakefulness and in the upright position but is markedly different during sleep. The worse value is noted in blue bloaters. There are no absolute criteria for determining which groups of COPD patients have more severe nocturnal hypoxemia. Patients must be monitored at night, which is impractical considering the large number of patients who should be monitored. "Blue bloaters" phenotype is considered emphysema-predominant COPD, whereas "pink puffers" phenotype is considered airway (nonemphysematous)-predominant COPD (based on chest CT scans). "Pink puffers" type is associated with an increased risk of diabetes mellitus. There are contentious issues to be resolved regarding definition and staging and phenotyping of COPD as we know today which may be different from the classic phenotypes of "pink puffers" and "blue bloaters." In some patients, COPD may coexist with OSAS—a condition called *overlap syndrome,* a term introduced by Flenley [295]. In a study [296] of 265 consecutive unselected OSAS patients, COPD was found to be present in 30 (11 %) of these patients. Coexistence of COPD and OSAS results in a higher risk of pulmonary hypertension and CCF than in those with only OSAS [286, 287]. In addition, Bednarek et al. [297] noted that the course of SDB is more severe in subjects with overlap syndrome, but these authors found that COPD in subjects with OSAS was as frequent as in the general population. OSAS has a major impact on quality of life in patients with overlap syndrome [298]. COPD patients who are hypoxemic during wakefulness become more hypoxemic during sleep, which is most severe during REM sleep. Alveolar hypoventilation and ventilation–perfusion mismatching are the two most important factors (alveolar hypoventilation being the predominant factor) for worsening of nocturnal hypoxemia in these patients. Several factors contribute to worsening of hypoxemia during sleep in COPD patients [299]. 1. Diaphragm may be flattened and lengthened due to hyperventilation; 2. COPD patients have increased "dead space" (i.e., does not participate in gas exchange) due to rapid shallow breathing pattern during phasic REM sleep; 3. Many have increased airway resistance during sleep; and 4. Hypoxic and hypercapnic ventilator responses are

more blunted in COPD patients than in normal. Hypoxemia is worse in patients with overlap syndrome [300–302]. The consequences of sleep hypoxemia include pulmonary hypertension due to hypoxic pulmonary vasoconstriction and cardiac arrhythmias [303].

Changes in Sleep Architecture

Disturbances in sleep architecture in COPD patients have been reported by several authors [278, 304–313]. These disturbances may be summarized as follows: a reduction of sleep efficiency, delayed sleep onset, increased WASO, frequent stage shifts, and frequent arousals. Arand et al. [304] correlated these findings with EDS. These patients are more likely to have difficulty with falling and staying asleep as well as EDS [311]. Chronic coughing and nocturnal wheezing in addition to nocturnal oxygen desaturation are mostly responsible for arousals from sleep in these patients.

Nighttime symptoms of COPD patients impacting their sleep quality are often "a forgotten dimension" of COPD [314, 315] in 2011; an expert panel was convened in Barcelona, Spain, to address this gap [314]. It has been suggested that the prevalence of nocturnal symptoms and sleep disturbance may exceed 75 % in COPD patients. The panel concluded that nighttime symptoms are of multifunctional origin and warrant further investigation.

A number of factors cause sleep disturbances in COPD patients, resulting in disturbed electroencephalographic (EEG) sleep patterns, including the use of drugs that have a sleep-reducing effect, such as methylxanthines; increased nocturnal cough resulting from accumulated bronchial secretions; and associated hypoxemia and hypercapnia [286, 316], and comorbid disorders (e.g., OSA, RLS, depression, and cardiovascular diseases) [317, 318]. In a study by Calverley [309], administration of supplemental oxygen at 2 L/min by nasal cannula during sleep improved both oxygen saturation at night and sleep architecture, in terms of decreasing sleep latency and increasing all stages of sleep, including REM and SWS. Other reports did not note improved sleep quality, but the nocturnal hypoxemia did improve after oxygen administration [304, 305].

Aoki et al. [319] noted four patterns of SDB in the desaturation group of COPD patients: hypoventilation, paradoxical movement, periodic breathing, and unclassified pattern. Urbano and Mohsenin [310] listed the following eight mechanisms to explain nonapneic oxygen desaturation during sleep in COPD patients: decreased functional residual capacity, diminished hypoxic and hypercapnic ventilatory responses, impaired respiratory mechanical effectiveness, diminished arousal responses, respiratory muscle fatigue, diminished nonchemical respiratory drive, increased upper airway resistance, and the position of baseline saturation values while awake on the oxyhemoglobin dissociation curve.

Diagnostic Considerations

The most important test to document airflow obstruction and determine severity of COPD is spirometry. An FEV_1/FVC ratio (FEV_1 divided by forced vital capacity [FVC]) of less than 0.70 defines an obstructive defect [317, 320]. The COPD severity is determined by observing FEV_1 percent, predicted as follows: mild, less than 80 %; moderate, 50–80 %; severe, 30–50 %; and very severe, less than 30 % [321]. The spirometric measurements are performed before and after bronchodilator therapy, and other pulmonary function tests may also be important. In addition, pulse oximetry and arterial blood gas determinations, chest radiograph and high-resolution computed tomography chest scan, ECG, and determinations of α_1-antitrypsin levels may be useful. In patients suspected to have an associated OSA (overlap syndrome), an overnight PSG is essential.

Treatment Considerations

The cornerstone of treatment for COPD includes smoking cessation, bronchodilators or inhaled steroids, and pulmonary rehabilitation [320, 322]. The ultimate goal is improvement of sleep quality and quality of life as a result of improvement of lung mechanics and gas exchange. All patients must avoid risk factors by instituting smoking cessation, getting early pneumococcal and influenza vaccinations, and receiving patient education and exercise training. The mainstay of COPD treatment is bronchodilators, which include anticholinergics and β_2-agonists. Metered-dose inhalers and nebulizers both work well. In severe cases, in addition to short- and long-acting bronchodilators (long-acting agents such as salmeterol have largely replaced short-acting agents [albuterol] which may still be used for "rescue" or as-needed basis), inhaled corticosteroids may be needed. In very severe cases, oral corticosteroids (but only on alternate days, using the lowest effective dose) combined with inhaled corticosteroids may have to be used. The role of supplemental oxygen therapy is discussed below. For patients not able to use inhaled medication, oral therapy including sustained-release theophylline in addition to a β_2-agonist or anticholinergic may have to be used. Theophylline can also be useful to control nighttime symptoms; however, nighttime symptoms may cause insomnia that itself needs separate treatment consideration. Insomnia is prevalent in COPD patients and needs to be treated to improve quality of life; however, use of hypnotics in the hypercapnic patient with severe COPD might be dangerous [311, 323]. Benzodiazepines may be dangerous for elderly COPD patients, particularly those with overlap syndrome. Nonbenzodiazepine receptor drugs may be used with some benefit, but even these drugs may promote apnea, thus exacerbating hypoxemia in COPD patients. Ramelteon has been shown to be safe and efficacious in mild-to-moderate COPD and OSA patients; however, further research is needed to determine

the safety in this population [311]. In patients with overlap syndrome, treatment with CPAP or BIPAP therapy may have to be used, but such treatment in these patients may not necessarily lead to an improvement in the coexistent COPD [324]. However, more recent studies have shown that treatment of OSA with CPAP in patients with overlap syndrome improves daytime arterial blood gas abnormalities, nocturnal oxygen saturation, and daytime sleepiness as measured by ESS [325]. Furthermore, in a prospective study of overlap syndrome, it was noted that patients who used CPAP had significantly lower risk of death compared with those who did not use CPAP [326].

In summary, current guidelines for medical therapy in COPD recommend "stepping up" triple therapy (a combination of long-acting beta agonists [e.g., salmeterol], muscarinic antagonists [e.g., triotropim], and glucocorticoids for moderate–severe COPD patients [327]). However, Magnussen et al. [328] have now shown in a recent trial that "stepping down" therapy (discontinuing inhaled glucocorticoids but keeping the other two agents) did not make a significant difference in terms of risks of moderate–severe exacerbations. In very severe cases not responding adequately to medical therapy, lung volume reduction surgery or lung transplantation should be considered [320].

Treatment of Nocturnal Oxygen Desaturation

Investigators have become aware of severe nocturnal hypoxemia in many COPD patients [278–280]. This nocturnal hypoxemia may or may not be accompanied by sleep-related apnea, hypopnea, or periodic breathing and impairment of gas exchange [281–283]. It is clear that repeated or prolonged oxygen desaturation at night may cause cardiac arrhythmias and may lead to pulmonary hypertension and cor pulmonale [329]. In addition, COPD patients show changes in sleep architecture [278, 304–309, 312, 313] that may be related to the poor quality of sleep or may be secondary to nocturnal hypoxemia causing disruption of nocturnal EEG sleep stages. Oxygen desaturation during sleep in COPD patients can be identified only if PSG, using sleep staging or continuous monitoring of oxygenation, is performed. Several studies show episodes of oxygen desaturation during sleep in COPD patients. An important study by Wynne's group [281] showed that oxygen desaturation could be associated with two types of patients: those with OSA (apnea and hypopnea) and those without OSA. In patients with OSA, the desaturation typically lasts less than 1 min and is mild. In the other group, the desaturation lasts 1–30 min and is associated with a profound decrease in oxygen saturation. The maximum episodes, lasting longer than 5 min, occur during REM sleep. Similar episodes of nocturnal oxygen desaturation have been described in patients with kyphoscoliosis [330, 331], in young patients with cystic fibrosis [285, 332, 333] and in patients with interstitial lung disease [334, 335].

Modern treatment of nocturnal hypoxemia is administration of oxygen by nasal cannula at a slow flow rate, usually less than 2 L/min. The multi-center study by the Nocturnal Oxygen Therapy Trial Group [336] and the Medical Research Council Working Party study [337] showed increased longevity for patients who used continuous supplemental oxygen at home. The Thoracic Society of Australia and New Zealand has published a position statement for oxygen therapy in COPD patients [338].

Particular indications for supplemental oxygen can be summarized as follows: daytime Pa_{O_2} below 55 mm Hg (Sa_{O_2} below 88 %) and daytime Pa_{O_2} between 56 and 60 mm Hg (or Sa_{O_2} of 89 %) accompanied by signs of right-side heart failure, unexplained polycythemia, pulmonary hypertension, and cor pulmonale [316, 339, 340], as well as significant nocturnal or exercise-induced oxygen desaturation. Oxygen administration may also improve sleep architecture [309]. O'Reilly and Bailey [341] reviewed the published evidence for and against the use of long-term oxygen treatment in COPD, summarized the problems with current guidelines, and suggested important areas for future research. Earlier, Croxton and Bailey [342] published recommendations for long-term oxygen treatment for COPD for future research based on a National Heart, Lung and Blood Institute Workshop report.

The question of safety of oxygen administration has to be determined [277]. Some patients become more hypercapnic after oxygen administration [278]. Furthermore, Motta and Guilleminault [343] showed the worsening effects of administration of oxygen at night in patients with OSAS. In an earlier study, Chokroverty et al. [344] reported worsening of apnea and prolongation of apnea after administration of 100 % of oxygen in four patients with obesity-hypoventilation syndrome. Many COPD patients may have OSA (overlap syndrome) [278, 295, 296], so physicians must be careful during administration of oxygen. Kearley and colleagues [345] have shown that administration of oxygen at 2 L/min reduces the episodic desaturation. Fleetham et al. [346] confirmed this finding, but Guilleminault et al. [283] contradicted these findings in five patients with excessive sleepiness associated with chronic obstructive airflow disease. The multiple institution studies by the Nocturnal Oxygen Therapy Trial Group [336] showed the relative safety of oxygen therapy, however, including home oxygen. In COPD patients undergoing long-term oxygen therapy, it may be useful to monitor breathing and oxygen saturation by finger pulse oximetry during sleep at night [347]. The role of noninvasive intermittent positive pressure ventilation (NIPPV) to improve hypoxemia in COPD patients remains undetermined [348, 349] in the absence of adequate clinical

trials using a large number of patients. However, in a recent prospective, multicenter, randomized control trial, Kohnlein and coworkers [350] investigated the effect of long-term NIPPV in 195 patients (102 NIPPV groups and 93 control groups) in advanced stable hypercapnic COPD. The authors concluded that addition of long-term NIPPV to standard therapy improved all-cause mortality after 12 months of follow-up of hypercapnic, stable COPD patients. This positive observation was reinforced later by Windisch et al. [351] after summarizing the current literature on NIPPV in COPD. These authors stated that there is now increasing evidence to support the role of NIPPV in hypercapnic COPD patients but how to select such patients needs to be determined.

Bronchial Asthma, Including Nocturnal Asthma

The characteristic clinical trials of asthma are the paroxysm of dyspnea, wheezing, and cough [352]. The paroxysmal attacks of wheezing and breathlessness may occur at any hour of the day or night, and the nocturnal attacks are distributed at random without any relationship to a particular sleep stage. Nocturnal symptoms of wheezing and coughing at least once per week are noted in as many as 75 % of asthmatics [353]. Breathing is characterized by prolonged expiration accompanied by wheezing and unproductive cough. There may be tightness of the chest and palpitation. The attacks typically last for 1–2 h. When the attacks last hours, the disorder is called *acute severe asthma* or *status asthmaticus;* this is a life-threatening condition because of extreme respiratory distress and arterial hypoxemia.

Pulmonary function tests and radiographic examination of the chest are important for confirming the diagnosis of bronchial asthma [352]. Abnormalities of certain pulmonary function tests [i.e., FEV_1, vital capacity (VC), and peak expiratory flow (PEF)] suggest airflow obstruction. An overnight fall in PEF of over 15 % associated with characteristic history is diagnostic of nocturnal asthma [354]. Chest radiography may reveal hyperinflated lungs and emphysema.

Sleep Disturbances in Bronchial Asthma

A variety of sleep disturbances have been noted in patients with asthma [355–364]. Janson et al. [363], using questionnaires and sleep diaries, studied the prevalence of sleep complaints and sleep disturbances prospectively in 98 consecutive adult asthma patients attending an outpatient clinic in Uppsala, Sweden. Compared with 226 age- and sex-matched controls, the authors found a high incidence of sleep disturbances in asthma patients, including early morning awakening, difficulty in maintaining sleep, and EDS. Sleep disturbances in general consist of a combination of insomnia and hypersomnia. Polysomnographic studies may reveal disruption of sleep architecture as well as sleep apnea in some patients. Nocturnal exacerbation of symptoms during sleep is a frequent finding in asthma patients [287, 353, 365].

There is evidence of progressive bronchoconstriction and hypoxemia during sleep in patients with asthma [354, 356]. In an important study by Turner-Warwick [357], 94 % of 7729 asthmatics surveyed woke up at least once a night with symptoms of asthma, 74 % at least one night a week, 64 % at least three nights a week, and 39 % every night. Nocturnal asthma is a potentially serious problem, as there is a high incidence of respiratory arrest and sudden death in adult asthmatics between midnight and 8:00 AM [358, 359].

To understand the relationship between the attacks of asthma and sleep stage and time of night, Kales et al. [360] studied six men and six women aged 20–45 years with PSG, each for 2–3 consecutive nights. They observed a total of 93 asthma attacks in these patients, 73 during NREM sleep, and 18 during REM. They did not find a relationship between asthma attacks and sleep stage or time of night. Sleep pattern showed less total sleep time, frequent WASOs, early final awakenings, and reduced stage 4 sleep. Kales' group [361] observed similar findings in a PSG study of 10 asthmatic children. Montplaisir and colleagues [362] studied 12 asthmatics, eight of whom showed nocturnal attacks on sleep studies (six women and two men aged 20–51 years).

Two questionnaire surveys from the European community [363, 364] found that bronchial asthma was associated with increased daytime sleepiness and impaired subjective quality of sleep (difficulty initiating sleep and early morning awakenings). One survey also noted increased prevalence of snoring and sleep-related apneas during sleep [363]. In the same survey, associated allergic rhinitis may have been a confounding variable. Twenty-six attacks were documented. No attacks occurred in stage 3 or 4 NREM sleep, nor were attacks more frequent during REM than NREM sleep. Thus, stages 3 and 4 sleep was "protective." Sleep efficiency was decreased. The number and duration of apneas were not significantly greater in asthmatics than in controls. Episodes of oxygen desaturation occurred only in the asthmatics. In a retrospective analysis of PSG recordings from children aged 5–17 years with (n = 113) and without (n = 104) asthma from a single pediatric sleep unit in Australia, Jensen et al. [366] reported that female asthmatic children had longer sleep latency but the male asthmatic children had shorter sleep duration, thus underscoring the gender difference in sleep disturbance among asthmatic children. Sleep efficiency and waking time after sleep onset were altered in asthmatics. When there were no attacks, no difference in sleep architecture was noted between the controls and the patients, which suggested that sleep disturbances are characteristic of unstable asthma with nocturnal attacks.

A number of pathogenic mechanisms for sleep disturbances and nocturnal exacerbations of asthma have been suggested [287, 353–355, 367–370]:

- Sleep deprivation [371]
- Impaired ventilatory function in the supine posture [372]
- A decrease in circulating epinephrine at night, with an increase in histamine [373]
- Gastroesophageal reflux [374, 375]
- Marked fluctuation in airway tone during REM sleep [376]
- Theophylline, a commonly used asthma drug that may cause insomnia [377, 378] and increased episodes of gastroesophageal reflux [379, 380] (a study by Hubert's group [381] found no such increase in asthmatics taking theophylline)
- Prolonged administration of corticosteroids in some asthmatics, which may have adverse effects on sleep and daytime functioning because of increased incidence of OSA [381, 382]
- Increased cellular inflammatory response in the bronchopulmonary region at night [369, 383]
- Miscellaneous factors, including allergens (e.g., house dust); increased bronchial secretions combined with suppression of cough, especially during REM sleep; airway cooling at night; increased pulmonary resistance; altered bronchial reactivity; normal propensity for worsening of lung function during sleep; normally increased vagal tone during sleep, which may be a major cause of nocturnal bronchoconstriction as evidenced by circadian desynchronization studies and cholinergic blockade studies [384, 385]; and suppressed arousal response to bronchoconstriction in severe nocturnal asthma [369]
- Certain circadian factors [367–370].

The following evidence supports the claim that circadian factors contribute to nocturnal exacerbation of asthma:

1. PEF typically is highest at 4:00 PM and lowest at 4:00 AM [369]. The variation is ordinarily approximately 5–8 %, but if it reaches 50 %, as it can in some asthmatics, there is the danger of respiratory arrest [369]. This circadian variation in PEF is related to sleep and not to recumbency or the hour [368–370].
2. Airway resistance as measured breath by breath is not increased in normal individuals at night, but asthmatics show a circadian rhythm of increased airway resistance at night that is related to the duration of sleep and not to sleep stages [369, 386].
3. OSA is more prevalent and more severe in severe asthmatics [365, 387–391]. Asthma in turn is more prevalent in OSA [392].
4. Finally, tonsillar hypertrophy has been reported to be more frequent in children with a history of wheezing

Treatment of Bronchial Asthma

Treatment of bronchial asthma, including nocturnal asthma, can be grouped into two main components: [352] 1. Rescue agents (acute relievers) and 2. The controller treatment (agents that modify the airway environment causing less frequent occurrence of airway narrowing).

The rescue treatment includes a rapid-acting β-agonist as inhaler; this is the mainstay of bronchodilator treatment of asthma: a short-acting β2-selective inhaler (e.g., albuterol) on an as-needed basis in patients with mild intermittent asthma (by nebulizer or metered-dose inhaler). The dose consists of two "puffs" from the inhaler with a separation of 3–5 min between the first and the second puffs. The first puff dilates the narrowed airways and then the second puff has a better chance of access to the affected areas of the lungs. This treatment can be repeated every 4–6 h. Another rescue treatment is an anticholinergic agent (e.g., ipratropium bromide, an atropinic agent) which inhibits acetylcholine release promoting bronchodilation. It is given as two puffs every 4–6 h in a metered-dose inhaler.

The controller treatment includes inhaled corticosteroids (e.g., fluticasone, budesonide, and triamcinolone) to improve lung function and prevent exacerbation of asthmatic attacks. One must consider adverse effects of steroids.

Other Modalities of Treatment [352] consist of antileukotrienes (e.g., montelukast, 10 mg tablet once a day), long-acting β-agonists (e.g., salmeterol), one-to-two puffs every 12 h as controller agents, and theophylline bromide for moderate to persistent asthmatics who are also receiving other agents as described above. Systemic corticosteroids may be considered as last resort for moderate-to-severe persistent asthma. Rarely monoclonal antibody treatment (e.g., omalizumab, lebrikizumab, and mepolizumab [not FDA approved in USA]) has been prescribed for severe cases of asthma. Finally in children with tonsillar hypertrophy, adenotonsillectomy is followed by improvement in asthma symptoms [393]. Other measures include treating the reversible factors such as allergens, nasal congestion, or bronchopulmonary infections, and using a humidifier [369].

In a double-blind, placebo-controlled crossover study, Kraft et al. [394] and Wiegand et al. [395] reported that salmeterol, an inhaled β_2-agonist with a prolonged duration of action, improved the number of nocturnal awakenings with nocturnal asthma. Wiegand et al. [395] found that salmeterol was superior to theophylline in maintaining nocturnal FEV_1 levels and in improving morning and evening PEF, and in an improvement in patient perception of sleep but not in PSG measures of sleep architecture. Previously, several studies showed efficacy of salmeterol in

nocturnal asthma, primarily in combination with inhaled corticosteroids [396–400].

Sleep disturbances in asthma caused by nocturnal asthma attacks should not be treated with hypnotic medicines; rather, the best treatment is vigorous treatment of the asthmatic attacks by using oral and preferably inhaled steroids, salmeterol, and anticholinergic medications (e.g., inhaled ipratropium bromide) as stated above [322, 352, 354, 369, 395, 401, 402]. Patients with PSG evidence of OSA should be treated with CPAP, which not only is effective for OSA but also helps nocturnal asthmatic symptoms. Ciftci et al. [389] reported moderate-to-severe OSA based on an AHI of 15 in 16 of 43 asthmatic patients with nocturnal symptoms. CPAP treatment improved nocturnal symptoms but did not correct pulmonary function test abnormalities. Patients with gastroesophageal reflux disease (GERD) often have worse symptoms of the disease at night, which may worsen the nocturnal asthmatic symptoms. Treatment of GERD with proton pump inhibitors (e.g., omeprazole) at bedtime may improve nocturnal asthmatic symptoms and sleep quality [403, 404]. However, the evidence is conflicting; Coughlan et al. [405], after a systematic review, concluded that clear evidence or improvement of nocturnal asthmatic symptoms after treating GERD is lacking.

Restrictive Lung Disease

Restrictive lung disease is characterized functionally by a reduction of total lung capacity, FRC, VC, expiratory reserve volume, and diffusion capacity but preservation of the normal ratio of FEV_1 to FVC [335]. This may be due to intrapulmonary restriction (e.g., interstitial lung disease) or extrapulmonary restriction resulting from diseases of the chest wall (e.g., kyphoscoliosis) or pleura; neuromuscular diseases; obesity; or pregnancy, which may abnormally elevate the diaphragm.

Interstitial Lung Disease

Etiopathogenesis

Interstitial lung disease (ILD) may result from a variety of causes, including idiopathic pulmonary fibrosis, fibrosing alveolitis associated with connective tissue disorders, pulmonary sarcoidosis, occupational dust exposure, pulmonary damage resulting from drugs, or radiotherapy to the thorax [406–410]. The common features of all these conditions include alveolar thickening due to fibrosis, cellular exudates, or edema; increased stiffening of the lungs causing reduced compliance; and ventilation–perfusion mismatch giving rise to hypoxemia, hyperventilation, and hypocapnia.

Clinical Features

Features of interstitial lung disease include progressive exertional dyspnea, a dry cough, clubbing of the fingers, and pulmonary crackles (crepitations) on auscultation of the lungs. The diagnosis is based on a combination of characteristic clinical features, radiographic findings (e.g., diffuse pulmonary fibrosis), and pulmonary function test results.

Sleep Abnormalities

Several authors [334, 408–416] reported on sleep studies in interstitial lung disease. Sleep abnormalities consist of repeated arousals with sleep fragmentation and multiple sleep stage shifts, increased stage 1, and reduced REM sleep accompanied by oxygen desaturation during REM and NREM sleep owing to episodic hypoventilation and ventilation–perfusion mismatch, and occasionally OSA. Mermigkis et al. [412], in a retrospective study, reported OSA in 18 patients with interstitial lung disease. These authors concluded that an increased body mass index and a significant impairment in pulmonary function tests may predict the occurrence of OSA in these patients, and it is important to make the diagnosis and treat comorbid OSA to improve quality of life. Milidi et al. [40] in a review article described fatigue as a disabling symptom of ILD, and the patients show poor sleep quality and SRBD correlating with impaired sleep quality. PSG studies document frequent sleep apnea–hypopnea as well as reduced sleep efficiency, SWS, and REM sleep in addition to REM-related hypoventilation. Treatment of sleep-breathing disorders improves quality of life. Schiza et al. [413] observed an increasing prevalence of OSA in idiopathic pulmonary fibrosis (IPF). The recently published IPF guidelines recognized OSA as an important comorbidity affecting patients' survival.

There is no effective treatment for interstitial lung disease except to treat the comorbid conditions such as OSA. Corticosteroids are found to be effective in some cases. George and Kryger [335] advocated symptomatic treatment with supplemental nocturnal oxygen therapy according to the guidelines developed by the Nocturnal Oxygen Therapy Trial Group [336]. In summary, supportive care, treatment of comorbid conditions, and ultimately lung transplantation are the only therapeutic options available for these conditions.

Kyphoscoliosis

Kyphoscoliosis is a thoracic cage deformity that causes extrapulmonary restriction of the lungs and gives rise to impairment of pulmonary functions, as described earlier for restrictive lung diseases. The condition may be primary (idiopathic) or secondary to neuromuscular disease, spondylitis, or Marfan syndrome [335].

In severe cases of kyphoscoliosis, breathing disorders during sleep (e.g., central, obstructive, and mixed apneas associated with oxygen desaturation) and sleep disturbances (e.g., disrupted night sleep, reduced NREM stages 2 through 4 and REM sleep, and EDS) have been described [330, 331, 335].

The best treatment for patients with chronic respiratory failure secondary to severe kyphoscoliosis is NIPPV. This

has been described in detail in Chap. 41. Long-term NIPPV treatment improves nocturnal and daytime blood gases, respiratory muscle performance, pulmonary function, and hypoventilation-related symptoms in patients with severe kyphoscoliosis [417–419].

Lung Transplant Recipients and Sleep Dysfunction

Lung transplantation has recently become a life-saving modality and a treatment of last resort in many patients with end-stage lung disease (ESLD) (e.g., idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease or COPD, and cystic fibrosis). However, these patients are at increasing risk for poor sleep due to comorbidities and use of immunosuppressants, steroids, and other medications [420, 421]. Insomnia and sleep-disordered breathing (SDB) are the most frequently reported sleep disorders in these patients. Often the sleep disorders are unrecognized and untreated. It is important to screen such patients for sleep disorder before and after transplantation. Sommerwerck et al. [422] polysomnographically studied 77 patients (45 men) and noted a prevalence of SDB of 49.4 % (42.9 % OSA and 6.5 % CSA). The authors concluded that the prevalence of SDB is high in stable lung transplant recipients and COPD is an independent predictor of SDB. High prevalence of SDB was also noted in several other reports [420, 421, 423–425]. Some of the factors cited are weight gain, altered chemosensitivity, and central control of breathing and medication use. Reilly-Spong et al. [420] using Pittsburg Sleep Quality Index and actigraphy in patients with various organs including lung transplant recipients reported poor sleepers in 41 %. Sleeplessness is mostly related to steroids and immunosuppressive medications.

Gastrointestinal Diseases

Peptic Ulcer Disease

A peptic ulcer is an ulcer in the lower esophagus, stomach, or duodenum [426]. The prevalence of peptic ulcer in the general population is fairly high—approximately 10 % of the adult population—and men are most often affected. The most common presentation of peptic ulcer is episodic pain localized to the epigastrium that is relieved by food, antacids, or other acid suppressants. The pain has a characteristic periodicity and extends over many years. The patient generally can localize the pain to the epigastrium. Occasionally, however, it is referred to the interscapular region at the lower chest and is usually described as burning or gnawing. Duodenal pain is often described as "hunger pain" and is relieved by eating. An important feature is that the pain awakens patients 2–3 h after retiring to bed, disturbing sleep. An important physical sign is the so-called pointing sign and localized epigastric tenderness.

The natural history of the disease is episodic occurrence over a course of days or weeks, after which the pain disappears, to recur weeks or months later. Between attacks the patient feels well. Presentation may be secondary to complications of ulcer, such as an acute episode of bleeding or perforation or even an episode of gastric obstruction. The differential diagnosis of ulcer pain should include cholecystitis, angina, gastroesophageal reflux, esophagitis, and pancreatitis. Definitive diagnosis is established by barium examination of the gastroduodenal tract and, if necessary, by endoscopic examination and biopsy.

In the last two decades, it has been clearly established that the most common cause of peptic ulcer disease is *Helicobacter pylori* infection [426–429]. The second most common cause is ingestion of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) [426, 427]. *Helicobacter pylori* infection is responsible for 95 % of duodenal and more than 85 % of gastric ulcers [427].

Sleep, Nocturnal Acid Secretion, and Duodenal Ulcer (See also Chap. 11)

To understand the role of nocturnal gastric acid secretion in duodenal ulcer, Dragstedt [430] studied hourly collections of nocturnal gastric acid from patients with duodenal ulcer and from normal subjects. The study found 3–20 times greater volumes of nocturnal acid secretion in patients than in normal controls (see also Fig. 11.10). Vagotomy abolished this increased secretion and improved healing of ulcers [431]. Studies by Orr et al. [432] have shown that patients with duodenal ulcer exhibit failure of inhibition of gastric acid secretion during the first 2 h after onset of sleep. A study by Watanabe et al. [433] confirmed the findings of Orr et al. [432] and found that the intragastric pH values increased during NREM and REM sleep in healthy controls and gastric ulcer patients, but the intragastric pH of duodenal ulcer patients did not change. Schubert and Peura [434] reviewed the physiology and pathophysiology of acid secretion and its inhibition in the management of acid-related clinical conditions.

Sleep disturbances in duodenal ulcer patients characteristically result from episodes of nocturnal epigastric pain. These symptoms cause arousals and repeated awakenings, thus fragmenting and disturbing sleep considerably in these patients.

Treatment

In light of the evidence about the role of *H. pylori* infection and NSAIDs in the pathogenesis of gastroduodenal ulcers, the theory of hypersecretion of acid in peptic ulcer patients has been relegated to a secondary role [427]. The first step is to find the causes of ulcer based on the history and laboratory tests such as serology, carbon-13 urea breath test, and endoscopic biopsy and histology, particularly in patients with gastric ulcer [426, 427]. The purpose of treatment is to

relieve symptoms; heal the ulcer; and either cure the disease, in the case of *H. pylori* ulcers, or prevent recurrences, in the case of NSAID ulcers [426, 427]. To cure the ulcer, the best approach is a triple combination of antimicrobial therapy as recommended and approved by the Food and Drug Administration as follows [426, 427, 435–437]: esomeprazole, amoxicillin, clarithromycin; lansoprazole, amoxicillin, clarithromycin; omeprazole, amoxicillin, clarithromycin; or rabeprazole, amoxicillin, clarithromycin. Antimicrobial agents effective against *H. pylori* infection include amoxicillin, clarithromycin, tetracycline, and metronidazole. Most commonly a 10- to 14-day regimen may be effective. To accelerate healing, the antimicrobial agent is combined with antisecretory agents [histamine$_2$ (H_2)–receptor antagonists such as cimetidine (Tagamet), ranitidine (Zantac), nizatidine (Axid), or famotidine (Pepcid)]. The most potent antisecretory agents are the proton pump inhibitors (e.g., esomeprazole, lansoprazole, omeprazole, and rabeprazole). Because of emergence of resistant strains of *H. pylori* and failure of eradication in 20–25 % of cases, quadruple [427, 438] and sequential therapy has been suggested for eradication of *H. pylori* infection [426, 435, 436, 439–441]. Sequential therapy includes an initial 5 days of therapy with a proton pump inhibitor and amoxicillin followed by 5 days of a proton pump inhibitor plus clarithromycin and tinidazole. For treatment of NSAID ulcers, NSAID therapy should be stopped and treated with traditional antisecretory agents. Patients who require continued NSAID therapy, however, may be treated with misoprostol, a synthetic prostaglandin E_1 analog (200 mg four times a day) [426, 427]. General measures of treatment of peptic ulcer disease should consist of avoidance of tobacco and alcohol. For detailed management of uncomplicated, complicated, and resistant ulcers, the reader is referred to Feldman [427] and Kuipers et al. [426].

Gastroesophageal Reflux Disease

Clinical Features

Gastroesophageal reflux disease (GERD) is preferable to the term *reflux esophagitis* [442]. GERD frequently occurs in middle-aged and elderly women, and sometimes in younger women during pregnancy. Hiatal hernia is often associated with reflux esophagitis. The characteristic symptom is heartburn, described as retrosternal burning pain exacerbated by lifting or straining or when the patient lies down at night [442, 443]. The nocturnal burning pain causes difficulty in initiating sleep, frequent awakenings, and fragmentation of sleep [431, 444– 447]. The nocturnal pain is characteristically relieved by sitting up or ingesting food or by acid-suppressant agents. An important differential diagnosis would be angina, particularly when the pain radiates to the neck, jaws, and arms, but an important point to remember is that the esophageal pain is usually not related to exertion. Other symptoms include transient or persistent dysphagia if the patient has developed stricture and regurgitation of gastric contents associated with coughing, wheezing, and shortness of breath due to the aspiration of the gastric contents into the bronchopulmonary region [431, 442, 443]. A serious complication of repeated episodes of gastroesophageal reflux and esophagitis is Barrett's esophagus, which may be a precursor to esophageal adenocarcinoma [442, 443, 448, 449]. Another potential complication is exacerbation of nocturnal asthma.

Differential Diagnosis, Pathogenesis, and Diagnostic Tests

Peptic ulcer disease, ischemic heart disease, sleep apnea, abnormal swallowing, and sleep choking syndromes may be mistaken for gastroesophageal reflux [442, 443, 445]. It has been shown that the fundamental mechanism of GERD is the inappropriate, transient, and frequent relaxation of the lower esophageal sphincter, causing episodes of acid reflux [431, 442, 443, 450]. The esophagitis resulting from acid reflux in the esophagus reduces the sphincter pressure and impairs esophageal contractility [431, 442, 450]. An additional mechanism is the presence of a hiatal hernia. Other factors, such as the acid clearance time, frequency of swallowing, and secretion of saliva, play an important role in the pathogenesis. The diagnosis of gastroesophageal reflux and prolonged acid secretion can be made by continuous monitoring of lower esophageal pH [431, 451]. When the pH falls below 4, gastroesophageal reflux occurs [452]. Repeated prolonged episodes of gastroesophageal reflux during sleep at night can cause esophagitis [453]. Physiologic changes during sleep consisting of suppression of saliva, decreased swallowing frequency, and prolonged mucosal contact with the gastric acid all contribute to the development of esophagitis [431, 442, 445, 454, 455]. After repeated prolonged episodes of gastroesophageal reflux at night for many years, patients may develop Barrett's esophagus, which results from replacement of the squamous epithelium of the lower esophagus by the columnar epithelium of the stomach [442, 443, 448, 449]. Documentation of spontaneous gastroesophageal reflux and prolonged acid clearance is important for diagnosis and treatment of esophagitis and of extraesophageal reflux and upper aerodigestive tract diseases resulting from repeated episodes of gastroesophageal reflux [431, 442, 454, 456–459].

Role of Gastroesophageal Reflux in Bronchopulmonary Disease

In some patients with asthma and chronic bronchitis or COPD, spontaneous gastroesophageal reflux at night plays a role in the pathogenesis of symptoms such as nocturnal wheeze, cough, or shortness of breath [431, 442, 443, 460–462]. In such patients, intraesophageal pH monitoring has shown prolonged acid clearance [461]. This is important from a therapeutic point of view, because administration of acid suppressants to such patients improves pulmonary

symptoms [443]. A study by Tan et al. [463], however, casts doubt on the relevance of gastroesophageal reflux to asthma.

The mechanisms of pulmonary symptoms in gastroesophageal reflux include aspiration of the gastric contents in the lungs causing pneumonitis and acid contact with the lower esophagus initiating reflex stimulation of the vagus nerve, causing bronchoconstriction. Actual aspiration of gastric contents into the lungs can be documented with the scintigraphic technique used by Chernow et al. [464]. These authors instilled a radionuclide into the stomach before sleep. A lung scan the next morning showed the radioactive material in the lung, suggesting nocturnal pulmonary aspiration. Children with asthma and bronchopulmonary disease may have sleep apnea, in addition to the other complications of gastroesophageal reflux [465]. Gastroesophageal reflux has been implicated in some cases of sudden infant death syndrome, possibly causing apnea and sudden death, but this has been found in only a small percentage of cases [466, 467]. The relationship between GERD and OSAS remains undetermined, although there is an increased prevalence of GERD in OSAS patients and CPAP treatment in such patients improves GERD symptoms [468–470]. These findings agree with the conclusion of Shepherd et al. [471] that the prevalence of nocturnal reflux symptoms is increased in those with or suspected of having OSA. This conclusion was based on 1116 patients with PSG-diagnosed OSA and 1999 participants of population health survey (2007 Busselton Survey). In a recent report Shepherd and Orr [472] suggested that obesity rather than airway obstruction is responsible for GERD symptoms.

Diagnostic Tests

No single test is diagnostic for GERD, but a combination of tests to assess the potential for reflux damage to the esophagus and actual presence of reflux is necessary to make the diagnosis. The diagnosis is confirmed by barium examination, and, if necessary, by endoscopic examination and biopsy [442, 443]. Measurement of lower esophageal sphincter pressure and a diagnosis of hiatal hernia may detect risk factors for reflux [442, 443]. Damage to the esophagus may be assessed by Bernstein's test (acid perfusion test), esophagography, esophagoscopy, and mucosal biopsy [442]. The actual presence of reflux may be established with the following tests: esophagography, acid reflux test, prolonged esophageal pH monitoring, and gastroesophageal scintigraphy [442]. The importance of 24-h ambulatory esophageal pH monitoring has been emphasized by Triadafilopoulos and Castillo [442].

Treatment

Treatment [442, 450] includes general measures such as avoidance of fatty foods and stooping, weight reduction, and elevation of the head of the bed to reduce reflux at night. Smoking should also be avoided. These simple measures decrease the frequency and length of reflux episodes as demonstrated by 24-h pH monitoring [452, 453]. If the patients fail to improve as a result of these simple measures, H_2-receptor antagonists (cimetidine, ranitidine, famotidine, and nizatidine) in the usual dose range as used for peptic ulcer patients (see earlier) will improve the symptoms of GERD [442, 443, 450]. For patients who are resistant to H_2-receptor antagonists, a proton pump inhibitor may be used [442, 443]. Proton pump inhibitors decrease gastric acid secretion through inhibition of the proton pump (H^+,K^+-ATPase) of the parietal cells (this is the most potent inhibitor of gastric acid secretion) and are in fact the treatment of choice for nighttime symptoms causing sleep dysfunction [442, 471–480]. Several studies have shown improvement of subjective measures of sleep without evidence of objective measurement after pharmacologic treatment for GERD [477, 479]. Other measures found to be useful are prokinetic agents (e.g., metoclopramide, 10 mg qid; cisapride, 10 mg qid; bethanechol, 10 mg qid) [346]. For patients who fail to respond to medical treatment, antireflux surgery (e.g., fundoplication) is indicated [442, 481]. Rarely, a Roux-en-Y near esophagojejunostomy is necessary for those intractable GERD patients who failed prior antireflux surgery [482].

In conclusion, an awareness of the role of sleep in the pathogenesis and treatment of peptic ulcer disease, particularly duodenal ulcer and esophageal reflux, is important for diagnosis and treatment. Facilities for all-night PSG study and 24-h esophageal pH monitoring have contributed to an understanding of the association between sleep and these diseases. These disorders are good examples of diseases that benefit from a multidisciplinary approach to patient management by a gastroenterologist, a pulmonologist, and a sleep specialist. This review also shows that sleep adversely affects patients with GERD by increasing the episodes of reflux and prolonging the acid clearance time. Furthermore, repeated spontaneous reflux episodes adversely affect sleep by causing arousals, frequent awakenings, sleep fragmentation, and excessive daytime sleepiness [444–446, 483].

Sleep in Functional Bowel Disorders

Functional bowel disorders include functional or nonulcer dyspepsia (NUD) and irritable bowel syndrome (IBS). NUD includes functional disorders of the upper gut and presents with upper abdominal pain or discomfort, nausea, gaseous distention, and early satiety [484–488]. A number of patients with functional bowel disorders have symptoms originating from the lower gut consistent with IBS, which is a common medical disorder characterized by symptoms of bowel dysfunction and abdominal pain [488]. In the last two decades, our understanding of IBS has grown considerably [488,

489], beginning with change in the classification and definition, which are the symptom-based Rome III criteria [490]. The basis for IBS symptoms is thought to be dysregulation of the brain–gut (central nervous system–enteric nervous system) relationship. The concept of IBS as a functional bowel disorder with no structural alteration has been dispelled by the functional and structural magnetic resonance imaging (MRI) findings of significant cortical thinning of the anterior cingulate cortex (ACC) and insula [491]. These findings confirm the investigators' previous observation of absent rectal pain-related functional MRI responses in the anterior insula and ACC in IBS [492]. These findings support the earlier abnormal EEG findings in IBS [493]. Davis et al. [491] also noted reduced gray matter in the anterior/medial thalamus and ACC on voxel-based morphometry in the IBS group relative to healthy controls.

Many patients with NUD and IBS have history of sleep complaints (e.g., frequent awakenings with or without pain and nonrestorative sleep) [494–496]. Such functional disorders may be associated with fibromyalgia syndrome (FMS) [489, 497–499]. Patients with FMS complain of a variety of sleep problems (see later). Jarrett et al. [500] and Eisenbruch et al. [501] reported that women with IBS associated with gastrointestinal symptoms complain of poor sleep and nonrestorative sleep more often than women without IBS. In a previous study, Eisenbruch et al. [502] reported poor sleep quality in the absence of objective sleep abnormalities (PSG findings), suggesting an altered sleep perception. In contrast to these findings, Fass et al. [503] prospectively evaluated 505 new patients with functional bowel disorders and 247 healthy controls using validated bowel symptom and sleep questionnaires. They concluded that functional dyspepsia patients, but not IBS patients, reported sleep disturbances more frequently than healthy control subjects. Another important observation is that IBS patients, compared with controls, had greater sympathetic dominance as indicated by increased LF/HF heart rate variability ratio during REM sleep because of vagal withdrawal, suggesting that autonomic functioning during REM sleep may be an useful biological marker to identify IBS patients [504]. However, in a later review of the literature, Mazurak et al. [505] concluded that most studies reported no difference in heart rate variability (HRV) when the IBS population was compared to healthy controls. Treatment of IBS patients includes an integrated pharmacologic and behavioral approach depending on the severity of symptoms and disability [488].

Miscellaneous Gastrointestinal Disorders and Sleep

There is circumstantial evidence that sleep deprivation or sleep disturbance may trigger flare-ups of two chronic autoimmune inflammatory bowel disorders: Crohn's disease or regional ileitis, and ulcerative colitis [506, 507]. Demonstration of exacerbation of colonic inflammation and tissue damage following acute and chronic sleep deprivation in a mouse model of colitis [508] supports such contention. Future research and clinical trials focusing on an improvement in the quantity or quality of sleep in patients with inflammatory bowel disorders are needed to provide definitive evidence.

Hepatic encephalopathy may cause hypersomnia, inversion of the sleep–wake rhythm, and recurrent stupor, which are most likely related to neurotransmitter alterations in the brain. There is an excessive accumulation of endozepines [benzodiazepine-like γ-aminobutyric acid (GABA) type A receptor modulators] in hepatic encephalopathy, explaining the recurrent stupor that is noted in some cases [509]. Prior hepatic encephalopathy may synergize with OSA in worsening sleep architecture and sleep disturbance in cirrhosis of liver [510] (nonrestorative sleep, reduced SWS, and increased stage N2). In a population-based cohort study from Chou et al. [511] observed that the risk of liver disease (particularly cirrhosis of liver and hepatitis c) was more than five times higher and among people with OSA compared with the control group. Previous studies [512–514] have also postulated a high prevalence of OSA in liver disease; however, a prospective study is needed to determine the factors responsible for such a high prevalence and also to evaluate the effect of CPAP therapy on the morbidity and mortality in liver disease.

Sleep disturbances have not been adequately studied in celiac disease (nontropical sprue or gluten-sensitive enteropathy) and Whipple's disease (a chronic multisystem disease due to infection with *Tropheryma whipplei*). Patients with celiac disease may have restless legs syndrome (RLS)—periodic limb movements in sleep (PLMS) [515], and Whipple's disease patients may present with insomnia or sleep–wake cycle changes.

Endocrine Diseases

Thyroid Disorders

It is important to be aware of the association between thyroid disorders, disordered breathing, and sleep disturbances. History and physical examination may direct attention to a thyroid disorder, in which case thyroid function tests should be performed to confirm the clinical diagnosis.

Hypothyroidism

The salient diagnostic features suggestive of myxedema consist of presentation in a middle-aged or elderly individual of fatigue, weight gain, decrease of physical and mental faculties, dryness and coarsening of the skin, pretibial edema, hoarse voice, cold sensitivity (sometimes presenting with hypothermia), constipation, and bradycardia or

evidence of ischemic heart disease in the ECG. Both upper airway obstructive [516] and central sleep apneas [517], which disappeared after thyroxine treatment, have been described in patients with myxedema. Mechanisms include deposition of mucopolysaccharides in the upper airways as well as central respiratory dysfunction as evidenced by impaired hypercapnic and hypoxic ventilatory response [518].

In an important study, Jha et al. [519] evaluated 50 newly diagnosed consecutive patients with primary hypothyroidism using PSG in all patients. Thyroxine replacement therapy was associated with improvement, including the findings in the repeat PSG study. This supports the previous findings of Rajagopal et al. [520]. Grunstein and Sullivan [521] recommended nasal CPAP treatment in patients with hypothyroidism and concomitant OSA while the patient is receiving thyroxine treatment. Routine screening for hypothyroidism in OSAS remains controversial [522–525]. Hashimoto's thyroiditis, an autoimmune disease diagnosed on the basis of high titers of antithyroid antibodies and histologic findings, is associated with higher prevalence of sleep-related breathing problems compared with controls [526]. A recent study [527] of 203 patients documented a total of 12.77 % of subclinical and clinical hypothyroidism in PSG proven OSAS patients.

Hyperthyroidism

Clinical features suggestive of thyrotoxicosis are presentation in a woman (female-to-male ratio, 8:1) of apparent increased energy, weight loss despite increased appetite, staring or bulging of the eyes (exophthalmos), tachycardia or atrial fibrillation, heat intolerance with excessive sweating, feelings of warmth, and a fine tremor of the outstretched fingers.

Few sleep studies have been made in patients with thyrotoxicosis. Dunleavy et al. [528] observed an increased amount of SWS, which returned to normal after treatment. In contrast, Passouant et al. [529] did not find any change in SWS but described an increase in sleep-onset latency in hyperthyroid patients. Johns and Rinsler [530] found no relationship between stages of sleep and alteration of thyroid function.

Ajlouni et al. [531] reported eight cases of patients with new-onset sleepwalking coinciding with the onset of thyrotoxicosis resulting from diffuse toxic goiter. Disappearance of sleepwalking with successful achievement of a euthyroid state supported a cause-and-effect relationship.

Diabetes Mellitus

For a discussion of sleep disturbance and sleep apnea in diabetes, see the section on autonomic neuropathy in Chap. 41.

Growth Hormone Disorders

Growth Hormone Deficiency and Sleep

In eight adults with isolated growth hormone (GH) deficiency (aged 18–28 years), Astrom and Lindholm [532] found a reduction of stage 4 sleep but increases in stages 1 and 2 NREM sleep, with a net result of an increase of total sleep time. In a later paper, Astrom and others [533] studied these patients after daily treatment with GH for 6 months and found a decrease in total sleep time that was due mainly to a reduction in stage 2 sleep, unchanged slow waves, and an increase in REM sleep time. In contrast to these findings, Pavel et al. [534] found no difference in sleep efficiency and daytime sleepiness in 16 GH-deficient adults (7 women and 9 men with a mean age of 36.8) after GH substitution. The subjective sleep parameters improved, however, and the authors suggested that this improvement might be caused by other indices of general well-being in this study with a small sample size. In 30 patients with GH deficiency (pituitary dysfunction in 26 and hypothalamic origin in four), Copinschi et al. [535] reported sleep dysfunction (high Pittsburgh Sleep Quality Index Scores, daytime sleepiness, and reduced QoL) compared with 30 controls. GH efficiency associated with morbid obesity, OSA, and hypogonadism is an important manifestation of Prader–Willi syndrome [536], a rare multi-system paternally inherited disorder of gene expression on chromosome 15q11–q13.

Excessive Growth Hormone Release and Sleep

Sullivan et al. [537] reported sleep apnea in association with GH release from the pituitary in patients with acromegaly. The most common explanation for sleep apnea in these patients is the enlargement of the tongue and pharyngeal wall, which causes narrowing of the upper airway. Sullivan's group [537] studied 40 patients with acromegaly and observed central sleep apnea in 30 %. Increased respiratory drive with increased hypercapnic ventilatory response is present in these patients. Sandostatin, a somatostatin analog, cured central apnea and normalized the ventilatory response.

Grunstein et al. [538] studied 53 patients with acromegaly who were consecutively referred for consultation. Sleep apnea was a reason for referral of 33 patients, whereas 20 patients were referred without any suspicion of apnea. Thirty-one patients of the group of 33 referred for apnea had sleep apnea; 12 of the 20 patients referred without suspected apnea were found to have apnea. Central apnea was predominant in 33 % of patients. The authors concluded that sleep apnea is common in individuals with acromegaly and central sleep apnea is associated with increased disease activity as reflected by biochemical measurement. They speculated that alteration of respiratory control may be a mechanism for sleep apnea in these patients. In a later study of 54 patients with acromegaly, Grunstein et al. [539] found

increased hypercapnic ventilatory responses in those patients with central sleep apnea but not in those with OSA or those without sleep apnea. These authors also found that acromegalic patients with central sleep apnea have increased GH and insulin-like growth factor-I levels compared with their counterparts with OSA. The authors concluded that increased ventilatory responsiveness and elevated hormonal parameters of disease activity contribute to the pathogenesis of central sleep apnea and acromegaly.

In contrast, later investigators found a high prevalence of sleep apnea, predominantly obstructive type and rarely central apnea [540, 541]. Suggested mechanisms for the development of OSA in acromegaly include an anatomic abnormality, especially at the base of the tongue [542]; craniofacial changes (e.g., increased vertical dolichofacial growth) causing narrowing of the posterior airway space, and displacement of the hyoid caudally [543].

Octreotide, a long-acting somatostatin analog, has been found to be an effective noninvasive treatment for sleep apnea in acromegaly [544, 545]. Sze et al. [546] reported a high prevalence of sleep apnea syndrome in acromegaly patients with resolution of SDB symptoms after transsphenoidal adenoidectomy. The relationship between sleep apnea and the GH level in active acromegaly remains unresolved [538, 541, 544]. Nonfunctional pituitary macroadenoma patients ($n = 69$) in long-term remission after trans-sphenoidal surgery on replacement therapy showed impaired sleep quality EDS and altered sleep–wake rhythmicity (decreased daytime and increased nighttime activities in actigraphic recordings) probably due to a dysfunction of the adjacent SCN [547].

Miscellaneous Endocrine Diseases and Sleep

In the only controlled study in patients with Cushing's syndrome (hyperpituitarism with corticosteroid excess), about one-third of the patients were diagnosed with sleep apnea [548]. There is one report of decreased delta sleep and increased stage 1 sleep and sleep fragmentation [549].

Addison's disease (adrenal gland insufficiency) patients may have increased sleep fragmentation and decreased REM sleep [550].

The male hormone testosterone is a risk factor for sleep apnea, as exogenous administration of testosterone induces sleep apnea in both normal and hypogonadal men [551] and worsens sleep apnea in older men [552]. Testosterone treatment transiently worsens severity of OSA [553], and serum testosterone levels are negatively correlated with severity of OSA [554]. However, CPAP therapy has no influence on testosterone level in men with OSA [555].

There is an increased prevalence of OSAS, insulin resistance, and type 2 diabetes mellitus in patients diagnosed with polycystic ovary syndrome, the most common endocrine disorder in reproductive-aged women, characterized by chronic anovulation and hyperandrogenism [556–558].

Renal Disorders

Sleep Disturbances and Chronic Renal Failure

Sleep dysfunction has been well described in cross-sectional studies of patients with chronic renal failure (CRF) on hemodialysis [559–567] and those not on hemodialysis [568–571], and even in patients with renal transplantation [572, 573]. Sleep dysfunction has been noted in up to 80 % of patients with CRF [560]. There is, however, no clear relationship noted between indices of renal failure and sleep disturbance in these studies.

Several studies have used PSG to objectively document the sleep disturbances, which consist of reduced sleep efficiency, increased sleep fragmentation, frequent awakenings with difficulty in maintenance of sleep, decreased SWS, and disorganization of the sleep cycle [559, 560]. Various studies have demonstrated a variety of sleep complaints in CRF patients that include poor-quality and nonrestorative sleep, difficulty in initiating and maintaining sleep, EDS, SDB, and sleep apnea. In a more recent study [574], Ezzat and Mobab sought to assess the prevalence of sleep dysfunction in patients with end-stage renal disease (ESRD) on hemodialysis ($n = 30$), chronic kidney disease (CKD) on conservative management ($n = 30$) comparing these two groups with normal controls ($n = 30$). In addition to standard blood biochemical studies and hemoglobin levels, all had one night of PSG study. They found a high percentage of sleep dysfunction in both patient groups. The types of sleep disorders and percentage were as follows in those on hemodialysis: insomnia (69); OSAS (24); RLS-PLMS (18); nightmares (13); EDS (12); sleepwalking (2); possible RBD (2); and possible narcolepsy (1.4). The figures in the CKD patients not on dialysis were as follows: insomnia (54); RLS (19); PLMS (12); OSAS (16); nightmares (15); EDS (1); sleepwalking (4); possible RBD (3); and possible narcolepsy (1). The authors concluded that sleep dysfunction is common in all kidney disease patients, and treatment of anemia, hyperphosphatemia, and hypoalbuminemia may improve their sleep problems.

In a prospective longitudinal study of 154 consecutive patients with CRF (78 completed the follow-up), Sabbatini et al. [575] determined sleep quality based on the Pittsburgh Sleep Quality Index (PSQI), and the data suggested that the progression of renal disease is accompanied by a progressive worsening of sleep quality. The data showed no correlation with creatinine clearance or with other indices of renal failure, but showed a correlation with age, which served as a

confounding variable. Four patients had high PSQI score at baseline and had further deteriorated at 3-year follow-up.

There are several factors which may contribute to the sleep problems in CRF patients [576]:

1. Disease-related factors (e.g., symptoms related to uremia, anemia, comorbid conditions, metabolic changes, and alterations in neurotransmitters)
2. Treatment-related factors (e.g., rapid changes in fluid, electrolyte, and acid-based balance; alterations in melatonin and thermoregulatory functions; medications; types of dialysis; alterations of cytokine metabolism in patients treated with hemodialysis causing abnormal somnolence [577] and proinflammatory cytokines (interleukin-1β), which might be associated with sleep complaints in hemodialysis patients [578])
3. Demographic factors (e.g., increasing age, male gender, and white race)
4. Psychological factors (e.g., anxiety and depression)
5. Lifestyle factors (e.g., increased intake of coffee, cigarette use, and poor sleep hygiene).

Sleep Apnea in Patients Receiving Dialysis

Sleep apnea is noted in up to 50 % of patients with renal failure [579]. Sleep apnea could be upper airway obstructive or central, but mainly an obstructive type of apnea is noted in most of the patients [577, 580–588]. This sleep apnea improves after nocturnal hemodialysis [488], which may be due to a decrease in chemosensitivity, suggesting also that, in some patients with kidney failure, increased chemoreflex responsiveness may contribute to the pathogenesis of sleep apnea. Beecroft et al. [589] studied 23 patients on hemodialysis and found decreased hypercapnic ventilatory response in sleep apnea patients who showed a significant reduction of the AHI after conversion from conventional to nocturnal hemodialysis. The authors suggested that increased chemosensitivity, by destabilizing respiratory control during sleep, may be responsible for both obstructive [590] and central sleep apnea [79, 591, 592]. An important study from the Sleep Heart Health Study identified an association between conventional hemodialysis and severe sleep apnea with nocturnal hypoxemia [593]. It should be noted that the prevalence of sleep apnea is similar in patients before and after receiving peritoneal dialysis or hemodialysis [594–596]. Although sleep problems may not be as common among transplantation patients as those on dialysis, the problems are still higher than in the general population [572, 573]. There are case reports indicating resolution of sleep apnea after renal transplantation [597]; however, many patients do not improve [584, 586, 598].

The following are the suggested mechanisms for the pathogenesis of sleep apnea in CRF:

- Upper airway edema causing partial airway obstruction coupled with decreased muscle tone during sleep [583].
- CNS depression during sleep resulting from so-called uremic toxins causing excessive reduction of upper airway muscle tone [583] (persistence of sleep apnea after dialysis speaks against this suggestion).
- Disturbance of the ventilatory control of breathing in renal failure and hemodialysis [577, 589, 597] making the respiratory control unstable, causing an imbalance between diaphragmatic and upper airway muscles. Beecroft et al. [599] reported an increased ventilatory sensitivity to hypercapnia in CRF patients with sleep apnea, suggesting an increase in respiratory control system "loop gain," which destabilizes central respiratory control and contributes to upper airway occlusion. Beecroft et al. [589] suggested that decreased chemoreflex sensitivity after conversion from conventional hemodialysis to nocturnal hemodialysis corrected sleep apnea by decreasing respiratory control system "loop gain," thus stabilizing the control of ventilation.
- CCF, which may occur in association with CRF, itself causing sleep apnea.
- Anatomic narrowing of the upper airway [600]. The same investigators also noted that there was an increase in pharyngeal size following conversion from conventional hemodialysis to nocturnal hemodialysis in those patients who previously had decreased pharyngeal cross-sectional area [601].
- Hypertension associated with CRF.
- Metabolic derangement associated with uremia. Soreide et al. [602] reported that an infusion of branched-chain amino acids stimulated nocturnal respiration and resulted in a decreased number of obstructive apneas.

Restless Legs Syndrome in Chronic Renal Failure Patients

There is an increased prevalence of RLS (20–50 % and even higher in patients with ESRD on dialysis [603–617]). Uremic RLS and idiopathic RLS resemble each other and cannot be distinguished clinically [609]. There are no specific biochemical risk factors identified with RLS associated with CKD except for low iron status as a predictor of poor outcome. Serum ferritin less than 70 μg/ml is the best cutoff for identifying possible iron deficiency which is the strongest predictor of RLS in CKD in older hospitalized patients [618]. Reports of disappearance or improvement of RLS symptoms after kidney transplantation suggest that some unknown biochemical or other factors are causing RLS symptoms in ESRD [606, 607]. Winkelmann et al. [607] investigated clinically the long-term course of 11 of 64 hemodialysis patients who underwent kidney transplantation. In all patients, RLS symptoms disappeared within 1–21 days after transplantation, and at follow-up visits up to

9 years, four patients remained free of RLS symptoms. In three other patients, RLS symptoms gradually reappeared. In 3 of 11 patients, transplantation failed and RLS symptoms reoccurred within 10 days to 2 months. In one patient, RLS symptoms reoccurred with transplant failure but disappeared after a second successful transplant. The authors concluded that kidney transplantation has a positive effect on RLS symptoms in hemodialysis patients. In an important cross-sectional study, Molnar et al. [606] assessed the prevalence of RLS in 992 kidney-transplanted patients using an RLS questionnaire. They found a prevalence rate of RLS of 4.8 % and concluded that the prevalence is significantly lower in kidney-transplanted patients than in patients with maintenance dialysis. The increasing prevalence of RLS in their series is associated with declining renal function and iron deficiency. In a preliminary study, Benz et al. [619] treated 10 hemodialysis patients having sleep complaints with recombinant human erythropoietin; in 9 of 10 patients, this therapy corrected the anemia and improved sleep quality. There is one report of MEIS1 and BTBD9 genetic association with RLS in ESRD [620]. Patients with ESRD and RLS showed an increased likelihood of cardiovascular and cerebrovascular events and mortality [621]. But a later report contradicted these findings [622].

Fibromyalgia Syndrome, Rheumatoid Arthritis, and Other Rheumatologic Disorders

All of these conditions are associated with chronic pain, and hence, some knowledge of human pain pathways is essential for understanding the pathophysiology of these disorders [623]. Pain pathways include afferent (ascending) fibers, central pain processing regions, and descending (efferent) fibers modulating these pathways. According to the current consensus, there are two central ascending pain pathways: a lateral sensory discriminative pathway and a medial affective pathway [624]. Impulses from peripheral pain-sensitive receptors are transmitted via thinly myelinated A delta and unmyelinated C fibers to the lateral pain pathway originating in the dorsal horn of the spinal cord in the region of zone of Lissauer, from where the fibers cross within one-to-three spinal segments to the contralateral spinothalamic tracts. The sensory afferent neurons in the spinothalamic tracts terminate in the ventral posterolateral nucleus of the thalamus. The third-order neurons from the thalamus terminate in the somesthetic cortex (SI and SII) for pain perception, discrimination, and central processing. Fibers also project directly both from thalamus and from SII to anterior insular cortex (the cortical pain center) [624]. The medical polysynaptic pain pathway includes spinoreticular and trigeminoreticular tracts projecting to the brain-stem reticular formation and then to the contralateral medial dorsal thalamic nucleus with upward projection to the anterior cingulate cortex which is responsible for the affective component of pain [624–629]. The other emotional pain pathway includes spinomesencephalic fibers to midbrain reticular formation with onward projection to the amygdala which is primarily responsible for the sense of fear [624]. Sensory descending pathways originating from the periaqueductal gray region, locus ceruleus, and hypothalamus [624, 630, 631, 632] modulate pain perception [633, 634]. These anatomic pathways are influenced by several neurotransmitters and neuromodulators [635–638] (e.g., noradrenalin, serotonin, and dopamine) as well as neuropeptides and their receptors. Dysregulation of ascending and descending pathways and alteration of central sensitization may be responsible for chronic pain in articular and nonarticular painful syndromes. Electrophysiologic [639–641] and functional neuroimaging [642–646], as well as SPECT and positron emission tomography (PET) [647, 648], studies have lent support to these hypotheses. This section briefly reviews sleep disturbances in FMS; rheumatoid arthritis (RA), including juvenile rheumatoid arthritis; osteoarthritis; and miscellaneous other painful conditions (e.g., ankylosing spondylitis, systemic lupus erythematosus, Sjögren's syndrome, and scleroderma) causing sleep disturbances.

Fibromyalgia Syndrome

FMS is a common but poorly understood syndrome characterized by chronic diffuse soft tissue pain and tenderness accompanied by a variety of somatic symptoms, including sleep dysfunction, in the absence of any structural lesion and without a single laboratory diagnostic test [649]. The condition has a prevalence rate of 1.3–4.7 % in the general population, with a female-to-male ratio of about 9:1, and onset typically occurs in the middle-aged and older women [650, 651]. The most common symptoms included morning stiffness, fatigue, nonrestorative sleep, pain, low back pain, impaired concentration, and memory "fog." Yunus et al. [652] originally listed specific diagnostic criteria for FMS, and this was followed by a description by Goldenberg [653] of an emerging but controversial condition. The American College of Rheumatology (ACR) in 1990 published the formal diagnostic criteria for FMS [654]. According to these criteria, the diagnosis is based on the presence of widespread diffuse pain affecting both upper and lower extremities lasting for at least 3 months and present in a symmetric fashion accompanied by 11 of 18 "tender points" when applying pressure of about 4 kg/cm^2 by digital palpation using the thumb or two fingers. The original ACR criteria are superseded by the 2010 ACR preliminary diagnostic criteria for FMS in which there was more emphasis on patient's symptoms [655] (Table 47.4). These criteria were later modified based on a self-report questionnaire (Fibromyalgia survey questionnaire [FSQ]) for improved specificity and sensitivity

Table 47.4 Diagnostic criteria for fibromyalgia

• Widespread diffuse pain lasting for at least 3 months
• Tender points in at least 11 of 18 anatomically defined sites (9 pairs of tender spots as listed below) after applying digital pressure of approximately 4 kg of force
– Second rib at the costochondral junctions
– Lateral epicondyle 2-cm distal to the epicondyle
– Suboccipital region
– Midpoint of the upper border of the trapezius
– Low cervical region
– Supraspinatus above the medial border of the scapular spine
– Gluteal region
– Greater trochanteric region posteriorly
– Medial fat pad at the knee joint proximal to the joint line

[656]. Based on a cutoff score ≥ 12, the modified ACR criteria had a sensitivity of 90.2 % and a specificity of 89.5 %; however, the modified ACR 2010 criteria questionnaire had a sensitivity of 97.4 % and a specificity of 85.2 %. Using a score of ≥ 13, the sensitivity was 93.1 % but the specificity increased to 91.7 %. The pathophysiology of the condition remains undetermined. However, based on the evidence that patients with fibromyalgia have dysfunctional pain processing in the CNS and perceive pain differently from the general population (see electrophysiologic, functional neuroimaging, SPECT, and PET studies cited above), suggested mechanisms included central sensitization, alterations in neurotransmitters, blunting of inhibitory pain pathways, genetic factors, neuroinflammation including viral infections, psychological stress, physical trauma, oxidative stress, and associated psychiatric comorbid conditions [623, 657]. A positive family history of fibromyalgia is found in some studies, and this is supported by the findings of a specific polymorphism in the 5-hydroxytryptamine$_{2A}$ receptor gene [658, 659], the serotonin transporter gene [660], and catechol-0-methyltransferese (COMT) gene [661, 662] which may predispose these patients to have psychiatric symptoms. Finally, genome-wide linkage of FMS to chromosome 17p supports a genetic factor in FMS [663].

An important item in the differential diagnosis is polymyalgia rheumatica, which is also characterized by diffuse muscle aches and pains but is often associated with accelerated erythrocyte sedimentation rate and evidence of temporal arteritis. Other differential diagnostic considerations include chronic fatigue syndrome (see later) and other myofascial pain syndromes. Sleep disturbance is very common in FMS [657, 665–671]. The characteristic PSG finding is intermittent alpha activity during NREM sleep giving rise to the characteristic alpha-delta or alpha-NREM sleep pattern in the recording (Fig. 47.2). It should be noted that although alpha-delta sleep is seen in this condition, this variant is not specific for the syndrome. Alpha-NREM sleep has also been reported in other rheumatic disorders [672], febrile illness, post-viral fatigue syndrome [673], psychiatric patients [674], and even normal individuals [675]. Nonrestorative sleep associated with nonspecific PSG abnormalities of sleep fragmentation, increased awakenings, decreased sleep efficiency, and alpha-NREM sleep is the most prominent complaint in these patients [665, 666]. In two retrospective reviews of PSG records and medical charts, there is a high prevalence of sleep apnea and RLS in addition to the other sleep complaints noted previously [669, 670]. Gold et al. [676] reported that, following CPAP treatment in women with FMS and upper airway resistance syndrome, the patients obtained considerable relief from fatigue, pain, and gastrointestinal symptoms. The most prominent feature in all of these studies is the subjective perception of poor sleep, which is out of proportion to objective measures of sleep [665, 666, 677]. Another objective measurement of sleep is actigraphy, which gave inconsistent results in FMS [678–681]. In summary, patients with FMS have a high prevalence of sleep difficulty, with up to 99 % reporting poor sleep quality [665, 666, 682]. The most common sleep difficulties reported are EDS, fatigue, and insomnia [665, 666, 683]. The observation of disassociation of subjective sleep complaints with objective sleep measures is strengthened by a pilot study showing high levels of dysfunctional beliefs and attitudes about sleep and perceived stress associated with poor sleep quality in FMS patients [684].

Treatment of FMS remains unsatisfactory. Treatment options should include both pharmacologic and nonpharmacologic therapies [657, 666, 686–688]. The nonpharmacologic treatment should include an exercise program [689] (more recent studies [690, 691] did not find exercise programs in FMS to be beneficial) good sleep hygiene measures, education and reassurance, and cognitive behavioral therapy [692–695]. Pharmacologic treatment [657, 665–677, 696] found to be useful includes tricyclic antidepressants (e.g., amitriptyline), nonbenzodiazepine hypnotic drugs, selective serotonin reuptake inhibitors (e.g., fluoxetine),

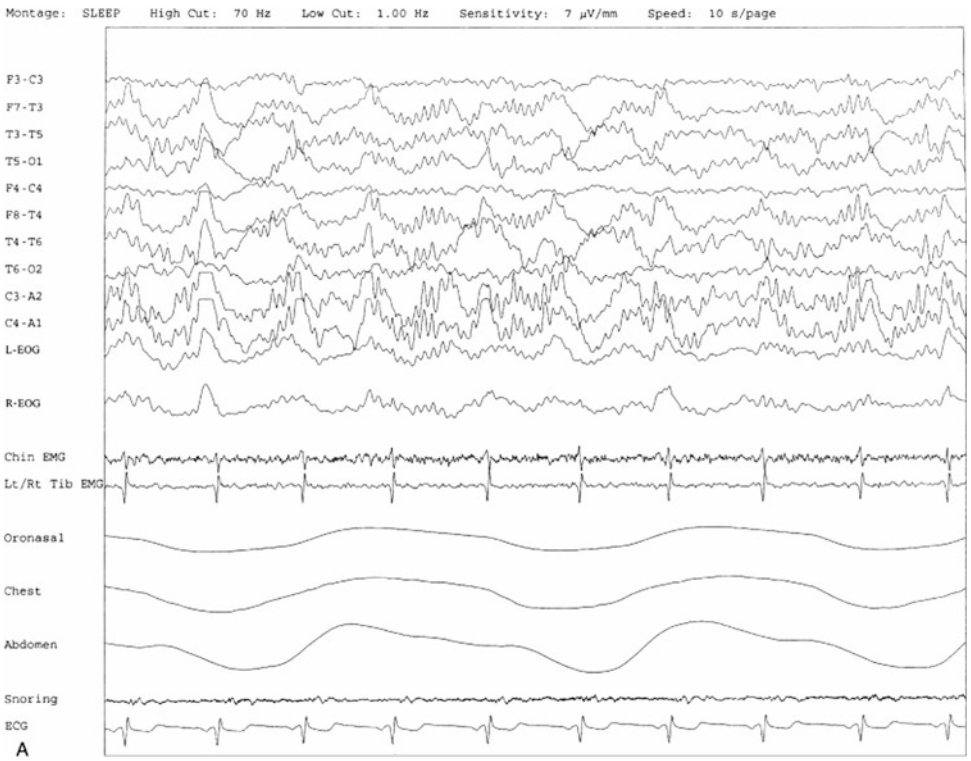

Fig. 47.2 Ten- (a) and 30 s (b) excerpts from a nocturnal PSG showing alpha-delta sleep in a 30-year-old man with history of snoring for many years. He denied any history of joint or muscle aches and pains. The alpha frequency is intermixed with and superimposed on underlying delta activity. Alpha-delta sleep denotes a nonspecific sleep architectural change noted in many patients with complaints of muscle aches and fibromyalgia. It is also seen in other conditions and in many normal individuals. (EEG, top 10 channels; Lt. and Rt. EOG, left and right electro-oculograms; chin EMG, EMG of chin; Lt./Rt. Tib. EMG, left/right tibialis anterior EMG; oronasal thermistor; chest and abdomen effort channels; snore monitor; EKG, electrocardiography) (From Ref. [685])

serotonin/norepinephrine reuptake inhibitors (e.g., venlafaxine, duloxetine, and milnacipran), gabapentin [657, 697], and pregabalin [698–700]. Pregabalin, a centrally acting drug used to treat neuropathic pain and adults with partial epilepsy, is the only drug approved by the Food and Drug Administration for treating and managing fibromyalgia. The recommended dose of pregabalin is 300–400 mg/day in two divided doses beginning with smaller doses of 75 mg twice a day and gradually increasing. Patients should also be treated for comorbid conditions (e.g., depression and sleep apnea). In a meta-analysis of five randomized placebo-controlled trials consisting of 2918 FMS patients (four with pregabalin and one with gabapentin), Hauser et al. [701] reported an improvement of sleep with reduction of pain in the patients. In a later Cochrane review, however, Moore et al. [702] reported that gabapentin 1200 mg or more per day reduced pain by 50 % in only 37 % of patients compared with 21 % on placebo.

Rheumatoid Arthritis and Other Rheumatologic Disorders

Arthritis, including rheumatoid and nonrheumatoid types, is the leading cause of disability in the USA, affecting approximately 70 million individuals. These conditions include RA (including juvenile RA), osteoarthritis, seronegative spondyloarthritis (e.g., ankylosing spondylitis, a reactive arthritis that was formerly known as Reiter's syndrome; and psoriatic arthritis, arthritis associated with ulcerative colitis, Crohn's disease, and Whipple's disease), systemic lupus erythematosis, Sjögen's syndrome, scleroderma, gouty arthritis, and polymyalgia rheumatica. Osteoarthritis is the most common type of arthritis, followed by RA. A systematic approach encompassing history, physical examination, and appropriate laboratory tests will help differentiate these conditions [703]. For appropriate diagnosis and differential diagnosis of these conditions, readers are referred to a standard text in internal medicine. Many of these patients suffer from sleep dysfunction, and in particular insomnia, fatigue, and depression; however, adequate scientific data correlating subjective with objective measures in a large number of such patients are lacking [683, 684].

In limited studies, sleep disturbances in osteoarthritis are commonly noted, consisting of sleep onset and maintenance insomnia (including early morning awakenings), correlating with the severity of joint pain, physical function, and

depression [686, 687]. Polysomnographic findings are not specific but correlate with sleep complaints, showing increased stage 1 sleep and repeated awakenings and arousals [688]. Sleep disturbances in adult RA patients consisting of difficulty in sleep onset and maintenance and fragmentation of sleep associated with EDS and fatigue are noted [689]. In a large percentage of patients [690], PSG studies show normal sleep architecture associated with alpha intrusions and increased PLMS [691, 692]. Studies generally show a positive correlation between sleep complaints and severity of the disease activity [694–696]. There is an increased prevalence of RLS in patients with RA [691, 697, 698]. There is also an increased prevalence of sleep apnea in these patients [691, 699, 700]. Similar sleep disturbances are also noted in juvenile RA [701, 702]. Similar sleep disturbances, particularly insomnia and daytime sleepiness, are also noted in systemic lupus erythematosis, Sjögren's syndrome, and seronegative spondylotic arthritis [411, 667, 703–728]. Comorbid upper airway OSA and PLMS are noted in systemic lupus erythematosis and ankylosing spondylitis. Gastroesophageal reflux, pulmonary fibrosis, and RLS are additional comorbid conditions disrupting sleep in scleroderma patients. Treatment of these conditions includes treatment of the primary diseases and associated sleep dysfunction following the general lines of management for insomnia, hypersomnia, and sleep apnea. Currently, there are no adequate studies describing the prevalence of and appropriate guidelines for treating sleep disturbances in these conditions.

Hematologic Disorders

The hematologic disorders that may cause sleep disturbance or be adversely affected by sleep include paroxysmal nocturnal hemoglobinuria (PNH), sickle cell anemia, hereditary hemorrhagic telangiectasia, and iron-deficiency anemia. Hansen [729] noted increased levels of plasma hemoglobin in five of seven patients with PNH, and the maximum values were found at midnight or at 4:00 AM. However, the author did not record EEGs or electro-oculograms to document any relationship with different sleep stages. Sleep impairment in the form of reduced total sleep time and REM sleep percentage and increased number of awakenings and sleep stage shifts is noted in patients with clinically stable sickle cell anemia, and these findings are probably due to hemoglobin desaturation [730, 731]. OSA and sleep disturbances resulting from reduced Sao_2 can occur in patients with sickle cell anemias and the prevalence of OSA in SCD is higher than in the general pediatric population [732]; when these diagnoses are suspected, overnight PSG recording should be obtained to confirm the diagnosis so that appropriate treatment with CPAP titration can be instituted [733]. Progressive somnolence accompanied by confusion has been described in a patient with hereditary hemorrhagic telangiectasia [734]. Iron-deficiency anemia in infancy is reported to be associated with altered temporal organization of sleep states and stages in childhood [735, 736]. Sleep alterations may persist for years after correction of anemia with iron treatment [736]. Furthermore, iron-deficiency anemia with low ferritin level may be combined with RLS. Zilberman et al. [728, 737] reported an improvement of anemia in congestive heart failure following administration of erythropoietin and intravenous iron, along with an improvement of sleep-related breathing disorder and daytime sleepiness. Finally, sleep deprivation in healthy individuals may cause a hypercoagulable state as evidenced by increased levels of prothrombotic hemostasis factors, which are risk factors for cerebrovascular and cardiovascular diseases [738, 739].

Dermatologic Disorders

Dermatologic disorders may cause sleep disruption because of pruritus and painful skin diseases [740, 741]. Patients may have sleep initiation and maintenance insomnia. In many dermatologic disorders, patients may have recurrent episodes of pruritus, which is most frequently noted during stages 1 and 2 NREM and least frequently noted in SWS; the intensity of symptoms is intermediate in REM sleep [741]. Patel et al. [740] reviewed the question of the high prevalence of nocturnal pruritus in many systemic and dermatologic diseases, causing sleep disturbance and diminished quality of life. Singareddy et al. [742] reported skin picking or pathologic excoriation in nearly 2 % of patients attending the dermatologic clinic in a mid-Western region of the USA. They found a significant correlation between skin picking and poor sleep as well as high anxiety. Nocturnal scratching may occasionally present as a parasomnia not associated with dermatological disorders [743, 744]. Mouzas et al. [745] reported a significantly higher occurrence of sleepwalking, sleep terrors, nightmares, and nocturnal enuresis in 116 patients suffering from vitiligo compared with 52 patients with other dermatologic diseases and 48 healthy controls.

Atopic dermatitis (AD), a common skin disorder beginning in infancy, may also cause disturbance of sleep in children because of nocturnal itching and scratching [746–748]. This can be documented by questionnaire and actigraphic recording [747]. There is a report of patients with OSA especially male younger patients with an increased risk for AD later in life [749]. Lichen simplex chronicus is another common pruritic disorder in which nighttime pruritus is a common feature disturbing sleep. This was documented by overnight PSG

study and the Epworth Sleepiness Scale in 15 patients with lichen simplex chronicus and 15 age-matched controls [750]. Polysomnographic findings in patients demonstrated increased arousals and awakenings associated with scratching bouts during sleep. PSG study and parental report of sleep quality (sleep disturbance scale of children) in 21 children with eczema and 20 healthy controls (ages 6-16 years) documented worse sleep quality on both PSG (increased nocturnal awakening and stage shifts) and parental report in addition to significant neurocognitive deficits [751].

Miscellaneous Disorders

Acquired Immunodeficiency Syndrome

Acquired immunodeficiency syndrome (AIDS) is a multisystem disorder caused by infection with human immunodeficiency virus (HIV). Its manifestations are protean. Neurologic manifestations include both CNS and peripheral neuromuscular dysfunction. Encephalitis, due to either opportunistic infection or direct invasion by the virus, may cause a variety of disorders such as memory impairment, seizures, and pyramidal or extrapyramidal manifestations. Some patients have sleep disturbances, but adequate studies utilizing PSG recordings and validated sleep scales have not been performed in a large number of these patients.

Norman et al. [752–754] found alterations in sleep architecture in groups of asymptomatic HIV-positive men that progressed as the disease became symptomatic in 17 of the initial group of patients followed for 19–63 months. Several other authors [755–758] also reported sleep architectural abnormalities after PSG recordings in asymptomatic HIV-positive patients. Darko et al. [757, 758] also suggested that there is evidence to support a role for the somnogenic immune peptides tumor necrosis factor-α and interleukin-1β in the sleep changes and fatigue commonly seen in HIV infection. These authors [757] stated that these peptides were elevated in the blood of HIV-infected individuals and are somnogenic in clinical use and animal models.

A more recent study utilizing the PSQI and the Medical Outcome Short-Form Health Survey in a sample of 144 HIV-infected African American women recruited from 12 health clinics and AIDS service organizations in three southern states in the USA showed a high prevalence of poor sleep quality associated with an impairment of health-related quality-of-life index in these patients [759]. Moyle et al. [760] also reported sleep disturbances and alterations of sleep architecture following initiation of efavirenz-containing triple antiretroviral therapy in HIV-positive individuals.

HIV infection can cause SDB. Epstein et al. [761] identified three HIV patients with OSA due to adenotonsillar hypertrophy. They also surveyed 134 patients with asymptomatic HIV disease with a self-administered questionnaire designed to detect OSA and EDS. Those patients whose responses suggested possible OSA were studied by overnight PSG recording. Twelve HIV-positive patients with OSA were identified. The consistent risk factor in this young and non-obese population was the presence of adenotonsillar hypertrophy, which was found in 11 of 12 patients with OSA. In a previous paper, these authors [762] reported the first cases of severe OSA in HIV-infected men. Garrigo et al. [763] obtained PSG recording in asymptomatic HIV-positive men and reported an elevated apnea index in 7 of 24 patients who did not have symptoms related to SDB. In a more recent retrospective review of the medical records of consecutively identified HIV-infected subjects, there was a high prevalence of SDB on PSG recordings. The authors suggested that clinicians caring for HIV patients should inquire about risk factors for OSA because overnight PSG study can aid the diagnosis of sleep disturbances in such patients [764]. This is important for treatment and improvement of quality of life.

Whether PSG can document significant and specific abnormalities in asymptomatic individuals or warn of the development of encephalopathy remains to be determined. A systematic study of a large number of cases needs to be done to answer these questions.

There are several recent reports documenting sleep dysfunction and the factors responsible for this in HIV/AIDS patients [765–769]. A recent meta-analysis [770] covering 9246 HIV-positive subjects documented a prevalence of 58 %. Sleep problems may have potential impact on antiretroviral therapy outcome.

Lyme Disease

Lyme disease [771–778] is a multisystem disease caused by the spirochete *Borrelia burgdorferi* and transmitted to humans by tick bite. The clinical manifestations may be divided into three stages:

1. Initially, there is a characteristic skin lesion, erythema migrans, which is followed in the course of time by a febrile illness (acute stage or stage I).
2. In the subacute stage or stage II, which occurs in several weeks to months after the onset of the illness, approximately 12–15 % of patients may develop neurologic manifestations and approximately 4–10 % may have cardiac involvement (conduction disturbance or cardiomyopathy) [771, 776]. Neurologic manifestations may present as axonal polyneuropathy, radiculoneuropathy, cranial neuropathy (particularly affecting the facial nerve), lymphocytic meningitis, encephalitis, or encephalopathy. Encephalitis is rare. Patients with CNS manifestations may have sleep disturbances.
3. In the chronic stage or stage III, which occurs weeks to as long as 2 years after the onset of illness, approximately 60 % of patients develop arthritis [771, 776].

Sleep complaints are common in Lyme disease [771], but no large-scale study using PSG is available to characterize the sleep disturbances in this condition. Greenberg et al. [779] obtained 2 nights of PSG in 11 patients meeting Centers for Disease Control and Prevention (CDC) criteria for late Lyme disease with serologic confirmation and 10 age-matched controls. In addition, the authors performed the Multiple Sleep Latency Test (MSLT) in the Lyme disease patients. All patients had complaints of difficulty initiating sleep, frequent nocturnal awakenings, and EDS; a small percentage had restless legs or nocturnal leg jerking. Polysomnographic findings included decreased sleep efficiency, increased arousal index with sleep fragmentation, and alpha intrusion into NREM sleep. These authors concluded that these sleep abnormalities may have contributed to the sleep complaints and fatigue that are commonly present in this disease.

Because Lyme disease is treatable, every attempt should be made to diagnose it accurately. Diagnosis depends on the serologic detection of antibodies against *B. burgdorferi* in the serum (or, in the case of CNS infection, in cerebrospinal fluid samples) [777]. The usual method of testing is the enzyme-linked immunosorbent assay [777], but antibodies usually are not detectable until 4–6 weeks after the initial infection. Diagnosis may be complicated by false-positive results and lack of a standardized technique to assay for antibodies. Polymerase chain reaction has been shown to be useful in demonstrating *B. burgdorferi* DNA in clinical material [777]. Recently developed serodiagnostic tools, such as the C6 assay, and appropriate use of Western blotting show considerable promise in improving the diagnostic accuracy [780].

In most patients, oral antibiotics are efficient, but in severe cases, 2- to 4-week parenteral therapy is needed. Practice parameters are available for treatment of nervous system Lyme disease developed by the American Academy of Neurology and Clinical Infectious Diseases Society of America [775, 781]. The most effective oral antibiotics include amoxicillin 500 mg three times a day, doxycycline 100 mg twice a day, and cefuroxime 500 mg twice a day given for 2–3 weeks. Treatment of more than 4 weeks' duration is not needed and carries substantial risk but minimal benefit [773, 782, 783].

Chronic Fatigue Syndrome

Chronic fatigue syndrome (CFS) is a complex, ill-defined heterogeneous debilitating condition. Patients complain of profound fatigue, functioning below their usual level of energy, that is not improved by bed rest. CFS affects 836,000 to 2.5 million in the USA and is more common in women than men. The diagnostic criteria for CFS were established from a consensus among international experts [784]. Diagnosis of CFS depends on the patient's history and the information obtained by physical examination as well as exclusion of other causes of the fatigue after extensive laboratory investigations. There is controversy in this case definition as the condition overlaps with many other disorders and because it is based on a consensus of experts without availability of any laboratory diagnostic test [785]. The concept of CFS has evolved over the years and has been modified since the original diagnostic criteria [784] were established. In view of the evidence in later research of widespread inflammation and multisystem involvement, the term myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [786] was thought to be appropriate to call this condition. The proposed new evidence-based diagnostic criteria by the Institute of Medicine (IOM) [664] focused on the central symptoms and one of two additional symptoms (Table 47.5). These symptoms should persist for at least six months at a moderate, substantial, or severe intensity at least half of the time. The IOM committee [664] noted that evidence of other manifestations of ME/CFS seen less frequently but these may support the diagnosis (Table 47.6). ME/CFS is thus a chronic multisystem debilitation condition manifested by chronic disability fatigue, post-exertional malaise and unrefreshing sleep associated with cognitive impairment or orthostatic intolerance [664, 787]. There are no diagnostic laboratory tests but all three national agencies [IOM, Agency for Healthcare Research and Quality (AHRQ) and National Institute of Health (NIH)] concluded that there are biological abnormalities [788]. A Positron Emission Tomographic (PET) scan showed evidence of neuroinflammation (activated microglia or astrocytes) [789], functional magnetic resonance imaging (fMRI) studies documented distinctive abnormalities when challenged with working memory tasks, and the NIH report gave evidence of neurotransmitter signaling disruption [788, 789]. There is, however, no conclusive evidence of any biomarker sensitive or specific enough to serve as a diagnostic test [788]. The cause and pathogenesis remain uncertain. Viral causes have been incriminated but no specific virus or other infectious agent has been indentified [787, 790]. There has been a suggestion of an external agent triggering an immune response leading to immune and neuroendocrine dysregulation [790, 791].

The clinical course of CFS follows a randomly cyclical pattern, and studies conducted by the CDC [792, 793] have found that 40–60 % of the people with CFS report partial or total recovery, particularly those who have received early treatment. Certain comorbid conditions with CFS include IBS, fibromyalgia, depression, Gulf War syndrome, and interstitial cystitis. There is some suggestion of increased familial aggregation of CFS because of increased concordance rates in monozygotic compared with dizygotic twins [794]. Several patients with CFS had orthostatic hypotension on tilt-table study, which was thought to be responsible for some of the

Table 47.5 Proposed IOM diagnostic criteria for ME/CFS [664]

Diagnosis requires for the patient to have the following three symptoms (core symptoms)
1. A substantial reduction or impairment in the ability to engage in preillness levels of occupational, educational, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest, and
2. Post-exertional malaise, and
3. Unrefreshing sleep
At least one of the two following manifestations is also required
1. Cognitive impairment
2. Orthostatic intolerance

Table 47.6 Additional symptoms of ME/CFS

• Pain which is variable and may manifest as myalgia, arthralgia, or headache
• Evidence of immune dysfunction
• Evidence of infection
• Gastrointestinal or genitourinary symptoms
• Sore throat
• Painful or tender cervical or axillary lymph nodes
• Sensitivity to food, drugs, or other chemical agents

symptoms [795]. It is notable that orthostatic intolerance is listed as one of the five symptoms in the proposed IOM diagnostic criteria [664] (see Table 47.5).

Sleep disturbances (e.g., disturbed unrefreshing and poor quality of nighttime sleep, insomnia, and EDS) are very common in ME/CFS patients, but in many cases these have not been adequately characterized by PSG studies. PSG abnormalities have been found in a few studies [796–801]. Fischler et al. [796], in a PSG study in 49 CFS patients and 20 healthy controls, found more sleep initiation and maintenance disturbances and a significantly lower percentage of stage 4 NREM sleep in the CFS patients than in the control group. However, they did not find any association between sleep disorders and the degree of functional impairment. Similarly, in a population-based study of CFS patients and nonfatigued controls from Wichita, Kansas, utilizing overnight PSG and MSLT tests, Reeves et al. [798] did not provide evidence that altered sleep architecture is a critical factor in CFS. Guilleminault et al. [799] reported that complaints of unrefreshing sleep and chronic fatigue were associated with an abnormal EEG cyclic alternating pattern and an increase in respiratory effort and nasal flow limitation, suggesting subtle undiagnosed SDB. Togo et al. [800] compared PSG findings and subjective scores for sleepiness and fatigue (visual analog scales) in 26 CFS patients (12 with and 14 without coexisting fibromyalgia) with 26 healthy subjects. Compared with controls, CFS patients had reduced total sleep duration and decreased sleep efficiency, which positively correlated with subjective sleepiness and fatigue. The authors suggested that this sleep disruption may explain the overwhelming fatigue and unrefreshing sleep. In conclusion, the entity of ME/CFS remains ill-defined and the treatment, at present, should be symptomatic, using both pharmacologic and nonpharmacological treatment. Nonpharmacologic treatment includes sleep hygiene measures and cognitive behavioral therapy (CBT). Symptomatic treatment for depression using appropriate antidepressants and nonsteroidal medications for pain is suggested. In a meta-analysis evaluating 35 treatment trials, the benefits of therapy remain inconclusive [787]. Limited evidence was seen with the immune modulator, rintatolimod along with counseling behavior therapies and graded exercise therapy (GET) in some patients with ME/CFS [802]. However, the ME Association [803] came out with a report contradicting some of the above conclusions. Their report showed no benefit from CBT and GET but Pacing courses (containing elements of CBT and "learning coping strategies" but not GET) have consistently shown to be the most effective, safe, acceptable, and preferred form of active management for ME/CFS.

Sleep of Intensive Care Unit Patients (Medical and Surgical)

Generally, patients are admitted to the medical ICU because of acute respiratory failure resulting from COPD, bronchial asthma, sleep apnea syndrome, restrictive lung disease, acute cardiovascular disorders (e.g., ischemic heart disease with or without myocardial infarction, cardiac arrhythmias, CCF),

acute neurologic disorders causing respiratory disturbances (e.g., brain-stem lesion, status epilepticus, high cervical cord lesions, neuromuscular disorders), renal failure, or gastroesophageal reflux causing acute respiratory tract symptoms. All of these conditions can be associated with sleep disturbances (insomnia, hypersomnia, and sleep-related respiratory dysrhythmia), which become intense in severely ill patients admitted to the ICU who require life-saving cardiorespiratory support [804–821].

Sleep disruption is very common in ICU patients; a figure of more than 50 % incidence has been quoted [811]. The causes of the sleep disruption include a variety of factors: (1) the ICU environment; (2) comorbid medical or surgical illnesses; (3) effects of many medications used to treat these critically ill patients; (4) individual factors, e.g., anxiety, psychological stress, pain resulting from the surgical procedures, and therapeutic interventions (e.g., use of ventilators, noise generated by the monitors) [804–821]. The ICU environment itself is deleterious to normal sleep and conducive to sleep deprivation with its attendant complications, such as ICU psychosis. In addition to sleep deprivation, physiologic and physical factors contribute to ICU psychosis. Noise, bright light, and constant activity on the part of the ICU personnel for monitoring and drug administration play significant roles in disturbing the sleep of ICU patients.

The ICU syndrome or ICU psychosis describes a cluster of psychiatric symptoms and is a characteristic mental state defined as a reversible confusional state developing 3–7 days after ICU admission secondary to sleep deprivation [812–814, 817, 821]. ICU psychosis is more common in surgical than in medical ICUs, and the prevalence has been estimated to be between 12.5 % and 38.0 % of patients admitted to the ICU [812–814]. Sleep deprivation has been cited as the major cause of the ICU syndrome [795, 822]. In a study by Helton et al. [812], 10 % of patients with moderate sleep deprivation and 33 % with severe sleep deprivation developed the ICU syndrome. There is evidence to suggest that the ICU syndrome is similar to delirium [785]. The question remains whether sleep deprivation is the cause of the delirium [823, 824]. There is evidence that higher morbidity and mortality increases the length of stay and cognitive impairment associated with ICU delirium [825, 826].

An important cause of sleep disruption in the ICU is noise [810, 811, 816, 817, 827–832]. Technological advances in the ICU setting (e.g., monitors and meters, ventilator alarms, television, phones, and beepers) have been cited as the major culprits for contributing to ICU noise and sleep disruption. The role of the noise in contributing to sleep disruption has been documented objectively by continuous sleep monitoring and recording of the environmental peak sound levels [831, 833].

In the surgical ICU, patients are usually admitted in the postoperative period because they are recovering from anesthesia, are beginning to suffer from pain, are experiencing metabolic disturbances, or have an infection related to surgical care. All these factors may cause severe disturbance of sleep and breathing.

Another condition noted in many patients admitted to the ICU is REM sleep behavior disorder. Schenck and Mahowald [834] evaluated over 200 adults with injurious, sleep-related behaviors during 8 years of clinical practice, and 20 of these had ICU admissions. Polysomnography with audio–video recordings documented REM sleep behavior disorder in 17 of these 20 patients.

Several authors have studied ICU patients using PSG to document disruption of sleep structure [827, 835–841]. These disturbances consist of marked diminution of SWS and REM sleep, frequent awakenings, sleep fragmentation, and reduced total night sleep time. The total sleep over a 24-h period appears to remain normal. Because of night sleep disturbances, ICU patients often have EDS [835, 837]. PSG recording in ICU patients has been a challenge. For one thing sleep of ICU patients is severely fragmented, especially those on mechanical ventilators [821, 835], and distributed in short segments throughout 24 h without any consolidated period of sleep containing atypical sleep prompting new scoring guidelines for ICU patients [840, 841].

Some studies have suggested that an impairment of the melatonin rhythm may play a role in explaining sleep disturbances and delirium in ICU patients [818, 819, 840–842]. The questions of ultimate outcome and functional status of patients in the ICU and the impact of improving poor sleep in ICU patients are not clearly known, and further research is needed in this direction [843]. It is stated that, overall, physical recovery is more complete than psychosocial recovery [844]. There have been reports of post-traumatic stress disorder following ICU admission for critical illnesses [845]. Roberts et al. [846] reported experiencing vivid dreams, hallucinations, or delusions associated with a longer ICU stay among 41 participants in three ICUs 24 months of post-discharge. The authors suggested that, because these dreams are disturbing, the patients should have information and counseling about delirium, particularly for those who remain in ICU for longer periods. Another factor known to play a role for sleep disturbance in ICU patients is sepsis which accounts for about 20–40 % of admissions to a medical ICU [817, 847]. Septic encephalopathy may show a characteristic EEG pattern (low-voltage mixed frequency

theta-delta waves) which has been reported to appear before the clinical manifestations of sepsis [827] along with reduced REM sleep and loss of circadian melatonin rhythm [817].

Treatment

The physicians and paramedical personnel who take care of ICU patients must be aware of the various ICU factors contributing to the problem of sleep disturbances, so that correct diagnosis and management of secondary complications (in addition to treatment of the primary disorders) can be effected promptly. The treatment for sleep disturbance in the ICU environment consists of nonpharmacologic and pharmacologic intervention. Nonpharmacologic treatment includes measures to decrease or eliminate many of the factors (noise, light, and others as described previously) causing sleep deprivation in ICU patients. Other nonpharmacologic measures include sleep hygiene rules, cognitive behavioral therapy, counseling the patients after discharge from the ICU, and adjusting ventilator settings to prevent dys-synchronous breathing and central apneas in those using mechanical ventilation [804, 817, 848]. Clinical practice guidelines to improve sleep in critically ill adults have been suggested [849]. These guidelines suggest an integrative approach to improve sleep in these patients, combining pharmacologic and nonpharmacologic measures. The suggested pharmacologic measures include hypnotics and benzodiazepine drugs (short and intermediate acting, such as alprazolam, lorazepam, and temazepam). These drugs should be used with caution because of adverse effects. Nonbenzodiazepine receptor agonists (e.g., zolpidem, eszopiclone, and ramelteon) are preferable to benzodiazepine drugs because of the lesser side effect profiles. The newer antipsychotic drugs (e.g., olanzapine, risperidone, and quetiapine) may be useful to treat delirium, but adequate studies have not been undertaken yet. Opiates and NSAIDs should be used for pain. In a report using a small sample size, significant improvement in postoperative delirium after surgery for esophageal cancer was noted following bright light therapy [850]. There is currently no standardized protocol to improve sleep of ICU patients [817]. Kamdar et al. [851] recently suggested controlling noise and light and increasing daytime activities.

In addition to treating the primary disorder, it is important to treat secondary sleep-related respiratory problems. If a sleep disturbance persists after the patient leaves the ICU, a primary sleep disorder may be suspected and appropriate investigations, such as PSG study and MSLT, should be performed.

African Sleeping Sickness (Trypanosomiasis)

African sleeping sickness is caused by *Trypanosoma gambiense* or *Trypanosoma rhodesiense* and is transmitted to humans by the bite of tsetse flies. The clinical features are characterized by lymphadenopathy, fever, and later (after several months or years) excessive sleepiness due to encephalopathy or encephalitis. In stage 1 of the disease, the parasites proliferate in the hemolymphatic system (hemolymphatic stage). In stage 2, the parasites invade the central nervous system, causing progressive neurologic dysfunction with disruption of sleep–wake patterns (meningoencephalitic stage) [824–856]. The clinical manifestations in the type caused by *T. rhodesiense* (Rhodesian sleeping sickness) are more rapidly progressive, resulting in cardiac failure and acute neurologic manifestations [853, 855]. Gambian sleeping sickness, caused by *T. gambiense,* is a more chronic illness with predominant neurologic manifestations [852]. Within 6 months to several years after the onset of the first symptoms, the Gambian type progresses into a late meningoencephalitic stage. CNS involvement is initially characterized by personality changes followed by delusions, hallucinations, and reversal of sleep–wake rhythm [852, 856]. The patient remains somnolent in the daytime and progresses gradually into the stage of stupor and coma. The cerebrospinal fluid examination shows increased cells and protein.

Several PSG studies lasting for at least 24 h and correlating with several plasma hormone levels have been conducted in patients with human African trypanosomiasis [854–865]. These studies documented disruption of the circadian sleep–wake rhythm, which is proportional to the severity of the illness. In less severely affected patients, the relationship between hormonal pulses (cortisol, prolactin, and plasma renin activity) and specific sleep stages persists. Sleep–wake rhythms are severely disturbed consisting mainly of circadian disruption and occurrence of sleep bouts lasting for 80–90 min throughout 24 h [856]. In addition, sleep-onset REM periods (SOREMP) are noted during many of these episodes which have been proposed to be a diagnostic marker and Buguet et al. [857] confirmed the usefulness of SOREMP in a five-year study of patients in Congo, particularly for diagnosing relapses following treatment. Circadian disruption of plasma cortisol, prolactin, and sleep–wake rhythms is noted in the most advanced patients, but not in patients with less severe illness [861–864]. These findings of circadian disruption suggest selective changes in the suprachiasmatic nucleus (SCN), resulting in circadian rhythm changes in the advanced stage of the illness. The association between SWS and GH secretion persisted in the patients, even in the presence of disrupted circadian rhythms [859]. In one study, circadian periodicity of the sleep–wake cycle was disturbed proportional to the severity of the illness, but the patients' melatonin rhythm was similar to that in normal individuals, suggesting additional control for melatonin beside the SCN [860]. In three advanced patients, the cytokine interferon-γ levels were increased 7- to 12-fold [862]. In an experimental study, rats infected with the

parasite *Trypanosoma brucei brucei* showed selective changes in c-*fos* expression in the SCN, supporting the hypothesis that, in human trypanosomiasis, changes in the SCN are responsible for circadian rhythm dysregulation and changes in the sleep–wake pattern [862]. Lundkvist et al. [866] suggested that the parasites target circumventricular organs in the brain, causing inflammatory responses in hypothalamic structures that may lead to dysfunction of the circadian timing and sleep-regulatory systems in patients with African trypanosomisis.

The possible role of hypothalamic hypocretin was evaluated by measuring cerebrospinal fluid hypocretin 1 levels in 25 untreated patients with human African trypanosomisis [867]. The authors observed that the cerebrospinal fluid hypocretin 1 levels were significantly higher in these patients than in narcoleptic patients but lower than in neurologic controls. The authors observed undetectable hypocretin levels in only one stage 1 patient and intermediate levels in one stage 2 patient. These results do not suggest a unique implication of the hypocretin system in African sleeping sickness, but the authors proposed that a dysfunction of the hypothalamic hypocretin region may participate in sleeping disturbances observed in African trypanosomisis. The diagnosis of trypanosomiasis is based on history as well as confirmation that the organism is in the blood, bone marrow, cerebrospinal fluid, lymph node aspirates, or a scraping from the chancre [852, 856]. The treatment of choice for patients in the meningoencephalitic stage is arsenical melarsoprol [852, 853, 856, 868, 869]. It is divided to have follow-up of these patients every 6 months for 18 months after treatment to diagnose relapse [856]. Actigraphic recording in a pilot study of none of the patients with human African sleeping sickness documented sleep–wake alterations correlating with PSG findings [870]. In a follow-up study, actigraphy showed improvement of sleep dysfunction and could be used for monitoring progress and treatment [870]. Because of growing resistance to melarsoprol, the World Health Organization (WHO) recommended the nifurtimox–eflornithine combination therapy [856, 869, 871]. However, because of adverse effects, lack of adequate synergistic effects, and possible resistance [872], there is ongoing research evaluating two new molecules [873, 874].

Sleep and Cancer

Sleep disturbance, although very common in patients with cancer, has not been systematically studied adequately in such patients as this complaint has been overshadowed by other major problems related to cancer [875]. A prominent complaint in the patient is fatigue [876–878], which may be secondary to insomnia in many of these patients. It is important to differentiate primary fatigue from that secondary to insomnia. Given the opportunity for sleep (e.g., relaxing on a couch or lying in bed during the daytime), a patient whose primary complaint is fatigue will not be able to fall asleep and will not complain of heaviness or drooping of the eyelids or head nodding. These patients remain alert and do not doze off. In contrast, patients with secondary fatigue will doze off under these circumstances. The most common sleep complaints in cancer include sleep initiation or maintenance insomnia, nonrestorative sleep, and impaired daytime function as a result of nighttime sleep dysfunction. Almost two-thirds of cancer patients and survivors have sleep problems [878–884]. Savard and Morin [885] quoted a figure of 30–50 % of patients with insomnia in newly diagnosed or recently treated cancer patients. This figure is much higher in patients with metastasis associated with pain.

The cause of sleep disturbance in cancer patients is multifactorial [878, 882, 886], including severe anxiety and depression related to cancer, cancer chemotherapy (e.g., tamoxifen in breast cancer), corticosteroids given to such patients to alleviate the medication side effects, environmental factors (e.g., hospitalization for surgical intervention), severe pain in patients with bone metastasis or compression of nerves or nerve routes, and radiation therapy. In addition to insomnia [875, 884, 887], which is the most common sleep complaint in cancer patients, some patients may have upper airway OSA after head and neck surgery as a result of edema in the pharyngeal space and reduction of upper airway dilator muscle tone [878, 888]. Sleep dysfunction in cancer patients adds to the burden of impaired quality of life and may also cause EDS in many of these patients. Most of the studies have involved breast and lung cancer patients, but there are scattered reports in patients with cancers in other sites causing sleep disturbances [822, 878, 882, 887, 889].

It is important to diagnose sleep dysfunction in both early and advances stages of cancer to improve the quality of life. The important first step is a history obtained from patients and the caregivers. Laboratory tests are not needed in most of the patients [885], but if upper airway OSAS is suspected (e.g., if the patient complains of snoring and EDS and has witnessed apneas), an overnight PSG study is recommended so that this patient can be adequately treated to improve quality of life in advanced stages of cancer and to prevent long-term adverse consequences of OSAS in early stages of cancer with long-term good prognosis

The relationship between hypnotic medication use and cancer remains contentious. A few studies linked sleep

Table 47.7 Medications causing sleep–wake disorders

Drugs used to treat general medical disorders
• Analgesics, including opioids
• Antiemetics
• Antihistamines
• Cardiovascular medications, including angiotensin-converting enzyme inhibitors and β-blockers
• Bronchodilators
• Appetite suppressants
• Sleeping medications
Drugs used to treat psychiatric disorders
• Antidepressants (e.g., tri- and tetracyclics, MAO inhibitors, SSRIs, trazodone, nefazodone, bupropion, mirtazapine, venlafaxine, duloxetine, and lithium)
• Antipsychotic drugs (e.g., haloperidol, phenothiazines, thioridazine, clozapine, olanzapine, and quetiapine)
Drugs used to treat neurologic disorders
• Antiepileptic agents
• Antiparkinsonian medications
• Drugs used to treat RLS and narcolepsy-cataplexy
Miscellaneous agents (including drugs of abuse and alcohol)
• Amphetamines
• Cocaine
• Marijuana
• Methylenedioxymethamphetamine (MDMA; ecstasy)
• Lysergic acid diethylamide (LSD)
• Phencyclidine (PCP or "angel dust")
• Testosterone
Over-the-counter (OTC) medications
• Nasal Decongestants
• Appetite suppressants
• Caffeine
• Sleeping medications

MAO Monoamine oxidase; *SSRIs* Selective serotonin reuptake inhibitors

medication to an increased risk of cancer [890–892]. A case-control study from Finland [882] observed that sleep medication use (both the yearly dosage and the years of use of hypnotic medications) was associated with increased cancer risk of the respiratory system. These findings should be interpreted with caution as some confounding factors (e.g., smoking and BMI) could not be addressed in this study. Further research is needed to resolve the controversial relationship between cancer and hypnotic medications and the mechanism for such association.

Management of sleep disturbance in cancer patients will follow the same general principles of management of insomnia and sleep apnea as outlined in other chapters of this book. Adequate hypnotic therapy [878, 887], preferably with non-benzodiazepine GABA agonists, should be tried first; for insomnia associated with pain in advanced stages of cancer, stronger hypnotics, including opiates, should be liberally used. Pharmacotherapy should always be combined with nonpharmacologic treatment (e.g., sleep hygiene and cognitive behavioral measures). It is important for physicians to be perceptive of sleep disturbance in cancer patients as treatment will largely improve the quality of life. Another important point to remember is that the patient's caregiver or spouse may also need treatment for insomnia as that individual's sleep is also disturbed as a result of a combination of psychological factors and sleep deprivation [875, 878, 883, 885].

Medication-Related Sleep–Wake Disturbances

Medications causing sleep–wake disturbances can be divided into five groups [893–907] (Table 47.7): (1) drugs used to treat general medical disorders; (2) drugs used to treat psychiatric disorders; (3) drugs used to treat neurologic disorders; (4) miscellaneous agents (drugs of abuse and alcohol); and (5) over-the-counter (OTC) medications. The importance of chronobiology, chronophysiology, and chronopharmacology should be kept in mind when discussing medication effects because biological responses to medications may depend on the circadian timing of administration of the drugs (see also Chap. 2). Responses of antibiotics to bacteria or cancer cells to chemotherapy may depend on the time of administration because pharmacokinetic or pharmacodynamic interactions vary depending on time of day.

Drugs for General Medical Disorders

Antihistamines (histamine$_1$ blockers), used to treat allergies, cause EDS as proven by the MSLT. These agents, however, are not recommended as hypnotics because of inadequate knowledge about their safety and efficacy as well as their daytime sedation and anticholinergic effects.

Narcotics (e.g., morphine, codeine, and other opioids), which are used to relieve severe pain and to induce sleep, can cause CNS sedation and respiratory depression. Other analgesic medications such as anti-inflammatory and antipyretic agents (e.g., acetaminophen and aspirin) have not been adequately studied to understand their effects on sleep, but they may have a mild hypnotic effect. It is shown in healthy individuals that the narcotics may increase wake time and reduce the amount of REM sleep and SWS. Antiemetics (e.g., metoclopramide, domperidone, phenothiazines, and the anticholinergic scopolamine) may produce drowsiness as a common side effect. Scopolamine may increase stage 2 NREM but decrease total REM sleep. Domperidone has the least side effects.

Cardiovascular drugs include ACE inhibitors, β-blockers, and clonidine. ACE inhibitors, used to treat hypertension, may affect sleep adversely, causing impairment of performance and mood. The β-blockers (e.g., propranolol, metoprolol, and pindolol), which are used to treat hypertension, cardiac arrhythmias, and angina pectoris, may cause difficulty initiating and maintaining sleep with frequent nightmares. They may also cause insomnia by suppressing the production of melatonin. Clonidine, a centrally acting α-adrenergic receptor agonist used to treat hypertension, may disrupt the quality of sleep by inducing shift changes to stage 1 or wakefulness and by suppressing REM sleep. Clonidine, like the β-blockers, may increase daytime sleep and sleepiness.

Bronchodilators used to treat COPD and bronchial asthma may cause insomnia. Theophylline may cause sleep fragmentation and increased awakenings during sleep.

Anorectics or appetite suppressants may act as CNS stimulants by increasing catecholaminergic activity, causing insomnia.

Sleeping medications such as benzodiazepine and nonbenzodiazepine (e.g., zolpidem and eszopiclone) receptor agonists may have the opposite effect after prolonged use, and an abrupt withdrawal may disrupt sleep due to severe withdrawal effects. There is individual variation and susceptibility to the withdrawal effects. Transient disruption of sleep after cessation of hypnotic medication is common. All sleeping medications, particularly long-acting ones, may affect daytime functioning. The short-acting drugs may cause rebound insomnia, daytime anxiety, and amnesia. Although benzodiazepines affect cognition and memory, these drugs are relatively safe and have low risk of abuse, and the side effect profiles are predictable. All sleeping medications may have respiratory depressant effect, particularly in COPD patients, bronchial asthma, and OSA. Sleeping medications should be used cautiously in the elderly as these may easily induce side effects because of alterations of metabolism and drug absorption in the elderly. All benzodiazepine agonists improve sleep quality by reducing latency to persistent sleep onset, reducing WASO, and increasing sleep efficiency and total sleep time. Benzodiazepine drugs may suppress SWS, but nonbenzodiazepine agonists do not do so.

Drugs Used to Treat Psychiatric Disorders

Antidepressant medications such as tri- and tetracyclics, monoamine oxidase (MAO) inhibitors, selective serotonin reuptake inhibitors (SSRIs), and others (e.g., trazodone, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, and lithium) may disrupt sleep, alter sleep architecture, and suppress REM sleep. Some of the tricyclics and MAO inhibitors are sedating, whereas others are stimulating, but most of the SSRIs are stimulating drugs. These antidepressants suppress REM sleep, may increase latency to REM sleep, and reduce percentage of REM sleep. Sedative antidepressants (e.g., amitriptyline, doxepine, and trazodone) may be used to treat insomnia, especially associated with depression. Most tricyclic antidepressants may cause daytime sedation. MAO inhibitors have alerting properties, so they are best used in the morning or early afternoon. Trazodone, a sedative antidepressant, increases SWS but is a weak REM suppressant. Fluoxetine has an alerting effect and can suppress REM sleep at high doses. Lithium increases

SWS and has a mild REM suppressant effect. Sudden withdrawal of these REM suppressant medications may cause REM rebound. Anxiolytics (e.g., buspirone and alprazolam) may cause sedation.

Antipsychotic drugs such as haloperidol, the phenothiazines, thioridazine, and the newer antipsychotic agents (e.g., clozapine, olanzapine, risperidone, and quetiapine) are used to treat psychotic conditions, including schizophrenia. Some of these drugs, particularly the phenothiazines, may cause drowsiness and impairment of performance. All neuroleptic drugs may produce serious side effects in combination with hypnotics, alcohol, or antihistamines. The newer antipsychotics have a better side effect profile.

Drugs Used to Treat Neurologic Disorders

Antiepileptic drugs (AEDs), especially benzodiazepines and barbiturates, cause sedation. Newer generation of AEDs is in general less sedating. However, well-controlled studies documenting the effects of antiepileptic agents and sleep architecture are lacking (see also Chap. 44). Effective control of seizures following treatment with antiepileptic agents results in the reduction of sleep disturbance due to the reduction of seizures and not due to any specific effect of antiepileptic agents on sleep architecture.

Drugs to treat RLS mainly include dopamine agonists (e.g., Pramipexole, Ropinirole, Rotigotine patch, α-2-delta ligands [Gabapentin, Gabapentin Enacarbil, Pregabalin], and opiates in refractory or intractable cases and those with augmentation). In addition to these short-term adverse effects of daytime sleepiness with these agents, especially α-2-delta ligands, the long-term vexing complication of dopamine agonists in dopamine-induced augmentation (DIA) [908] causing also severe sleep disturbance seen in a large percentage of patients, notably with Pramipexole and Ropinole. A rare side effect with long-term opiate use is opioid-induced hyperalgesia (OIH) resembling DIA [909]. The most serious effect of opiate besides addiction is its adverse effect on breathing causing or aggravating coexisting sleep apnea [898].

Stimulants used in narcolepsy-cataplexy (e.g., Provigil, Nuvigil, methylphenidate, and amphetamines) may adversely affect night sleep if taken late in the afternoon with reduction of SWS and REM sleep [898, 907]. Sodium oxybate, indicated mainly for cataplexy but also for consolidating night time sleep, is a CNS sedative and has an increased risk of sleep apnea [903–905].

Antiparkinsonian medications such as L-dopa may cause nocturnal hallucinations and agitated confusion during sleep at night. Some of the dopaminergic agonists (e.g., pergolide, pramipexole, ropinirole, and cabergoline) may cause nightmares.

Miscellaneous Agents

Drugs of abuse and alcohol (although not a drug, alcohol can be considered a social drug) have potentially deleterious effects on sleep. Stimulant drugs of abuse (e.g., amphetamines and cocaine) may cause insomnia. Amphetamines increase wakefulness, suppress REM sleep, and delay sleep onset. Cocaine reduces REM sleep and increases sleep latency and REM latency. On cessation, these may cause REM rebound. Hallucinogens such as lysergic acid diethylamide (LSD) and mescaline may cause a state resembling dreaming. Marijuana, through its active ingredient tetrahydrocannabinol (THC), may cause sedation at lower doses and hallucinations at higher doses. THC increases SWS and reduces REM sleep. Drugs of abuse mostly alter the amount and timing of REM sleep and produce REM rebound on discontinuation.

Alcohol has profound effects on sleep/wakefulness. Acute alcohol administration, by acting as a CNS sedative, will cause shortening of sleep onset, increase SWS, and reduce REM sleep. However, after the initial sedative effects lessen and as the blood alcohol level falls, the patient will have repeated awakenings causing sleep fragmentation and REM rebound. REM rebound is also noted on discontinuation after several nights of alcohol consumption. The sedative action of alcohol may be due to facilitation of GABA function and inhibition of glutamate. Alcohol, barbiturates, tricyclic antidepressants, and SSRIs may produce REM sleep behavior disorder and other complex phenomena such as status dissociatus.

Testosterone levels in men with sleep apnea have been reported to be low which improved after CPAP therapy, but testosterone administration may worsen sleep apnea by adversely affecting neuromuscular control of upper airway potency [898].

Over-the-Counter Medications

OTC medications include nasal decongestants and anorectics, which are stimulants (e.g., pseudoephedrine and phenylpropanolamine) and will cause insomnia. Caffeine, which is present in coffee, tea, colas, and chocolates, also is a stimulant and may promote wakefulness by blocking adenosine A_{2a} receptors. As little as 150 mg of caffeine, which is the equivalent of 1–2 cups of coffee, may disturb sleep quality by increasing sleep latency and reducing total sleep time. During sleep deprivation, high doses of caffeine reduce total sleep time, increase stage 1 NREM sleep, and reduce SWS but do not affect neurocognitive functions.

OTC sleeping medications are widely used for the induction of sleep. The active ingredients in these agents are antihistamines (diphenhydramine and doxylamine), and

these drugs represent the most common use of antihistamines in OTC preparations. These histamine$_1$ blockers have undesirable anticholinergic effects (e.g., dryness of the mouth, palpitations, dilation of pupils, tachycardia, and difficulty in urination) and cause daytime sedation.

Summary and Conclusions

There has been explosive growth in sleep medicine and increasing awareness about the importance of sleep in everyday life. It is therefore important for sleep specialists, general internists, and family physicians to have adequate knowledge about sleep dysfunction in general medical disorders to practice their trade effectively. This chapter attempts to summarize in a comprehensive manner general medical disorders that may account for a variety of sleep complaints (e.g., insomnia, hypersomnia, parasomnias, sleep-related breathing disorders, and circadian rhythm sleep–wake dysfunction) or may be comorbid with sleep disorders. General medical disorders may affect sleep–wake neurons by indirect mechanisms through metabolic, toxic, or anoxic disturbances. The possibility of medically induced sleep disturbance should always be kept in mind because the natural history of medical illness may be altered by this comorbidity. It is unfortunate that the ICSD-2 eliminated medical disorders as a separate category of classification and introduced these conditions in a scattered manner throughout the eight major categories and appendices.

All major categories of general medical disorders were addressed in this chapter, and some conditions were addressed in greater details than others because of the importance of sleep complaints affecting quality of life and because of long-term adverse consequences of sleep-related breathing disorders in many of these medical conditions. In the final section, a brief description was also given of a variety of medications used to treat general medical, neurologic, and psychiatric illnesses that may affect sleep and breathing, causing acute and emergent events during the course of the practice of sleep medicine.

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Evaluation and Management of Circadian Rhythm Sleep Disorders

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Sabra M. Abbott and Phyllis C. Zee

Introduction

Circadian rhythms are the near 24-h oscillations in physiology and behavior that persist in the absence of external time cues. The sleep–wake cycle is one of the most apparent of these behaviors, the timing of which is regulated by a combination of a homeostatic drive for sleep, which builds up the longer one is awake, and the circadian clock which regulates the appropriate timing of sleep [1].

In mammals, the primary circadian pacemaker is located in the suprachiasmatic nucleus (SCN), a set of paired nuclei located in the hypothalamus, lying on either side of the third ventricle, directly above the optic chiasm [2]. In the absence of external time cues, the SCN is able to maintain a near 24-h period through a complex transcription/translation feedback loop, but is also capable of being reset by various signals within the environment. The most well studied and presumably strongest of these signals is light. Light exposure during the evening and before the core body temperature minimum delays the circadian clock, while light in the early morning, after the core body temperature minimum advances the circadian clock [3–5]. In addition to light, melatonin also has resetting effects on the circadian clock. Endogenous melatonin levels normally rise 2–3 h before sleep onset, peaking in the middle of the night [6]. Opposite to the effects of light, exogenous melatonin given during the early evening causes advances, while melatonin in the morning causes delays [7, 8]. Other factors, including exercise [9] and restricted feeding [10], are also known to affect the circadian clock, though are not as well studied, and are not believed to be as strong a signal as light. The ability of these signals to reset the circadian clock can be used for treatment of the circadian rhythms sleep–wake disorders (CRSDs) which will be detailed below.

The CRSDs result when either an individual's internal clock is unable to maintain appropriate alignment with the external environment, or social/work obligations force an individual to follow a schedule that is misaligned with their internal clock. The principles of circadian physiology can be used to understand and diagnose these disorders, as well as provide treatment options for these individuals.

Circadian Rhythm Sleep Disorders

Delayed Sleep Phase Disorder

Delayed sleep phase disorder (DSPD) results in a stable sleep–wake cycle that is delayed by around 3 h with respect to the general population [11], with patients generally reporting being unable to fall asleep before 2–6 am. When allowed to sleep during their preferred schedule, sleep duration and quality are normal for age. DSPD has an estimated prevalence of 0.7–8 % depending on the population studied, with the highest prevalence among adolescents [12], and affects up to 5–10 % of chronic insomnia patients [13].

There does appear to be a familial component to DSPD. Certain haplotypes of hPER3 appear to occur with increased frequency in DPSD [14, 15] and may result in altered timing of the degradation of hPER3, prolonging the overall period. Polymorphisms in the Clock gene have also been associated with morningness–eveningness preference, though not specifically with DSPD, and this also has not been consistent across ethnic groups [16, 17].

DSPD has also been associated with traumatic brain injury (TBI). There are several case reports of individuals developing DSPD following TBI [18–20], and in a large case series of 42 individuals with TBI, 15 developed a CRSD, either DSPD or irregular sleep–wake rhythm [21]. This may

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be due to disruption of the melatonin signaling pathway, which normally projects from the hypothalamus, through the intermediolateral cell column in the cervical spine then back through the sympathetic chain to the pineal. Injuries to the cervical spine could potentially disrupt this pathway, resulting in alterations in melatonin secretion, with concomitant effects on circadian rhythms [22].

Advanced Sleep Phase Disorder

Individuals with advanced sleep phase disorder (ASPD) have a stable sleep–wake cycle that is several hours earlier than the conventional time [11]. Bed times are generally reported to be between 6 and 9 pm and wake times range from 2 to 5 am. ASPD is thought to be less prevalent than DSPD; however, this may simply be due to under-reporting, as individuals with ASPD and extreme morning types generally have fewer work and social disruptions resulting from their sleep patterns.

There is a strong heritable component to ASPD, with several cohorts of families with ASPD identified. The common feature to all of these families is a mutation either in CK1e or the binding site on hPER2 for this kinase [23–25]. CK1e normally phosphorylates and stabilizes hPER2 and slows the translocation back into the nucleus [26]. In the absence of this phosphorylation, the transcription–translation feedback loop progresses more quickly, resulting in an overall shortened period [27–29].

Irregular Sleep–Wake Rhythm

The hallmark of irregular sleep–wake rhythm (ISWR) is an absence of a clear major sleep and wake period, with at least 3 distinct sleep periods occurring with a 24-h window. While irregularly distributed, the total sleep obtained during a 24-h period is normal for age. Symptoms include complaints of both insomnia and excessive sleepiness related to the abnormal timing of sleep [11]. ISWR is most commonly seen in individuals with neurodevelopmental disabilities and elderly institutionalized individuals [30]. Symptoms are believed to result from a combination of dysfunction or degeneration of the SCN, in conjunction with either decreased exposure or decreased sensitivity to entraining time cues [31].

Non-24-h Sleep–Wake Disorder

Non-24-h sleep–wake disorder (N24SD) results when an individual's intrinsic pacemaker is unable to entrain to the 24-h environment. Symptoms include both insomnia and excessive daytime sleepiness as the circadian drive for sleep moves progressively later each day, moving out of phase with the surrounding environment [11]. N24SD is most commonly seen in blind individuals, who are unable to receive the daily signals of light to maintain entrainment with the surrounding environment. However, more rarely, this disorder can also be seen in sighted individuals. The etiology remains unclear at this point; however, there is some evidence that these individuals have a longer intrinsic period, which may make it more difficult for them to entrain to a 24-h environment [32].

Shift Work Disorder

Shift work disorder (SWD) consists of symptoms of insomnia or excessive sleepiness associated with a recurring work schedule that overlaps with the usual sleep time. To account for adaptation to a change in schedule, symptoms should be present for at least one month [11]. SWD is most commonly seen among individuals who work either night or rotating shifts, however, can also be seen in individuals working early morning or late evening shifts, if this work period is not aligned with their preferred sleep and wake times [33]. SWD is more common in individuals who are morning types, those who require longer sleep times, and those with significant daytime family or social responsibilities [34].

Jet Lag Disorder

Jet lag disorder consists of symptoms of insomnia or excessive daytime sleepiness secondary to travel over two or more time zones. In addition to sleep complaints, there are often symptoms of generalized malaise, cognitive impairment or somatic symptoms including gastrointestinal distress [11]. The severity of symptoms depends on many factors, including the distance and direction of travel. Eastward travel is generally more difficult to adapt to than westward travel, as eastward travel requires a phase advance of the circadian clock, which is generally more difficult to achieve than a phase delay of the circadian clock. In addition, older adults tend to have more difficulty adapting to time zone changes when compared to younger adults [35].

Evaluation of Circadian Rhythm Sleep Disorders

The diagnosis of the CRSDs depends primarily on taking a careful history; however, additional diagnostic testing can also be used. Clinical history should focus on getting a sense of when the individual's preferred sleep and wake times are. Both DSPD and ASPD can often be mistaken for insomnia, with individuals with DSPD complaining of inability to fall asleep, and individuals with ASPD complaining of early morning awakenings. The key distinguishing feature, however, is that when allowed to sleep at their preferred time, sleep will be of normal quality and duration. Irregular sleep–wake disorder may be more difficult to

distinguish with history alone, however, should be suspected, particularly in individuals with developmental delay, or dementia in whom caregivers note frequent prolonged napping throughout the day, with difficulty staying asleep at night. All non-sighted individuals should be questioned regarding possible symptoms of N24, with complaints of going through periods where they are unable to sleep at night, but feel tired during the day. In sighted individuals, N24 often presents in individuals who initially had extreme DSPD, but eventually are unable to maintain a 24-h pattern of rest and activity. SWD should be readily apparent from the history; however, it is important to question all individuals with a sleep complaint regarding their daily schedule.

Sleep Logs

Sleep logs provide useful adjunctive information for the clinical history, particularly for individuals who may have difficulty recalling their daily schedules, and are considered a guideline for the diagnosis of CRSD by the American Academy of Sleep Medicine (AASM). A variety of sleep logs are available but at a minimum should collect information regarding bedtime, wake time, and any naps. In individuals where there is a concern for insomnia, information regarding the timing of caffeine, alcohol, and medication intake is also useful. General recommendations are to obtain sleep log data for at least 2 weeks; however, particularly in individuals with suspected N24SD, collecting this information for at least 3–4 weeks may be useful [36].

Actigraphy

Actigraphy consists of an accelerometer that is usually worn on the non-dominant wrist to provide objective measurements of activity and rest periods. Actigraphy has been validated as a means of measuring sleep and wake [37] and recently was demonstrated to be approximately 80 % accurate in determining sleep and wake when compared to polysomnography (PSG) [38]. Newer devices also are capable of measuring both the intensity and wavelength of light exposure, which can provide additional data that can aid in diagnosis and management. The use of actigraphy is considered a guideline in the diagnosis of CRSDs and can also be used to evaluate the response to treatment [36]. Actigraphy should generally be performed for at least 2 weeks, preferably longer, particularly if evaluating for N24SD (Fig. 48.1a–c).

Circadian Phase Markers

Measurement of circadian phase markers can potentially be useful in demonstrating the presence of a circadian rhythm disorder and is considered an option under the AASM guidelines [36]. Melatonin release peaks in the middle of the night, and the onset of melatonin secretion in dim light (DLMO) generally occurs 2–3 h prior to the habitual sleep time [39]. Melatonin can be measured in the plasma; however, this is often impractical in the outpatient setting, as samples need to be collected every 30–60 min through an indwelling venous catheter. As an alternative, melatonin can also be collected in the saliva and has been validated as a comparable measure to plasma [40]. Samples should be collected every 30 min starting 5–7 h prior to expected sleep time, either under dimly lit conditions or while wearing light-blocking goggles. The timing of DLMO can be used both as a marker of circadian phase, but can also be used to assess response to treatment [41].

Core body temperature is another marker of circadian timing; however, the standard method of collection, using an indwelling rectal thermometer, is often impractical or undesirable in the clinical setting. Newer techniques are being developed, using a wrist mounted thermometer to measure the daily fluctuations in temperature. Core body temperature normally falls as an individual is falling asleep, reaching a nadir, and then beginning to rise $\sim$2 h prior to waking. Skin temperature, on the other hand, begins to increase prior to bedtime and drops just after awakening [42]. Validation studies have shown good correlation between the evening temperature increase measured at the wrist and DLMO suggesting that this may be another, less invasive means of measuring circadian timing [43].

Questionnaires

The Horne-Ostberg Questionnaire (MEQ) is a 19-item questionnaire that evaluates an individual's subjective sense of morningness–eveningness [44]. However, there has been some criticism of the MEQ, as it primarily assesses subjective sleep preferences, without evaluating the actual timing of sleep. More recently, the Munich Chronotype Questionnaire (MCTQ) was developed, which determines sleep times on work and non-work days and can also be modified to account for shift work [45]. Using this assessment, chronotype has been found to strongly correlate with morningness–eveningness preferences [45]. Based on current AASM guidelines, while questionnaires are an option for obtaining additional information, they are not required for the diagnosis of CRSDs [36].

Polysomnography

Unless there are concerns for other comorbid sleep disorders, polysomnography (PSG) is generally not indicated in individuals in whom a primary CRSD is suspected, as the disorder is primarily one of abnormal timing, rather than quality of sleep [36]. Patients should be carefully screened for potential symptoms of obstructive sleep apnea (OSA) and restless legs syndrome (RLS). In addition, PSG should be considered if individuals are still complaining of significant fatigue, despite being allowed to sleep during their preferred sleep window.

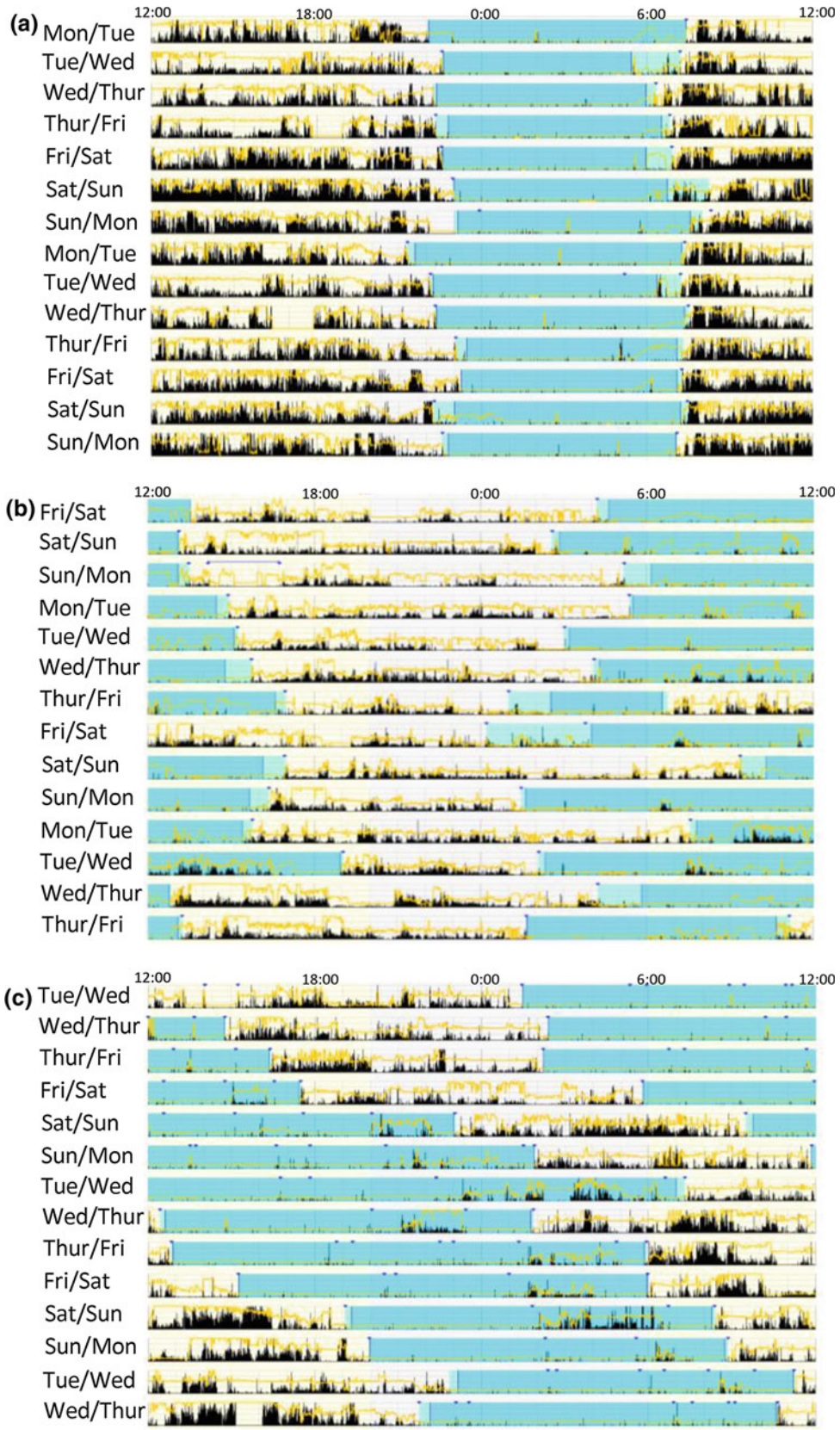

Fig. 48.1 Representative 2 week actigraphy data from an individual with normal sleep timing (**a**), delayed sleep phase disorder (**b**), and non-24-h sleep disorder (**c**). Each *horizontal line* represents 24 h. *Black vertical lines* indicate periods of activity, *blue shaded* areas represent reported self-reported sleep periods, and *yellow line* indicates light exposure

Treatment of Circadian Rhythm Sleep Disorders

Delayed Sleep Phase Disorder

Successful treatment of DSPD relies primarily on a combination of bright light and melatonin to advance the circadian clock. Bright light, given either immediately after or shortly before the habitual wake time (after the core body temperature minimum) can successfully advance the circadian clock. In addition, low doses of evening melatonin (0.5–3 mg) can provide additional advancing signals. A recent randomized controlled trial with bright light and melatonin showed improved subjective daytime sleepiness, fatigue, and cognitive function. Subjects were instructed to use the bright light for 30–45 min on awakening, take melatonin (3 mg) 12 h after the light exposure, and progressively advance their wake time by 1 h each day until the desired sleep window was reached [46].

While chronotherapy, consisting of progressively delaying the sleep time until the desired sleep window is reached, can sometimes be effective, caution should be exercised, as there have been case reports of this technique actually inducing N24SD in individuals with DSPD [47]. Hypnotics are generally not recommended for treatment of DSPD [36], as this is a disorder of sleep timing, rather than a primary insomnia, so the focus should be on adjusting the timing of sleep, rather than using medications to induce sleep at a time when the circadian system is not in a permissive state for sleep.

Advanced Sleep Phase Disorder

Perhaps due to the lower prevalence or fewer complaints associated with ASPD, there are fewer treatment trials for this disorder. There are case reports of progressively advancing the sleep period until the desired sleep time is reached [48]. In addition, there are a few small studies supporting the use of bright light in the evening, from 7 to 9 pm to delay the circadian clock, with results showing a delay on average of 1–2 h, as well as increase in total sleep time [49, 50]. In addition to light, exercising in the early evening has been demonstrated to delay the circadian clock [51] so may be a useful intervention in this population, though trials have not been performed looking specifically at individuals with ASPD. Theoretically, melatonin taken in the early morning should also delay the circadian clock [52]; however, there are no trials to date looking at its use in individuals with ASPD.

Irregular Sleep–Wake Rhythm

In treating ISWR, a focus on overall sleep hygiene is very important, as this often affects institutionalized individuals who are living in environments with few time cues and frequent nocturnal disruptions. A multi-modality approach is often most effective. Daytime bright light exposure can improve activity during the day and consolidate sleep at night [53–55]. Melatonin administered prior to bedtime has been shown to improve sleep in children with ISWR [56–58]; however, similar results have not been observed in elderly patients [59]. In elderly patients, a combination of daily light exposure, physical activity during the day, and a structured bedtime routine has been shown to be most effective [60].

Non-24-h Sleep–Wake Disorder

N24SD affects two distinct populations, sighted and non-sighted individuals, and treatment differs depending on the individual. In blind individuals, there is strong evidence that regularly scheduled melatonin, given one hour prior to the desired bedtime can serve as an effective entraining signal. Study doses have ranged from 0.5 to 10 mg, though generally lower doses are preferred [61, 62]. More recently tasimelteon, a synthetic melatonin agonist has been FDA approved for treatment of N24SD in non-sighted individuals [63].

In sighted individuals with N24SD, treatment is more complicated and is often multifaceted. There is a focus on enforcing strong social cues, with regular sleep–wake schedules, meal times, and exercise. In addition, the use of bright light upon awakening [64, 65], and melatonin prior to bedtime can also be beneficial [66, 67].

Shift Work Disorder

The treatment of SWD relies on multiple strategies. There is strong evidence that planned napping prior to the beginning of the shift can improve alertness and decrease accidents during the work shift [68]. During the work shift and commute home, close attention should be paid to the lighting conditions. During the work shift, increased exposure to bright light toward the beginning of the shift can improve alertness and mood. However, to avoid significant circadian phase shifting, which could impair work time performance, care should be taken to avoid bright light exposure during the commute home [69]. Shift workers often complain of insomnia related to difficulty sleeping during the day. Simple measures to improve sleep include making the bedroom as conducive for sleep as possible. Interventions include adding black out curtains to minimize light exposure, white noise machines to limit external noise, and instructing family members to minimize disrupting the individual during their sleep time. If this alone is not effective, studies have shown benefits from taking either a low dose of melatonin [70, 71] or hypnotic prior to sleep [72–74]. Particularly with hypnotic use, patients must allow enough time for sleep after taking the hypnotic to minimize any carryover of sedative effects into the next work period. While often attempts to improve daytime sleep are enough to minimize fatigue during work, if

Table 48.1 Clinical features and recommended treatment strategies for the circadian rhythm sleep disorders

Disorder	Clinical features	Diagnosis	Treatment
Advanced sleep–wake phase disorder (ASPD)	Stable advance of the major sleep period, resulting in early morning awakenings and difficulty staying awake in the evening	Sleep logs and when possible actigraphy for at least 7 days demonstrating a stable advance	Bright light therapy for 2 h in the evening
Delayed sleep–wake phase disorder (DSPD)	Stable delay of the major sleep period, resulting in difficulty falling asleep at night, and difficulty waking up in the morning	Sleep logs and when possible actigraphy for at least 7 days demonstrating a stable delay	Bright light therapy for 2 h on awakening, and melatonin (0.5–3 mg) 5–7 h before bedtime
Non-24-h sleep–wake rhythm disorder (N24SD)	Sleep period does not follow a 24-h pattern, instead usually delaying by 1–2 h every day	Sleep logs and actigraphy for at least 14 days demonstrating a pattern of sleep and wake times that delay each day	Blind: 0.5 mg of melatonin 1 h before bedtime Sighted: Bright light therapy for 2 h on awakening and melatonin (0.5–3 mg) 1 h before bedtime
Irregular sleep–wake rhythm disorder (ISWR)	Chronic disorganized pattern of sleep and wake with insomnia during the usual sleep period and hypersomnia during the usual wake period	Sleep logs and when possible actigraphy for at least 7 days demonstrating at least 3 irregular sleep bouts in a 24-h period	Mixed modality treatment, including increased daytime light and social activity, with decreased evening light and noise. Evening melatonin may also be helpful
Shift work sleep disorder	Insomnia or excessive sleepiness associated with a work schedule that overlaps the usual time for sleep	Sleep log and actigraphy, with measurement of light exposure if possible, for at least 14 days demonstrating a disturbed sleep–wake pattern	Sleep hygiene, scheduled naps, modafinil/armodafinil, and timed light exposure at the beginning of the work shift, melatonin at bedtime
Jet lag	Insomnia or excessive sleepiness associated with travel across at least 2 time zones	Clinical history	Timed melatonin (0.5–5 mg) 3 to 5 days prior to and after travel. Gradually change the sleep/wake time by 1 h each day

sleepiness during the work period remains a problem, modafinil [75] and more recently armodafinil [76] have been demonstrated to improve alertness and work performance in shift workers.

In addition to the above strategies for work days, one must also pay close attention to behaviors on non-work days as well. While ideally one would have a patient follow the same schedule on both work and non-work days, family and social responsibilities on non-work days often make this difficult. To accommodate for this, a compromise phase position has been proposed, where individuals sleep from 8 am to 4 pm on work days and from 3 am to noon on non-work days, allowing for daytime activity on days off, without completely losing entrainment to the night shift schedule [77, 78]. While following this schedule, it is important to also take advantage of the other strategies described above, including bright light exposure during the beginning of the work shift.

Jet Lag Disorder

The treatment of JLD depends on the direction, distance, and duration of travel. For short trips (<48 h), it is generally easier just to maintain the home time rather than trying to reset the clock multiple times during such a short time window [79]. For longer trips, options are to either gradually start resetting the clock before departure or adapt once arriving at the new destination. In either case, appropriately timed light and melatonin are the mainstays of treatment. Along with resetting strategies, the addition of hypnotics may be beneficial for some individuals; however, there is somewhat mixed data regarding their overall efficacy [80–82].

When traveling eastward, it is necessary to advance the circadian clock, which is generally more difficult to adapt to. Prior to departure, one option is to move the sleep schedule earlier by one hour each day, combined with morning bright light exposure, so that the clock is already advanced to the new time zone by the day of travel. Alternatively, if waiting to reset until the time of travel, once arriving at the destination the goal should be to avoid bright light during the morning (before the core body temperature minimum) when it can further delay the clock, but seek out light in the afternoon (after the core body temperature minimum) to help advance the clock. In addition, a low dose of melatonin (0.5 mg) at bedtime can be beneficial. Along with the above strategies, the addition of armodafinil during the daytime has been shown to increase alertness in individuals traveling >6 time zones east [83].

Westward travel is generally easier to adapt to, as it involves delaying the circadian clock. If attempting to transition prior to departure, the recommendation is to use bright light in the evening and gradually delay the bedtime

by one hour each day. On the other hand, if the preference is to wait until arriving at the destination, bright light exposure during the afternoon and a low dose of melatonin in the evening should both help to facilitate delays.

For travel in either direction, close attention to the timing of meals can also be beneficial. There is evidence in rat models of jet lag that scheduled food exposure can increase the speed of entrainment to the new time zone [84].

Conclusion

The CRSDs encompass a variety of disorders of the timing of sleep. Diagnosis depends on a complete clinical history, with adjunctive information obtained from sleep logs, actigraphy, and circadian phase markers. Treatment relies primarily on the resetting effects of light and melatonin on the circadian clock, with appropriate timing depending on the nature of the disorder, summarized in Table 48.1.

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Rapid Eye Movement Sleep Behavior Disorder 49

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Introduction

REM sleep behavior disorder (RBD) was first described in humans in 1986 after a series of patients reported curious nocturnal behaviors that resulted in injury to patients or their bedpartners [1]. Due to the loss of normal REM sleep muscle atonia, RBD patients often "act out their dreams," most commonly expressing violent complex movements that often mirror dream content [1–10]. RBD patients are primarily divided into two groups: idiopathic RBD, with no obvious cause, and symptomatic RBD, which is primarily associated with synucleinopathy neurodegenerative disorders, including Parkinson's disease (PD), Lewy body dementia (DLB), and multiple system atrophy (MSA) [3–12]. However, RBD is also common in patients with narcolepsy and in patients receiving antidepressant treatment and may be seen rarely in those with brainstem lesions in dorsal pons and medulla [10, 13–26]. In addition, RBD has also been associated with the use or withdrawal of drugs or alcohol, high chocolate intake [27], and migraine headaches [27–31]. However, because up to 82 % of idiopathic RBD patients develop parkinsonism or dementia over longitudinal follow-up, growing evidence suggests that idiopathic RBD may be a prodromal feature of a neurodegenerative disease, often preceding other characteristic more overt neurological manifestations by several years to decades [3, 5, 7, 8, 12, 32–37]. In addition, recent neuropathology data suggest that up to 94 % of patients with RBD, and 98 % of RBD patients confirmed by polysomnography (PSG), have synucleinopathy neurodegeneration at autopsy, furthering the presumption that RBD may represent the *forme fruste of* neurodegeneration in many patients [37].

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Diagnosis and Classification of RBD

The minimal diagnostic criteria according to the International Classification of Sleep Disorders (ICSD) 2 include: (A) presence of REM sleep without atonia on PSG; (B) sleep-related injurious or potentially injurious disruptive behaviors by history, and/or abnormal REM sleep behaviors during PSG; (C) absence of epileptiform activity during REM sleep (unless RBD can be clearly distinguished from any concurrent REM sleep-related seizure disorder); and (D) sleep disturbance is not better explained by another disorder [38]. However, an evolving diagnostic standard for probable RBD (pRBD) for patients having dream enactment behaviors but who lack PSG evidence for RSWA (due to either unavailability of PSG or failure to record REM sleep) is included in ICSD 3, given the resource intensive nature of confirmatory PSG (38a).

The core clinical feature of RBD is a history of witnessed dream enactment by the patient's bed partner, with or without recall of dream mentation by the patient himself or herself [1, 5, 11, 34, 39]. Patients are often able to vividly recall their dreams for weeks or longer, and when enacted dreams are recalled, patients typically report that their dream mentation contains a theme of being chased, or defense against an attack by animals or people [11, 40]. However, less aggressive themes such as playing sports or performing household chores are also common [41, 42]. Collateral history obtained from the patient's bed partner is crucial in diagnosing RBD patients, since NREM parasomnias like sleep walking or sleep terrors also often report frightening dream content. However, dreams of patients with sleep walking or sleep terrors more often involve natural disasters with a "flight" response, as opposed to the "fight" response reported by patients with RBD [5, 11, 39, 42, 43].

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RBD patients often have coherent vocalizations such as shouting, screaming, laughing, crying, and swearing, most often matching recalled dream content described by the patient [4–6, 11]. Excessive, repetitive phasic muscle jerking during REM sleep is the most frequent RBD clinical phenomena captured during PSG; however, complex motor behaviors such as punching, kicking, and running can lead the patient to leave the bed, potentially resulting in injuries [5, 11, 44]. Due to the violent nature of dreams, injuries prior to treatment are frequent and have been reported in approximately 55 % of patients [41]. While most often minor injuries such as bruises occur, more serious injuries such as fractures, lacerations requiring suturing, and subdural hematomas occur in as many as 12 % of patients [1, 5, 11, 41].

While PSG is required for a formal diagnosis of RBD, PSG is expensive and requires expertise for accurate interpretation, and is not readily accessible in many locations. Given the resource intensive nature of PSG, several validated screening measures for pRBD are available [39, 43, 45–49]. The RBD-HK consists of 13 questions regarding frequency and severity of dream enactment behavior. Out of 100 possible points, a cutoff score of 18 yields positive and negative predictive values of over 80 % [43]. The REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ), a 10-item patient self-rating questionnaire (maximum total score of 13 points) covering core clinical features of RBD, demonstrated that RBD patients scored an average of 9.5, compared to 4.6 in controls [45]. This survey has been adapted for use in Japanese patients, with a score of 5 yielding a sensitive, specific, and reliable diagnosis of RBD [47]. The Mayo Sleep Questionnaire (MSQ) is another validated diagnostic questionnaire tool for RBD screening in older patients with or without cognitive impairment and/or parkinsonism [39, 48]. While other surveys utilize patient-reported symptoms, one of the main strengths of the MSQ is completion by bed partners, providing valuable collateral history verifying dream enactment symptoms, which may be more reliable for patients who are cognitively impaired and in those who have little recall of their dreams. In addition, the MSQ is 100 % sensitive and 95 % specific for diagnosis of RBD, indicating its utility for screening for RBD when PSG is unavailable [48]. The RBD1Q is a multicenter validated screening questionnaire consisting of a yes or no answer to a single question about dream enactment (which is almost identical to the core RBD question on the MSQ), with a sensitivity of 93.8 % and specificity of 87.2 % for a diagnosis of RBD in patients with Parkinson's disease [46]. These questionnaires may be valuable for future epidemiological studies given their brevity, efficiency, and accuracy for diagnosis of RBD.

While surveys have been shown to be useful measures for RBD screening, exclusion of RBD-mimics such as nightmares, sleep walking, sleep terrors, nocturnal seizures, obstructive sleep apnea with atypical arousals from REM sleep, post-traumatic stress disorder, nocturnal panic disorder, psychogenic dissociative states, and delirium may be difficult by reliance on questionnaire instruments alone [5, 6, 42, 50, 51]. Given that violent behaviors during sleep in the general population are often associated with vivid dreams in sleep terrors and sleepwalking, the "gold standard" for clinical RBD diagnosis should remain a combination of clinical diagnostic interview with a thorough history, neurological examination, and PSG to confidently diagnose and differentiate RBD from other sleep disorders and parasomnias, and to confirm the necessary diagnostic feature of REM sleep without atonia [1, 5, 11, 38].

Diagnosis of RSWA

PSG diagnosis of RSWA requires the presence of abnormally elevated muscle tone during REM sleep, most often observed in the mentalis and tibialis muscles, but also in arm EMG leads [9, 38, 52, 53]. While most clinical laboratories primarily use mentalis, anterior tibialis, and forearm muscles to identify RSWA, some studies have suggested that an expanded EMG montage including the biceps brachii, flexor digitorum superficialis, and abductor pollicis brevis muscles is the most sensitive for RSWA determination [52, 53]. RSWA is classified as short phasic bursts, with muscle tone reaching at least two to four times larger than the amplitude of the lowest background EMG during REM or NREM sleep, or tonic segments with twice the background amplitude, usually lasting longer than 10–15 s in duration [52–54]. RSWA may also be found incidentally on PSG recording without dream enactment behavior. However, the significance of incidental RSWA for future development of dream enactment or neurodegeneration remains to be elucidated [5, 55]. In addition, RSWA without dream enactment is not uncommon in PD, suggesting that lesions in separate specific structures may be necessary to cause RSWA and DEB [55]. Since a small amount of phasic or tonic muscle activity can also be found during REM sleep in normal individuals [56], the AASM has established a standard for abnormal or potentially clinically relevant RSWA, defined as at least 5 mini-epochs of 3-s duration containing abnormally excessive phasic muscle activity within a single 30-s epoch of REM sleep, or excessive tonic muscle activity in the chin EMG channel lasting over 15 s in duration [38].

Quantitative Methods of RSWA Analysis

In addition to AASM criteria, several manual and automated methods of RSWA quantification have been developed, resulting in definitive cutoff values for a RBD diagnosis [9, 51–53, 57–60]. Many of the manual methods employ variations of the AASM standard, including the percentage of 3-s mini-epochs containing phasic muscle activity, as well as the percentage of 30-s epochs containing tonic activity [53]. In addition, 3-s mini-epochs containing the presence of either scorable phasic or tonic activity have been defined as "any" muscle activity, resulting in percentage of "any" muscle activity [61]. Various phasic, tonic, and "any" percent muscle activity cutoff values have been established for a diagnosis of RBD with 100 % specificity. For the common montage of mentalis and muscles in the submentalis region combined with anterior tibialis muscles, cutoffs of 46.4 % and 44.2 % have been reported for "any" and phasic percent muscle activity. In addition, a submentalis tonic percent muscle activity cutoff of 9.6 % has been reported [61].

Recently, similar methods have been extended to define appropriate density cutoffs for RBD patients with comorbid obstructive sleep apnea, as is commonly seen in clinical populations. Diagnostic RSWA percent muscle activity (phasic, "any") cutoffs were as follows: submentalis (SM) (15.5, 21.6 %); anterior tibialis (AT) (30.2, 30.2 %); and combined SM/AT (37.9, 43.4 %) [54]. A tonic percent muscle activity cutoff of 1.2 % was 100 % sensitive and specific, while an automated chin REM atonia index of 0.88 is appropriate in this patient population [54]. This manual methods also showed that in addition to standardly determined RSWA percent muscle activity measures, RBD patients have longer phasic muscle burst duration when compared with controls, and that measurement and consideration of phasic muscle burst durations further increases the specificity and sensitivity for diagnosis of RBD when combined with cutoff values for phasic and "any" percent muscle activity [54]. However, whether phasic muscle burst duration measurement may identify which patients with "incidental" RSWA are at greater risk for the development of RBD and future synucleinopathy is yet to be determined [54].

In addition to manual scoring methods, automated methods of chin RSWA analysis have been developed. The REM atonia index (RAI) is a computer generated value from 0 to 1, with a score of 0 indicating absolute absence of REM muscle atonia, and a score of 1 indicating completely preserved REM muscle atonia [58, 62, 63]. RAI of <0.9 has been found to be highly sensitive and specific for a diagnosis of RBD [54, 62]. Another automated method of chin tone analysis found that the number of both short duration (<0.2 s) and long duration (>0.2 s) muscle bursts was significantly greater in RBD patients than controls [60].

While both automated and manual methods of RSWA analysis have been shown to be accurate in the diagnosis of RBD, both have serious limitations. Manual methods are extremely time intensive, and many clinical sleep laboratories do not use expanded recording montages used to determine RSWA cutoff values for RBD diagnosis in some studies. Automated methods, while less time and labor intensive, have yet to be developed for limb muscles, limiting application toward RBD diagnosis in patients with RSWA primarily limited to the limb muscles [64].

Epidemiology

RBD most commonly presents after the age of 50, with 70–90 % of RBD cases occurring in men [34, 37, 65–68]. The prevalence of RBD has traditionally been estimated to be between 0.38 and 0.5 % in large population-based studies, [4, 11] but RBD patients represent up to 4.8 % of patients presenting to sleep disorders clinics, with the most common complaint being self or bedpartner injury due to dream enactment behaviors [67, 69]. More recent data suggest that pRBD (based on the MSQ) may be more common than previously believed, occurring in over 6 % in a community-dwelling subjects aged 70–89 years [70], and a very recent study from a large Korean cohort demonstrated a frequency of RBD of 4.8 % [71]. In addition, data on over 19,000 individuals found that violent behaviors during sleep are present in 1.6 % of the general population and occur more often in male individuals [11]. However, violent behaviors were also associated with NREM parasomnias such as sleep terrors, sleep walking, and confusional arousals, so not all violent behaviors during sleep can be attributed to RBD [11]. While the majority of RBD patients are older men, DEB can begin at any age, and may, in fact, occur as commonly in women as men, although RBD may be under diagnosed in women due to less violent dream enactment behaviors [72–74]. In patients with RBD diagnosed before the age of 50, and in those with comorbid narcolepsy, prevalence is nearly equal between genders [28, 75]. In younger patients with RBD, the most frequent causes are antidepressant use, drug or alcohol withdrawal, underlying narcolepsy, brainstem lesions, or congenital or neurodevelopmental disorders [28–30, 72–74]. In addition, evidence for coexistent autoimmunity is found in 20 % of women with RBD [28, 29]. Psychiatric diagnosis and antidepressant usage have also been reported to increase the likelihood of RBD as much as 10-fold [30]. In addition, limited evidence suggests that there may be a genetic association of RBD with human leukocyte antigen DQw1 [76]. However, this link has not been fully explored. RBD has

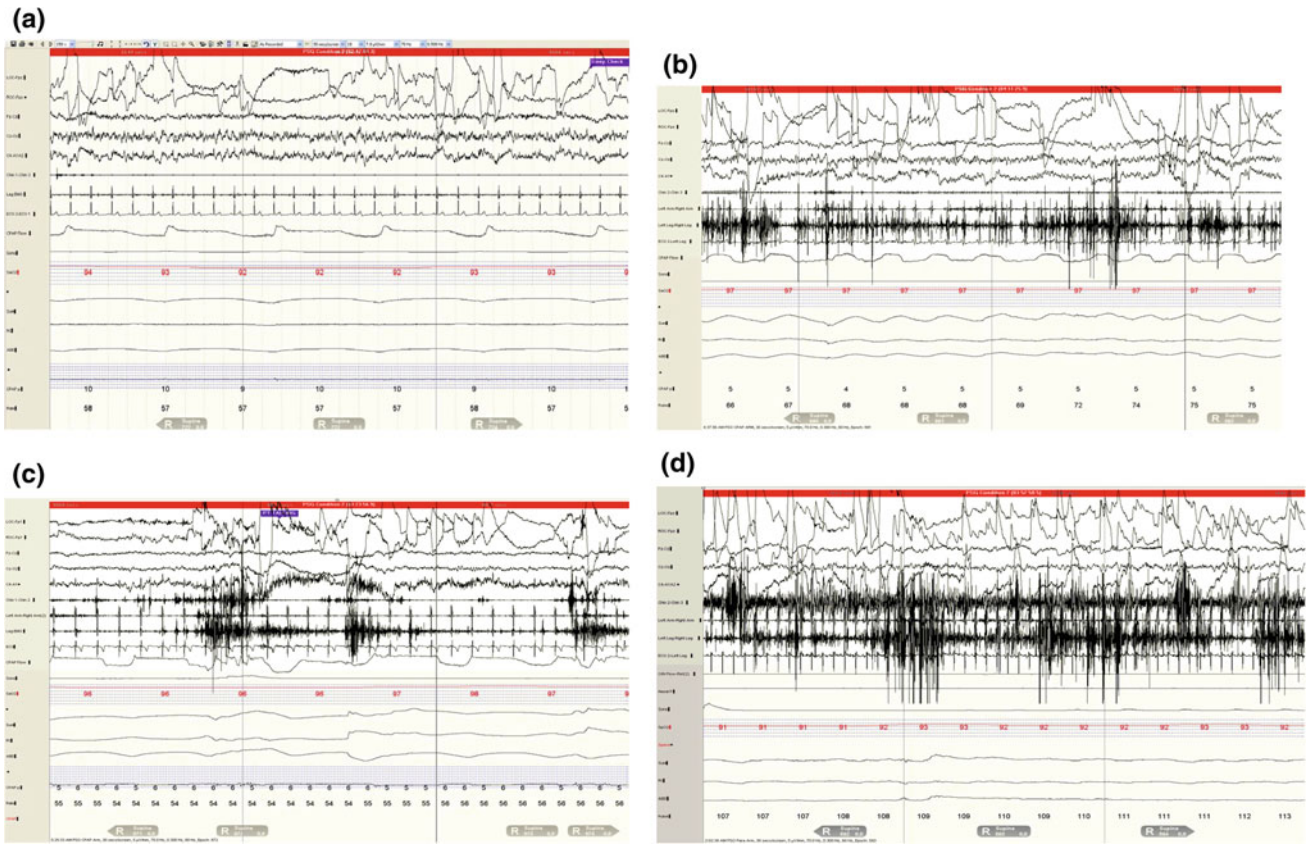

Fig. 49.1 Muscle tone during REM sleep in a normal subject, and in patients with REM sleep behavior disorder. The figure shows representative examples of 30 s polysomnogram epochs recorded during REM sleep. Muscle tone in the chin (submentalis), legs (linked tibialis), and arms (linked extensor digitorum communis) are shown in the sixth, seventh, and eighth channels of each example epoch, respectively. **a** demonstrates a normal level of REM sleep muscle atonia, while **b**–**d** demonstrate clear excessive phasic and tonic muscle tone, **b** shows predominantly excessive phasic muscle activity, especially in the leg, where there is also subtly increased tonic muscle activity. **c** demonstrates predominate excess phasic burst activity in the chin, arm, and leg muscle channels, accompanied by probable dream enactment manifested by vocalization; **d** shows excessive phasic and tonic muscle activity in the chin and leg muscle channels. Each of the examples seen in **b**–**d** is consistent with REM sleep without atonia, the neurophysiologic substrate of REM sleep behavior disorder

also recently been shown to be four times more likely in primary relatives (i.e., parents or siblings) of patients with iRBD when compared to primary relatives of individuals without RBD suggesting that there may be familial link in RBD [65]. In addition, history of head injury, smoking, pesticide exposure, lower level of education, and occupation as a farmer have been reported as potential risk factors for RBD. However, further research in this area is needed [77] (Fig. 49.1).

The Association of RBD with Neurodegenerative Synucleinopathy Disorders

RBD can result from several synucleinopathy phenotypes, as shown in Table 49.1. Both idiopathic and symptomatic RBD have been shown to be especially strongly associated with the synucleinopathies, a group of neurodegenerative disorders of unknown etiology related to intracellular accumulation of the protein alpha-synuclein, including Parkinson disease (PD), Lewy body dementia (DLB), multiple system atrophy (MSA), and pure autonomic failure (PAF) [5, 8, 12, 33, 37, 38, 67, 78]. Mild cognitive impairment (MCI), especially the non-amnestic subtype, has also been associated with RBD [5]. RBD is strongly associated with parkinsonism and/or cognitive impairment, which affects more than 82 % of RBD patients [36, 79]. Idiopathic RBD patients have an approximate 12–45 % risk of developing parkinsonism or dementia within five years of RBD symptom onset, which rises to 60 % within fifteen years, and to approximately 84 % risk 20 years after RBD symptom onset [5, 8, 79, 80].

There is growing evidence in iRBD patients of frequent presence of "soft," subtle neurological and neuropsychologic abnormalities (also known as non motor signs) consistent with the early stages of a developing synucleinopathy [5, 81–83]. Patients with iRBD show abnormalities in smell and

Table 49.1 Symptomatic causes of RBD

Synucleinopathy disorders • Parkinson disease • Lewy body dementia • Multiple systems atrophy • Pure autonomic failure
Tauopathies (rare) • Progressive supranuclear palsy • Alzheimer disease
Narcolepsy
RBD associated with antidepressant medication
Paraneoplastic disorders
Brain stem lesional pathology

color vision, similar to that seen in patients with PD [81–84]. Some useful batteries for assessment of vision and olfactory function include the Farnsworth-Munsell-100-Hue test (FM 100) for color vision, and the University of Pennsylvania Smell Identification test (UPSIT) and Brief University of Pennsylvania Smell Identification test (B-SIT) to test olfaction [81, 83]. These clinical assessments may help clinicians clarify which RBD patients are most likely to develop parkinsonism, and poor performance on the FM-100 and UPSIT tests appears to be good predictors for the development of impending neurodegenerative disease in patients with iRBD [81, 82, 84]. RBD patients without impaired olfaction have an 86 % chance of remaining disease free for 5 years, contrasting with a 35.4 % chance in those with abnormal olfaction [12]. Abnormal olfaction in RBD appears similar to olfactory deficits in previously diagnosed PD patients, indicating that progressive neurodegeneration in RBD leads to PD [81, 83]. In addition, RBD patients with impaired color vision have an 18–26 % chance of 5-year disease-free survival [12, 83].

Patients with idiopathic RBD and PD with RBD have difficulties with object identification compared to controls and patients with PD lacking RBD [82]. Neuropsychological performance can also be used as a potential predictor of progressive neurodegeneration in iRBD patients [78, 85]. Impairments in attention, executive function, decision-making abilities, verbal memory, and verbal learning are most common in RBD patients, similar to deficits seen in synucleinopathies [86, 87]. Because iRBD is likely an early manifestation of synucleinopathy, serial neuropsychometric testing may help determine the timeline and progression of neurodegeneration in iRBD patients. Similarly, quantitative electroencephalography (EEG) has demonstrated temporo-occipital slowing in patients with iRBD, with higher theta power similar to that seen in patients with DLB and PDD [86, 88]. Of note, mild cognitive impairment appears to be the driver of EEG slowing in iRBD patients and likely heralds impending MCI [89, 90].

Cognitive impairment in iRBD likely varies due to the time point at which patients are sampled. Patients with iRBD are a heterogeneous group and are considered "idiopathic" because they do not yet express clinical symptoms of neurodegenerative disease, but that does not mean patients in the reported studies are at the same point in the disease progression. Because we do not sample patients at a uniform time point in their supposed disease process, and we do not fully understand why patients progress at different rates, it is difficult to draw conclusions about accompanying cognitive, motor, and autonomic dysfunction that would apply to all iRBD patients [91]. RBD patients that have progressed further toward overt clinical manifestations of neurodegenerative disease would very likely have greater impairments in cognition; therefore, differences seen between controls and iRBD patients may be driven by those patients closer to the clinical expressions of synucleinopathies. To our knowledge, no studies have yet examined cognition in the very early stages of dream enactment behavior with subsequent longitudinal, serial follow-up to determine whether or not there is a discernible common pattern of temporal progression of cognitive decline in iRBD. Future studies examining early RBD are of significant importance in the hopes of better understanding the underlying neurodegenerative process in iRBD.

Autonomic dysfunction may be the earliest predictor of impending neurodegeneration in iRBD. Orthostatic blood pressure drop may present as early as 20 years prior to development of overt neurological signs of synucleinopathy [92]. Urinary incontinence (13 years), constipation (15 years), and erectile dysfunction (11.5 years) also begin long before other neurological symptoms [92]. In addition, there is increased cardiac denervation in patients with iRBD and PD, further indicating that RBD may be an early expression of PD in many cases. However, the amount of cardiac denervation does not appear predictive of neurodegenerative disease development [84, 93, 94]. Reduced ^{123}I-MIBG uptake may begin as early as Braak Stage 1, indicating that cardiac

scintigraphy may be useful in early identification of PD development. Since cardiac denervation is present in the earliest stages of PD and RBD, but the amount of denervation does not predict neurodegeneration, RBD may represent early PD in a subset of patients [94]. Notably, while ^{123}I-MIBG scintigraphy may be significantly decreased in RBD and PD, iRBD patients have been shown to have even greater reduction of MIBG uptake when compared to PD patients without RBD and neurologically normal controls, possibly indicating that PD-RBD may be a specific PD phenotype [95, 96]. Recently, plasma urate levels have also been shown to be a possible predictive factor of synucleinopathy neurodegeneration, with higher uric acid levels reportedly associated with a decreased risk for PD development [97] and a longer duration of RBD without conversion to PD, suggesting that plasma urate may modulate the progression of neurodegeneration in RBD. However, significantly more research is required to draw definitive conclusions [97].

Imaging in RBD

Similarly, advances in objective neuroimaging tests have begun to allow the non-invasive identification of patients at risk of development of a neurodegenerative disorder [5, 7, 98]. These tests include dopamine transporter uptake ^{123}I-FP-CIT SPECT (DaTscan) and transcranial sonography (TCS), which have shown to be effective in detecting subclinical changes in the substantia nigra that may reflect evolving synucleinopathy; and ^{99}mTc–ethylene cysteinate dimer SPECT (ECD-SPECT), a measure of regional cerberal blood flow (rCBF) which has been shown to predict future development of PD and DLB [98]. These tests may be useful in the identification of patients who could participate in future clinical trials of neuroprotective therapies designed to slow progression or arrest neurodegeneration in patients with iRBD [7]. Abnormalities on TCS (i.e., substantia nigra hyperechogenicity) and DaTscan (i.e., ^{123}I-FP-CIT binding deficiencies in the striatum) in iRBD patients appear predictive of those who subsequently develop more classic features of a synucleinopathy, whereas patients with no abnormalities on neuroimaging remained disease free during follow-up [7]. The sensitivity of combined TCS and DaTscan scans was 100 % for predicting development of neurodegenerative disease within 2.5 years, so DaTscan and TCS may be useful in diagnosing neurodegenerative disease before clinical symptoms of parkinsonism, cognitive decline, or dysautonomia appear [7].

ECD-SPECT scan showed increased hippocampal rCBF in all iRBD patients who developed PD or DLB when compared to iRBD patients who remained disease free [98]. Notably, patients who developed PD displayed increased perfusion in the hippocampus, pons, and anterior cingulate cortex, while patients who developed DLB had increased rCBF confined to the hippocampus. Increased rCBF was also associated with several clinical markers of neurodegeneration. UPDRS-III was positively correlated with rCBF in the right hippocampus, and olfaction was correlated with increased rCBF in the medial frontal gyrus, while impairments in color vision were correlated with increased perfusion in the pons and left hippocampus [98].

Cortical afferent inhibition during transcranial magnetic stimulation (TMS) study was shown to be decreased in iRBD patients when compared to controls and correlates strongly with poor performance in episodic verbal memory and executive function tasks, suggesting that cholinergic dysfunction may underlie cognitive impairment in iRBD [99]. In addition, voxel-based MRI morphometry (VBM) has recently shown gray matter loss in the left and right anterior cerebellum, pontine tegmentum, and left parahippocampal gyrus in iRBD patients, a pattern similar to neurodegeneration in DLB and MSA [100]. These findings indicate the utility of SPECT, TCS, TMS, and MRI scans to predict future neurodegeneration, and possibly synucleinopathy subtype in patients with iRBD, which may enable more accurate prognostication and individualized diagnostic and therapeutic approaches.

Finally, the degree of RSWA appears predictive for future PD development. Patients with a more significant degree of elevation in baseline mentalis tonic density were more likely to develop PD in one study [33]. RSWA increases over time in patients with iRBD, suggesting a progressive neurodegenerative process leading to the destruction of brainstem regions responsible for the control of REM sleep toward clinical manifestations of parkinsonism and dementia [101, 102]. However, RBD symptom duration may not be the correct measure to determine group comparability, and patients with higher RSWA densities may have been studied further along in their disease course toward the eventual expression of PD, so additional prospective studies are necessary to determine whether the degree of RSWA is a marker for progression to PD.

RBD and RSWA Association with Specific Synucleinopathy Disorders: Parkinson Disease, Lewy Body Dementia, and Multiple System Atrophy

RBD and Parkinson Disease

RBD is common in Parkinson disease (PD) with as many as 55 % of PD patients reporting RBD symptoms [12, 32, 103–105]. RBD symptoms can develop prior to the development

of clinical PD symptoms or during any of the six stages of PD [67]. Depression has been shown to be a risk factor for future development of PD [106]. In addition, depression and antidepressant use have also been associated with RBD [28, 30, 51, 107]. PD patients with RBD are more likely to have a comorbid psychiatric disorder compared to PD patients without RBD, and iRBD patients with comorbid depression have an increased risk for development of PD compared to RBD patients without comorbid depression [96, 108].

There is some evidence that PD-RBD may be a specific PD subtype. PD patients with RBD are less likely to be of the tremor predominant phenotype, less levodopa responsive, have higher Hoehn–Yahr scores, more frequent hallucinations, a greater degree of autonomic dysfunction, and most important, an increased risk for dementia [95, 96, 105, 109]. PD-RBD patients have a 45 % risk of development of dementia within four years compared to a 0 % risk in PD patients without RBD [95]. Of note, only PD patients with clinical RBD symptoms were at an increased risk for future development of dementia, when compared with PD patients with RSWA on PSG but no history of dream enactment and PD patients with normal REM sleep [109]. This suggests that PD-RBD may be a more widespread disease process compared to PD patients without RBD.

PD-RBD patients may have a gender disparity for the type of dream enactment behaviors similar to that seen in iRBD [110]. Men with PD-RBD report more aggressive and violent dreams with a higher percentage of violent movements during sleep. However, women with PD-RBD report more disturbed sleep with less violent movements during sleep [110]. Clinical RBD symptoms may remit in PD patients and appear less injurious when compared with iRBD patients [41, 111, 112], possibly due to decreased functionality as PD progresses. However, motor activity appears improved during dream enactment behavior compared with awake motor activty, so decreased functioning may not be fully responsible for clinical RBD remission and the lesser injury potential due to RBD behaviors in PD patients [113, 114]. The smoothing of movements during dream enactment represents sleep-related intact corticofugal and corticospinal neural circuitry that bypasses the basal ganglia, where functioning is impaired by synucleinopathy during wakefulness [114].

RBD and Lewy Body Dementia

Cognitive impairment is frequent in RBD and many patients develop dementia, primarily DLB or PDD [67, 84, 115–117]. While DLB and PDD are similar, important differences exist in the time course for the development of cognitive symptoms relative to development of motor symptoms. If motor symptoms are present for >1 year before cognitive decline, patients are considered to have PDD. If motor symptoms are present for <1 year prior to cognitive decline, or if they develop anytime after the onset of cognitive decline, patients have DLB [118]. Dream enactment is common in DLB, and PSG-confirmed RBD is present in as many as 83 % of DLB patients [119]. In fact, DLB and RBD are so closely associated that including RBD as a core feature of DLB increases the likelihood of DLB diagnosis sixfold [117]. Visuospatial impairment is one of the hallmarks of DLB, but can also be present in PDD. In addition, executive functioning is also affected in patients with DLB and PDD [84, 115, 116]. Idiopathic RBD patients show visuospatial and visuoconstructive dysfunction similar to patients with DLB, indicating that RBD may be a predictor for the development of dementia [82, 84]. In addition, many RBD patients eventually express clinical and/or pathologic features of Lewy body dementia/disease [5, 78, 107, 116, 117, 120, 121]. DLB patients with RBD have a shorter duration of dementia, earlier onset of parkinsonism and visual hallucinations, and lower neuritic plaque scores than DLB patients without RBD, indicating that DLB-RBD is a specific subtype of DLB which may have more widespread neurodegeneration than DLB without RBD [121]. Further insights clarifying the association between dementia and RBD, especially determining which patients are at highest risk for deteriorating cognitive functioning, are needed.

RBD and Multiple System Atrophy

Of the synucleinopathies, multiple system atrophy (MSA) appears to be the most strongly associated with RBD, with 68–100 % of patients having RBD or RSWA [85, 122, 113, 123]. Why MSA is more strongly associated with RBD than PD or DLB remains unclear. RBD symptoms in MSA appear to be less severe, even though RSWA is increased, when compared with PD-RBD and iRBD patients, a possible consequence of the more widespread neurodegeneration in MSA and its impact on functionality [124]. A diagnosis of RBD may help differentiate MSA from pure autonomic failure (PAF); in one case series, four patients with MSA had dream enactment behaviors, while all six patients diagnosed with PAF had no sleep disturbances [123]. However, other studies have shown RBD also occurs in PAF, indicating that further research is required on the association of PAF with RBD [122]. RBD has been found to be equally common in both MSA-P and MSA-C subtypes, suggesting that RBD is not a reliable finding to differentiate between subtypes of MSA [125].

RBD and Tauopathies

There have been reported cases of RBD in Alzheimer's disease, but the pervading theory is that concomitant Lewy body pathology instead may more likely explain the RBD symptoms [126]. REM sleep without atonia and RBD have been variably reported in patients with progressive supranuclear palsy (PSP) and rarely in patients with corticobasal degeneration [127–130]. Evidence is contradictory on whether the amount of RSWA in PSP is similar to the amount seen in Parkinson disease [128, 130, 131]. Regardless, RBD rarely presents years in advance of PSP features, instead tending to occur concurrently with the motor dysfunction [5, 126, 130]. RBD has not been found in other primary tauopathies. Yet rare examples of autopsy-proven Alzheimer's disease and PSP with RBD have been documented [5]. While it is possible that RBD can occur with a variety of the neurodegenerative proteinopathies, the frequency of RBD associated with synucleinopathies is far greater than in non-synucleinopathy disorders [5].

Narcolepsy and RBD

Since narcolepsy is a boundary state disorder, RSWA and RBD frequently co-occur in up to 60 % of cases [57]. Unlike RBD associated with synucleinopathy neurodegenerative disorders, RBD occurs equally in female as in male narcolepsy patients and has less complex and violent dream enactment behaviors which begin at an earlier age [57, 132]. RSWA without dream enactment occurs more frequently in patients with narcolepsy–cataplexy compared to both idiopathic hypersomnia patients and neurologically normal controls, correlating with the degree of hypocretin cell loss [57]. RSWA may be a useful diagnostic marker when unsure of a diagnosis between narcolepsy and idiopathic hypersomnia [133]. Antidepressants or stimulants may induce clinical RBD symptoms in narcolepsy patients, so sleep neurology clinicians must regularly inquire about dream enactment symptom occurrence and frequency in narcolepsy patients during follow-up care.

RBD Associated with Brainstem Lesions and Autoimmunity

Lesions of the brain stem caused by tumors, paraneoplastic, and autoimmune neurological disorders such as anti-Ma2-associated encephalitis or Morvan syndrome have been associated with clinical RBD symptoms and RSWA [13, 15, 16, 18, 19, 22–25, 128, 134, 135]. In addition, autoimmune disorders have been reported to occur in up to 20 % of women with RBD [29]. Brain stem lesions in patients with subsequent development of RBD symptoms have been helpful in localizing the structures responsible for control of REM sleep muscle tone in humans. One recent case identified RBD due to a discrete lesion in the right dorsomedial pons, the presumed location of the human sublateral dorsal nucleus/subcoeruleus that is believed to play a major role in generation of REM sleep muscle atonia [136]. Other lesional cases of RBD have also impugned the dorsal pontine tegmentum [26, 135]. Further case reports of brain stem lesions may allow insights into RBD pathophysiology. RBD or RSWA has also been found in up to 13 % of patients following traumatic brain injuries, indicating damage to brainstem structures responsible for REM sleep muscle control [137].

RBD Associated with Psychiatric Disorders and Antidepressants

There is growing evidence that RBD is common in psychiatric populations [28, 30, 51, 138]. Depression and antidepressant use are common, with as many as 60 % of RBD patients using antidepressant medications [30, 66]. In addition, RBD patients report significantly greater feelings of anxiety and depression when compared with matched control patients [107]. However, it remains unclear whether psychiatric RBD is a specific RBD subtype with a different pathophysiologic mechanism or simply an early manifestation of synucleinopathy neurodegeneration unveiled by antidepressant medications. A recent longitudinal study comparing iRBD patients taking antidepressant medications compared with antidepressant naïve iRBD patients showed a decreased rate of conversion to symptomatic RBD in the antidepressant users [139]. These findings, along with similar RSWA profiles between iRBD patients taking antidepressants and those not taking antidepressants, support the contention that psychiatric RBD is not a distinct RBD subtype, but simply iRBD that has been unveiled by antidepressant medication use [107, 139]. Notably, patients with depression have shown to be at an increased risk for developing PD, indicating that depression may be an early maker of PD [140, 141]. In addition, iRBD patients with depression appear to be at a significantly greater risk of future development of PD when compared to iRBD patients without depression [108]. PD patients with depression have been shown to have decreased norepinephrine binding in the locus coeruleus compared to PD patients without depression, providing evidence for a possible link between RBD and depression [142]. However, while there appears to be some relationship between psychiatric disease, RBD, and PD, idiopathic and symptomatic RBD patients have significantly

greater tonic RSWA elevation when compared to patients with psychiatric RBD on antidepressant medications, indicating that there may be mechanistic differences between these RBD types [107]. Further research in this area is needed to understand these relationships.

Selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants have been shown to exacerbate RBD symptoms and increase REM sleep muscle tone in patients without clinical dream enactment [29, 30, 138]. However, it remains unclear whether neurochemical effects mediated by antidepressants cause a reversible state of RSWA and RBD, or these drugs simply unveil RSWA and RBD in predisposed individuals [6, 29, 30]. Patients without a history of dream enactment on antidepressant medications have been reported to have increased RSWA when compared to normal volunteers not on antidepressants [107, 143]. In addition, limited evidence suggests that patients who previously received antidepressant medication use but who were not using antidepressants at the time of polysomnography had normal RSWA indices, suggesting that antidepressant medications do not cause a permanent alteration in REM sleep muscle tone [107]. Clinically, it is important to consider the impact of antidepressant effects in patients with RBD. Gradual cessation of SSRI medications or changing to an alternate antidepressant medication such as bupropion, which may have lesser propensity to aggravate RBD, may help decrease the frequency of dream enactment behaviors [144].

Pathophysiology of RBD

The mechanisms for RSWA and RBD remain poorly understood. Animal studies involving the rat and cat have informed much of our understanding of REM sleep atonia control. RBD-type behaviors were first demonstrated by selective lesioning of the cat locus coeruleus in 1965 [145]. Further study of sleep in the cat and rat has shown that the regulation of REM sleep is complex, and primarily located within the pons and medulla, especially the noradrenergic locus coeruleus (LC) and the cholinergic pedunculopontine nucleus (PPN) and laterodorsal tegmental nucleus (LDTN). Glutamatergic projections from the medullary magnocellular reticular formation (MCRF) also play a role in motor inhibition. In addition, the glycinergic/GABAeric nucleus raphe magnus, and the ventral and alpha gigantocellular nuclei have been implicated in the suppression of REM sleep muscle tone [146]. The hypothalamus, thalamus, substantia nigra, basal forebrain, and frontal cortex also participate in REM sleep regulation [145, 147].

Brainstem regions thought to be involved in the pathophysiology of RSWA and RBD are the MCRF, locus coeruleus/subcoeruleus (LC/SC) complex, PPN, LDTN, and the substantia nigra [145, 148]. Lesions in the LC/SC cause RSWA, and the site and severity of the lesion determines whether simple or complex behaviors result [3]. However, the rat sublateral dorsal nucleus (SLD), analogous to the cat SC, appears to have a vital role in the regulation of normal REM atonia, and when lesioned, mediating the pathophysiology of RSWA and RBD [149–153]. The SLD is located in the dorsal pontine tegmentum [152]. Lesions in the SLD result in RSWA in rats. The SLD contains primarily excitatory glutamatergic neurons with both caudal and rostral projections [153]. Rostral projections excite thalamocortical neurons, the basal forebrain, and lateral hypothalamus to generate REM sleep (EEG) [153]. Caudal projections to the ventromedial medulla (VMM), the premotor glycinergic/GABAergic neurons of the nucleus raphe magnus, and the ventral and lateral gigantocellular nuclei are responsible for activating hyperpolarization within spinal motorneurons and subsequent generation of REM sleep muscle atonia [153]. Rats also possess a "REM-on" and "REM-off" region [154]. The REM-on region is inhibited by GABAergic and galaninergic projections from the forebrain ventrolateral preoptic nucleus (VLPO), in addition to cholinergic projections from the PPN/LDTN which are active during wakefulness and non-REM sleep [153, 155]. The REM-off nuclei are activated by projections from the noradrenergic LC, serotonergic raphe nucleus (RN) and by hypocretinergic pathways from the lateral hypothalamus [3]. The REM-on nuclei in the SLD and the precoeruleus (PC) also interact with REM-off nuclei and are mutually inhibitory [154].

Recent research from a RBD transgenic mouse model has illustrated the importance of ionotropic glycine/$GABA_A$, and metabotropic $GABA_B$ receptors for generation and maintenance of REM sleep muscle atonia [151]. Only simultaneous inhibition of both ionotropic and metabotropic receptors results in heightened REM sleep muscle tone similar to that of wakefulness [151]. Inhibition of only single neurotransmitter receptors results in incomplete muscle activation, and it is very likely that the large degree of variation of RSWA seen between different patients, and within the same patients on repeated studies over different nights, is a direct result of how many receptors are inhibited [151, 156]. While large lesions to the SLD result in RSWA, they also cause a large decrease in total REM sleep time [153, 154]. Therefore, because RBD patients often have a normal amount of REM sleep, it is unlikely that RBD and RSWA in iRBD result from lesions directly to the SLD [150, 153]. Two populations of SLD/SC neurons have been found in the cat brain; ascending glutamatergic projections responsible for generation of REM sleep EEG activity, and descending glutamatergic projections inducing REM sleep muscle atonia [153]. Possibly only the descending projections are disrupted in iRBD, resulting in RSWA and dream enactment, while

the ascending projections are relatively spared [153]. Another possible hypothesis is that the selective degeneration of premotor REM-on GABA/glycinergic neurons of the nucleus raphe magnus and the ventral and alpha gigantocellular reticular nuclei occur in RBD as a result of alpha-synuclein aggregation, which is also in accordance with the Braak hypothesis [157]. Both noradrenergic and serotonergic influences also play a role in REM sleep muscle tone. Decreased serotonin and noradrenaline concentrations have been found in the nuclei of hypoglossal motor neurons, with a subsequent increase in REM muscle tone with direct injection of serotonin into these nuclei [153, 158]. On the other hand, noradrenaline does not appear to directly increase muscle tone, but instead amplifies glutamatergic driven muscle excitation [159]. Dream enactment behavior and phasic muscle twitches during REM sleep are hypothesized to result from direct or indirect glutamatergic inputs from the motor cortex projecting to spinal motor neurons [153]. The fact that movements during DEBs in patients with PD appear faster and less stereotyped than movements during wakefulness argues for direct activation of spinal motor neurons resulting from corticospinal and corticofugal projections bypassing the smoothing contributions of the basal ganglia during REM sleep [153, 160]. Ultimately, REM sleep muscle atonia likely results from a powerful combined glycinergic/GABAergic drive stimulated by glutamatergic projections from the SLD, with additional mediation by seratonergic and noradrengergic influences [153].

Since most of our understanding of REM sleep comes from animal models, there are very likely interspecies differences between humans and animals. However, lesional cases of RBD in humans also propose that human dorsomedial pontine structures analogous to the SLD and MCRF play similar roles to the animal models. Discrete dorsomedial pontine lesions in SLD-analogous structure lead to decreased motor inhibition, as well as decreased excitation of the MCRF, thereby potentially causing RBD symptoms [136]. It remains unclear whether lesions causing RBD in humans may involve the MCRF alone, or whether lesions must have additional involvement of the REM-off regions [154].

Because patients with narcolepsy frequently have RBD, the relationship between orexin-A and orexin-B (hypocretin-1 and hypocretin-2) and REM sleep muscle tone has also been examined. Decreased levels of CSF hypocretin-1 from damage to the lateral hypothalamus have been associated with a greater amount of muscle activation during REM and non-REM sleep in patients with narcolepsy with and without cataplexy [161]. Hypocretin has also been shown to play a role in REM sleep muscle activation by directly acting on LC neurons, in addition to REM sleep muscle tone suppression by action on the pontine inhibitory area [162, 163], suggesting that hypocretin likely plays a large role in the stabilization of REM sleep muscle control, and that disruptions in hypocretin expression, whether deficient or excessive, could result in RSWA [161, 162, 163]. Decreased hypocretin levels have been associated with RSWA in narcolepsy, while increased hypocretin levels have been associated with RSWA in PD [161, 164]. In addition, in a small case study of patients with idiopathic RBD, hypocretin levels were normal, so further research on the role of hypocretin in mediating RSWA and RBD is needed [165]. Dopamine may also play a stabilizing role in the control of REM sleep muscle tone, with both dopamine deficiency and excessive levels of dopamine resulting in increased REM muscle tone [166, 167]. Because RSWA is occasionally seen in PD patients without RBD, it is possible that dopaminergic dysfunction in these patients contributes to the RSWA without DEB [55]. Further exploration of this relationship is needed.

The Braak Staging Hypothesis and RBD

Because of the strong association of RBD with PD, the Braak staging hypothesis of PD may provide a possible explanation for the occurrence of RSWA and RBD symptoms in PD and perhaps also in DLB [3, 5]. Braak has postulated six stages of progressive and selective Lewy body deposition and Lewy neurite accumulation based on the clinical phenotype of PD, corroborated by pathologic examination [157]. Each successive stage has increased Lewy bodies and Lewy neurites compared to the previous stage. In addition, some structures are almost never affected in the six stages, while others are affected in most, indicating a selective vulnerability in the synucleinopathy neurodegeneration [168]. In stage 1, Lewy bodies and neurites begin to accumulate in the dorsal motor nucleus of the vagus in the medulla, while in stage 2, Lewy bodies and neurite progress rostrally through the magnocellularis reticular nucleus, subceruleus–ceruleus complex, olfactory bulb, and anterior olfactory nucleus. RBD symptoms are also considered to be part of stage 2, given common impairments in olfaction and cardiac denervation reported in idiopathic RBD patients [83]. Stages 1 and 2 are considered the "preclinical" phase of parkinsonism, preceding the evolution of motor or cognitive symptoms, in which RBD is the most distinguishing feature [168]. The parkinsonian stage is encompassed by stages 3 and 4 with the progression of Lewy deposits to the substantia nigra, the pedunculopontine nucleus, and the amygdala occurring in stage 3, while stage 4 results from progression of Lewy deposits into the temporal mesocortex. Widespread neurodegeneration occurs in stages 5 and 6, with Lewy deposits affecting the neocortex, causing cognitive

impairment [157]. Further evidence for the relationship between RBD and Braak staging stems from reportedly impaired olfaction and dysautonomia in patients with idiopathic RBD, indicating that RBD may be a precursor of PD [81–83, 94, 103]. As PD progresses from stage 1 to stage 6, there is an increasing loss of hypocretin cells, possibly supporting the hypothesis that hypocretin deficiency either plays a role in RBD pathology, or occurs concurrently and causes other PD-associated features [169]. However, a recent small case series reported increased levels of RSWA associated with increased hypocretin, so this relationship remains incompletely understood [164]. In addition, Braak staging does not well explain why some Lewy body disease patients never display RBD symptomatology, nor why some RBD patients never develop PD.

Treatment of RBD

Suppression of nightmares and prevention of patient and bed partner from injuries are the main goals of RBD treatment. Prediction of injury occurrence in RBD is very difficult. Patients with idiopathic RBD and those who remember their dreams have been recently found to be at significantly greater risk of injury [41]. However, frequency of dream enactment behaviors has not been shown to be predictive of possible injury, highlighting the importance of RBD treatment, even in patients with infrequent episodes of dream enactment [41]. All dangerous objects should be removed from the bedroom. Moving furniture away from the bed, padding the corners of bedside tables, and placing a mattress next to the bed may help prevent injury if the patient falls or leaves the bed during dream enactment [44]. If injury to the bed partner occurs, sleeping in separate beds or separate rooms minimizes risk of injury. Bed rails or barriers between the patient and bed partner may also be utilized, and bed alarms may be useful if the bedpartner has had to move to another room. A novel bed alarm designed to provide RBD patients with a calming instruction to return to sleep has been effective in reducing DEB in medication refractory patients [170]. The alarm system includes a pressure sensitive pad underneath the shoulders of the patient, as well as a clothing tether that is attached magnetically to the alarm system that detaches from the alarm system, activating the alarm and waking the patient from sleep, thereby averting the RBD episode [170]. The device is most effective in patients with a history of leaving the bed during dream enactment behavior. Confusional arousals resulting from obstructive sleep apnea, a common comorbidity in RBD patients, may mimic RBD episodes [171]. Treatment of apnea with continuous positive airway pressure may result in improvement in the frequency and severity of these episodes; however, treatment of OSA has not been shown to decrease RSWA, indicating there may be no direct effect of treatment of comorbid OSA on the pathophysiology of RBD [54].

Clonazepam and Other GABA Agonists

Melatonin and clonazepam are considered to be the two mainstays of pharmacologic treatment for RBD [32, 66, 68, 172, 173]. Melatonin and clonazepam appear to be equally effective in reducing frequency and severity of DEB, but only melatonin has been reported to significantly reduce injuries, with fewer side effects than clonazepam [66]. The $GABA_A$ receptor modulator clonazepam was the initial treatment reported as effective for decreasing RBD symptoms, with a median effective dose of 0.5 mg and a range of 0.25–2.0 mg given approximately 30 min before bedtime [8, 28, 59, 66–68, 75, 108]. Of note, while patients on clonazepam have decreased motor activity during REM, REM sleep muscle atonia is not restored, indicating that clonazepam may act on the motor cortex to inhibit glutamate induced phasic muscle bursts, but not on regions responsible for control of REM sleep muscle atonia [153, 174–176]. While clonazepam effectively reduces RBD symptoms, it can also increase the severity of obstructive sleep apnea and cognitive impairment. Additional side effects include sleepiness, dizziness, unsteadiness, and sexual dysfunction [32, 66, 176]. Therefore, patients with cognitive impairment, dementia, and sleep apnea must be monitored carefully when treated with clonazepam. While most patients with RBD associated with neurodegenerative disorders tolerate clonazepam well and benefit from its use, melatonin has been shown to be more effective in treating this population with fewer side effects [66]. Other GABA receptor modulators may also be useful in treating RBD; however, very little research on the effectiveness of these drugs on RBD symptoms exists [177]. Zopiclone has been reported to be effective in reducing RBD symptoms in a small number of patients [35, 177]. Zopiclone is a selective GABA α-1 and α-5 agonist with a short half-life and may impact the pathophysiology of RBD and reduce REM muscle tone by selectively acting on $GABA_A$ receptors [35]. However, further research is needed to validate this hypothesis.

Melatonin

Melatonin has recently been shown to be equally effective for RBD treatment, with fewer side effects than clonazepam [32, 66, 172, 173]. Adverse effects are dose related and primarily include daytime sleepiness; however, headache and hallucinations have been reported [32, 66, 178]. Melatonin may be a more efficacious treatment for patients with symptomatic RBD due to its more tolerable side effect

Table 49.2 Treatments for RBD

Drug	Mechanism	Dose (mg)	Adverse effects
Clonazepam	$GABA_A$ receptor modulator	0.25–2.0	Sedation, sexual dysfunction, and cognitive respiratory depression
Melatonin	Unknown	3–12	Sedation
Pramipexole	Dopamine agonist	0.125–0.5	Sedation, nausea, impulse control disorders

profile [66]. The median effective dose of melatonin has been reported to be 6 mg at bedtime [66]. However, ranges of 3–25 mg have also been reported as tolerable and effective [66]. Melatonin has been shown to increase REM sleep atonia during treatment; however, the mechanism by which this occurs remains unknown [35, 172, 173].

Other Potential Treatments of RBD

Other treatments of RBD have been limited to case reports and small case series. The association between RBD and PD has prompted interest in the role of dopamine in the pathophysiology of RBD. While levodopa decreases the amount of REM sleep time, possibly providing less opportunity for dream enactment behaviors, high doses of levodopa have been shown to increase both REM muscle tone and hallucinations which may be mistaken for RBD [166, 179]. Pramipexole has shown mixed results, varying from little or no effect, to reduction of RBD episodes [180–182]. In a recent large series, 62 % of patients treated with pramipexole monotherapy reported improvement in RBD symptoms, compared to 88 % improvement reported by patients treated with clonazepam, suggesting that pramipexole is likely not a suitable first-line therapy for RBD [183]. In this study, pramipexole was more effective in treating patients with lower amounts of RSWA compared to patients with significant amounts of RSWA, indicating that dopaminergic agents may help stabilize control of REM muscle tone early in the early course of PD [183]. Zonisamide, which is used to treat motor symptoms of PD, has been reported to decrease DEB in one PD patient [184]. Zonisamide has been shown to increase GABA-ergic neurotransmission and decrease glutamate in the rat brain, indicating that zonisamide could influence RBD symptoms both by inhibition of glutamatergic phasic muscle bursts as well as through GABA induced hyperpolarization of motor neurons [185, 186]. Given the high frequency of RBD in PD, further research on the effects of zonisamide on RBD symptoms is warranted. If efficacious in treatment of RBD symptoms, zonisamide may allow for the use of one treatment for both motor dysfunction and RBD symptoms, eliminating the need for polytherapy in a cognitively vulnerable patient population that may be impacted more severely by polypharmacy. Donepezil has also rarely been reported to reduce motor events related to RBD [187, 188]. Agomelatine is a novel antidepressant with a melatoninergic mechanism that has been reported to effectively decrease RBD symptoms with minimal side effects [189]. In addition, RSWA decreased in patients taking agomelatine, suggesting a relatively potent melatoninergic effect [189]. Because agomelatine has also shown similar efficacy to other antidepressant medications with fewer side effects, agomelatine may be considered a very useful medication in RBD patients with depression [190]. In addition, the herbal supplement Yi-Gan San has been shown to suppress RBD symptoms in three patients, possibly by acting on serotonergic and GABAergic systems [191]. While clonazepam and melatonin are effective in reducing RBD symptoms, only rarely do these or other treatments completely eliminate potentially injurious dream enactment behaviors. Therefore, future large, prospective comparative treatment trials are needed to develop better and more tolerable treatments that completely eliminate injury potential (Table 49.2).

Conclusions

RBD is a potentially injurious parasomnia that can reflect an early manifestation of synucleinopathy neurodegenerative disorders in many individuals, especially Parkinson disease, Lewy body dementia, and multiple system atrophy. Injuries are frequent to both patients and bedpartners, occurring in at least 50 % of cases, and not infrequently, injuries are serious enough to require medical intervention [1, 66, 67]. Currently, addressing bedroom safety in addition to pharmacologic treatment is the most effective form of therapy. A 6 mg bedtime dose of melatonin, with its relatively benign side effect profile and comparable efficacy to clonazepam, may be considered the first-line treatment of RBD, especially in patients with neurodegenerative disorders. Unfortunately, no neuroprotective therapies to prevent the progression of RBD to other clinical manifestations of neurodegenerative disorders exist at this time.

Early identification of patients with RBD could enable entry of individuals vulnerable to developing future synucleinopathy neurodegenerative disorders into clinical trials of neuroprotective therapies, with the goal of preventing

further neurodegeneration and arresting its course at a time point before clinically significant motor or cognitive sequelae unfold, or at least delaying the onset of these features [192]. Symptomatic treatment of RBD is focused on injury prevention by advising environmental measures to assure bedroom safety, and reduction of the frequency and severity of RBD episodes through administration of pharmacotherapy with clonazepam or melatonin. Future research of RSWA and RBD is necessary to determine sensitivity and specificity as biomarkers for conversion to overt synucleinopathy, to more effectively manage dream enactment so as to prevent injury, and to better understand the time course and causes of progressive neurodegeneration to inform design of future neuroprotective treatment trials.

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Parasomnias

50

Jacques Montplaisir, Antonio Zadra, Tore Nielsen, and Dominique Petit

Introduction

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines parasomnias as "disorders characterized by abnormal behavioral, experiential, or physiological events occurring in association with sleep, specific sleep stages, or sleep-wake transitions" [1]. Parasomnias can sometimes be considered benign sleep phenomena, especially when occurring during childhood, and do not necessarily have serious impacts on sleep quality or quantity, or on daytime functioning. In some cases, however, injuries, psychological distress, and/or sleep disruption can ensue and seriously disturb the individual and his or her spouse or family.

True parasomnias are classified by the second edition of the International Classification of Sleep Disorders (ICSD-II) [2] into (1) disorders of arousal, or nonrapid eye movement (NREM) parasomnias; (2) parasomnias associated with rapid eye movement (REM) sleep; and (3) other parasomnias. Disorders of arousal (from NREM sleep) comprise somnambulism (or sleepwalking) and sleep terrors. Parasomnias associated with REM sleep consist of nightmare disorder, recurrent isolated sleep paralysis, and REM sleep behavior disorder (RBD). Other parasomnias include sleep enuresis and sleep-related groaning, among other conditions. The classification is slightly modified in the ICSD-3 published in 2014 (see Chap. 27). Sleep-related bruxism, sleep-related rhythmic movement disorder, and somniloquy (or sleep talking) were classified under parasomnias in the first edition of the ICSD but not in the second (see Chap. 27). We have, however, included these topics in this chapter.

The clinical presentation, polysomnographic (PSG) characteristics, prevalence, associated factors, pathophysiology, and treatment of the diverse conditions forming this heterogeneous group are reviewed in this chapter. Secondary parasomnias (disorders of specific organ systems that manifest preferentially during sleep) are not discussed here.

Disorders of Arousal (From NREM Sleep)

The symptoms and manifestations of the disorders of arousal can be considered along a spectrum. The patient's emotional expression can range from calm to extremely agitated while the actual behavioral manifestations can range from simple and isolated actions (e.g., sitting up in bed, mumbling, fingering bed sheets) to complex organized behaviors (e.g., rearranging furniture, inappropriate sexual activity, playing a musical instrument, driving a vehicle). Moreover, an episode can be composed of two overlapping disorders such as a sleep terror followed by sleepwalking.

The two disorders of arousal share many characteristics. Generally, episodes develop from sudden but incomplete arousals from slow-wave sleep (SWS: NREM sleep stage N3) [3–5] and sometimes from stage 2 sleep [5–7]. As a consequence, these parasomnias tend to take place in the first third of the night when SWS is predominant. In all disorders of arousal, episodes are typically characterized by misperception and relative unresponsiveness to external stimuli, mental confusion, automatic behaviors, and variable retrograde amnesia. Conditions that intensify sleep, such as sleep deprivation [6, 8, 9], intense physical activity [10], hyperthyroidism [11], fever [12–14], neuroleptics [15, 16], or medications with depressive central nervous system effects [17], can precipitate disorders of arousal in predisposed individuals. Finally, a common genetic component is suspected. People with an arousal disorder often have a positive family history for one of the two disorders [18–21].

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Somnambulism

Clinical Presentation

Somnambulism (or sleepwalking) is characterized by complex behaviors usually initiated during arousals from SWS; it may begin with simple movements (e.g., sitting up in bed) and culminate in walking, bolting from the room, or worse [2]. Table 50.1 presents the diagnostic criteria established by the American Academy of Sleep Medicine [2]. Although usually considered a benign condition in children, sleepwalking in adults is potentially injurious. Episodes of surprising complexity have been reported: cooking or eating [22], driving a car [23], even homicide [24–28]. Accordingly, the duration of episodes may vary from a few seconds to several minutes [22]. The number of legal cases of sleep-related violence is on the rise [29–33] and raises fundamental questions as to the medicoforensic implications of these acts [23, 24, 34–39]. Associated mental activity includes instances of confusion, perceived threat, dreaming, and even pseudohallucination.

Experimental sleep deprivation can be used to trigger episodes of somnambulism in the sleep laboratory, since these rarely occur spontaneously in laboratory conditions. In fact, 25–38 h of sleep deprivation can significantly increase the number of actual somnambulistic events recorded in the laboratory by a factor of 2.5–5 when compared to baseline [6, 40, 41]. The fact that none of the control subjects investigated in these studies experienced nocturnal behavioral manifestations in the laboratory demonstrates that sleep deprivation alone does not lead to somnambulistic episodes, but rather that it increases the probability of somnambulistic behaviors in predisposed individuals. Experimentally triggered arousals using auditory stimulation during slow-wave sleep can also be used to successfully induce episodes during sleepwalkers' normal sleep and even more so during recovery sleep [40]. Diagnosis may thus be substantially aided by such techniques.

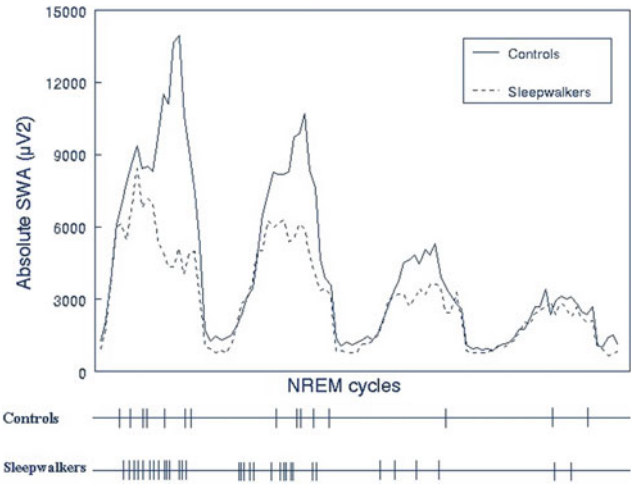

Fig. 50.1 Slow-wave activity (SWA) over 4 consecutive NREM-REM cycles in 15 sleepwalkers and 15 healthy paired controls. Power is significantly reduced in the second half of the first NREM period. Awakenings from SWS are indicated on the two *horizontal lines* below the graph (reproduced with permission from Gaudreau et al. [44])

Analyses of sleep architecture reveal no significant differences between adult somnambulistic patients and control subjects [42–47], except for a greater number of arousals selectively out of SWS in sleepwalkers, even for nights without sleepwalking episodes [3, 42, 44]. On quantitative analysis of their electroencephalograms (EEGs), sleepwalkers were found to have lower power in slow-wave activity (0.75–4.5 Hz) during the first NREM cycle [44]. They also had a higher number of awakenings during SWS than control subjects (Fig. 50.1) [44].

Several studies have documented the presence in the EEG of high-amplitude delta waves, termed *hypersynchronous*

Table 50.1 ICSD-2 diagnostic criteria for somnambulism and sleep terrors

Somnambulism	Sleep terrors
(A) Ambulation occurs during sleep (B) Persistence of sleep, an altered state of consciousness or impaired judgment during ambulation demonstrated by at least one of the following: i. Difficulty in arousing the person ii. Mental confusion when awakened from an episode iii. Amnesia (complete or partial) for the episode iv. Routine behaviors that occur at inappropriate times v. Inappropriate or nonsensical behaviors vi. Dangerous or potentially dangerous behaviors (C) The disturbance is not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder	(A) A sudden episode of terror occurs during sleep, usually initiated by a cry or loud scream that is accompanied by autonomic nervous system and behavioral manifestations of intense fear (B) At least one of the following associated features is present: i. Difficulty in arousing the person ii. Mental confusion when awakened from an episode iii. Amnesia (complete or partial) for the episode iv. Dangerous or potentially dangerous behaviors (C) The disturbance is not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder

delta (HSD) activity, occurring during SWS or immediately prior to somnambulistic episodes [4, 42, 45, 48]. However, more comprehensive studies have shown that HSD has a low specificity for the diagnosis of somnambulism [47, 49, 50] and that actual episode onset is often not preceded by a gradual accumulation of HSD waves [49]. However, episodes may be preceded by an abrupt change in high-amplitude slow oscillations (<1 Hz) [51], a process that may reflect cortical reactions to brain activation.

With regard to postarousal EEG, Schenck et al. [47] described three patterns that characterized the first 10 s of most SWS arousals in adults with sleepwalking/sleep terrors: pattern I, diffuse rhythmic, and synchronous delta activity (0–4 Hz), most prominent in bilateral anterior regions; pattern II, diffuse and irregular moderate- to high-voltage delta and theta activity intermixed with, or superimposed by, alpha- and beta-activity; and pattern III, prominent alpha- and beta-activity, at times intermixed with moderate-voltage theta activity. A follow-up investigation [52] of adult sleepwalkers showed that patterns II and III were the two more frequently observed forms of postarousal activity and that these patterns were also the only two that occurred during stage 2 episodes.

There is a strong genetic component to somnambulism [18]. About 80 % of somnambulistic patients have at least one family member affected by this parasomnia, and the prevalence of somnambulism is higher in children of parents with a history of sleepwalking [53–55]. A population-based twin study [18] showed a considerable genetic effect in adulthood sleepwalking (proband-wise concordance five times higher in monozygotic than dizygotic pairs), although the effect in childhood sleepwalking was not as pronounced (1.5 times higher in monozygotic than dizygotic pairs). In fact, this parasomnia was recently found to be linked to excessive transmission of the human leukocyte antigen DQB1*05 and *04 alleles [56]. However, the functional significance of this finding remains unclear. More recently, a genomewide scan conducted on a single family composed of 22 members found evidence for a significant linkage at chromosome 20q12-q13.12 [21]. Of particular interest is the fact that the candidate interval includes the adenosine deaminase gene which is believed to play a role in slow-wave sleep [57].

Although daytime somnolence or impairment in daytime functioning has never been part of the clinical portrayal of sleepwalking, there is increasing evidence showing that adult sleepwalkers often complain of excessive daytime somnolence. The association between somnambulism and daytime sleepiness has been found in a large population-based survey [58], in laboratory-based studies based on sleepwalkers' mean sleep latencies on the Multiple Sleep Latency Test [59] as well as on their scores on the Epworth Sleepiness Scale [60, 61], The EDS reported by adult sleepwalkers does not appear to be explained by the presence of concomitant sleep disorders or PSG signs of nocturnal sleep disruption and may thus be part of the sleepwalking phenotype and linked to its underlying pathophysiology [60].

Associated Factors and Pathophysiology

Although considerable progress has been made in the conceptualization of sleepwalking and its correlates [62], the exact pathophysiologic mechanisms of somnambulism remain unclear. Several factors have been proposed, including psychopathology, genetics, and deregulation of serotonergic systems.

Traditionally, the presence of somnambulism in adulthood has been viewed as a sign of major psychopathology [52, 63, 64]. However, several studies have shown that most adult patients do not have a *Diagnostic and Statistical Manual of Mental Disorders*-based [1, 65] Axis I psychiatric disorder, nor do they necessarily present with highly disturbed personality traits [46, 66–69]. However, anxiety may increase its occurrence in both children and adults [70, 71]. Based on clinical and research experience, Rosen and colleagues [70] proposed that somnambulism and sleep terrors may be nocturnal expressions of repressed anger concerning major life events such as separation, divorce, marital conflict, or family relocation.

Serotonin has also been hypothesized to be involved in the pathophysiology of sleepwalking on the basis that certain factors implicating the serotonergic system (e.g., certain drugs, fever) can precipitate sleepwalking [72]. In addition, sleepwalking episodes are four to nine times more common in conditions associated with abnormalities in the metabolism of serotonin, such as Tourette's syndrome or migraine headaches [73–75].

Finally, one single-photon emission computed tomography study was performed during sleepwalking in a 16-year-old boy with a history of somnambulism [76]. It showed that sleepwalking arose from the selective activation of thalamocingulate circuits and the persisting inhibition of other thalamocortical arousal systems. During the episode, the EEG showed diffuse, high-voltage rhythmic delta activity. This supports the notion that sleepwalking is a dissociated state consisting of motor arousal and persisting mind sleep.

Prevalence

The peak incidence of somnambulism (approximately 17 %) is around age 12 years [77]. For adults, a suggested prevalence of 2–2.5 % [78, 79] is probably an underestimate. Although many studies report no gender difference in older children, adolescents, or adults [77, 80], a study of two large cohorts of young children (2.5–6 and 4–9 years old) found it to be more common in boys than in girls [81, 82].

Treatment

Treatment is often unnecessary when the episodes are benign and not associated with potential injury. In this case, reassuring the patient/family about the benign nature of the episodes and demystifying the events is often sufficient. However, identifying and avoiding the potential precipitating factors, such as sleep deprivation, stress, and environmental disturbances, is effective in preventing episodes. Precautions should also be taken to ensure a safe sleep environment.

In children, the preferred treatment for somnambulism consists of a behavioral technique called anticipatory or scheduled awakening [83]. The parents keep a diary of their child's episodes and determine an average time at which the episodes take place. They then awaken their child about 15–20 min before the typical time of occurrence of the episode for a period of 1 month. It has been reported that the episodes cease as soon as this intervention is started, and the benefit is maintained on long-term follow-up [84, 85]. Hypnosis (including self-hypnosis) has been found to be effective in both children and adults with sleepwalking or sleep terrors [84, 86–91].

Pharmacologic treatment should be considered only if the behaviors are hazardous or extremely disruptive to the bed partner or other household members. Benzodiazepines (clonazepam or diazepam) and tricyclic antidepressants (imipramine) can be effective [92–97]. However, pharmacotherapy does not always result in adequate control of sleepwalking [68]. Treatment should always include instructions on sleep hygiene and stress management.

Sleep Terrors

Clinical Presentation

Sleep terrors (also known as night terrors or *pavor nocturnus*) are "arousals from SWS accompanied by a cry or piercing scream and autonomic nervous system and behavioral manifestations of intense fear" [2]. The American Academy of Sleep Medicine [2] diagnostic criteria for sleep terrors are presented in Table 50.1. Historically, sleep terrors have been confused with nightmares, a distinct REM sleep parasomnia. In 1965, Gastaut and Broughton [98] first observed by PSG that sleep terrors were not associated with REM sleep but rather occurred suddenly during SWS. Typically, within 90 min after sleep onset, the individual will scream loudly and sit up in bed with a panic-stricken expression. There is usually intense autonomic activity (sweating, flushing of the skin, mydriasis, tachycardia, rapid breathing) and, less often, complex behavioral manifestations such as leaving the bed, fleeing the room, or thrashing around. Injuries may result in such cases. The distinction between sleep terrors and somnambulism is ambiguous, although the activity displayed during sleep terrors is usually more rapid and abrupt than it is during somnambulism [95]. Inconsolability is a key feature of sleep terrors; attempting to console or awaken an individual during an episode will only unduly prolong or intensify it. As is the case for somnambulism (and contrary to a nightmare), the individual usually does not fully wake up and remains amnesic for the event the next day.

As for somnambulism, sudden awakenings from SWS (even without an actual episode starting) are typical of this condition, especially in the second half of the first two SWS sleep episodes. Instability of the NREM EEG pattern was also demonstrated [99]. However, a normal PSG does not rule out a diagnosis of sleep terrors. Time spent in SWS preceding an episode appears to be positively correlated with severity of the episode [95]. Rarely, sleep terrors may arise from stage 2 sleep.

Associated Factors and Pathophysiology

Sleep terrors that occur in childhood are usually not associated with a neurologic condition, whereas onset in adulthood could indicate a neurologic disease. Sleep terrors in adulthood have been described in relation to various psychopathologies, but many studies have shown that such parasomnias can occur in otherwise mentally healthy individuals [3, 46, 100]. As is true for somnambulism, genetic factors play a major role. Monozygotic twins are more concordant than dizygotic twins for sleep terrors [101]. A model-fitting analysis showed that sleep terrors were explained by a two-component model at 18 and at 30 months (about 42–44 % of additive genetic effects and 56–58 % of nonshared environment) [102]. Sleep terrors are twice as frequent in children for whom one or both parents have a sleepwalking history than in children with nonaffected parents [103]. These data and the clinical similarities between these two parasomnias suggest a common genetic predisposition and similar pathophysiologic mechanisms.

As for somnambulism, the incidence of sleep terrors in the sleep laboratory is lower than in the patient's normal environment [95, 104]. However, sleep terrors can be induced in predisposed individuals by auditory stimulation during SWS [46, 95]. Indeed, in individuals with sleep terrors, the orienting response to auditory stimuli has been reported to be more intense and persistent than in normal subjects, suggesting a hyperexcitability of the nervous system in these individuals [105]. In the sleep laboratory, the severity of the sleep terror, as assessed by heart rate increase and maximum heart rate after arousal, has been found to be proportional to the duration of the preceding SWS episode [106]. The prearousal delta power was also proportional to the sleep terror's intensity [107]; the EEG preceding sleep terrors contained significantly more delta power in central and frontal regions than control EEG (no event) sections.

This was confirmed by Espa et al. [3], who showed that sleep terrors were preceded by an increase of slow-wave activity with the main increase occurring immediately prior to the episode. During the sleep terror itself, the EEG activity demonstrated that the subject was neither fully asleep nor fully awake [95].

Prevalence

Reported incidence estimates are wide ranging [80, 108–110]. For childhood sleep terrors, the estimate is influenced by the age range studied, the sampling method, and definition used. Further, some parents may fail to differentiate between nightmares and sleep terrors. When an operational definition was supplied to parents, a high overall prevalence (40 %) was found for preschool period [82]. More specifically, the prevalence of sleep terrors was found to be 36.9 % at 18 months and 19.7 % at 30 months [102]. As for somnambulism, sleep terrors tend to resolve during adolescence and do not display a gender difference [80, 82]. The prevalence in the general adult population is about 2.2 % and declines gradually with age to attain about 1 % at 65 years of age and older [79]. In adults, there is a high degree of overlap among the two principal disorders of arousal.

Treatment

The scheduled awakening technique was shown to be effective to treat sleep terrors in children [83, 111]. Results of a randomized study in children with sleep terrors indicate satisfactory treatment with L-5-hydroxytryptophan [112]. In adults, when the episodes are not associated with injury potential, treatment is often unnecessary. If a treatment is needed, the same pharmacologic and nonpharmacologic approaches as for somnambulism can be tried.

Parasomnias Associated with REM Sleep

Nightmare Disorder

Clinical Presentation

Nightmare disorder consists of persistent disturbing dreams that arise primarily from REM sleep (and more rarely from stage 2 NREM sleep) and that usually awaken the sleeper [2, 113]. Nightmares are often distinguished from bad dreams precisely because the nightmare triggers an awakening. These awakenings are usually abrupt, not confused, and accompanied by detailed recall of disturbing content. However, there is typically a much lower level of autonomic activation during nightmares than during sleep terrors. Dream-enacting behaviors are not frequent but can occur during transitions to wakefulness [114], e.g., racing heart, perspiration, limb contraction, or bodily start. Nightmares are associated with varying levels of heart rate and respiratory activation during REM sleep, but often the autonomic arousal appears much less than might be expected from the emotions or thematic content of the disturbing dream [115].

Associated Factors and Pathophysiology

Bad dreams among 29-month-old preschoolers are predicted by material ratings of difficult temperament as early as 6 months of age and by parental ratings of child anxiety as early as 17 months [116]. Among adults, nightmares are also associated with demographic factors (e.g., low income) [117], psychopathologic traits [118–120], and personality variables such as physical and emotional reactivity [118, 121, 122], fantasy proneness [123, 124], and thin boundaries [125–128]. Nightmares are more frequent and prevalent in psychiatric populations [129–134] and are associated with pathologic symptoms such as anxiety, neuroticism, post-traumatic stress disorder, borderline symptoms, schizophrenia spectrum symptoms, dissociative phenomena, problematic health behaviors, and sleep disorders (see review by Levin and Nielsen [113]). Several studies converge on the finding that frequent nightmares signal an elevated risk for suicidal and self-harm behaviors [135–138].

Nightmares are also reactive to stressful life events [118, 122, 139–143]. This general pattern of comorbidity among nightmares, pathologic symptoms, and stress has been explained as due to an underlying distress-prone personality style [113]. More frequent nightmares are also associated with the eveningness chronotype [144, 145]. Finally, genetic contributions to nightmares have been suggested by population studies. The estimated proportion of genetic effects to the phenotypic variance in childhood was 44 % for males and 45 % for females in one study [146] and 51 % for all adults combined in another [147].

The few available PSG studies of frequent nightmare sufferers provide inconsistent findings but nonetheless all suggest disruption of REM and NREM sleep regulation. For REM sleep, there is more frequent skipping of early REM periods, longer REM latency and REM/NREM cycle length, lower REM%, and altered REM density across the night—all changes consistent with a possible disruption in REM/NREM cycle timing and duration and low REM sleep propensity in nightmare sufferers [148]. Another study found none of these differences, but did find an increase in REM% [149]. For NREM sleep, reduced NREM sleep duration, more NREM sleep awakenings, increased WASO [149], and anomalies in cyclic alternating pattern (CAP) subtypes (reduced A1, increased A2 and A3) also suggest a disruption of the regulation of sleep-promoting and arousing mechanisms during sleep [150].

A neurocognitive model has been proposed to explain nightmares [151]. The affect network dysfunction model of nightmare production is based on a combination of findings in brain imaging, sleep physiology, post-traumatic stress disorder, fear memory, and anxiety disorders. It complements a neurophysiologic description of nightmare formation, the AMPHAC model, which describes key roles for amygdala, medial prefrontal cortex, hippocampus, and anterior cingulate cortex [113]. Accordingly, nightmares result from dysfunction in a network of affective processes that, during normal dreaming, serves the function of fear memory extinction. Evidence for the involvement of prefrontal and limbic areas in nightmares has been reported [152]; frequent nightmare sufferers have impaired reaction times on Emotional Go/NoGo and Stroop tasks and more perseveration and word generation disturbance on a verbal fluency task.

Prevalence

Prevalence of nightmare disorder is difficult to assess precisely because of different operational definitions, response scales, age ranges, and study samples used (see reviews by Levin and Nielsen [113] and Spoormaker et al. [153]). In addition, prevalence studies usually evaluate nightmares as an isolated symptom but rarely as a disorder per se. The prevalence of nightmare symptoms is estimated in tandem with their temporal frequency. Accordingly, nightmares as a symptom occur occasionally in over 85 % of the general population, at least once a month in 8–29 %, and at least once a week in 2–6 % [78, 121, 129, 154, 155]. There is a consensus (e.g., DSM-5) that a frequency of one nightmare per week reflects clinical pathology.

Surprisingly, bad dreams are not frequent among preschoolers (1.5–3.9 % report them *often* or *always*). They can appear as early as 29 months, and the prevalence remains stable until age 6 years [116]. An Internet survey of 23,839 respondents found that the typical monthly recall of nightmares peaks between the ages of 20 and 29 and declines steadily thereafter. There is a gender difference in prevalence favoring girls that appears in adolescence [156, 157] and continues throughout the life span (Fig. 50.2) [158].

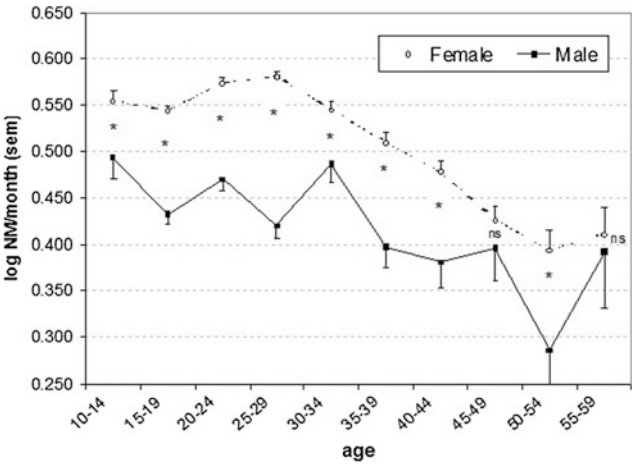

Fig. 50.2 Retrospective estimates of monthly nightmare frequency by 5-year age strata in an Internet sample of 23,839 respondents. *Asterisk* significant difference between female and male subjects at that stratum ($p < 0.05$) (reproduced from Nielsen and Petit [158])

Treatment

Treatments for nightmares include psychotherapy, systematic desensitization and relaxation, eye movement desensitization, imagery rehearsal, hypnosis, and pharmacological approaches [159–164]. A best practices guide to treatment of nightmares recently proposed by the Standards of Practice Committee of the American Academy of Sleep Medicine recommends only a single Level A drug treatment for nightmares—prazosin—and this only for PTSD nightmares [165]. The same committee also recommends only a single Level A nondrug treatment, Imagery Rehearsal Therapy, for Nightmare Disorder. However, more recent meta-analyses suggest that the recommendations for psychological therapies may need updating. One meta-analysis [166] found empirical support for both psychological and pharmacological (prazosin) treatments. Effect sizes for the psychological treatments (0.47–0.48) were higher than those for drug treatments (0.15–0.29), but equal to the effect size for prazosin alone (0.50). Further, studies of individual therapies had higher effect sizes than did those of self-help therapies. The second meta-analysis [167], examining only nondrug treatments, found that methods of *imagery rescripting and rehearsal*, which includes IRT, had lower effect sizes than did methods of *imaginal confrontation with nightmare contents*, such as self-exposure therapy [168].

Recurrent Isolated Sleep Paralysis

Male sex, poor mental health, drinking alcohol, taking a long daytime nap, early or late bedtime, difficulty initiating sleep, low subjective sleep assessment, presence of excessive daytime sleepiness, and presence of nightmares had higher odds ratios than other factors for sleep paralysis [133].

Clinical Presentation

Previously known as isolated sleep paralysis or simply sleep paralysis, recurrent isolated sleep paralysis is a common, generally benign, parasomnia characterized by brief episodes of motor or vocal paralysis combined with a waking state of consciousness [2]. Its benign status is perhaps responsible for its removal from the DSM-5 list of sleep disorders; it is now considered a subcategory of nightmare disorder. During

sleep paralysis episodes, fear-provoking dreamlike hallucinations often intrude and produce considerable distress. Episodes occur primarily at sleep onset (hypnagogic) and upon awakening (hypnopompic). Feelings of fear and terror are accompanying sleep paralysis experiences [169], and they are often linked to a feeling of presence (i.e., a vivid impression that a sentient being is nearby, but without a clear visual image of it) [170, 171].

Sleep paralysis episodes usually arise from sleep-onset REM periods [172, 173], suggesting that they are periods of state dissociation in which some REM sleep characteristics, muscle atonia and dreaming, intrude upon wakefulness [174, 175].

Associated Factors

Stress, shift work, and irregular sleep–wake schedules are factors associated with sleep paralysis episodes [173, 176–178]. Several studies link sleep paralysis to various neurologic and psychiatric disorders. It is predicted by bipolar disorder, automatic behavior, and use of anxiolytic medications [79]. It is also comorbid with post-traumatic stress disorder [179–181], depression symptoms [182, 183], anxiety disorder with agoraphobia [184], panic disorder [181, 185–188], generalized anxiety disorder, anxiety sensitivity [189], social anxiety [190, 191], excessive daytime sleepiness, and poor sleep [192]. This wide comorbidity has been attributed to mediation by an affect distress personality style ("sleep paralysis distress" [171]) in a manner analogous to that proposed for nightmare disorder ("nightmare distress" [113]).

Associations of sleep paralysis with psychiatric conditions vary among ethnic groups [193, 194]. Some of these differences may stem from cultural interpretations of sleep paralysis hallucinations, sensed presence in particular, as a form of spiritual entity, such as "ghost oppression" in China [178], "Old Hag" in Newfoundland [195], "kanashibari" in Japan [176], and "the ghost that pushes you down" in Cambodia [179]. Finally, a genetic component has also been reported: About 36 % of respondents in a Japanese sample had family members who experienced sleep paralysis [196].

Prevalence

Variations in prevalence estimates (5–40 %) depend upon differences in operational definitions, age of subjects, ethnicity, and other sociocultural factors [79, 176, 177]. One meta-analysis [197] of 35 studies (total N = 36,533) found lifetime prevalence rate to be 7.6 % of the general population, 28.3 % of students, and 31.9 % of psychiatric patients, with a slightly higher value for females (18.8 %) than for males (15.7 %). A study, which queried over 90,000 Japanese junior and senior high school students (90 % response rate) about whether or not they had experienced sleep paralysis ("kanashibari") in the last month, found a prevalence of 8.3 % with prevalence increasing monotonically with age (Fig. 50.3) [133]. Age of onset for sleep paralysis is typically 14–17 years. Accompanying vivid dreams are common (e.g., intruders, vestibulo-motor sensations); sensed presence hallucinations are particularly characteristic, occurring in 60–69 % of cases [170, 171, 198, 199].

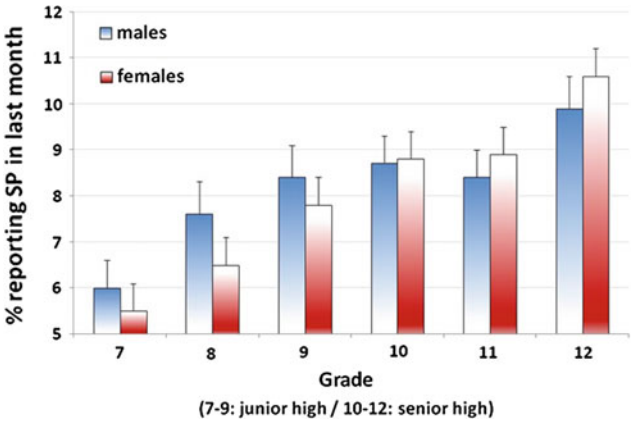

Fig. 50.3 Percent of 43,380 male and 44,769 female students reporting any occurrence of sleep paralysis in the last month by grade. Age may be approximated by adding 6 to grade (adapted from Munezawa et al. [133]. Table 50.1)

Treatment

Snyder and Hams [200] report three cases of isolated sleep paralysis controlled by L-tryptophan.

REM Sleep Behavior Disorder

Clinical Presentation

RBD was first described as a clinical entity in 1986 [201]. It is characterized by the loss of skeletal muscle atonia normally present during REM sleep and accompanied by complex dream-enacting motor activity. Behaviors can range from simple motor activities such as laughing, talking, shouting, or excessive body and limb jerking to complex, seemingly purposeful and goal-directed behavior, such as gesturing, punching, kicking, sitting up, leaping from bed, and running [2]. The close relationship between the dream content and the observed RBD behaviors has been demonstrated in a PSG video study with blind judges [202]. Too often, these sleep behaviors produce injuries to the patient or the bed partner such as ecchymoses, lacerations, fractures, and subdural hematomas. Injuries are a main reason for consultation, being reported by 79–96 % of consulting cases [203]. RBD episodes may also cause severe sleep disruption for the bed partner and lead to major marital discord, mood changes, and even suicide attempts [204]. In addition, the dream process and its content appear altered. Most patients

(87 %) report that their dreams became more vivid, intense, action filled, and violent with the onset of RBD [203]. Dream themes associated with behaviors are largely stereotyped in structure and emotional content. The most frequent pattern is that of vigorous defense against attacks by people (58.8 %) and animals (23.5 %) (see review by Nielsen [205]).

It has been observed that the aggressiveness displayed during nocturnal behaviors stands out against the good-natured daytime personality [203]. Indeed, a controlled study using content analyses of recently remembered dreams revealed an elevated proportion of aggressive content, yet normal levels of daytime aggressiveness [206]. The mechanism by which dream content is changed is unclear. However, it has been proposed that hyperactivity (disinhibition through degeneration) at the brain stem level activating motor, perceptual, and affective pathways may be responsible for both REM sleep behaviors and altered dreams [206]. The fact that clonazepam reduces both behavioral manifestations and disturbed dreaming [203, 207] supports the notion that the two phenomena share a common neurophysiologic substrate.

Clinical diagnostic criteria include (1) complaints of violent or injurious behaviors during sleep, (2) limb or body movements associated with dream mentation, and (3) one of the following: harmful or potentially harmful sleep behaviors, dreams that appear to be acted out, and sleep behaviors that disrupt sleep continuity. Polysomnographic recordings reveal an intermittent or complete loss of REM sleep muscle atonia and an excessive phasic electromyographic (EMG) activity during REM sleep [92]. This excessive tonic and phasic EMG activity during REM sleep worsens over time [208]. Diagnostic criteria are listed in Table 50.2. Early studies reported a substantial loss of REM sleep muscle atonia in patients with RBD. For example, three large series reported that 92–100 % of patients had some loss of REM sleep muscle atonia [209–211]. Changes in REM sleep in patients with RBD seem to be restricted to the excessive tonic and phasic motor activity. All other features of REM sleep, including REM latency, REM percentage, REM density, number of REM periods, and REM/NREM cycling, are usually preserved [46, 212].

Table 50.2 ICSD-2 diagnostic criteria for RBD

1. Presence of REM sleep without atonia: electromyographic finding of excessive amounts of sustained or intermittent elevation of submental electromyographic tone or excessive phasic submental or (upper or lower) limb electromyographic twitching
2. At least one the following is present:
   - Sleep-related injurious, potentially injurious, or disruptive behaviors by history
   - Abnormal REM sleep behaviors documented during polysomnographic monitoring
3. Absence of electroencephalographic epileptiform activity during REM sleep unless RBD can be clearly distinguished from any concurrent REM-related seizure disorder
4. The sleep disturbance is not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use or substance use disorder

In contrast, Schenck et al. [210] originally reported an increase in the proportion of SWS in patients with RBD. In one series, 80 % of patients over the age of 50 years had more than 15 % of sleep time spent in SWS. This was not associated with prior sleep deprivation. In the Mayo Clinic series, 33 % of patients over the age of 58 years had more than 15 % SWS [209]. These observations were confirmed in a comparison with age-matched controls: RBD patients demonstrated a higher percentage of SWS and more delta power in NREM sleep [213]. Patients with RBD also showed lower occipital beta power during REM sleep [214], as well as markedly higher theta power in frontal, temporal, and occipital regions, lower occipital beta power, and lower dominant occipital frequency during wakefulness [214].

Another polygraphic characteristic of RBD is the presence of periodic leg movements in sleep (PLMS). In a study of RBD and restless legs syndrome (RLS) patients, RBD patients showed a mean PLMS index of 39.5 per hour of sleep, a value not significantly different from the mean PLMS index found in patients with RLS [215]. In this study, 70 % of RBD patients had a PLMS index greater than 10. This percentage is similar to the prevalence of PLMS previously reported in RLS patients and significantly higher than the prevalence rate found in healthy subjects of the same age [216]. One difference between RLS and RBD patients, however, is that the periodicity of leg movements was shown to be lower in RBD patients compared to that of patients with RLS [217]. Another more important difference is that, in RBD patients, PLMS occurred mainly during REM sleep [215]. This is most likely due to the lack of motor inhibition during REM sleep in this condition, and this suggests that PLMS have a different pathophysiologic basis in RBD. Also, PLMS were significantly less likely to be associated with microarousals in RBD compared to RLS patients [216], and a markedly reduced amplitude of cardiac response was found in patients with RBD [215]. These findings suggest the presence of dysautonomia and/or reduced cortical reactivity in RBD.

Until recently, the diagnosis of RBD was based on clinical manifestations; PSG recordings of patients were not necessary for diagnosis. However, there are some limitations in using clinical criteria only. RBD-like features can occur with other sleep conditions, such as obstructive sleep apnea syndrome, sleepwalking, night terrors, and sleep-related seizures. Therefore, it is important to ensure that behavioral manifestations occur exclusively during REM sleep. In addition, PSG allows the detection of subclinical forms of RBD, such as REM sleep without atonia, which can be

observed in the absence of behavioral manifestations. In the ICSD-2 and ICSD-3, PSG features are essential (see also Chap. 27) to the RBD diagnosis [2]. The first essential criterion is the presence of REM sleep without atonia, that is, the EMG finding of excessive amounts of either sustained or intermittent elevation of submental EMG activity or excessive phasic submental or limb EMG twitching. The second criterion is the presence of either sleep-related injurious or disruptive behaviors by history, or abnormal REM sleep behaviors documented during PSG recording. Time-synchronized video recording is essential for helping to establish the diagnosis of RBD during PSG. The last two criteria are the absence of epileptiform activity during REM sleep and the absence of other sleep disorders or medical or neurologic disorders that could better explain the sleep disturbance.

One limitation of these new criteria was the absence of a validated and universally accepted method for scoring REM sleep in RBD. Assessing REM sleep without atonia by using standard criteria is impossible—muscle atonia is an essential defining criterion for REM sleep [218]. Montplaisir et al. [212] developed a scoring method for REM sleep based on the EEG and electro-oculography only (Table 50.3). In this method, the occurrence of the first REM is used to determine the onset of the REM sleep period. The termination of the REM sleep period is identified either by the occurrence of specific EEG features of a different sleep stage (K complexes, sleep spindles, EEG signs of arousals), or by the absence of REMs for 3 consecutive minutes. Then, tonic and phasic components of REM sleep are scored separately. Each epoch is scored as tonic or atonic depending on whether tonic chin EMG activity is present for more or less than 50 % of the epoch duration. Phasic EMG density is also scored from the submental EMG recording and is expressed as the percentage of mini-epochs (2 or 3 s depending on epoch duration of 20 or 30 s) containing phasic EMG events. Using this method, the following criteria have been proposed to diagnose RBD patients: chin EMG tonic density ≥ 30 % or phasic chin EMG density ≥ 15 %. Although some night-to-night variability in REM atonia has been shown [219], these cutoffs show a high degree of sensitivity and specificity. A study investigating 11 different muscles showed that upper limb muscles provided the highest discriminative power for RBD diagnosis, even higher than that of the chin EMG [220]. Computer-assisted scoring methods have also been developed (see [221] for a review of the various EMG scoring methods for RBD).

Finally, validated questionnaires have also been put forth to either help screen patients [222, 223] or diagnose RBD [224, 225] and assess its severity for large-scale epidemiological studies.

Associated Factors (Idiopathic and Secondary RBD) and Pathophysiology

RBD may be associated with a great variety of medical conditions or with the use of various psychotropic medications. Therefore, RBD has been divided into primary and secondary forms [1]. Primary or idiopathic RBD is diagnosed when none of the conditions listed for secondary RBD is present. Potential risk factors for idiopathic RBD have nonetheless been identified; they include smoking, head injury, pesticide exposure, and farming [226].

Secondary RBD has been classified into acute and chronic subtypes depending on the time course of clinical manifestations [2]. Acute RBD is usually associated with intoxication or withdrawal from psychotropic substances. Abuse of caffeine, tricyclics antidepressants, biperiden, and monoamine oxidase inhibitors have been reported to trigger episodes of acute RBD as well as withdrawal from alcohol or from medications such as meprobamate, pentazocine, barbiturates, and nitrazepam (for review, see [92]). Chronic secondary RBD may occur during long-term use of several medications: cholinesterase inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, or newer serotonergic agents such as fluoxetine, paroxetine, citalopram, sertraline, and venlafaxine (for review, see [227]). RBD has been reported in patients with psychiatric disorders, and several

Table 50.3 Polysomnographic scoring criteria for RBD

REM sleep onset	Occurrence of the first REM
REM sleep termination	Occurrence of a specific EEG feature of another sleep stage (K complex, sleep spindle, EEG sign of arousal) *or* absence of REMs for 3 consecutive minutes
Muscle atonia	Each 30-s epoch is scored as tonic or atonic depending on whether chin EMG activity is present for more or less than 50 % of the epoch duration. Presence of EMG activity is defined by chin EMG amplitude at least twice that of the background or greater than 10 μV
Phasic EMG activity	Percentage of 3-s mini-epochs containing chin EMG events. EMG events are defined by any burst of EMG activity lasting 0.1–5 s, with amplitude exceeding 4 times the amplitude of background EMG activity
REM density	Percentage of 3-s mini-epochs of REM sleep containing at least one REM

Modified from Montplaisir et al. [212]
EEG electroencephalogram; *EMG* electromyographic; RBD REM sleep behavior disorder; *REM* rapid eye movement

indices suggest that use of psychotropic drugs might not be the only cause of the RBD symptoms in this population [228]. Secondary RBD can occur in association with narcolepsy [229, 230], especially narcolepsy with cataplexy and hypocretin deficiency [231], and other neurologic disorders, such as olivopontocerebellar degeneration, ischemic cerebrovascular disease, multiple sclerosis, Guillain–Barré syndrome, Shy–Drager syndrome, and Arnold–Chiari malformation [92]. Finally, RBD is strongly associated with neurodegenerative diseases, especially the synucleinopathy subtype [232–236], which includes Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). In a sleep laboratory study, one-third of patients with PD (11/33) had RBD based on PSG criteria [232]. Of note, a video-monitored PSG study revealed that patients with PD show a striking improvement of their movements during their RBD episodes (compared to wakefulness) almost as if they were disease-free [237]. RBD has been shown to coexist, albeit to a lesser extent, with Alzheimer's disease [238] and progressive supranuclear palsy [239], two tauopathies.

Patients with primary (or idiopathic) RBD are, conversely, at high risk of developing a neurodegenerative disease. As more patients with so-called idiopathic RBD are studied in a longitudinal manner, it is becoming increasingly clear that most patients will eventually develop neurodegenerative disorders, especially PD or DLB. Initially, Schenck et al. [233] had found that a parkinsonian syndrome developed in 38 % of 29 patients with idiopathic RBD after 5 years of follow-up. Seven years later, 65 % of patients from the same cohort had developed a parkinsonian syndrome [240]. Now, two prospective studies have estimated that up to 82 % of the patients with iRBD will eventually develop a neurodegenerative disease at a 10 to 16-year follow-up [241, 242]. It was shown that symptoms of RBD can precede the initial manifestation of synucleinopathies by up to 50 years [243]. Since RBD patients are at risk of developing PD, studies have looked at a variety of potential early markers of PD in patients with idiopathic RBD who were free of parkinsonism. Multiple dysfunctions have been described in the last 10 years for idiopathic RBD patients (Fig. 50.4), such as olfactory and color identification deficits [244], decreased motor speed [245], EEG slowing [214], mild dysautonomia [215, 246–250], subtle neuropsychological dysfunctions [214, 251–255], and brain perfusion anomalies [256–258]. These abnormalities are similar to those found in early stages of PD [259] and many are good predictors of conversion to PD with different prodromal period lengths and variable sensitivity and specificity (for review, see [260]). Finally, fluorodeoxyglucose positron emission tomography brain imaging of cognitively normal patients with dream-enacting behaviors revealed lower metabolic activity in several brain regions known to be affected in DLB [261]. In this respect, idiopathic RBD is considered a prodrome of neurodegenerative disease and, consequently, a form of neurodegeneration itself as the following paragraphs on pathophysiology demonstrate.

Due to the close association between RBD and PD, the striatal dopaminergic system was investigated as a possible candidate in the pathophysiology of RBD. Single-photon emission computed tomography showed a reduction in striatal dopamine transporters in patients with idiopathic RBD [262]. A reduced density of striatal dopaminergic terminals has also been shown with positron emission tomography [263]. In addition, there appeared to be a continuum of reduction in striatal dopamine transporters on single-photon emission computed tomography from patients with subclinical RBD to clinical RBD and finally to PD [264]. Moreover, a significant correlation was found between the percentage of REM sleep muscle atonia and striatal dopaminergic transmission [264], but not with thalamic cholinergic transmission [265]. However, the dysfunction of the nigrostriatal dopaminergic system is not likely the primary cause of RBD.

Animal studies using various methodological approaches (electrophysiology, lesions, and neuropharmacology) have shown that REM sleep muscle atonia results from the interaction of several neuronal systems located in the brain stem. Bilateral tegmentopontine lesions in animals can produce both a loss of muscle atonia and the presence of motor behaviors during REM sleep [266, 267], a model for human RBD. To produce RBD in animals, two different systems must be involved: the atonia system and the locomotor system. Lesions to the atonia system will produce only REM sleep without atonia, a phenomenon frequently encountered in neurodegenerative diseases and thought to be a form of incomplete RBD. To produce RBD in animals, the lesions should also involve the system that normally suppresses the brain stem motor generators during REM sleep. Therefore, RBD may result from a dysfunction in these two systems: either a loss of REM sleep atonia, excessive locomotor drive, or both [268]. Two different reviews of a large amount of animal physiological data recently proposed that the degeneration of the glutamatergic sublaterodorsal nucleus and of the GABA/glycinergic neurons located in the raphe magnus and gigantocellular reticular nuclei is at the heart of REM sleep without atonia in RBD patients [269, 270].

Neuropathologic and imaging studies of patients with RBD, associated with or without neurodegenerative disorder, also provide answers which are consistent with this hypothesis. Autopsied cases of RBD [66, 235, 241, 271, 272] revealed histopathologic anomalies (i.e., Lewy bodies, neuronal loss, or gliosis) in the locus coeruleus–subcoeruleus complex (the structure homologous to the sublaterodorsal nucleus in humans) and the substantia nigra for all patients and anomalies in the raphe, dorsal vagus, gigantocellular reticular, and pedunculopontine nuclei in

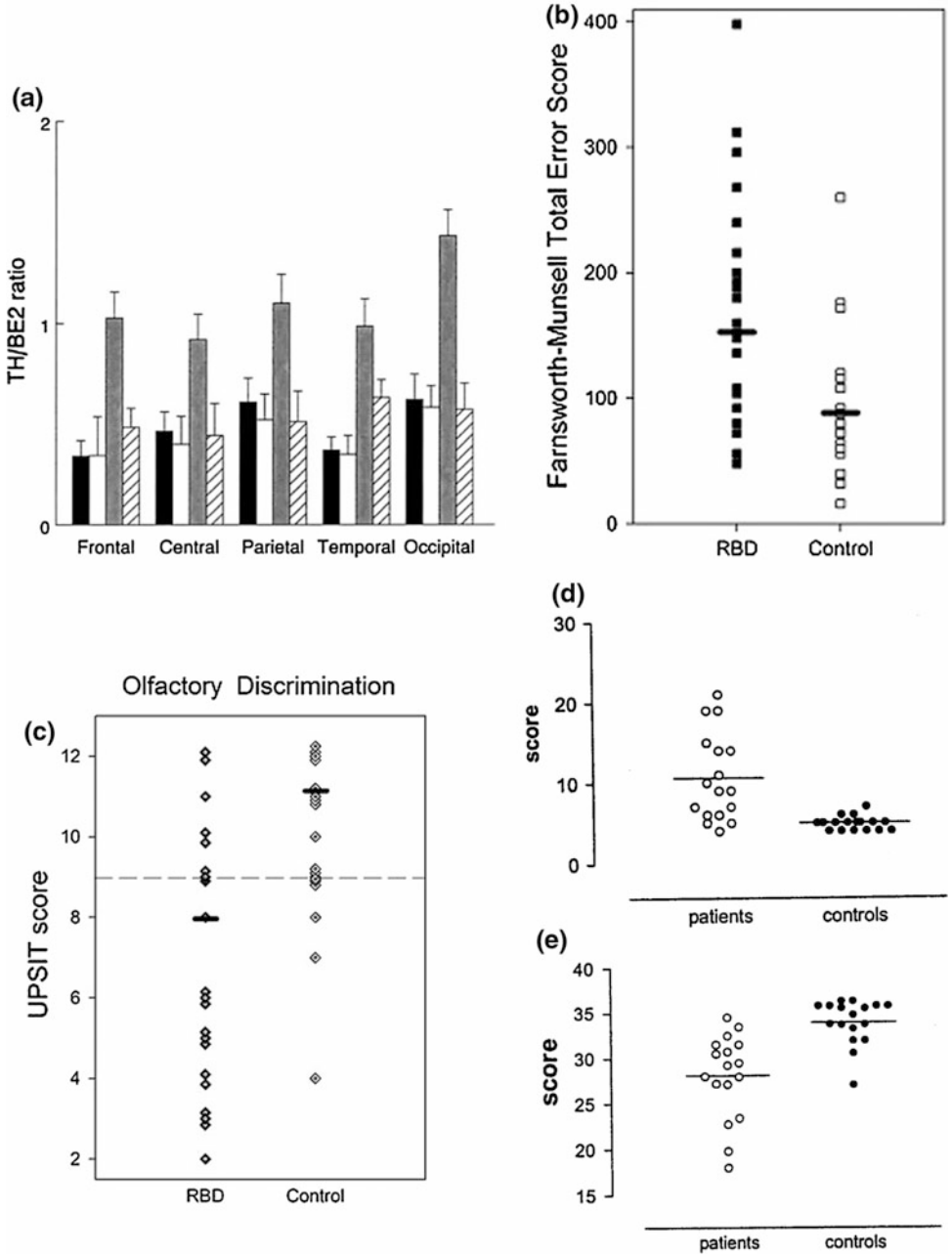

Fig. 50.4 Electroencephalographic changes and sensory and neuropsychological deficits associated with REM sleep behavior disorder (RBD). **a** Electroencephalographic slowing during wakefulness is indicated by a generalized increase in the theta/beta2 ratio in male RBD patients (*dark blue bars*) relative to male controls (*black bars*), female controls (*light blue bars*), and female RBD patients (*hatched bars*). **b** Visual discrimination deficits are apparent as higher error scores on the Farnsworth-Munsell 100-Hue Test for RBD patients. **c** Olfactory discrimination deficits are apparent as lower average scores on the University of Pennsylvania Brief Smell Identification Test. **d** and **e** Neuropsychological deficits are shown by higher error scores on the Corsi Supraspan Learning Test (**d**) and lower scores on the Rey-Osterrieth Complex Figure Design (**e**) (**a** reproduced with permission from Fantini et al. [214]. **b** and **c** reproduced with permission from Postuma et al. [403]. **d** and **e** reproduced with permission from Ferini-Strambi et al. [253])

most patients. Magnetic resonance imaging revealed ischemic lesions in pontomesencephalic regions in three patients with RBD [273]. Other studies have also demonstrated that tumor, ischemic infarct, or surgery in the pontine region are sufficient to trigger RBD [274–277].

In conclusion, in humans there are probably different anatomical and neurochemical (GABAergic, dopaminergic, cholinergic) dysfunctions that, alone or in combination, could lead to RBD. This could account for the efficacy of various families of medications.

Prevalence

The overall prevalence of RBD remains largely unknown. A large telephone survey assessing violent behaviors during sleep in the general population (15–100 years of age) suggested a prevalence of about 0.5 % [278]. Another study of 1034 individuals (70+ years of age) in the Hong Kong area found a prevalence of PSG-confirmed RBD of 0.4 % [279]. However, these studies screened only for people who suffered sleep injury inclusion of those without injury [280] would likely result in a higher prevalence rate [281]. To that effect, a sleep laboratory study in a population-based sample of 348 individuals 60 years and older found a prevalence of PSG-confirmed RBD of 2.01 % [282]. There is a male predominance (87 %) with primarily men over the age of 50 being affected [174]. When RBD is triggered by antidepressant medications, demographics include younger patients and more women [283]. A certain degree of familial aggregation was recently revealed for RBD by a multicenter study. A positive family history of dream enactment behaviors was found in 13.8 % of iRBD patients compared to only 4.8 % for controls (odds ratio = 3.9, 95 % confidence interval 2.0–7.7) [284].

Treatment

Since 2010, a best practice guide for the treatment of RBD is available [165]. This guide is based on numerous reports of case series of RBD treated with a variety of medications; there are no large randomized double-blind clinical trials. In addition, many of these reports have important methodological limitations and few have included PSG assessments.

Clonazepam, a sedating benzodiazepine, is considered the treatment of choice for RBD. Two large case series have reported substantial improvement in a majority of patients treated with clonazepam [209, 210]. In most cases, a suppression of problematic sleep behaviors and nightmares was reported during the first week of treatment. Sustained efficacy was reported during long-term administration of up to 17 years [92], although some degree of tolerance did occur. Polysomnographic recordings revealed that clonazepam suppresses behavioral manifestations and decreases phasic EMG activity without restoring REM sleep muscle atonia [212]. Clonazepam was also shown to decrease NREM sleep instability in RBD patients [285]. The mechanism of action of clonazepam is unclear but likely results from its serotonergic properties [286]. This hypothesis is based on observations made in animals where selective destruction of brainstem serotonergic neurons produced a disinhibition of REM sleep phasic activity and triggered hallucinatory behaviors, whereas the administration of serotonin inhibited motor activity in several experimental designs [287, 288]. However, clonazepam is ineffective in approximately 10 % of patients [209, 210]. In addition, some patients experience serious side effects, such as an increased risk of confusion and falls in elderly individuals [289] and a worsening of sleep-related respiratory disturbances in patients with obstructive sleep apnea syndrome [290]. Therefore, alternative treatments must be considered.

A 6-week open-label trial of 3 mg of melatonin given 30 min before bedtime demonstrated a dramatic clinical improvement in five of six RBD patients [291]. A PSG recording showed a significant restoration of REM sleep muscle atonia without any significant reduction of phasic motor activity. This initial observation was confirmed in a study of 15 idiopathic RBD patients treated with melatonin 3–9 mg [292]. These authors noted a nearly threefold suppression of REM sleep tonic activity after melatonin therapy. More recently, Boeve et al. [293] looked at the efficacy of melatonin (3–12 mg) in 14 patients with RBD associated with neurologic conditions. RBD was controlled in six patients, significantly improved in four, and initially improved but subsequently returned in two. No improvement occurred in one patient and increased RBD frequency/severity occurred in one patient. Melatonin and clonazepam were recently compared in a clinical practice setting, and it was concluded that both treatments were comparably effective in reducing RBD behaviors and injuries. However, adverse effects were reported less frequently with melatonin than with clonazepam [294]. In summary, melatonin can be considered as an alternative therapy in both idiopathic and secondary RBD, but long-term, controlled trials are needed to ascertain the efficacy of melatonin in this condition. The mechanism of action of melatonin in RBD is still unknown; it appears that melatonin restores REM sleep muscle atonia, whereas clonazepam exerts its therapeutic effect by suppressing phasic motor activity.

Another drug family was shown to produce therapeutic benefit in RBD. Indeed, some studies of acetylcholinesterase inhibitors (donepezil and rivastigmine) demonstrated increased sleep quality and reduced motor events in patients with idiopathic RBD [295] and in patients with RBD associated with DLB [296–298]. However, neither of these studies used PSG recordings to confirm treatment efficacy. Other studies of patients with RBD associated with DLB did not find any change in the frequency or the severity of RBD symptoms with donepezil [293, 298].

Based on the strong association between RBD and PD, dopaminergic agents have been considered as a treatment of RBD. Pramipexole, a dopamine D_2 receptor agonist with a high affinity for D_3 receptors, was shown to reduce the intensity and the frequency of clinical motor events reported by patients and to decrease the number of simple motor manifestations seen on PSG video recordings [299, 300]. In neither of those studies was REM without atonia reduced. The second study postulated that the improvement in symptoms could rather be due to changes in dream content or dream frequency since the improvement observed

correlated with the reduction of REM density. A third study on 98 patients concluded that pramipexole was more effective for mild iRBD cases with a lower rate of REM sleep without atonia [301]. The therapeutic effect of pramipexole was not found in RBD associated with PD [302].

Finally, since injury to the patient or to the bed partner is the most common reason that brings patients to consultation, the treatment program should start with a discussion on risk of accidents, indication of sleeping in different beds and safety measures such as removal of dangerous objects in the room, protection of the windows, and placement of cushions around the bed or the mattress on the floor. These recommendations are important even in treated patients since cases of injuries were reported in patients apparently successfully treated for RBD.

Other Parasomnias

Sleep Enuresis

Clinical Presentation

Sleep enuresis is characterized by recurrent involuntary voiding during sleep at least twice a week among individuals who are at least 5 years of age [2]. If the child has never been constantly dry during sleep, it is considered primary. Sleep enuresis is secondary when the child (or adult) had been previously dry for at least 6 consecutive months and started wetting at least twice a week for at least 3 months.

A common belief among parents is that sleep enuresis is the result of sleeping too deeply. However, changes in sleep depth and sleep architecture have not been consistently demonstrated [303]. For most enuretic children, voiding occurs in the first half of the night and is not associated with a specific sleep stage [303]. Conversely, a PSG study has demonstrated that enuretic boys are more difficult to arouse from sleep than are age-matched controls [304].

Associated Factors and Pathophysiology

A three-system model has been proposed to explain enuresis, which has wide clinical appeal [305]. It identifies three processes that alone or in combination can engender nocturnal enuresis: (1) increased nocturnal urine production due to lack of arginine vasopressin release during sleep; (2) overactivity of the bladder (uninhibited bladder contractions) or low functional bladder capacity; and (3) decreased perception of full bladder sensations during sleep [306]. Tachycardia and short EEG arousals are often present prior to enuretic events [303].

Some evidence indicates that bed-wetting may reflect delayed development of the central nervous system. It has been shown that premature and/or low-birth-weight children were bed-wetting more often than normal-birth-weight children [307, 308]. Moreover, several studies or clinical observations have suggested an association between bed-wetting and developmental delays in motricity, [309, 310] language [310–313], physical growth [311], and skeletal maturation [314, 315]. Microstructure abnormalities were found in the thalamus, medial frontal gyrus, anterior cingulate cortex, and insula of enuretic children [316]. The authors propose that, since these regions are involved in micturition control, a developmental delay in these areas may be the cause of nocturnal enuresis. The full intelligence quotient (IQ), the verbal IQ, and the performance IQ appear to be normal in older enuretic children, but impairments in memory and attention were reported, together with some structural abnormalities of the right dorsolateral prefrontal cortex and left cerebellum [317].

Children with nocturnal enuresis show a higher prevalence of sleep problems, such as disorders of initiating and maintaining sleep, excessive daytime somnolence, sleep-disordered breathing, disorders of arousals, and disorders of the sleep–wake transition [318]. Obesity is a risk factor for nocturnal enuresis in children and adolescents [319]. Enuresis is not linked with anxiety in preschoolers [82] but is in older children [320, 321]. However, anxiety is more likely a consequence than a cause of enuresis, brought about by perplexity or a sense of immaturity, humiliation, social embarrassment, or fear of detection. Similarly, lower scores on self-esteem and higher scores on depression were found in adolescents and adults with nocturnal enuresis [322].

Finally, hereditary factors have been recognized; it is inherited via an autosomal-dominant mode of transmission (for a review, see von Gontard et al. [323]). The odds ratios for severe child nocturnal enuresis were found to be 3.63 times higher in maternal and 1.85 times higher in paternal nocturnal enuresis [324].

Prevalence

In 5-year-old children, population-based studies [82, 312, 325] found a prevalence between 20 and 33 %. A male predominance in childhood prevalence is well established [80, 82, 312, 325]. Prevalence is 77 % when both parents were enuretic as children and 44 % when one parent was enuretic [326]. A Korean population-based study on the prevalence of enuresis in adolescents and adults found that 2.6 % of individuals had at least one episode in the last 6 months and 4.5 % had one in the last 12 months [322]. The percentage of people with at least one episode in the last 6 months was about the same for both genders (men = 2.1 %, women = 3.0 %) and for the different age groups: 16–20 years = 2.8 %, 21–25 years = 2.5 %, 26–30 years = 3.2 %, 31–35 years = 1.8 % and 36–40 = 2.6 %. Enuresis occurs in about 3 % of elderly women (65 years and older) and in 1 % of elderly men living at home [327].

Treatment

Practical guidelines and checklists for the diagnosis and management of enuresis now exist [328, 329]. Most cases of nocturnal enuresis can be treated with bedwetting alarms (devices that alert and sensitize the child to respond quickly to a full bladder by waking up) and by specific treatment programs integrating cognitive-behavioral elements [328, 329]. Concomitant counseling is always recommended. When bed-wetting is caused by lack of arginine vasopressin release during sleep, a pharmacologic intervention using desmopressin, a synthetic analog of vasopressin, can be indicated. The anticholinergic agent oxybutynin is preferred in cases in which the cause is bladder overactivity. Oxybutynin is a smooth muscle relaxant with specific effects on the bladder. Combining treatments is also possible when mixed causes are present (for review, see Butler [330]). In a meta-analysis of randomized trials for the treatment for enuresis (other than with desmopressin or tricyclics), bedwetting alarms were found to be more effective than amphetamine, oxybutynin, and oxybutynin plus holding exercises [331]. The treatment of nonmonosymptomatic nocturnal enuresis is more problematic (for review, see the standardization document from the International Children's Continence Society [332].

Sleep-related Bruxism

Clinical Presentation

An international consensus [333] was recently reached for the definition and grading of bruxism. The adopted definition is as follows "Bruxism is a repetitive jaw-muscle activity characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the mandible. Bruxism has two distinct circadian manifestations: it can occur during sleep (indicated as sleep bruxism) or during wakefulness (indicated as awake bruxism)." This activity results in tooth wear, headaches, jaw dysfunction, and pain. However, it does not seem to affect occlusal and functional parameters [334].

The international group of experts proposes the following diagnostic grading system for both sleep and awake bruxism: possible (self-report), probable (self-report and clinical examination), and definite (self-report + clinical examination + PSG findings preferably with audio/video monitoring). The definitive diagnosis therefore rests on the presence of rhythmic masticatory muscle activity and grinding sounds during all-night PSG recording. Bruxism episodes most frequently occur in stages 1 and 2 but can occur in all stages [335, 336]. Surprisingly, bruxers have a normal sleep architecture and high sleep efficiency (>90 %) [335]. However, rhythmic masticatory muscle activity is associated with blood pressure surges during sleep [337].

Associated Factors and Pathophysiology

Various hypotheses have been put forward to explain sleep bruxism. The first one was changes in dental occlusion, but no strong evidence-based data support this hypothesis [338]. Orofacial morphology and temporomandibular disorders were shown not to be causal factors [339, 340]. Anxiety has been reported as a strongly associated factor in children [80, 341, 342], adolescents, and adults [343, 344]. Smoking also exacerbates bruxism [345]. A deficiency of the dopaminergic system has been implicated, but that remains to be confirmed since most randomized trials with dopaminergic medications have only marginally reduced sleep bruxism episodes [346, 347]. Finally, a 2013 meta-analysis revealed that bruxism can be triggered by esophageal acidification [348]. It also confirmed that bruxism has an important dose-dependent relationship with smoking and that disturbances in the central dopaminergic system are involved in the etiology of bruxism.

A clear sequence of cortical to cardiac activation preceding jaw motor activity in bruxism patients [349] suggests that sleep bruxism is secondary to microarousals. In fact, both microarousals and rhythmic masticatory muscle activity/sleep bruxism episodes were shown to increase concomitantly just before each REM sleep period [350]. Periodic limb movements during sleep, microarousals, and bruxism often occur concomitantly during sleep and in a time-linked manner [351]. It has been suggested that the sudden apparition of sleep bruxism is under the influence of brief and transient activity of the brainstem arousal–reticular ascending system contributing to the increase of activity in autonomic cardiac and motor modulatory networks (Fig. 50.5) [352].

Finally, as it is the case for many parasomnias, there is a strong genetic influence on bruxism in both childhood and adulthood [353]. Children of sleep bruxers are more likely to be affected than those of individuals who never had the problem or who suffer from daytime bruxism only [354]. Twin studies in bruxism have suggested that genetic factors account for half of the phenotypic variance [355] and are important to both the genesis and pattern of bruxism [356].

Prevalence

Sleep bruxism is common in childhood. However, prevalence estimates reported are variable between the studies due to the different age groups studied (for review on prevalence, see [357]). A longitudinal, population-based study found that the prevalence increases from 2.5 years to reach 33 % at 6 years of age [82]. Another population-based study found prevalence of 36.8 % for preschoolers and 49.6 % for first graders for a frequency of more than once a week [358]. Another longitudinal study reported a progressive decrease from age 10 to 13, attaining 9 % at age 13 [80]. A nationwide Japanese study of adolescents reported a low

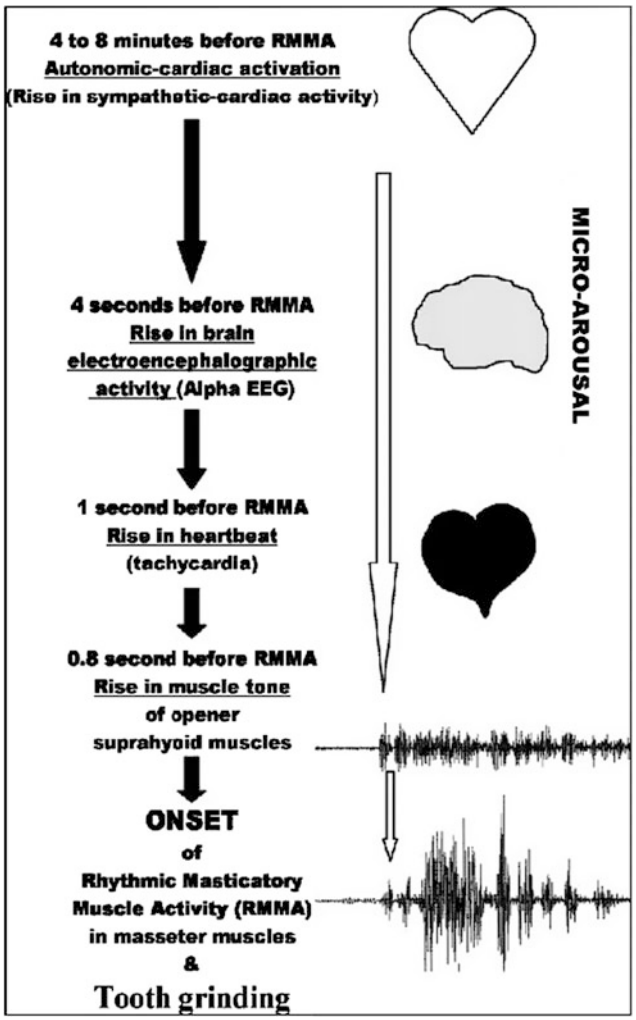

Fig. 50.5 Sequence of physiological events preceding rhythmic masticatory muscle activity (RMMA) associated with sleep bruxism (reproduced with permission from Lavigne et al. [352])

prevalence of 2.3 % in boys and 3.0 % in girls [359]. A self-reported adult prevalence around 8 % had been found in Canadian [360], European (UK, Italy [361]), Finnish [355], and Japanese [362] populations. Using a representative population of 1042 adults, the overall prevalence in Brazil was found to be 12.5 % if using questionnaires alone, 7.4 % when only PSG was used as diagnosis and 5.5 % when using both questionnaires and confirmation by PSG [363]. Usually, no striking gender difference is found for either children [80, 357] or adults [360]. The presence of sleep bruxism in childhood is highly predictive of bruxism in adulthood [353].

Treatment

A meta-analysis study evaluated randomized controlled studies of seven pharmacologic treatments and three oral devices [364]. The mandibular advancement device and clonidine are the most promising experimental treatments, although both are associated with adverse effects (discomfort for the device; REM suppression and morning hypotension for clonidine). Clonazepam appears to be an acceptable short-term alternative. Occlusal appliances (soft mouth guard, occlusal stabilization splint, splint with vibration) can protect orofacial structures. A PSG study comparing the efficacy of a stabilization splint and gabapentin showed significant reductions in the total duration of bruxism episodes per night and in the number of episodes per hour and per night with both treatments [365]. A recent randomized, double-blind, placebo-controlled, clinical trial reported that hydroxyzine was effective and well tolerated for treating bruxism in children [366]. Finally, the use of biofeedback technology as treatment for bruxism was reviewed and it was concluded that there is no strong evidence of efficacy [367].

Sleep-related Rhythmic Movement Disorder

Clinical Presentation

Sleep-related rhythmic movement disorder is characterized by the repetitive, stereotyped, and rhythmic activity of large muscle groups that occurs predominantly during drowsiness (sleep onset) or sleep [2]. It is largely a parasomnia of infancy and early childhood and usually disappears around age 10 [2]. The most frequent rhythmic movements are body rocking, head rolling, and head banging, although it can involve any body part. Body rocking may be difficult to distinguish from head banging because the former sometimes includes banging of the head into a solid object. The frequency of movements is more typically around 1 Hz (one per second) but can range from 0.5 to 2.0 Hz [368]. Episodes of rhythmic movement can last from a few seconds to more than an hour [368]. In most sufferers, they will occur nightly or almost every night [369]. The majority of episodes (around 80 %), at least for head banging, occur at sleep onset [369]. When appearing at sleep onset, rhythmic movements are considered to be a self-soothing or tension-releasing behavior linked with pleasurable sensations that have hypnotic properties. However, more violent movements, usually in cases of mental retardation, have been reported to cause head or eye injuries [370, 371].

Polysomnographic recordings show that rhythmic movement disorder can arise from REM sleep, NREM sleep, or sleep onset with persisting activity in light sleep [372]. Longer movements are usually observed at sleep onset and during stage 1 sleep, whereas shorter movements are seen in stages 2, 3, and 4 NREM sleep and in REM sleep [368]. Rhythmic movements are not preceded by EEG changes, as are nocturnal seizures, and do not provoke arousals or interrupt SWS even in older children [369, 373].

Associated Factors and Pathophysiology

There are reports of rhythmic movement disorder in association with other sleep-related problems such as RLS, which is associated with body rocking [374, 375], insomnia [376], and RBD [377, 378]. Familial forms are rare but have been reported [372, 376, 379]. Adult cases of rhythmic movement disorder are not usually associated with severe psychiatric disorders as previously believed [372], but a relationship with ADHD has been documented [368, 380]. Finally, some studies have reported daytime complaints such as attentional difficulties, sleepiness, morning headaches, fatigue, and poor concentration—and even more serious problems such as anxiety, depression, hyperactivity, and irritability [368, 372, 381]. Whether or not the daytime symptoms result from poor sleep caused by the rhythmic movements remains to be determined.

The etiology of rhythmic movement disorder is still unknown. The involvement of the central motor pattern generator in the genesis of motor phenomena during sleep has been suggested [382]. This network is involved in the control of early locomotor function [383] and is thought to be under the inhibitory control of the cortex. Immaturity of the inhibitory cortical system in early infancy might account for rhythmic movements occurring during sleep, coinciding with the acquisition of motor milestones.

Prevalence

This parasomnia is quite common in infancy but decreases rapidly in prevalence with increasing age. Incidences of 66 % at 9 months, 26 % at 2 years, and 6 % at 5 years had been reported using a sample of children [384], but an epidemiologic study reported lower incidences of about 6 % at 2.5 years, 3 % at 4 and 5 years, and 2 % at 6 years [82]. Body rocking was found to be present in 3 % of children ages 11–13 years [80]. Rhythmic movement disorder can persist into adulthood [372]. No gender difference has been demonstrated for childhood cases, but there is a male preponderance in adult cases [372].

Treatment

There are no systematic pharmacologic studies or behavioral trials for rhythmic movement disorder; it generally has a benign course and is not usually associated with a severe clinical picture. Benzodiazepines, especially clonazepam, or tricyclic antidepressants can be effective [379, 381, 385]. For rhythmic movement disorder associated with RLS in adulthood, pramipexole seems to be effective in alleviating both conditions simultaneously [375].

Somniloquy

Clinical Presentation

Somniloquy, also known as sleep talking, is defined as talking during sleep "with varying degrees of comprehensibility" [2]. Somniloquy is such a prevalent phenomenon that it is considered to be a normal sleep behavior, especially in childhood.

Somniloquy can arise from all sleep stages [386]. Since there are few systematic PSG studies, no clear profiles have been identified. However, EMG-induced artifact is common and may begin several seconds prior to, and continue several seconds following, verbalizations [387]. Temporary suspension of eye movements and occurrence of sustained alpha-EEG trains during REM sleep somniloquy episodes have also been noted [387], as has suppression of theta- and alpha-activity prior to utterances [388]. Episodes frequently occur in parallel with sleep mentation, but concordance between verbal utterances and ongoing dreamed speech may vary from isomorphic to completely absent [389].

Associated Factors and Pathophysiology

The pathophysiology is unknown. In addition, since somniloquy is so prevalent, it is virtually impossible to isolate predisposing factors. Nonetheless, a clear genetic influence has been demonstrated [390]. Somniloquy is also the parasomnia that most often co-occurs with other parasomnias. It often accompanies the behavioral manifestations of either RBD or somnambulism. Stereotyped vocalizations can also be heard during nocturnal seizures. Recently, somniloquy (especially loud sleep talking) has been found helpful in the differential diagnosis of DLB versus Alzheimer's disease and other forms of dementia [391]. In most cases, however, somniloquy is idiopathic.

Prevalence

Although considered the most frequent parasomnia, somniloquy is usually without consequences and thus rarely a reason for consultation. Its prevalence among preschoolers (84 %) [82] is much higher than among older children and adolescents. A prevalence of 30 % was found for children ages 11–13 years using prospective reports [80], while in adults, an estimate of 24 % was found using a telephone sampling method [278]. A current prevalence of 17.7 % and a lifetime prevalence of 66.8 % were found for adults in a recent population-based Norwegian telephone interview study [392]. There is no apparent gender difference.

Treatment

There is no known treatment for somniloquy. It is usually considered too benign to treat.

Sleep-related Groaning

In ICSD-3 (see Chap. 27) this is classified under sleep related breathing disorder as an isolated symptom.

Clinical Presentation

Sleep-related groaning, also known as catathrenia, is defined as "a chronic, usually nightly, disorder characterized by expiratory groaning during sleep, particularly during the second half of the night." [2] Groaning or moaning sounds typically begin 2–6 h after sleep onset. The sounds produced are usually loud, but the pitch and timbre vary among individuals: groaning, loud humming, roaring, and high-pitched sounds have all been observed. The length of each groaning period was observed to be between 11 and 168 s [393]. By contrast, within individuals, the type of sound is usually fairly constant. Catathrenia is not associated with abnormal motor activity and is qualitatively different from somniloquy. Degree of concordance with sleep mentation is unknown. The affected individual is usually unaware of the problem and, apart from occasional complaints of daytime sleepiness, typically has no other sleep complaints. However, production of the sounds may disturb the bed partner. The identification of this disorder is relatively new, with less than 50 cases reported in the literature [394–398].

Catathrenia occurs during either REM or NREM sleep, but episodes arise predominantly from REM sleep [395]. Three-quarters to all of the groaning events occur in REM sleep, and most of the events were associated with arousals; the latter were preceding or coinciding with the groaning [393, 399]. Polysomnographic tracings reveal bradypneic events, often occurring in clusters, with deep inspirations followed by long expirations and monotonous vocalization (Fig. 50.6). There is a high night-to-night consistency of the groaning episodes [394]. Although catathrenia is associated with bradypneic events, only one [396] of the reported cases had significant obstructive apnea–hypopnea, and oxygen saturation remained above 90 % across the night; body position does not seem to have any influence [395]. In addition to the typical absence of apnea–hypopnea, the subjects are reportedly slim and young [398, 400, 401]. Whereas the loud sounds of snoring or obstructive sleep apneas occur during the inspiratory phase, the vocalizations of catathrenia occur during expiration. Unlike sleep apnea, sleep architecture for nocturnal groaners is usually preserved. However, a few patients will show either reduced total sleep time combined with reduced sleep efficiency, or a reduction of either slow-wave or REM sleep [395].

Associated Factors and Pathophysiology

No particular anomaly was found on neurologic and physical (including otorhinolaryngologic) examination, on routine laboratory testing, or in the medical history [394, 395, 398]. The close temporal association between microarousals and groaning episodes points to the involvement of arousal activation mechanisms in the pathogenesis of this parasomnia [399]. Bruxism is sometimes found in association with catathrenia [399, 402]. As is the case for many parasomnias, catathrenia is, at least in part, genetically determined. In about 15 % of cases, there is at least one family relative also affected, sometimes in a way consistent with an autosomal-dominant pattern of inheritance [395].

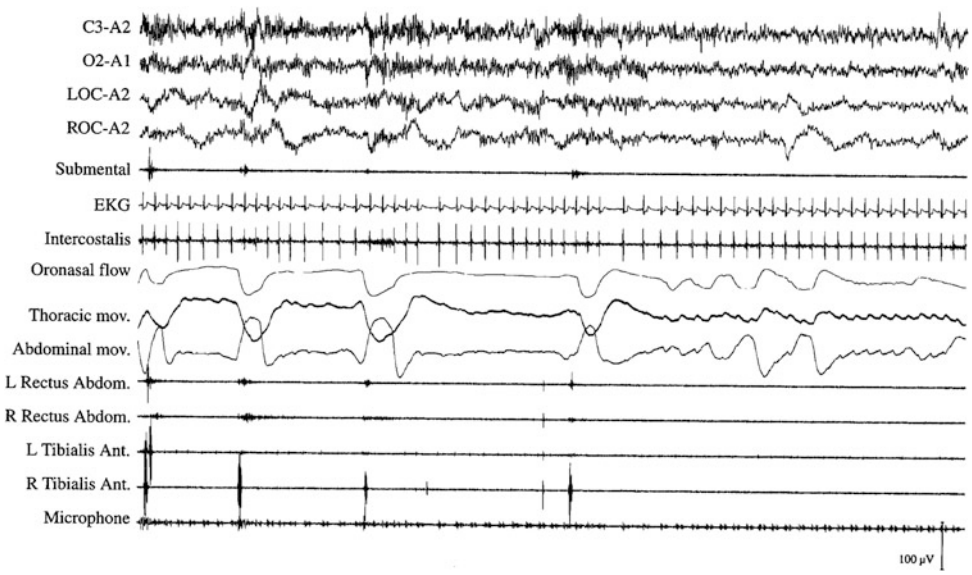

Fig. 50.6 PSG recording of a nocturnal groaning episode. A deep inspiration is followed by a short expiration and long, relatively flat period of reduced breathing during which the vocal groan is heard (reproduced with permission from Oldani et al. [395]

Prevalence

Nocturnal groaning represents less than 1 % of the population consulting at a sleep disorder center [393, 395]. However, since this parasomnia is without major consequences, there are probably a large number of affected individuals who do not seek medical help. It appears to be three times more prevalent in men than in women, although too few cases have been reported so far to be able to determine the gender ratio accurately. Onset is habitually during adolescence or early adulthood, and the parasomnia persists for several years [395]. The precise time course of the condition is unknown due to lack of follow-up on this recently identified condition.

Treatment

A few bedtime treatments have been tried with no sustained therapeutic effect: clonazepam, gabapentin, pramipexole, carbamazepine, trazodone, paroxetine, and dosulepin [394, 395]. Treatment with nasal continuous positive airway pressure produced inconsistent effects [394, 397, 400].

Conclusion

As stated in the DSM-5, some parasomnias, such as the disorders of arousal and RBD, "serve as a reminder that sleep and wakefulness are not mutually exclusive and that sleep is not necessarily a global, whole-brain phenomenon" [1].

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Sleep Disorders in the Elderly

51

Sudhansu Chokroverty

Introduction

To understand sleep disorders of the elderly, it is important to know what changes in sleep structure and sleep cycle are normal in disease-free-aged individuals. It is also important to understand the neurology of aging and, in particular, changes in central nervous system (CNS) physiology and morphology in normal healthy older individuals.

In 1900, 4 % of the American population was older than age 65; according to the best current estimate, that figure was 13 % in the year 2000 and will be 21 % by 2050 [1]. It is the life expectancy that has been increasing rather than the human life span, which is determined biologically and genetically and remains fixed [2]. We do not know what determines aging and the changes associated with aging (see Behnke et al. [3] and Comfort [4] for a review of this topic). Older individuals are at risk for sleep disturbances owing to a variety of factors, including social and psychosocial problems; increasing prevalence of concurrent medical, psychiatric, and neurologic illnesses; increasing use of medications (often sedative hypnotics) and alcohol; and alterations in circadian rhythms.

Neurology of Aging

Clinical Aspects of Central Nervous System Changes

Before discussing the neurology of aging, it is important to define what is meant by *aging*. No standard definition is available, but for this discussion I arbitrarily define age 65 as the start of old age. A normal elderly person is one who is free of obvious diseases of the central and peripheral neurologic systems as well as of general systemic diseases (e.g., cardiovascular, respiratory, renal, metabolic, hematologic, skeletal, and muscular diseases). Accepting this definition, a variety of changes in mental functions and the general nervous system of healthy elderly individuals have been noted. At the outset, I must point out certain difficulties in studying the neurology of aging. It is difficult to get a large number of elderly subjects who meet the criteria by being free of neurologic and other systemic disorders. Even if a number of such subjects can be recruited, without many years' subsequent longitudinal study, it often remains problematic to decide whether certain abnormal findings are related to a subclinical affliction of the nervous system that is expressed in overt manifestations later in life [5]. A large number of elderly individuals have general medical and neurologic disorders, particularly mild cognitive impairment (MCI) and dementia of the Alzheimer's type. In addition, there could be subclinical cerebral infarction, as noted in large series of autopsy examinations [6] in which half the individuals with cerebral infarction remained asymptomatic. The following discussion of the neurologic changes of normal aging is written with these limitations in mind.

A variety of physiological changes occur in the CNS which increase with aging. On mental function examination, the most striking changes in old age are in learning new information and in central processing of information [5]. In the Wechsler Adult Intelligence Scale [7], the performance scale declines much more rapidly than the verbal tests [5, 8]. This has been confirmed in several cross-sectional and longitudinal studies comparing young and old individuals [7–11]. The past and the immediate memory remain relatively intact until approximately the middle 70s, but recent memory is impaired. There is often forgetfulness and difficulty remembering names and remembering several objects at one time, which suggests impairment of central processing time. Speed of learning is retarded, as is speed of processing new information [5]. The reaction time to simple and complex stimuli is often delayed, and there is

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impairment of motor speed [12–16]. The cognitive impairment of the normal elderly is often termed *benign forgetfulness of senescence* [17] or *age-associated memory impairment* [18, 19]. The term MCI defines a transitional state between physiological aging and dementia [20]. It has been suggested that age-associated cognitive and other neurological changes may be mediated through subtle microvascular-induced damage to cerebral white matter as noted in neuroimaging [21]. In the Baltimore longitudinal study of aging, the investigators using serial imaging assessments sought to determine changes in cortical thickness in a cohort of 66 older adults (ages 60–84) without dementia over a mean follow-up of eight years [22]. They found widespread age-related decline in cortical thickness with an anterior–posterior gradient (frontal and parietal regions showing greater rates of decline than temporal and occipital areas). At the cellular level, researchers documented marked reduction in firing of prefrontal cortex (PFC) neurons with advancing age [23]. It is notable that the cognitive decline in normal aging (e.g., executive dysfunction, forgetfulness, distractibility) is thought to involve dorsolateral PFC dysfunction. The investigators had also shown that this age-related decline in the firing rate can be partially rescued by addressing molecular aspects of PFC circuits (e.g., by inhibiting cyclic-AMP signaling or by blocking HCN or KCNQ potassium channels).

In a classic paper in 1931, Critchley [24] first directed attention to certain changes in the nervous system of normal healthy elderly individuals. Since then, several studies have appeared in the literature documenting the presence of abnormal neurologic signs in a small number of such people [25, 26], but these signs may represent asymptomatic subclinical disease [5] (e.g., cerebrovascular disease or cervical spondylosis), and without longitudinal studies, it is impossible to exclude these definitely. Despite this limitation, there is a general consensus about the presence of certain findings in normal elderly individuals. There are changes in both the somatic and autonomic nervous systems (ANS) [5, 27, 28]. In the somatic system, an important finding is impairment of gait and stance [5, 29, 30]. It is difficult to stand on one leg with the eyes closed [25, 26, 30]. The so-called senile gait is characterized by stooped flexed posture accompanied by short steps, reduced arm swings, shortening of the stride, and impaired speed and balance [2, 5, 29]. The gait resembles that of patients in the early stage of Parkinson's disease, which may be due to the loss of dopaminergic neurons and striatal dopamine receptors [5, 29]. Grip strength declines with age [26]. The ankle reflex may be diminished, which may be related to the loss of large-diameter nerve fibers [5]. In the sensory examination, the striking abnormality is impairment of the vibration sense in the lower extremities [26]. Rowe and Troen [31] suggested that old age represents a hyperadrenergic state. If this is the case, sympathetic overactivity may explain some of the changes noted in the cardiovascular reflex, galvanic skin response, erection, maturation, and pupillary response of elders. Overactivity of the sympathetic nervous system may also interfere with cognitive function.

Physiologic Changes in Old Age

Electroencephalographic Changes

Awake Electroencephalography

The question remains whether electroencephalography (EEG) changes in old age are maturational changes or are related to pathologic alterations of the CNS. Many elderly individuals are afflicted with a variety of dementing illnesses, cerebrovascular disease, or systemic medical disorders that may cause metabolic encephalopathy [32]. Thus, it is important to select healthy elderly individuals who are free from any of these diseases for EEG study. Such a selection was made in the study of healthy septuagenarians by Katz and Horowitz [33]. The subjects were screened by careful neurologic, psychiatric, and neuropsychological examination and found to represent normative EEG data with an average alpha frequency of 9.8 Hz similar to that of young and middle-aged adults. This study can be contrasted with the report by Torres et al. [34], in which they found that 52 % of a group of normal volunteers with a mean age of 69 years had mild-to-moderate EEG abnormalities.

Obrist [35] summarized the EEG changes in old age as follows: slowing of the alpha rhythm and an increase in fast activities, diffuse slow activity, and focal slow waves. In an important longitudinal study by Obrist et al. [36], alpha frequency fell from 9.4 Hz at age 79 to 8 Hz intermixed with 6- to 7-Hz theta waves at age 89. Spectral analysis by Matejcek [37] and Nakano et al. [38] supported the progressive slowing of the alpha rhythm with aging. Duffy et al. [39] found no significant change in the frequency of the posterior EEG rhythm in a study of 63 men between 30 and 80 years of age. Oken and Kaye [40] analyzed conventional EEG and computerized EEG frequency in 22 extremely healthy subjects between 84 and 98 years old. The posterior peak frequency was higher than 8 Hz in those younger than 84, but between 7 and 8 Hz in 5 of 22 subjects older than 84 years. Alpha slowing appears to be related to the decline in mental function, which may be an early stage of progressive dementia of old age [41]. Alpha blocking and photic driving response to intermittent photic stimulation are also diminished in old age [42]. These findings may be related to the structural CNS alterations in elderly individuals (see *Pathologic Central Nervous System Changes of Normal Aging* later).

An increase in fast activity was noted by Busse and Obrist [43] in elderly volunteer community subjects, especially women. In an EEG spectral analysis, Brenner et al. [44] found more beta activities in elderly women than men. Kugler [45] also reported an increase in fast activity with the increase in age. The significance of this is uncertain, but Kugler [45] stated that the presence of fast activity in old age correlates with preserved mental functioning.

Intermittent focal slow waves in the temporal regions (particularly in the middle and anterior temporal regions and greater on the left side) are noted in 17–59 % of healthy elderly individuals (Fig. 51.1) [34, 35, 40, 46–48]. This temporal slow activity may be accompanied by sharp transients, which may be related to cerebral vascular disease causing asymptomatic small infarction of the temporal lobe [41], ventricular enlargement with cerebral atrophy [49], or white matter hyperintensities on magnetic resonance imaging (MRI) [40]. Klass and Brenner [50] listed some of the characteristics of what they called *benign temporal delta transients of the elderly* as follows: slow waves occur in patients older than 60 years and are maximally noted in the left temporal, particularly anterior temporal, region; the voltage is usually less than 70 μV, and these waves do not disrupt background activity; these delta transients are attenuated by mental alerting and eye opening and are increased by drowsiness and hyperventilation; the transients generally occur as single waves or in pairs but not in rhythmic trains; and the transient waves are present for up to 1 % of recording time. The elderly may also have an increased amount of theta activity [46, 51].

There is no clear relationship between intellectual deterioration and EEG slowing [35, 40]. Whether the EEG changes are correlated with cerebral blood flow (CBF) study remains controversial. There is no correlation, however, between areas that show the maximum blood flow reduction and those that show prominent EEG slowing, or between the blood flow changes and the alpha frequency changes in normal elderly subjects [52, 53]. The other suggestion is that the alpha slowing is related to the loss of choline acetyltransferase, the enzyme for synthesis of acetylcholine [5].

Sleep EEG Changes, Including Changes in Sleep Architecture and Organization

In addition to awake EEG changes, there are changes during sleep in the elderly (Box 51.1) [54, 55]. As early as 1945, Liberson [56] described paroxysmal bursts of sleeplike EEG lasting 1–10 s in the eyes-resting state in elderly subjects, and the incidence of these bursts increased with the age of the subject. Liberson [56] termed these episodes *microsleeps*. Transient bursts of anteriorly dominant rhythmic delta waves are often noted in elderly subjects in the early stage of sleep. Gibbs and Gibbs [57] used the term *anterior bradyrhythmia* for this finding. Katz and Horowitz [58] obtained sleep-onset frontal intermittent rhythmic delta activity in normal elderly subjects, which should be differentiated from that associated with a variety of neurologic disorders. These are highly stimulus-sensitive and disappear in deeper stages of sleep. In demented elders, however, one can see diffuse slow waves in the delta and theta frequencies.

Box 51.1 Age-related changes in EEG and Sleep Architecture

- Awake EEG
  - Progressive slowing of alpha frequency
  - Occasional focal temporal (left > right) sharp and slow transients
- Sleep Architecture
  - Reduced slow-wave sleep
  - Reduced sleep efficiency
  - Decreased night sleep time
  - Decreased sleep spindle density (number per minute), frequency, and amplitude
  - Decreased REM density (number of eye movement bursts per minute of REM sleep), but the percentage of REM sleep seems unaltered
  - Sleep fragmentation with multiple awakening including early morning awakening and arousals
  - Advanced circadian phase.

Normal elders show normal sleep patterns with certain modifications (Box 51.1). The delta waves during slow-wave sleep (SWS) are reduced in amplitude and incidence [27, 59, 60]. The amplitude of delta waves decreases, and therefore, in the standard scoring technique, SWS decreases. Feinberg et al. [61] discussed this point and suggested that quantification of the amount of time spent in a specified frequency be used for scoring SWS in elderly individuals, rather than using an amplitude criterion. Mann and Roschke [62] in a later study using EEG frequency and cross-correlation analysis in a group of 59 healthy young and middle-aged men confirmed a significant decline of the delta/theta bands during NREM sleep but an increase in EEG power in beta frequency during rapid eye movement (REM) sleep with increasing age. Recent authors [63–65] also commented on the age-related decline in slow waves. Mander et al. [64] thought that prefrontal atrophy, disrupted NREM slow waves, and hippocampal-dependent memory in aging are all interrelated. Colrain and co-investigators reported a linear decline in amplitude of sleep-evoked delta waves across the adult lifespan. This reduction in amplitude of delta waves could be related to the following factors: (1) reduction in neuronal synchronization in the neocortex [27, 58], (2) alterations in the skull [27, 60], (3) changes in the subarachnoid spaces [27, 60], (4) reduction in specific subpopulation

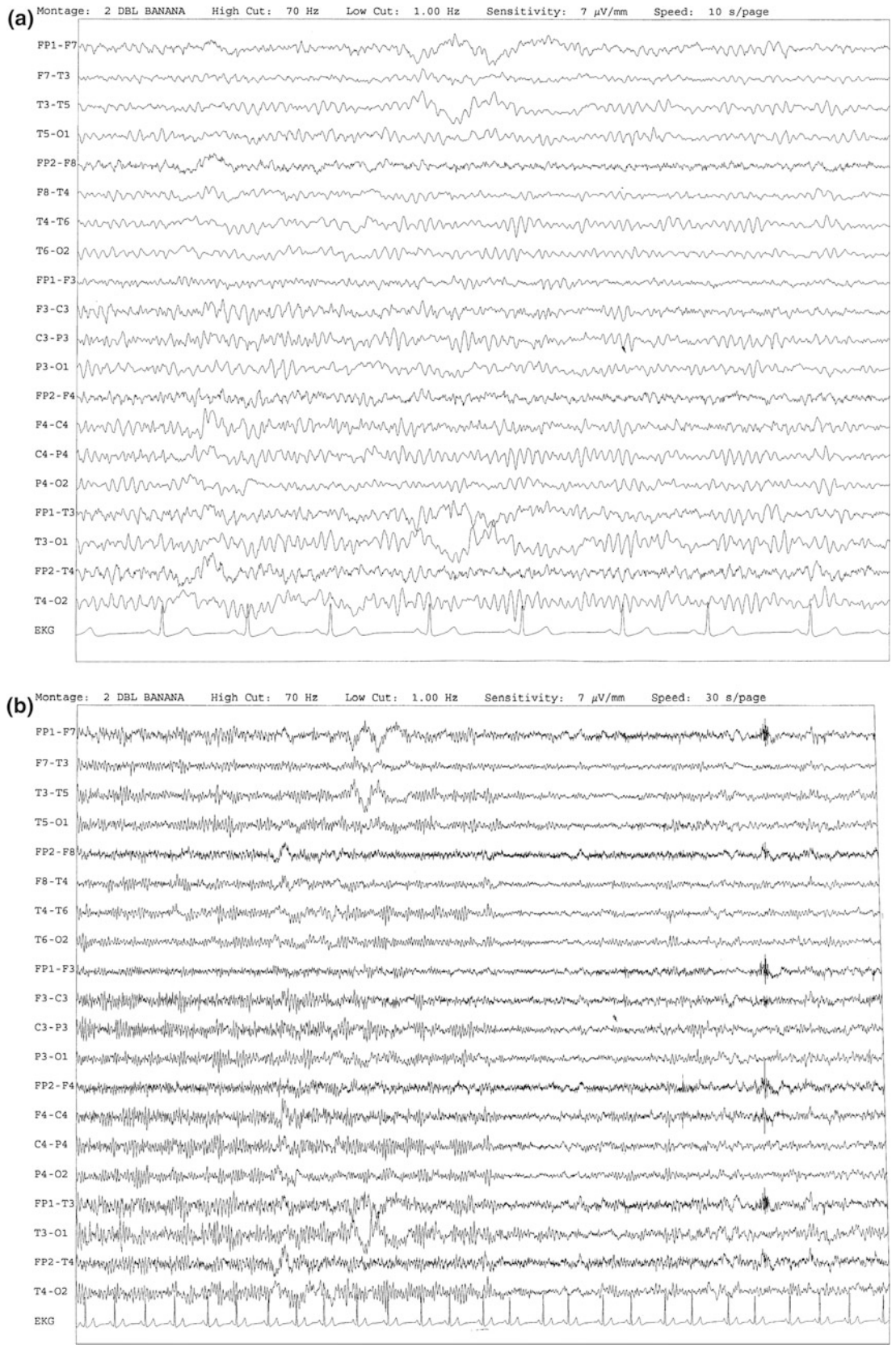

Fig. 51.1 **a** Electroencephalogram shows transient burst of delta activity in the left temporal, and occasionally also in the right temporal, region in a 94-year-old woman with a history of syncope. **b** Same subject data as in **a** viewed at a 30-s epoch. (From Chokroverty S, Bhatt M, Goldhammer T: Electroencephalography for the sleep specialists. In Chokroverty S, Thomas RJ, Bhatt M (eds), Atlas of Sleep Medicine. Philadelphia: Elsevier, 2005:29.)

(s) of neurons [66], (5) a steady decline of synaptic density resulting in a decline of intracerebral connectivity [67], and (6) changes in receptor functions and neurochemical alterations affecting synaptic communication and connectivity [68].

Sleep spindles may show a variety of changes in old age [69–71], including decreased frequency, amount, and amplitude. The frequency may decrease from 16 to 14 Hz, and then from 14 to 12 Hz. The spindles are often poorly formed and poorly developed. Sleep spindle changes thus resemble those noted with alpha frequency in old age.

The cyclic pattern from REM to NREM remains unchanged, but the first cycle may be reduced [27, 72, 73]. REM density (i.e., number of eye movement bursts per minute of REM sleep) and total REM sleep time are reduced, but the percentage of REM in relation to total sleep time (TST) remains unaltered [27, 74, 75]. Sleep fragmentation is due to frequent interruptions at night. In addition, there are frequent sleep stage shifts and, thus, frequent awakenings [27, 56]. Regarding nocturnal TST (lights out to lights on), there is discrepancy between subjective report and objective data based on the technician's schedule [27].

Nighttime sleep of elders usually is reported to be decreased (e.g., 5.5–6.5 h, in contrast to the usual 7.5–8.0 h TST average of young adults) [76]. This may not be an accurate observation, because elders often take daytime naps; 24-h TST of elders probably is no different from the 24-h TST of young adults.

Increased fragmentation of sleep and increased numbers of transient arousals accompanied by increased daytime sleepiness have been described in the studies by Carskadon et al. [77], Carskadon and Dement [78], and Boselli et al. [79]. Kales et al. [80] and Feinberg et al. [59] demonstrated the following changes in sleep with advancing age: state changes; frequent stage shifts; reduction in SWS and the EEG amplitude of delta waves; and increased NREM stage 1 owing to frequent arousals, decreased total nocturnal sleep, and reduction in total REM sleep time but normal REM percentage in relation to the TST.

Williams et al. [81] recruited 120 healthy seniors through advertisements, without mentioning sleep. They tried to carefully screen out sleep disorders by excluding those who had sleep complaints. These authors found that the seniors' sleep quality was poorer than that of young individuals. In particular, there was a decrease in stages 3 and 4 sleep and an increase in nighttime wakefulness [81, 82]. Prinz and Vitiello [83] considered these findings as a benchmark level of sleep change associated with aging per se. In another study involving the Veterans Administration Survey, Cashman et al. [84] found that nighttime hypoxemia, which correlated with sleep apnea, was worse in several medical disorders (i.e., diabetes, cardiovascular disease, history of alcoholism, and vascular headaches). Thus, the data suggest that the disease states may interact with sleep disorders.

Between the ages of 60 and 90 years, there are differences in the sleep architecture of men and women [71, 85]. Between 60 and 70 years, men have more frequent arousals and more decrements in slow-wave sleep. Between 60 and 80 years, women spend 9 % of TST in the slow-wave stage, whereas men spend only 2 %. The percentages of REM and total REM sleep are not different for men and women between 60 and 90 years. In a meta-analysis of normative sleep data across the human life span, Ohayon et al. [86] also reported a reduction in SWS beginning in middle age, with complete absence after the age of 90 years. In a recent population-based cross-sectional Sao Paulo epidemiological study [87, 88] including 1042 individuals (468 men and 574 women) with an age range of 20–80 years, Moraes et al. [87] noted after polysomnographic (PSG) study that their findings were similar to those of Ohayon et al. [86] except that the reduction in SWS percentage correlated with age in men but not in women, whereas the reduction in REM sleep percentage correlated with age in women but not in men.

In a longitudinal PSG and diary-based study, Hoch et al. [89] found deterioration of measures of sleep quality, continuity, and depth but not other sleep measures over a 3-year follow-up period in a group of 27 healthy "old old" subjects (75–87 years) as contrasted with a group of 23 "young old" subjects (61–74 years). The decline in sleep measures was manifested by impaired sleep efficiency, prolonged sleep latency, increased wakefulness after sleep onset, and decreased SWS percentage. These changes were accompanied by increased napping in the "old old" group.

Changes in the Circadian Rhythm

Circadian rhythm changes [85, 90] in the elderly result from fundamental changes in social activity, including family interaction. Interaction is governed by alterations of daily routine and activities, health needs, and psychosocial factors (e.g., loneliness, divorce) [27]. There may also be intrinsic changes in the circadian rhythm related to the pathologic changes noted in apparently normal individuals. Animal studies lend support to this conclusion [91–95]. In long-term care facilities, circadian rhythm disturbances may be related to alterations in *Zeitgebers* (external time cues), such as bedtime, medication time, mealtime, and special institutional regulations on lights out and lights on [17]. Wessler et al. [96] made an intensive study of 69- to 94-year-old institutionalized patients under strict environmentally controlled conditions and found a remarkable regularity in circadian synchronization. In a study involving 69- to 86-year-old subjects, however, Scheving et al. [97] did not find support for the other group's conclusion. In all of these studies

involving institutionalized patients, the effect of chronic illnesses must be considered in explanations of circadian rhythm disturbances. Thus, these changes may not be related to "normal" old age.

A study of evolution of sleep shows that the strong monophasic circadian rhythm of youth gives way to a polyphasic ultradian rhythm in old age. Frequent awakenings at night, with reduction in wakefulness, are accompanied by increased daytime naps. These physiologic changes may be related to the structural alterations noted in the suprachiasmatic nucleus (SCN) and brain stem hypnogenic neurons in experimental studies in several species of animals [98–100]. The human central circadian clock in the suprachiasmatic nucleus is subject age-associated changes [101] (e.g., molecular rhythms, ion channels, neurotransmitters, intracellular messenger); however, little is known about the underlying mechanisms. These changes may cause a reduction in the amplitude of the circadian timing signal, a deduction in amplitude of daily rhythms in physiology and a weakening of the peripheral oscillators. These changes partly explain some of the sleep disturbances in the elderly.

There is also phase advance in the elderly—that is, there is a tendency to go to sleep early and awaken early. These changes may be related to age-related changes in the core body temperature rhythm [102, 103]. In elderly individuals, the amplitude of the temperature rhythm is attenuated and phase-advanced [103].

Autonomic Nervous System Changes with Age

There are striking functional and structural changes noted in the elderly in the ANS [27, 28, 104–107]. Changes are found in autonomic nerves and ganglia; ANS-controlled cardiovascular, respiratory, and gastrointestinal functions; sympathetic nerve activity; thermoregulation; and nocturnal penile tumescence in men. The age-related structural alterations in the human superior cervical ganglia may explain the deterioration of neuronal functional capacity and affect neuronal plasticity and regenerative characteristics [106].

Sympathetic Nerve Activity

The most consistent abnormalities in old age are increased muscle sympathetic nerve activity and elevated plasma concentration of the sympathetic neurotransmitter norepinephrine [104, 108, 109]. Age-related changes are noted in circulating catecholamine levels and microneurographic recordings from sympathetic nerves of skeletal muscles. In contrast, the reactivity of the sympathetic and parasympathetic activities is reduced with aging [104].

Thermoregulation

Thermoregulation is impaired in old age [28]. In response to passive heating, the sweating response of elders is impaired [110]. They are susceptible to hypothermia (both postoperatively and in response to low ambient temperature in the environment) [111, 112] and hyperthermia [113]. There is a paucity of studies that show ANS changes during sleep in elders.

Cardiovascular Changes

Blood pressure (BP) and pulse rate fall at sleep onset, rise on awakening, and fluctuate during the night [114]. The increased incidence of stroke in elders during sleep may be related to these factors [27]. Orthostatic hypotension is common in elders and may be due to impaired baroreflex responsiveness and neuroeffector function [28]. Aging is associated with decreased cardiovagal baroreflex sensitivity (i.e., blunted reflex changes in the R–R interval in response to a change in BP) [105]. These alterations may cause increased levels in BP variability and increased risk of sudden cardiac death [105]. However, baroreflex control of sympathetic outflow is not impaired with age. Baroreflex functional changes with aging may cause an impaired ability to buffer BP changes.

Respiration

Age-related changes in the respiratory system and pulmonary function include a reduction in vital capacity, chest wall compliance, diffusion capacity, elastic recoil, and arterial oxygen tension; mismatch of the ventilation–perfusion ratio; decreased respiratory muscle strength; and respiratory center sensitivity [27, 115–117]. There is a higher incidence of periodic breathing, including Cheyne–Stokes breathing and snoring, in elders at night [114, 118–120]. Patients with chronic obstructive pulmonary disease, who are often elderly, are at special risk for periodic breathing during sleep (both at night and during the day) because of increasing oxygen desaturation, hypercapnia, and apnea during sleep [121, 122]. The recent population-based cross-sectional study also supported a decrease in oxygen saturation and an increase in apnea–hypopnea index (AHI) with aging [87].

Nocturnal Penile Tumescence

Penile erection occurs during REM sleep. This REM-related penile tumescence shows a linear decrease from youth to old age (from 88 % at 20–26 years old to 64–74 % at 60–90 years old) [123, 124].

Gastrointestinal Function

Selective degenerative changes may occur in the aging enteric nervous system, which regulates gastrointestinal functions [107]. These age-associated changes in intestinal innervation may contribute to the gastrointestinal disturbances that increase in incidence in the elderly (e.g., dysphagia, gastroesophageal reflux, constipation) [125].

Endocrine Changes with Age

Plasma Cortisol

Cortisol secretion has a circadian rhythmicity that remains intact in the elderly. There is an age-dependent increase in mean nocturnal cortisol levels and an advancement of the morning rise [126]. However, normal diurnal rhythm of salivary cortisol is maintained in older adults [127]. Magri et al. [128] observed a significant increase in nocturnal cortisol levels in 23 healthy elderly and 23 demented elderly individuals as compared with levels in 10 healthy young subjects. MRI of the brain correlated these higher nocturnal cortisol levels with a reduction in hippocampal volume in these elderly subjects. Poor sleep in the elderly may be related to an activation of the hypothalamic–pituitary–adrenal (HPA) axis associated with hypersecretion of cortisol and increased inflammatory cytokines (e.g., interleukin-6), which stimulate the HPA axis.

Growth Hormone

Sleep-related growth hormone release is diminished in old age [129], but the response of the growth hormone secretion to insulin hypoglycemia is normal [130]. There is a parallel decrease in SWS and growth hormone in the elderly [131].

Prolactin Secretion

Prolactin secretion in old age shows a normal pattern of episodic secretion with a sharp rise just after sleep onset and a sharp fall during morning awakening [27, 132]. Although older subjects wake up several times during the night and have daytime naps, these episodes are not correlated with the prolactin secretion pattern [27].

Gonadotropins (Follicle-Stimulating Hormone and Luteinizing Hormone)

No good studies correlate sleep changes in the elderly with gonadotropin secretion [27].

Plasma Insulin and Glucose

Insulin secretion shows a clear circadian variation in healthy young adults, but there is no adequate study of aged individuals [27].

Thyroid-Stimulating Hormone

Plasma thyroid-stimulating hormone shows a circadian periodicity in adults: Peak levels occur just before sleep onset at night [114, 133, 134]. In subjects older than 50 years, there are progressive changes in thyroid function causing a modest decrease in serum triiodothyronine concentration and minimal changes in thyroid-stimulating hormone and thyroxine concentrations [135].

Melatonin Secretion

Serum melatonin concentration shows an age-related decrease in old age [136]. Impaired melatonin secretion has been reported to be associated with sleep complaints in the elderly [137, 138].

Changes in Cerebral Blood Flow and Cerebral Metabolism

Despite some inconsistent early findings [5], there is a direct relationship between normal aging, CBF, and cerebral metabolism. The xenon-133 inhalation method related a clear-cut decline in the regional blood flow exclusively to advancing age, without the confounding factors of associated diseases [139, 140]. This decline with advancing age was noted more in the gray than in the white matter CBF values. Maximal declines were seen in the prefrontal and parietal regions and minimal declines in the frontal and frontotemporal regions [5]. This decline in old age seems to be related to a progressive decrease in the cerebral metabolic rate [141] and possibly also to the morphologic changes in the neurons in the brains of elderly individuals. It should be noted that the decrease in CBF during SWS and the increase during REM sleep are similar in normal subjects of all ages. In elderly sleep apnea patients, however, this decrease during SWS becomes excessive, placing elderly individuals at increasing risk for sudden death and development of stroke during sleep when combined with hypoxemia related to apnea.

Pathologic Central Nervous System Changes of Normal Aging

Aging represents biologic maturation, which may be accompanied by a variety of pathologic changes in the CNS. The neuropathologic changes of old age can be summarized as follows [5, 142]: Shrinkage of the brain; alterations in the outline; and loss of neurons in various locations; lipofuscin accumulation; collection of corpora amylacea; intraparenchymal vascular changes; loss of dendritic arbor and dendritic spines; and presence of senile plaques, amyloid deposits, neurofibrillary tangles, granulovacuolar degeneration, and Hirano bodies. The presence of senile plaques, amyloid deposits, neurofibrillary tangles, granulovacuolar degeneration, and Hirano bodies is correlated with dementia, but the other neuropathologic changes are considered nonspecific changes of aging.

From the standpoint of sleep disorders medicine, the cell loss in the locus coeruleus, pontine and midbrain reticular formation, selective hypothalamic regions, and SCN, as well as accumulation of neurofibrillary tangles and abnormal pigment in the hypothalamus, are important morphologic

correlates for widespread sleep disturbances in the elderly. Animal experiments on the SCN show the relationship between destruction of these nuclei and alteration of circadian rhythmicity of adrenal cortical secretion, body temperature, activity–rest cycle, and sleep cycle loss [27].

Sleep Complaints in Old Age

In an epidemiologic study, Ford and Kamerow [143] interviewed 7954 subjects and observed that 40 % of patients with insomnia and 46.5 % of those with hypersomnia had a psychiatric disorder, compared with 16 % of those with no sleep complaints. Complaints of persistent insomnia are important late in life. There is a high incidence of depression with insomnia in the elderly. Among the 1801 elderly respondents aged 65 and older, the prevalence of insomnia was 12 % and the incidence of insomnia was 7.3 % [143]. For hypersomnia, the figures for prevalence and incidence were 1.6 and 1.8 %, respectively. There was a strong association between persistent insomnia (longer than 1 month) and the risk of major depression. Clayton et al. [144] noted that, in late-life spousal bereavement, there is also a persistent and debilitating complaint of insomnia.

Brabbins et al. [145] noted an overall prevalence of 35 % for insomnia complaints (more in women) after an interview of 1070 noninstitutionalized elderly individuals. In contrast, after interviewing 59 institutionalized and 874 community-dwelling residents, Henderson et al. [146] found a prevalence of approximately 12 % in the institutionalized and approximately 16 % among the community-dwelling elderly at 70 years or older. Insomnia complaints are more prevalent among women; whites; and those with depression, pain, and poor health. In another study from Germany, Stepnowsky et al. [147] investigated the prevalence of insomnia in 330 patients older than 65 years attending the offices of five general practitioners. Using the *Diagnostic and Statistical Manual of Mental Disorders* (3rd revision) diagnostic criteria, they found severe insomnia in 23 %, moderate insomnia in 17 %, and mild insomnia in another 17 % of the patients. There was a significant association between insomnia, depression, and dementia.

Foley et al. [148] conducted an important epidemiologic study limited to interviews in more than 9000 elderly subjects aged 65 years and older from three communities in the United States in the National Institute on Aging's multicentered study entitled "Established Populations for Epidemiologic Studies of the Elderly". These authors observed at least one of the following complaints in over half the subjects: trouble falling asleep, multiple awakenings, early morning awakening, daytime naps, and tiredness. These complaints are more common in women than in men and are often associated with respiratory symptoms, depression, nonprescription and prescription medications, poor self-esteem, and physical disabilities. The authors observed 33 % of men and 19 % of women with snoring and 13 % of men and 4 % of women with observed apneas. In this cross-sectional study, the authors did not find a clear relationship of loud snoring, observed apneas, or daytime sleepiness to hypertension or cardiovascular disease in the elders. In a later epidemiologic study of 6800 persons over 3 years, Foley et al. [149] reported that 28 % of older adults had complaints of chronic insomnia but, in the absence of risk factors (e.g., depression, medical disorders, circadian rhythm disorders, medications), only 7 % had insomnia. In a 2003 National Sleep Foundation Sleep in America poll, sleep complaints common in older adults are found to be secondary to comorbidities rather than aging per se [149].

Excessive daytime somnolence (EDS) is often associated with fragmentation of nocturnal sleep, which may have been due to sleep-disordered breathing and periodic leg movements in sleep (PLMS) [150]. Other factors are changes in the circadian rhythms of temperature, alertness and sleepiness, and social time cues. Frequent daytime sleepiness in older adults is associated with an impairment of physical functioning and decreased exercise frequency [151]. Based on the National Sleep Foundation 2003 Sleep in America poll, Foley et al. [148] reported frequent napping associated with EDS, depression, pain, and nocturia in older adults.

Many other factors can disrupt sleep: Nocturia, leg cramps, pain, coughing or difficulty in breathing, temperature sensitivity, and dreams [149, 150]. There is an increased prevalence of nocturia in the elderly causing sleep disturbance [151–153]. Sleep disturbances, particularly complaints of insomnia, may contribute to increasing risk of falls and fractures in the elderly [150, 154–157]. There is controversy whether the increasing risk of falls in the elderly is related to the sleep disturbance per se or greater use of hypnotics by the elderly [154]. In a multicenter community-dwelling questionnaire-based study involving over 8000 white women aged 69 and older (mean = 77 years), self-reported long sleep (at least 10 h per 24 h) and daily napping were associated with greater risk of falls and fractures [155]. In a recent [157] prospective observational sleep study in 3101 community-dwelling men aged 67 and above (mean = 76 years), Stone et al. reported that subjective (Epworth Sleepiness Scale and Pittsburgh sleep quality index) and objective (actigraphy and in-home polysomnography) sleep disturbances were associated with risk of falls in older men, independent of confounders. These authors found that reduced hours of sleep (five hours or less compared with those with seven to eight hours) and nocturnal hypoxemia ($\geq$10 of sleep time with arterial oxygen saturation <90 %) but not apnea–hypopnea index were associated with greater risk of falls.

Vitiello and Prinz [158] found that CNS degenerative disorders (e.g., dementia of the Alzheimer's type) may cause

polyphasic sleep–wake patterns, which constitute a significant problem among old nursing home residents. In demented elderly subjects, nocturnal agitation, night wandering, shouting, and incontinence contribute to a variety of sleep disturbances. There are many other factors in the pathogenesis of nocturnal agitation, including loss of social *Zeitgebers* and circadian timekeeping, sleep apnea, REM-related parasomnias, low ambient light, and cold sensitivity [159].

An important behavioral disturbance during sleep late in life is snoring [150]. According to Koskenvuo et al. [160, 161], habitual snoring was found in 9 % of men and 3.6 % of women ages 40–69 years in their study done in Finland. Hypertension, ischemic heart disease, and stroke are risk factors for snoring. In an epidemiologic survey, Lugaresi et al. [162] found that approximately 60 % of men and 40 % of women between the ages of 41 and 64 years were habitual snorers. Enright et al. [163] recruited 5201 adults ages 65 and older who were participants in a cardiovascular health study that enrolled a random sample of Medicare subjects in four US communities. In this study, there was no positive correlation between aging and self-reported snoring. Loud snoring, however, was independently associated with body mass index, diabetes mellitus, and arthritis in older women, and with alcohol use in elderly men.

What is the relationship between sleep duration and mortality in elders? In 1989, Ancoli-Israel [164] re-examined the 1979 data of Kripke et al. [165] and concluded that 86 % of deaths associated with short (<7 h) or long (>8 h) sleep occurred among those older than 60 years. Thus, it could be concluded by extrapolation from these data that older individuals who sleep less than 5 h or more than 9 h may be at greater risk for death.

The high frequency of sleep complaints in aged individuals may be related to the physiologic sleep changes of normal aging as well as to concomitant medical, psychiatric, neurologic, and other disorders that are prevalent in this group [54, 85, 149, 153, 154, 159, 166]. Subjective sleep complaints are common in older subjects, as many reports attest [167–170]. The subjective complaints were corroborated by objective laboratory data. In contrast to the increasing incidence of subjective complaints from women, however, elderly men had more sleep disturbances than elderly women by objective reports [171].

Clinical Assessment of Sleep Disorders

Clinical assessment consists of a sleep, medical, drug, and psychiatric history. A general approach for making a clinical assessment is described in Chap. 26; only the points relevant to elders are emphasized in this section.

Sleep History

Kales et al. [172] developed excellent guidelines for taking an adequate sleep history, summarized as follows:

1. The specific sleep problem should first be defined from the history. It is important with elders to understand the significance of daytime fatigue, which may result either from insomnia at night or from EDS. The latter condition can be an indirect effect of repeated arousals at night owing to sleep-related respiratory disorders, with or without PLMS. The other important factor to note is that the sleep of elders becomes polyphasic, associated with frequent daytime naps and less sleep at night. Therefore, every daytime nap is not necessarily indicative of EDS.
2. The onset and the clinical course of the condition should be assessed from the history. The course of the illness in some sleep disorders (e.g., night terrors, nightmares, sleepwalking) is different [173]. Nightmares have a chronic course, whereas night terrors may be of recent onset. It should be noted that the relatively sudden onset of sleepwalking or night terrors in an elderly person is indicative of an organic CNS disorder, and appropriate investigation should be directed toward that diagnosis [174].
3. Inquiries should be made into a family history of a sleep disorder. Certain sleep disorders (e.g., narcolepsy, hypersomnia, sleep apnea, sleepwalking, night terrors, restless legs syndrome) may have a family history [172–178].
4. Various sleep disorders should be distinguished from one another, and any previous diagnosis should be reassessed.
5. It is important to obtain a complete 24-h sleep–wakefulness pattern. This is important in elderly individuals, because in old age the sleep cycle becomes polyphasic, rather than monophasic as in young adults. In elders, because of the tendency to take frequent naps, the sleep–wake schedule becomes irregular and may cause circadian rhythm disorders.
6. It might be important to keep a sleep diary or sleep log, and it is very important to question the bed partner or other caregivers about sleep disturbances of elders. Keeping a sleep diary may help assess the 24-h sleep–wake cycle pattern.
7. The bed partner or caregivers should be questioned carefully, as they may have clues to the diagnosis of sleep apnea syndrome (SAS). For example, excessively loud snoring, temporary cessation of breathing, or restless movements in the bed are important pointers to the diagnosis of SAS or PLMS.

8. It is essential to evaluate the impact of the sleep disorder and to determine the presence of other sleep disorders. The history may suggest a diagnosis of sleepwalking, night terrors, or REM sleep behavior disorder (RBD). A careful sleep history may also suggest nocturnal epilepsy, which is sometimes mistaken for a sleep disorder.

Medical History

It is vital that a complete medical history be obtained from the patient [172, 179]. Elderly individuals often have a variety of medical disorders, including congestive cardiac failure, hypertension, ischemic heart disease, chronic bronchopulmonary disorders, gastrointestinal disorders, arthritis and musculoskeletal pain syndromes, cancer, chronic renal disorders, endocrinopathies, and a variety of neurologic disorders. All of these conditions may disrupt sleep by virtue of the uncomfortable symptoms or because of the medications prescribed for them. Therefore, patients often complain of insomnia, but sometimes also of hypersomnia.

Drug History

It is important to obtain a drug history [172] because many medications can cause insomnia, including [180] CNS stimulants; bronchodilators; β blockers; antihypertensives; benzodiazepines, particularly the short-acting ones; steroids; and theophylline. Withdrawal from short- and intermediate-acting benzodiazepines and nonbenzodiazepine hypnotics causes rebound insomnia. Many CNS depressants, such as hypnotics, sedatives, and antidepressants, may cause EDS. Finally, drinking coffee or cola at night may cause difficulty initiating sleep. Alcohol consumption may cause difficulty maintaining sleep.

Psychiatric History

Psychophysiologic and psychiatric problems are the most common causes of insomnia in elders [180]. Elderly insomniacs can have a variety of psychological and psychiatric problems, such as anxiety, depression, organic psychosis, and obsessive–compulsive neurosis. A patient with depression complains of early morning awakenings, whereas a patient with obsessive–compulsive neurosis has difficulty initiating sleep. Some drugs (e.g., thioridazine) may increase nightmares [146]. Marital and sexual problems may give rise to interpersonal problems that cause sleep disturbances, particularly insomnia [179].

Sleep Disorders in Old Age

It is well known that the prevalence and intensity of sleep disturbances increase with age [149, 150, 179, 181–183]. Factors that affect the prevalence of sleep disturbances in the elderly are (1) physiologic (e.g., age-related changes in sleep patterns); (2) medical; (3) psychiatric; (4) pharmacologic (e.g., use, misuse, and abuse of drugs); and (5) social (changing rest–activity schedules, and, therefore, sleep–wake patterns) [149, 150, 179–185].

The prevalence of sleep-related breathing disorders, PLMS, and snoring are all greater among elders. The prevalence of sleep apnea increases with age and is greater in men than in women, and in menopausal women than in premenopausal women [164]. There is controversy over the exact prevalence of sleep apnea in the older population. The prevalence rates for sleep apnea—defined as repetitive episodes of upper airway obstruction—in elders in various studies have been estimated to range from 5.6 to 70 % [164, 186–194]. The prevalence is greater in the elderly than in younger adults, and in men than in women [195, 196]. There is a lack of consistency in study methods, so it is very difficult to generalize from these studies. In the Sleep Heart Health study involving a large cohort of about 6400 subjects (aged 40–98 years, with a mean of 63.5), Young et al. [194] reported an increased prevalence of SAS by 10-year age groups: 32 % of those ages 60–69 years had an apnea–hypopnea index (AHI) of 5–14 and 19 % had an AHI of ≥ 15; 33 % of those ages 70–79 years had an AHI of 5–14 and 21 % had an AHI of ≥ 15; and 36 % of those ages 80–98 years had an AHI 5–14; and 20 % had an AHI of ≥ 15. Thus, there was a small increase in the AHI index by 10-year age groups. In an earlier study, Hoch et al. [188] also found increased AHI and prevalence of SAS from 60 to 90 years. It should be noted, however, that based on a definition of 15 or more apneas or hypoapneas per hour of sleep accompanied by EDS, the recent Wisconsin sleep cohort study data listed prevalence of moderate-to-severe SAS at 10 % in men and 3 % in women among 30–49 years, but 17 % in men and 9 % in women among 50–70 years [197]. Because of the high prevalence of SAS in elders, questions have been raised as to the significance of sleep-disordered breathing in the elderly. Prinz et al. [198] stated that, because apneic episodes in the elderly may not have the same clinical symptoms as noted in younger people, it is more difficult to determine whether further investigations are needed. Fleury [199], suggested that SAS in the elderly not be considered different from SAS in middle-aged men, however, assuming that an appropriate diagnostic apnea index (AI) or respiratory disturbance index (RDI) was taken into consideration. Ancoli-Israel and Coy [193] agreed that, if SAS is severe enough to cause symptoms in the elderly, treatment should be similar to that in a younger patient.

The controversy as to whether SAS in the elderly represents a specific entity or the same disease in younger subjects continues [150, 200–202]. Further research is needed to resolve this issue. Launois et al. [201] contended that untreated SAS in the elderly appears to have less impact on mortality than in middle-aged adults; however, symptomatic elderly SAS patients tolerate continuous positive airway pressure (CPAP) as well as the younger patients. Based on a retrospective study in Poland, Bielicki et al. [202] concluded that SAS is more frequent in elderly than in younger patients but is more severe in younger patients requiring higher CPAP titration pressure. In an important longitudinal follow-up study of elderly patients with SAS for 18 years, Ancoli-Israel et al. [203] observed that the AHI did not continue to increase if the patient's body mass index remained stable. Some of the risk factors predisposing the elderly to SAS are as follows [204, 205]: age, gender, obesity, smoking, family history, race, upper airway anatomic configuration, use of sedative hypnotics, and alcohol consumption.

Reasons for the variation in the prevalence of sleep apnea could be the sampling of different populations without using a random sampling method, small sample size, or the use of different criteria to define sleep apnea. An important problem has been the scoring criteria for apnea and hypopnea and the definition of AI, AHI, or RDI. In the current American Academy of Sleep Medicine guidelines for scoring [206], these questions have been addressed and standardized (see Chap. 25). Another problem has been the clinical significance of an AI or RDI of 5. Some authors have suggested that an AI of 20 or more is related to increased risk of death [207]. In a survey among 427 randomly selected community-dwelling people, 65–95 years of age, in San Diego, California, Ancoli-Israel et al. [186] reported that 81 % of the subjects had an AHI of ≥ 5 with a prevalence rate of 62 % for an AHI of ≥ 10, 44 % for an AHI of ≥ 20, and 24 % for an AHI of ≥ 40. Night-to-night variability in sleep apnea has been the other confounding problem in the elderly [186, 208–211].

The question of the relationship between sleep apnea or sleep-disordered breathing and increased morbidity or mortality remains controversial, several studies, however, have found a positive relationship [207, 212, 213]. In a nearly 10-year follow-up of a randomly selected, population-based probability sample of 426 men and women (65–95 years old), Ancoli-Israel et al. [214] found that those with severe sleep-disordered breathing (RDI of 30 or more) had a significantly shorter survival but that the RDI was not an independent predictor of death. Similar results were reported from a sleep disorders clinic patient population study by Lavie et al. [215], Ancoli-Israel et al. [214] stated that other confounding variables such as age, hypertension, and cardiovascular or pulmonary disease might be responsible for the increased morbidity and mortality. Chronologic or biological age (determined by biological markers of physiologic aging) may be the single most important factor for increased morbidity and mortality in sleep-disordered breathing (i.e., sleep apnea may be an age-dependent condition). To address this controversy, well-designed controlled clinical studies are needed.

Diagnosis of Sleep Disorders in Old Age

Recognition of a variety of sleep disorders in elders is important for treatment of sleep disturbances and the associated medical or psychiatric conditions. Some examples of sleep disorders that have been recognized in the aged population [171, 198, 216–224] are insomnia; sleep-related respiratory dysfunction with periods of apneas and hypoapneas; PLMS; sleep disturbances secondary to a variety of medical or psychiatric illnesses (particularly depression in the elderly); sleep disturbances associated with dementia (particularly of the Alzheimer's type); and sleep disturbances related to the abuse of alcohol and sedative-hypnotic drugs, narcolepsy, restless legs syndrome, parasomnias, and circadian rhythm sleep disorders (Box 51.2).

Box 51.2 Common Sleep Problems in Old Age

Primary Sleep Disorders

- Insomnia
- Sleep-related breathing disorders
- Restless legs syndrome/periodic limb movements in sleep
- REM sleep behavior disorder
- Advanced sleep phase state.

Other Disorders associated with sleep difficulty

- Comorbid psychiatric illnesses
- Comorbid general medical disorders
- Comorbid neurodegenerative and other neurologic disorders
- Medication related
- Abuse of alcohol and use of sedative-hypnotic drugs
- Nocturia and sleep problems.

Insomnia and EDS are the two most common symptoms noted in normal aged individuals [198]. There is a high incidence of insomnia in the elderly, particularly elderly women [179] (see Chap. 37 for further details about insomnia). Epidemiological studies have shown that sleep

problems increase with age and are associated with comorbid insomnia, depression, dementia and cardiovascular disease, and increased mortality [225].

Sleep Apnea Syndrome

For the diagnosis of SAS, questioning the bed partner is very important. A history of loud snoring with periods of cessation of breathing at night accompanied by EDS and daytime fatigue suggests SAS [226]. The diagnosis is strongly suspected if the patient is also obese and hypertensive. For a definitive diagnosis, and to quantify the severity, an all-night PSG study is essential. The usual type is upper airway obstructive sleep apnea, but often it is mixed with central apnea, giving rise to mixed apnea (see Chap. 32). It is important to diagnose the condition because of possible adverse consequences [226], such as congestive cardiac failure, cardiac arrhythmias, hypertension, neuropsychological impairment [193, 224, 226, 227], increased risk of traffic accidents [228, 229], and increased mortality related to cardiovascular events [230, 231]. In a 6-year follow-up prospective longitudinal study in a population-based cohort of 394 noninstitutionalized elderly subjects (ages 70–100 years, median 77 years; 57 % men), Munoz et al. [230] found that severe obstructive sleep apnea–hypopnea (AHI index of ≥ 30) at baseline had an increased risk of ischemic stroke in the elderly population independent of known confounding factors (e.g., age, sex, smoking, alcohol consumption, body mass index, blood pressure, serum cholesterol levels, presence or absence of diabetes mellitus, and atrial fibrillation). Lugaresi et al. [162] reported a high prevalence of snoring in elderly individuals, and this can be the forerunner of full-blown SAS.

Periodic Limb Movements in Sleep

PLMS is reported more often in older normal subjects than in younger ones [189, 232–236]. According to Coleman et al. [234], the occurrence of PLMS may be related to disturbance of circadian sleep–wake rhythm in the elderly. In the study by Kripke et al. [233], 20–30 % of subjects 65 years and older had PLMS, whereas Ancoli-Israel et al. [232] reported an incidence of 37 % of PLMS in 24 older subjects. Pennestri et al. [236] noted PLMS rarely in normal subjects under the age of 40 years, but then the index increased dramatically after that age. They found a mean index of two/hour in subjects between 30 and 40, 11 between 40 and 50, 17 between 50 and 60, and 22 in those 60 years and older. PLMS is often associated with SAS independently of respiratory-related PLMS.

Sleep Disturbances and Medical Illnesses

A variety of medical disorders may be associated with insomnia—congestive cardiac failure; ischemic heart disease; arthritis and musculoskeletal pain syndrome; chronic respiratory disorder associated with bronchospasm; and dyspnea, which is often worse at night (see Chap. 11). Diabetics with autonomic neuropathy may have SAS [237]. Foley et al. [147] reported more sleep complaints in those with comorbid cardiopulmonary diseases and depression compared with those without associated medical disorders. Wilcox et al. [238] reported difficulty falling asleep in 31 % of patients with osteoarthritis and 66 % of those with chronic pain, whereas 81 % of patients with arthritis and 85 % with chronic pain complained of sleep-maintenance difficulty. There is an increasing prevalence of sleep-maintenance problems in patients with diabetes mellitus [239]. For information on medical disorders that cause sleep-disordered breathing, EDS, and other sleep disturbances, see Chap. 47. Treatment should be directed at the primary condition to alleviate secondary sleep disturbances.

Sleep Disturbances and Comorbid Psychiatric Illness

An important psychiatric illness that causes sleep disturbances in the elderly is depression [146, 216, 240–249], which should be carefully evaluated through a thorough psychiatric history. The condition is treatable, and misdiagnosis and prescription of hypnotics for insomnia would lead to a vicious cycle of worsening sleep complaints. An important sleep complaint in these patients is early morning awakening, resembling advanced sleep phase syndrome [240–242]. Untreated insomnia is also a strong predictor of depression [250]. Treating insomnia may also improve comorbid depression [251]. Anxiety disorders also cause sleep disturbances [243–245], and various psychotic disorders may cause both hypersomnolence and insomnia [242–245] (see Chap. 46).

Sleep Disturbances and Comorbid Neurodegenerative and Other Neurologic Disorders

Alzheimer's disease and related dementias in the elderly may cause sleep disturbances, including nocturnal confusional episodes (sundowning syndrome), which may require antipsychotic medication [250–253] (see Chap. 41). For information on other neurologic disorders causing sleep disturbances in the elderly, see Chap. 41).

Sleep Disturbances Associated with Drugs and Alcohol

A careful drug and alcohol history is important, as elderly individuals often take a variety of medications, including sedative hypnotics for associated medical conditions, and over-the-counter drugs to promote sleep [146, 149, 150, 171, 179, 216]. Sleeping medications produce secondary drug-related insomnia. Alcohol worsens sleep disturbances and may exacerbate existing SAS. Some examples of medications [149] that may cause insomnia include β blockers (probably by interfering with nocturnal melatonin secretion), bronchodilators, corticosteroids, decongestants (e.g., pseudoephedrine), and CNS stimulants (e.g., caffeine, theophylline), as well as drugs to treat gastroesophageal reflux (e.g., cimetidine), cardiovascular disorders (e.g., methyldopa, furosemide), neurologic diseases (e.g., phenytoin, modafinil, ritalin, amphetamines, dopaminergic drugs), and depression (e.g., bupropion, fluoxetine, venlafaxine, sertraline, paroxetine). Some antidepressants may cause sedation (e.g., nortriptyline, desipramine, amitriptyline, trazodone). Sedating medications should preferably be administered at bedtime and stimulating medications should be ingested during daytime hours.

Nocturia and Sleep Problems

The frequency of nocturia increases with age, and there is a significant association among nocturia, sleep-maintenance difficulty, bone fracture, and cardiovascular disease [254–258]. A recent study found an increased prevalence of EDS in elderly females with nocturia [259].

Narcolepsy

Narcolepsy (see Chap. 38) is a disease of earlier onset than old age, and the diagnosis will probably have been made much earlier, but it is a lifelong condition, and therefore, may be seen in older patients [260, 261]. The diagnosis rests on a history of sudden sleep attacks lasting a short time and associated with auxiliary symptoms such as cataplexy, hypnagogic hallucinations, and sleep paralysis. A history of narcoleptic sleep attacks and cataplexy is a strong indicator for diagnosis, but an all-night PSG study, followed by the Multiple Sleep Latency Test (MSLT), which will show reduced sleep-onset latency and sleep-onset REM (SOREM) in two of five recordings, is required for confirmation. (A SOREM within 15 min of sleep onset in previous nightly PSG may replace one of the SOREMs in the MSLT).

Restless Legs Syndrome

Restless legs syndrome (see Chap. 40) is primarily a lifelong condition, although it may be secondary to diabetic or uremic peripheral neuropathy. In addition to the characteristic features (five essential criteria) during quiescence and evening, nighttime sleep is severely disturbed. The prevalence increases with age, and the symptoms may occur initially in old age [262].

Parasomnias

The important parasomnias in the elderly are RBD, sleepwalking, and night terrors. The latter two conditions usually present in childhood or adolescence, but if they have a relatively sudden onset in an elderly person, an acute neurologic condition should be suspected and excluded by appropriate laboratory investigations [184]. RBD can be suspected from the history given by the bed partner and by simultaneous video-PSG evaluation at night (see Chap. 50 for a general discussion of parasomnias). RBD is frequently a preclinical manifestation of a neurodegenerative disorder, particularly synucleinopathies (e.g., Parkinson's disease, diffuse Lewy body dementia, and multiple system atrophy) in the elderly [263, 264].

Disorders of Circadian Function

Morgan et al. [265] reported that occasional sleep complaints are noted by 40 % of older individuals, and according to Garma et al. [266], older individuals complain of frequent and prolonged awakenings during the night. It has been speculated by Czeisler et al. [267] that these disorders may be due to changes in the human circadian pacemaker with advancing age. Work with light by Czeisler et al. [268, 269] showed that, with appropriately timed exposure to bright light, one can change the temperature cycle—that is, circadian phase—and may be able to correct the circadian sleep disorder. Further research is needed in this area.

In 1962, McGhie and Russell [168] reported that 15 % of older individuals complained of early morning awakenings, and in 1988 Mant and Eyland [270] reported that 33 % of elderly individuals woke up early in the morning several times a week. Sleep parameters thus show an advanced phase, which is also noted with other circadian markers such as activity rhythm, body temperature rhythm, and timing of REM sleep and the cortisol rhythm [267]. An advance in the

circadian phase due to a reduction in the endogenous period of the circadian pacemaker with advancing age is suggested by animal experiments [91, 271]. Human data for such studies are lacking, but a cross-sectional study by Weitzman's group [103] documented that the free-running period of the temperature rhythm was significantly shorter in six subjects aged 53–60 years than in six healthy young adults. A study by Czeisler et al. [268] suggested a strong relationship between period reduction and phase advance in the circadian rhythms of older people.

The pathophysiologic mechanism of these changes remains speculative. In 1972 [99, 272], a cluster of neurons was discovered in the anterior tip of the hypothalamus on either side of the third ventricle, the SCN. This is the circadian pacemaker. With advancing age, the volume of SCN cells shrinks—that is, the number of neurons decreases [273–275], which may result in functional impairment. Other factors may contribute to circadian dysrhythmia in the elderly [136, 150, 276]: gradual decrement of nocturnal endogenous melatonin secretion with age; and inadequate time spent in daylight, thus weakening exogenous cues (*Zeitgebers*) to entrain the circadian rhythm, causing sleep fragmentation and circadian dysrhythmia. In addition, weakening of the circadian and homeostatic mechanism in the elderly may explain age-related changes in sleep pattern and cognition [277, 278].

Laboratory Assessment

The diagnostic evaluation should begin with a thorough history of sleep disturbances, which may be EDS, difficulty initiating or maintaining sleep, and intrusions of unusual behavior during sleep. Physical examination may direct attention to systemic disease. Based on the history and findings of the physical examination, a decision should be made regarding referrals to specialized sleep centers for PSG and MSLT studies. Tests should be performed when clinical interview and examination cannot resolve the problems.

Most of the sleep disturbances of elders can be diagnosed by a careful history and physical examination. For some conditions, however, laboratory assessment is important. In SAS, it is important to have an all-night PSG study to quantify and determine the severity of sleep-related respiratory disturbances. Sleep apnea is a treatable condition, so it is important to make this diagnosis correctly. In addition, MSLT and PSG studies are important for a narcolepsy diagnosis, although in elderly people this diagnosis may have been made many years earlier. All-night video recordings are necessary to diagnose some conditions, such as RBD, that require the examiner to differentiate from among a number of sleep disorders with similar symptoms. Appropriate tests should be performed if other medical or neurologic disorders are suspected.

Treatment

The objective of treatment is to reduce the risk of mortality and morbidity and improve quality of life (Box 51.3) [279]. The first step is accurate assessment and diagnosis.

Box 51.3 Principles of Treatment of Sleep disturbances in the Elderly

- Initial step is an accurate assessment of diagnosis.
- Treat associated conditions causing or exacerbating sleep dysfunction.
- Treat primary sleep disorder according to standard medical practice (e.g., sleep apnea, insomnia, RLS-PLMS, RBD, advance sleep phase disorder).
- Consider altered pharmacokinetics and drug metabolism in the elderly (start with a small dose and gradually increase paying attention to drug–drug interactions).
- Pay special attention to lifestyle considerations, situational stress, and environmental situations.
- Encourage regular exercise (e.g., walking).
- Be aware of special situations in the elderly (e.g., confusional episodes, disorientation, and agitation) and treat accordingly.

Indications for Treatment of Obstructive Sleep Apnea

Indications for treatment of obstructive sleep apnea are reviewed briefly in this section; the reader is referred to Chaps. 32 and 34 for details. Obstructive sleep apnea is a major cause of hypersomnia in elders, and it is often a reversible condition if appropriately diagnosed and treated. For moderate-to-severe obstructive sleep apnea, treatment is recommended. Polysomnography should be able to decide the severity of the apnea when findings are considered with the AHI, the degree of oxygen saturation, and daytime sleepiness. Before instituting any specific treatment, certain general measures are recommended, including weight loss; smoking cessation; avoidance of alcohol, sedatives, and hypnotics before bedtime; avoidance of the supine sleep position; and management of nasopharyngeal disorders. The majority of patients respond to CPAP treatment. Weaver and Chasens [280] reviewed findings from clinical trials including CPAP therapy for older individuals. These studies clearly showed the benefit of CPAP therapy in an

older population, with improvement of cognition, memory, executive function, sleep quality, and cardiovascular function. CPAP treatment is well tolerated by older adults, and patterns of adherence are similar to those noted in younger adults. In general, older patients require lower CPAP titration pressure than younger patients, and this may be related to the physiologic differences in respiratory structure and function.

If all measures including CPAP fail, surgical procedures such as uvulopalatopharyngoplasty (UPP) may be appropriate, particularly if the site of obstruction is in the pharyngeal region. The success rate of UPP is variable. Tracheostomy, which is modified to keep the trachea closed during the day and open at night, has been an option in most severe cases. The primary criteria for recommending tracheostomy [175] include severe daytime symptoms that interfere with function, severe hypertension or dangerous cardiac arrhythmias, and an AI of 20 or greater or a decrease in oxygen saturation of more than 10 % below average baseline values. Tracheostomy is now rarely used and reserved for morbidly ill patients who cannot tolerate CPAP. In selected patients with a moderate degree of sleep apnea, oral appliances [281] have been tried with moderate success.

Indications for Treatment of Insomnia

Multiple factors are responsible for insomnia in elders, and, therefore, evaluation and treatment of insomnia should be multidisciplinary [179]. Elimination or avoidance of factors that are causing insomnia is the first step in treatment. The next important general measure is paying attention to sleep hygiene. See Chap. 37 for more information on the treatment of insomnia.

Insomnia is a very common complaint in the elderly and may be the result of a variety of medical or psychiatric conditions. Insomnia may also result from PLMS, or occasionally from sleep apnea. An important cause is pharmacologic agents (i.e., drugs and alcohol), so a careful history and physical examination are important before any treatment is instituted.

PLMS is an important condition in elders, but its incidence and natural history are unknown. Even the relationship between PLMS and insomnia is not clear. Therefore, any pharmacologic treatment for PLMS is subject to controversy, and the long-term effect of drug treatment on patients is unknown. For selected cases in which PLMS clearly disrupts sleep, therapy may be indicated (see Chap. 40).

Circadian rhythm disorder, another important cause of insomnia, results from changes in the daily routine or sleep pattern, shift work, or trans-meridian travel. Therefore, environmental control and adequate counseling should be the first line of treatment.

When a medical or psychiatric disorder causes insomnia, appropriate treatment should be directed toward the primary condition. In the case of depression, appropriate treatment with tricyclic antidepressants, often those with sedative effect (e.g., amitriptyline, doxepin, trazodone), or with selective serotonin reuptake inhibitors could be used to advantage.

Medical conditions such as cardiac failure, hyperthyroidism, respiratory disorders, arthritis and other painful conditions, and esophageal reflux syndrome should be treated appropriately. It should be remembered, however, that medications themselves may cause sleep disturbance.

For transient or temporary disturbances of sleep, short-term intermittent use of hypnotics and sedatives may be useful. Long-term use of hypnotics is not recommended (see Chap. 26). The National Institutes of Health State-of-the-Science Conference on Insomnia [282] concluded that there is no systematic evidence for the effectiveness of a variety of medications used to treat insomnia in the past and even now in the elderly (e.g., antihistamines, antidepressants, antipsychotics, anticonvulsants). The conference panel also warned about the risks of using these medications in the elderly. For chronic insomnia, nonpharmacologic treatment (see later and Chap. 37) is the mainstay of therapy.

Currently, the drugs of choice for treating insomnia in the elderly are the newer nonbenzodiazepine receptor agonists [149, 150, 283–287] (see Chap. 37). Before the advent of these agents, intermediate- and short-acting benzodiazepines were used to treat insomnia in the elderly [286, 288, 289] (see Chaps. 37, 55). The benzodiazepine group of drugs may have to be used even now in some patients if they fail to respond to the newer nonbenzodiazepine agonists or the recently approved Ramelteon, a melatonin agonist [290]. However, benzodiazepine hypnotics must be used conservatively and with caution in the elderly because of their adverse side effect profile, including next-day hangover effects with a risk of falls and fractures [291]. The specific type of insomnia (e.g., sleep-onset or sleep-maintenance insomnia) should be assessed first before determining the appropriate type of sleeping medication. The best agent for sleep-onset insomnia should be a short-acting, rapidly absorbing medication (e.g., zolpidem or zaleplon), whereas for sleep-maintenance insomnia an intermediate-acting hypnotic (e.g., zolpidem extended release, eszopiclone) is best [292, 293]. Zaleplon is an ultra-short-acting hypnotic that may be used at bedtime and again in the middle of the night if needed, but the patient must remain in bed for at least 4 h to avoid residual next-morning sedation. In an

open-label trial of long-term hypnotic therapy with zaleplon 5 and 10 mg, Ancoli-Israel et al. [293] found this to be safe and effective for insomnia treatment in older patients.

There is a relative lack of data regarding the use of nonbenzodiazepine receptor agonists in the elderly. In an earlier report, Reynolds et al. [294] reviewed 1082 patients in 23 randomized, double-blind trials in elderly patients with chronic insomnia and found scientific support for the short-term (up to 3 weeks) efficacy of zolpidem and triazolam in the elderly, as well as temazepam, flurazepam, and quazepam. Triazolam, an ultra-short-acting benzodiazepine hypnotic, has since been restricted by the US Food and Drug Administration and suspended in the UK because of serious behavioral disturbances. Dolder et al. [283] reviewed five drugs: zolpidem, zaleplon, eszopiclone, ramelteon, and zopiclone. Based on limited data, all these drugs are modestly effective and well tolerated for treatment of insomnia in older subjects [289, 292–294]. Comparative head-to-head trials of these drugs, however, are lacking.

Melatonin, an indoleamine secreted by the pineal gland at night, has received considerable attention as a hypnotic based mostly on anecdotal rather than scientific evidence. Garfinkel et al. [138] found melatonin to be superior to placebo in improving sleep efficiency in the elderly in a double-blind, placebo-controlled study. However, later studies did not find melatonin to be an effective hypnotic [282, 295]. In a subgroup of elderly insomniacs with a melatonin deficiency, Haimov et al. [296] found melatonin replacement therapy to be beneficial in the initiation and maintenance of sleep in these patients.

Special Pharmacologic Considerations

Vestal and Dawson [297] directed attention to the important factor of alterations of drug metabolism, with attendant changes in pharmacokinetics, in the elderly. It is important to start with a dose smaller than younger subjects require and then gradually to increase the dose, depending on the response. It is also extremely important to obtain a drug history, to prevent drug–drug interactions and exacerbation of sleep disturbances by hypnotics or other agents.

Situational and Lifestyle Considerations

Lifestyle factors are different for elders [216]. Retirement, with disturbance of the sleep–wake schedule (e.g., napping in the daytime and consequent inability to sleep at the scheduled nighttime); so-called empty nest syndrome that develops when children leave home; and bereavement over the death of a spouse or close friend may lead to loneliness and depression with attendant sleep disturbances. Other causes of sleep disturbances in the elderly include institutionalization, prolonged bed rest, poor sleep hygiene, unsatisfactory bed environment, poor dietary habits, and caffeine and alcohol consumption.

Treatment of Sleep Cycle Changes Related to Age

Treatment of sleep cycle changes related to age consists of educating the patient about sleep disruptions in old age, discouraging multiple naps, and urging participation in special interests and other activities and hobbies [150, 184].

For the treatment of circadian rhythm disorder in the elderly, bright light therapy is the treatment of choice [150] as light is the strongest cue for circadian sleep–wake cycle entrainment. In community-dwelling elderly patients and nursing home residents, evening exposure to light is found to delay circadian rhythms, correcting the advanced sleep phase state seen in the elderly [298]. Such patients are advised to avoid bright light in the morning and spend more time outdoors during late afternoon and early evening. Such light exposure outdoors or exposure to artificial light by a bright light box (5000–10,000 lx) not only may help correct the advanced circadian state in the elderly but also may improve sleep-maintenance insomnia in some subjects [298, 299].

Treatment of Situational Stress

Patients should be given supportive psychotherapy and behavior modification treatment, as well as clear explanations, to reduce stress and sleeplessness [184].

Treatment of Nocturnal Confusional Episodes

Nocturnal confusional episodes are characterized by disorientation, agitation, and wandering at night, and often result from acute or chronic organic neurologic dysfunction (see Chap. 41) [184, 300]. Relatively sudden onset of night terrors or sleepwalking indicates an organic brain disorder, and an appropriate investigation should be made. Nocturnal confusional episodes can be precipitated by other associated medical illnesses. The treatment should be directed toward the precipitating or causal factors for these confusional episodes. Often episodes are precipitated when the patient is transferred from home to an institution. As much as possible, the home environment of such patients should be preserved. The darkness of night often precipitates episodes, so a night light is helpful. A careful drug history should be obtained, and medications that are not absolutely necessary should be gradually reduced and eliminated. The use of hypnotics may further aggravate the condition. The treatment of choice is high-potency antipsychotics, such as haloperidol and thiothixene, in small doses [216, 300] or the newer antipsychotics (e.g., risperidone, olanzapine, quetiapine) [216, 300].

Treatment of Medication-Induced Sleep–Wakefulness Disturbances

Some medications cause insomnia, whereas others cause EDS. Elderly individuals often take a variety of medications because of the increased prevalence of other illnesses. Furthermore, because of their altered metabolism, they are susceptible to the side effects of various medications. The patient should avoid alcohol, caffeine, and cigarettes, and should gradually eliminate drugs that are not essential.

Special Environmental Considerations in Treatment

Treatment should be designed and tailored to different environmental situations (e.g., nursing home, hospital, home), as different types of sleep disturbances have been noted in different environments [54].

Exercise Program

Exercise, particularly 5–6 h before sleep, is thought to have a beneficial effect on sleep quality. However, there is a dearth of well-controlled studies. King et al. [301] found that older adults with moderate sleep complaints can improve self-rated sleep quality by initiating a regular, moderate-intensity, endurance exercise program. Sugaya et al. [302] reported an improvement of deep sleep and nocturia in 18 (60 %) of 30 men (average age 71 years) after walking rapidly for 30 min or longer in the evening for 8 weeks. Preliminary study findings by Gary and Lee [303] suggested that a progressive walking program may improve TST and quality of life in older women with diastolic heart failure. Some recent studies [304, 305] have confirmed previous observations that exercise exerts a beneficial effect on sleep irrespective of the timing (morning vs. evening) of the exercise in relation to bedtime.

Nonpharmacologic Treatment

Time-limited and sleep-focused nonpharmacologic interventions have been found to improve sleep in many chronic insomniacs [306–309] (see Chap. 37). The nonpharmacologic intervention consists of cognitive behavioral therapy, including stimulus control therapy, sleep restriction therapy, relaxation techniques, and sleep hygiene education. There are some limited studies combining nonpharmacologic interventions with pharmacotherapy to improve the quality of sleep [310–315], but none in elderly insomniacs.

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Evolution of Sleep from Birth to Adolescence and Sleep Disorders in Children

52

Timothy F. Hoban

Introduction

The maturational changes that occur in sleep between infancy and adolescence exhibit complex interrelationships with the other physical and developmental changes that occur as children grow older. For example, the nighttime sleep of young infants is necessarily interrupted by the frequent feedings required at this age. During adolescence, the frequently observed tendency toward delayed sleep phase can make morning waking difficult for teenagers whose classes begin at an early hour. The first part of this chapter examines the evolution of sleep from birth through adolescence and how age-related changes influence vulnerability to the common non-respiratory sleep disorders of childhood. The second part of this chapter reviews sleep-related breathing disorders in children, including obstructive sleep apnea, hypoventilation, upper airway resistance syndrome, and snoring.

The Evolution of Sleep from Birth Through Adolescence

Infant Sleep

For extremely premature infants, sleep and wakefulness do not always represent distinct or easily recognizable states. Behavioral assessment of these states becomes possible after 28 weeks of gestation, when infants begin to demonstrate episodes of spontaneous alerting and when gentle stimulation during apparent sleep results in several minutes of increased alertness and activity [1]. Longer periods of spontaneously sustained alertness become apparent by 32 weeks and are accompanied by crying or otherwise easily recognized by 36 weeks.

Electroencephalography (EEG) in premature infants does not clearly distinguish between wakefulness and sleep prior to 36 weeks of gestation [2]. By 36 and 38 weeks of gestation, periods of quiet behavioral sleep come to be characterized by *tracé alternant,* a distinctive EEG background in which bursts of high-amplitude slow waves lasting several seconds alternate with 3–15 s periods of lower amplitude fast frequencies. This activity represents the major EEG marker of *quiet sleep*, the infant equivalent of non-REM sleep. Quiet sleep is additionally characterized by regular respiration, regular heart rate, and a paucity of body movements.

The EEG activity of *active sleep*—infant REM sleep—resembles that of wakefulness in many respects. Both states are characterized by continuous, low-to-medium voltage background activity associated with less regular respiratory rhythm and increased variability of heart rate. The presence of rapid eye movements and low EMG tone during active sleep usually allows the polysomnographer to distinguish this state from wakefulness, but concurrent video or behavioral assessment is sometimes required for complete certainty. This is particularly true for infants of less than 37 weeks of gestation, whose inhibition of muscle tone during active sleep may be variable or incomplete [3].

Healthy infants who are born at term often sleep in excess of 16 h daily in the form of short sleep periods lasting 2–4 h which are initially equally distributed throughout the daytime and nighttime hours. The fragmented nature of sleep in the newborn infant is thought to be related to both the biologic necessity for frequent feedings at this age and to the fact that circadian regulatory mechanisms may not yet be sufficiently strong or well-entrained to sustain longer periods of nighttime sleep [4]. Although there is initially little day-to-day consistency in the timing and duration of sleep periods for most newborns, subtle changes in the length and organization of sleep periods begin within weeks after birth [5]. Over the span of several months, recurring

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environmental and social cues foster gradual lengthening and consolidation of nighttime sleep in a process known as *settling*. The majority of healthy infants achieve prolonged nighttime sleep periods—interrupted only briefly for feedings—by 3 months of age, but 10 % fail to achieve uninterrupted nighttime sleep during the first year of life [6].

As the first year of life progresses, daytime sleep diminishes and consolidates into several daily naps. Total duration of daily sleep declines to an average of 14.2 h at 6 months of age and 13.9 h at 1 year [7]. As napping and nighttime sleep achieve greater regularity, many families establish regular bedtime and naptime routines which provide cues and structure that supplement underlying circadian mechanisms in promoting transition to sleep. Nighttime feedings gradually diminish and disappear during the first year for most infants. Although nocturnal feedings are no longer a biological necessity for most healthy infants after 5–6 months of age, they may persist after that age as a learned habit for some [8]. Between 6 and 12 months of age, normal developmental milestones such as teething and separation anxiety have the potential to disrupt previously well-established sleep routines [9].

Persistent insomnia or chronically excessive night waking during infancy often occurs in the context of suboptimal sleep onset associations, where a child habitually settles to sleep while being fed, held, rocked, or having a parent present. Some children become so reliant upon these routines that they are unable to fall asleep or return to sleep without them. Treatment typically consists of parental education and extinction-based therapies designed to eliminate maladaptive sleep onset associations and provide infants with the opportunity to learn to fall asleep independently [10, 11].

Electroencephalography and polysomnography studies of infant sleep reveal profound differences in the character and organization of sleep compared to those of older children and adults. Within the first month of life, the tracé alternant pattern of quiet sleep evolves into more clearly recognizable non-REM patterns, including the high-amplitude delta activity of slow wave sleep [12]. Sleep spindles are first seen by about 4 weeks of age and are well developed by 6–8 weeks [8, 13]. K-complexes become evident by 6 months of age and demonstrate mature forms by 2 years [14].

REM sleep also evolves considerably during the first year of life. Newborns spend 50 % of total sleep time in REM sleep, declining to 40 % at 3–5 months and 30 % at 6–23 months [15, 16]. The question of whether the high proportion of REM sleep during infancy reflects any vital function remains unanswered, although it is postulated that the REM sleep may play an important role in brain maturation during early development [17, 18]. Newborns often enter sleep via an initial REM period, but by 3 months enter sleep through non-REM stages [8]. The recurring ultradian cycling of REM and non-REM states is shorter for infants (50–60 min) than for adults (90–100 min), and lengthens gradually through childhood and adolescence [15].

Sleep in Toddlers and Preschoolers

Sleep during the toddler and preschool years is characterized by further evolution of sleep duration and architecture. Total daily sleep duration declines from an average of 13.2 h at age two to 11.8 h at age four [7]. Daytime napping typically diminishes to a single nap during the second year of life, and most children outgrow regular naps after age three.

Sleep for toddlers and preschoolers is strongly influenced by the developmental and environmental factors. Intrinsic aspects of a child's temperament—particularly the ability to self-settle—may substantially affect the ease with which a child is able to fall asleep independently at bedtime or following nighttime waking [19]. Sleep may be transiently disturbed during the minor illnesses common at these ages or more persistently disrupted if well-established sleep routines and sleep schedule are suddenly changed.

Persistent bedtime struggles represent a common clinical problem in this age-group, affecting over 10 % of toddlers and preschoolers [20]. Bedtime resistance can take the form of crying, repeatedly leaving the bedroom, or engaging in other behaviors which delay or disrupt sleep onset. Lack of structured bedtime routines, irregular sleep habits, and inconsistent parental limit-setting at bedtime represents the most common predisposing influences and the primary focus of the structured behavioral interventions used for treatment in this age-group [21]. Cosleeping—sleeping with a parent or sibling—is also common in this population and associated with increased risk of both bedtime struggles and excessive night waking [22].

Polysomnography changes during these years are more modest and gradual compared to those seen during infancy. REM sleep declines to 20 % of total daytime sleep by age five, similar to older children and adults [16] Despite declines in REM sleep and total sleep time, the duration of non-REM sleep increases by about one hour daily between infancy and age three, with gradual reductions thereafter. PSGs of toddlers and preschoolers often exhibit lengthy and highly consolidated periods of slow wave sleep during the early portions of the night.

Sleep cycles in toddlers and preschoolers remain somewhat shorter than those of older children and adults, but overall sleep architecture rapidly assumes a mature pattern in which slow wave sleep is predominantly distributed during the first third of the night and REM sleep is more prominent in the last third. The temporal distribution of these sleep states is additionally reflected by the parasomnias often exhibited by toddlers and preschoolers. Sleep terrors,

confusional arousals, and other parasomnias arising from non-REM sleep tend to occur during the first hours of sleep, whereas nightmares—which arise from REM sleep—more often transpire during the latter hours of the child's habitual sleep period.

Sleep in Preadolescent Children

Overall sleep duration gradually declines for school-age, preadolescent children, from a mean of 11.4 h at five years of age to 9.3 h by age twelve [7]. Napping is uncommon for healthy children in this age range, and the presence of habitual napping is often an indication of insufficient nighttime sleep or an underlying sleep disorder. Declining sleep duration is associated with later bedtimes for most children as they grow older, but morning waking times often vary depending on the child's schedule for school and other activities [23].

Social, environmental, and developmental factors are integrally related to the most common clinical sleep problems encountered in this age-group. For many children, evening time activities such as homework, use of electronic devices, or athletic pursuits may be stimulating enough to delay bedtime or forestall sleep onset even if the regular bedtime can be maintained. Consumption of caffeinated beverages or use of sleep-influencing medications (e.g., antidepressants, stimulants prescribed for attention-deficit/hyperactivity disorder) can also disrupt sleep onset or continuity. Older children usually gain increasing autonomy with respect to bedtime and sleep schedule, commonly resulting in insufficient sleep for age and irregular sleep schedule. The clinical sequelae of insufficient or irregular sleep in preadolescent children often take the form of inattention, impaired school performance, or emotional/behavioral dysregulation rather than overt sleepiness [24]. Unfortunately, these daytime symptoms are often misattributed to causes other than the underlying sleep disorder, sometimes resulting in misdirected or suboptimal treatment.

There are limited data regarding the evolution of PSG findings for healthy preadolescent children. It is thought that the relative proportion of REM sleep remains fairly constant at 18.5 % to 20 % of total sleep time [16]. Although total non-REM sleep also remains relatively constant, slow wave sleep declines from 24 % of total sleep time for six- and seven-year-olds to 21 % for ten- and eleven-year-olds while stage 2 sleep increases from 47 to 52 % [25]. By ages ten and eleven, the average sleep cycle length of 87 min is close to that of mature sleepers.

Multiple sleep latency testing (MSLT) data for healthy school-age children reveal mean sleep latencies that are substantially higher than those for adolescents and adults, suggesting that preadolescents are normally less sleepy during daytime hours compared to teenagers and adults [26–28]. It has been postulated that this may represent one of the reasons why children with sleep disorders do not always "act sleepy" and are more likely to exhibit alternative daytime symptoms such as inattention, hyperactivity, or behavioral disturbances rather than frank somnolence.

Adolescent Sleep

Total sleep time declines further during adolescence, from a mean of 9.0 h at the age of thirteen years to 8.1 h by age sixteen in one large cohort [7]. Despite only gradual reduction in sleep duration during the adolescent years, mean sleep latency on the MSLT for healthy normals declines substantially during early adolescence and remains at a reduced level thereafter, suggesting that sleepiness and/or sleep need may increase during puberty [26, 29]. Reductions in mean sleep latency on the MSLT are more closely correlated with Tanner stage of sexual development than age, and detailed MSLT norms for children have been reported [26, 28].

Polysomnography findings evolve only modestly during adolescence. REM sleep remains constant at about 20 % of total sleep time [29, 30]. Slow wave sleep diminishes by 35 % during adolescence, balanced by proportionate increases in stage 2 sleep [26, 29]. Sleep cycling and overall sleep architecture otherwise approximate those of young adults.

Although a detailed review of sleep disorders affecting adolescents is beyond the scope of this chapter, several common sleep problems affecting this age-group merit brief discussion. Foremost among these is the well-recognized "night-owl" tendency toward delayed sleep phase affecting many adolescents and young adults [31]. While many teenagers successfully adapt their sleep times to meet the needs of their school schedule despite this tendency, others adapt less well and may experience difficulty falling asleep at their desired bedtime or waking up at the appropriate time in the morning. It is also common for adolescents to have longer sleep periods on non-school days—typically associated with delay of both bedtime and waking times—compared to the school day schedule [26, 29]. This irregularity of sleep schedule may contribute to clinically significant sleep disruption for some adolescents, particularly when the sleep schedule on non-school days reinforces an underlying phase delay which is often already problematic.

Mildly delayed sleep phase in adolescents sometimes responds to rigorous enforcement of the desired sleep schedule, including elimination of any daytime napping or "sleeping in" on non-school days. Severely delayed sleep phase is more effectively treated using chronotherapy, a treatment in which bedtime and waking time are delayed by

two or three hours on a daily basis until the desired sleep schedule is attained [32]. Although this treatment is safe, rapid, and non-pharmacologic, symptoms can quickly relapse if the target sleep schedule is not rigorously maintained for weeks to months.

It is also common for suboptimal sleep hygiene and other medical influences to negatively impact adolescent sleep. Teenagers typically have even greater autonomy in determining their sleep schedules than preadolescent children, whose bedtimes are more closely regulated by parents and caregivers. This often results in irregular sleep habits, habitually insufficient sleep, or otherwise suboptimal sleep hygiene. Evening time activities including reading, television or computer use, and use of portable electronic devices may be associated with decreased time in bed and higher levels of daytime tiredness [33, 34]. Consumption of caffeinated beverages—on average three times higher for adolescents than for preadolescents—may also disrupt sleep for some teenagers [35]. As is the case for younger children, prescription medications may disturb nighttime sleep or daytime alertness for adolescents. In addition, alcohol and drugs of abuse represent occasional but under-recognized causes of tiredness and sleep problems in this population [36].

Sleep-Disordered Breathing in Children

> It is not at all uncommon to find children who suffer from … enlargements of the lymphoid (tonsillar) tissues of the nasopharynx and fauces, described by their parents and teachers as backwards and stupid. … The fact, however, that children, the victims of nasal and pharyngeal obstructions, often suffer from headaches, especially when engaged in study, and frequently evince marked inability to fix their attention on their lessons or work for any length of time, has in recent years led many to suspect that these symptoms [are] in part a reflection of some evident hampering of the cerebral functions.
>
> —William Hill, B.Sc., M.B.Lond, 1889 [37]

History and Classification of Sleep-Disordered Breathing in Children

Astute observations regarding the clinical manifestations of sleep-disordered breathing (SDB) in children date from the late nineteenth century, as illustrated above. Sir William Osler eloquently reported: "At night, the child's sleep is greatly disturbed; the respirations are loud and snorting, and there are sometimes prolonged pauses, followed by deep noisy inspirations" [38]. It is thought that Charles Dickens may have provided a description of daytime somnolence secondary to SDB in the Posthumous Papers of the Pickwick Club, where the character Joe is depicted as an obese, red-faced, and perpetually sleepy child (Dickens Published in serial form, 1836–1837) [39].

Modern descriptions of childhood SDB date from 1965, with initial reports of reversible cor pulmonale in children with upper airway obstruction due to adenotonsillar enlargement [40]. **Obstructive sleep apnea** (OSA) affecting eight children between five and fourteen years of age was formally described by Guilleminault and colleagues in 1976 [41]. Subjects in this series had relatively severe disease—exhibiting 78–824 apneic episodes per night during PSG—with prominent daytime symptoms including headache, behavioral disturbances, poor school performance, hypertension, and excessive somnolence. This and subsequent reports initially characterized childhood OSA as consisting of episodic partial or complete airway obstruction resulting in hypoxemia, hypercapnia, or arousal from sleep similar to adult OSA (Figs. 52.1 and 52.2).

Over time, it was discovered that children with SDB often exhibit non-apneic respiratory disturbances during sleep, and it is currently thought that prolonged partial airway obstruction may represent the predominant form of respiratory disturbance for many children as opposed to discrete events such as apneas and hypopneas (Fig. 52.3) [42, 43]. **Obstructive hypoventilation** is characterized by prolonged partial obstruction resulting in diminished pulmonary ventilation causing hypercapnia and/or hypoxemia [44]. **Upper airway resistance syndrome** (UARS) represents a form of prolonged partial airway obstruction in which increased work of breathing disrupts the quality or continuity of sleep even in the absence of gas exchange abnormalities [45].

These varieties of sleep-related airway obstruction are not mutually exclusive, and it is common for children with obstructive SDB to exhibit elements of both chronic partial obstruction and "classic" OSA during PSG.

Sleep-disordered breathing in the absence of upper airway obstruction is substantially less common than obstructive SDB in children. **Non-obstructive hypoventilation** during sleep usually occurs in the context of diminished respiratory drive, weakness of the respiratory muscles, intrinsic lung disease, or a combination of these factors. Ventilation or gas exchange during sleep becomes insufficient to meet the body's needs, resulting in hypercapnia and/or hypoxemia. Predisposing conditions include disorders of the brainstem and cranial nerves (e.g., Chiari I malformation), cervical spinal cord injuries, neuromuscular disorders (e.g., Duchenne muscular dystrophy, myotonic dystrophy), and restrictive lung disease (e.g., severe scoliosis).

Congenital central hypoventilation syndrome (CCHS) is a distinct variety of non-obstructive hypoventilation that is usually present—but not always recognized—at birth. Affected children exhibit impaired ventilatory responses to hypercapnia and occasionally to hypoxemia [46]. As a

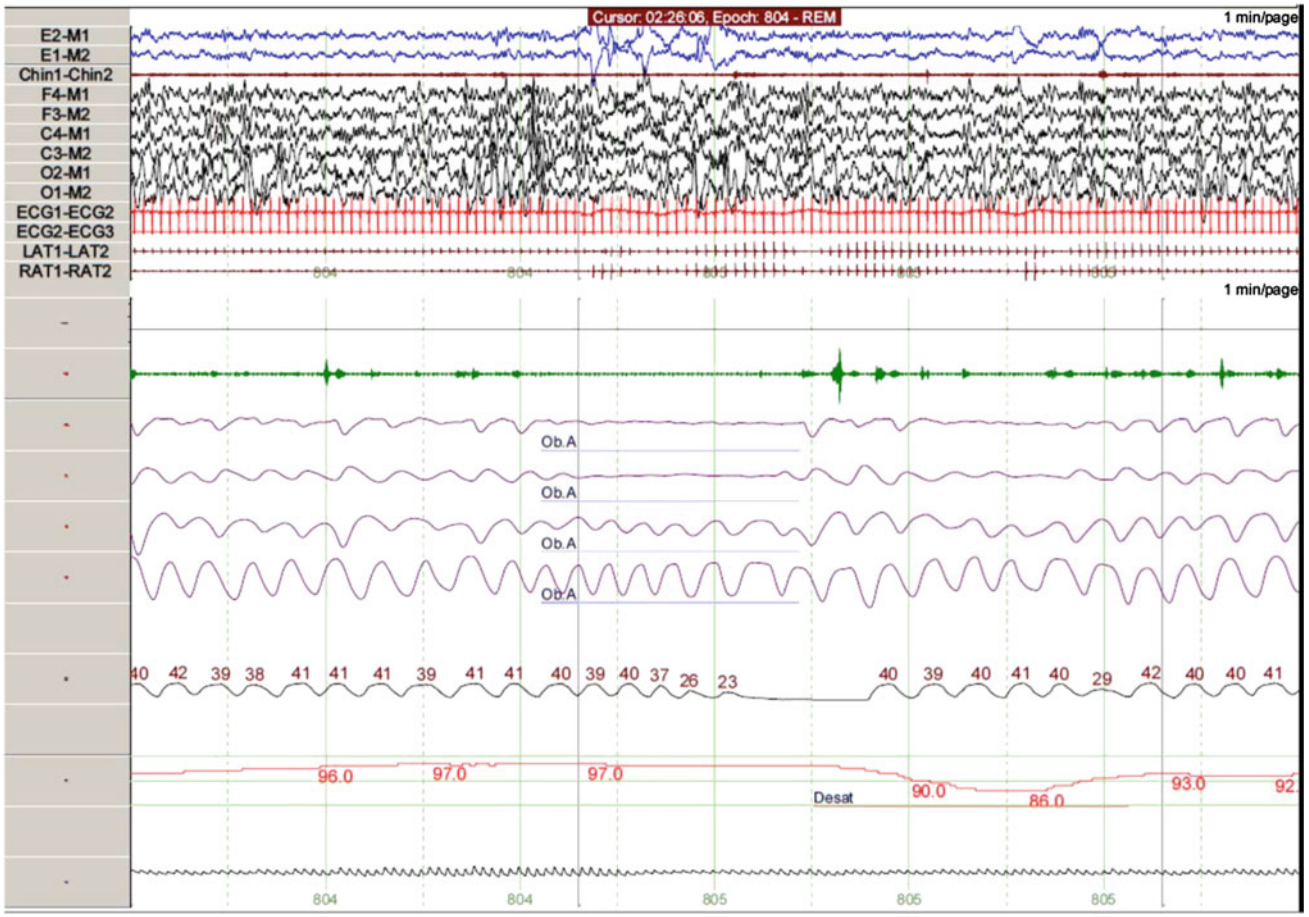

Fig. 52.1 Obstructive apnea during REM sleep (60 s PSG epoch). The event is characterized by cessation of nasal/oral (N/O) and nasal pressure (NPRE) airflow with preserved respiratory effort (THOR and ABD). Obstruction is associated with transient desaturation of SpO_2 from baseline. Note that cessation of flow on the capnogram is delayed compared to other measures of flow due to cannula transit time

result, ventilation during wakefulness may be normal or only modestly impaired, whereas ventilation during sleep is characterized by hypoventilation of a degree that may be life-threatening if the condition is not promptly identified and treated. Mutations of the PHOX2B gene have been identified in the majority of cases studied, and CCHS may be associated with Hirschsprung disease, neural crest tumors, and disturbances of cardiac autonomic regulation [47, 48]. Central hypoventilation syndromes are thought to be clinically and genetically heterogeneous, and late-onset forms with hypothalamic dysfunction have been described [49–51].

Central sleep apnea affecting children is identified most frequently in the context of **primary central sleep apnea of infancy**, formerly called apnea of prematurity. This condition is characterized by prolonged central apneas exceeding 20 s in duration or the presence of periodic breathing for greater than 5 % of total sleep time [52]. The central apneas that characterize this condition are sometimes accompanied by obstructive or mixed respiratory patterns as well. Primary sleep apnea in small or premature infants is thought to result primarily from dysmaturity of respiratory control mechanisms and usually improves with maturation. Apnea in infants may also occur as an associated manifestation of gastroesophageal reflux, infection, metabolic disturbance, upper airway obstruction, seizure, or other serious illness.

Clinically significant **central sleep apnea** is otherwise uncommon in children and has received scant scientific study. Brief central apneas are frequently observed during REM sleep or following arousals in otherwise healthy children, but seldom are accompanied by significant oxygen desaturation. Central apneas may also occur in the context of **periodic breathing**—recurring cycles of regular respiration interrupted by pauses lasting several seconds (Fig. 52.4). This stereotyped respiratory pattern is frequently observed in young infants, where it can be benign, and is occasionally seen in older children during sleep–wake transitions.

Primary snoring in children is defined as snoring which does not disrupt sleep, cause gas exchange abnormalities, or result in pathologic daytime symptoms [53]. Although this

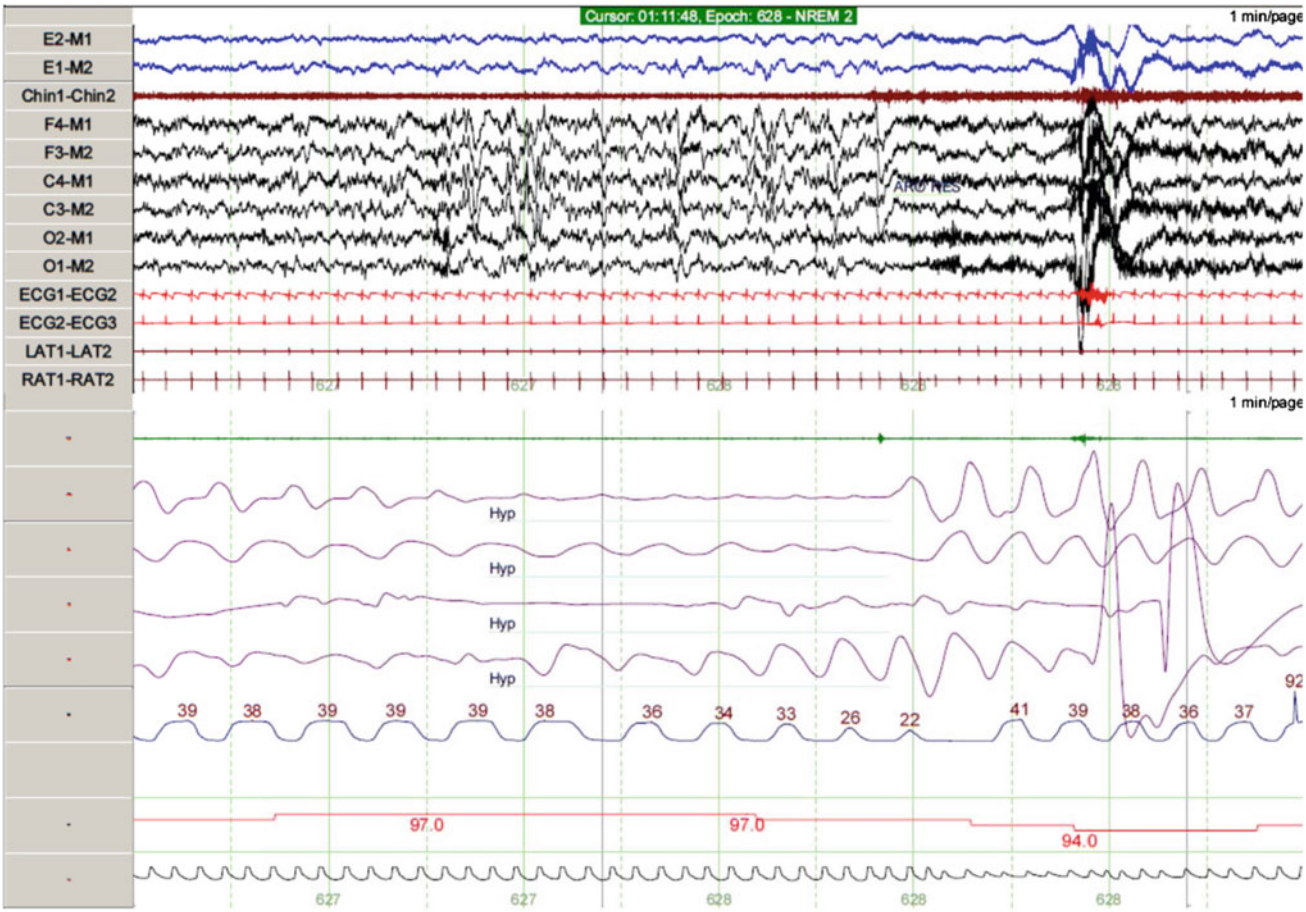

Fig. 52.2 Obstructive hypopnea (60 s PSG epoch). The event is characterized by diminished nasal pressure airflow (NPRE) and nasal–oral thermistor flow (N/O) associated with arousal and 3 % desaturation of SpO2 from baseline

condition by definition should not be associated with any secondary symptoms, subtle deficits in mood, behavior, and cognitive function have been reported in children with primary snoring compared to non-snoring controls [54–56]. It is thought that primary snoring may sometimes progress to more serious varieties of SDB. In one small series of children with PSG-documented primary snoring, 10 % were found to have developed OSA when reassessed 1–3 years later [57]. In a larger cohort, 37 % of school-age children with primary snoring had developed OSA at 4-year follow-up [58].

Epidemiology of Childhood SDB

Estimated prevalence rates for SDB in children remain imprecise because universally accepted diagnostic criteria for these conditions were only recently established and because large population-based studies using PSG have not been undertaken. It is estimated that between 5 and 12 % of children snore habitually, with some reports suggesting an increased risk of children exposed to tobacco smoke [59–63]. The prevalence of OSA in children is generally estimated to be 1–3 % [64–67].

Data are not available regarding the prevalence of UARS, central sleep apnea, and hypoventilation in children. CCHS is a rare disorder conservatively estimated to affect at least 300 children worldwide [46]. Prevalence for primary sleep apnea of infancy varies with size and gestational age. Symptomatic apnea of infancy affects 84 % of newborns weighing less than 1000 g, 25 % of newborns weighing less than 2500 g, and less than 0.5 % of term infants [52].

Clinical Features of Childhood SDB

The clinical manifestations of SDB in children (see also Chap. 32) differ from those exhibited by adults, as summarized in Table 52.1. Children with obstructive SDB tend to be noisy breathers during sleep, but severity may range from heroic snoring or stridor to only minimally loud respiration. Snoring may be continuous, intermittent, or vary with body

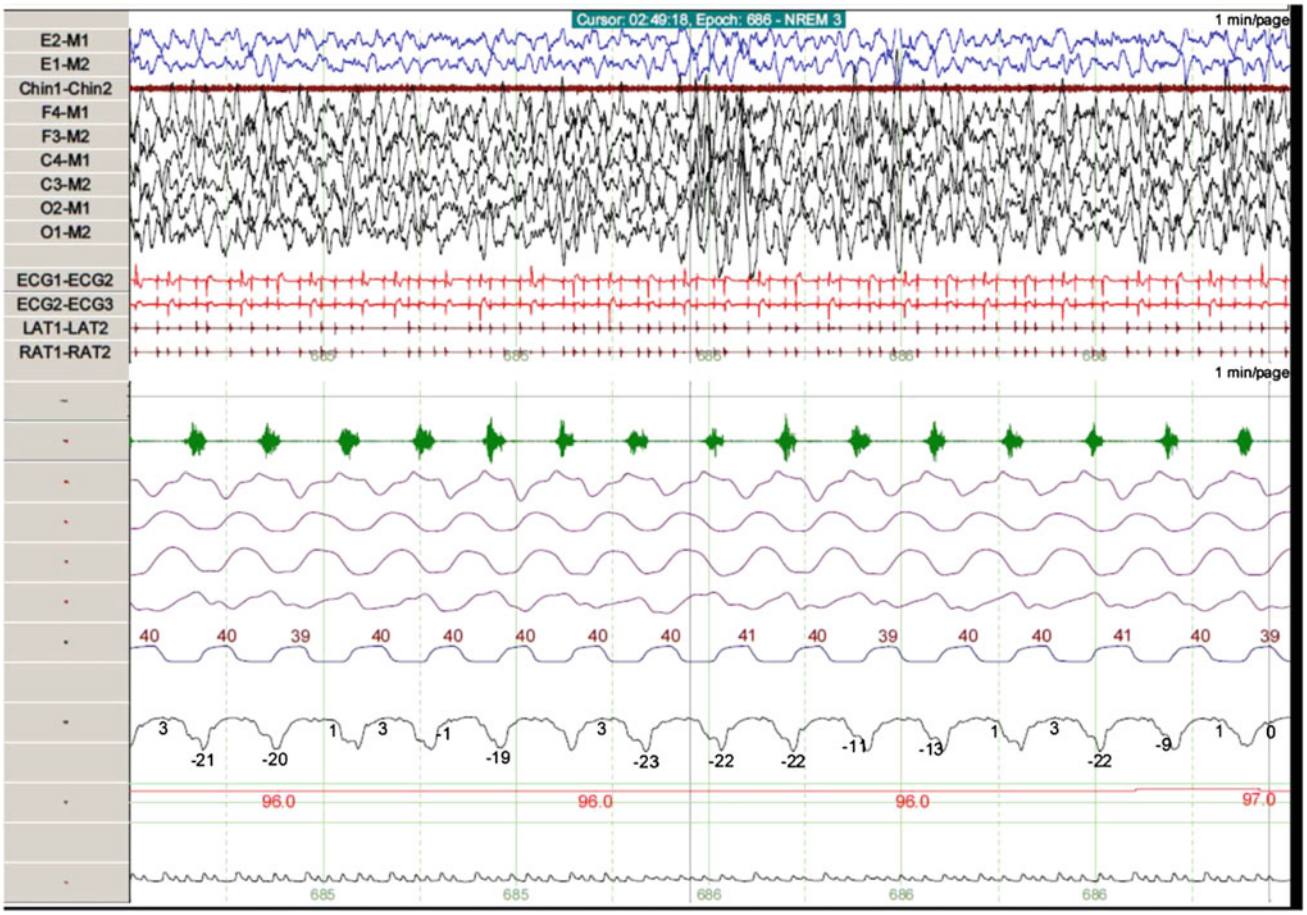

Fig. 52.3 Prolonged partial airway obstruction during stage N3 sleep (60 s epoch). Continuous snoring and excessively negative esophageal pressure fluctuations (measured peak-to-trough on ExPES with normal being 0 to −10 cm of water) indicate prolonged partial airway obstruction. *Note* normal oxygen saturation (SpO_2) and end-tidal CO_2 levels (CAPN) despite increased work of breathing

position. Snoring often worsens during upper respiratory infections or with exacerbations of allergic rhinitis and sometimes improves during treatment with decongestants or nasal steroids. Snoring in children with obstructive SDB is often accompanied by prominent mouth breathing and unusual sleeping positions such as neck hyperextension or excessive propping upon pillows, which represent compensatory mechanisms that may improve airway patency.

Witnessed apneas are only occasionally reported for children with obstructive SDB. This observation is consistent with the premise that prolonged partial airway obstruction during sleep is more common in children than the recurring episodes of brief obstruction followed by arousal that characterize typical adult OSA. When an obstructive apnea is witnessed in a child, parents may report paradoxical chest wall motion or the presence of snorting or gasping noises as respiration resumes.

Children with obstructive SDB demonstrate greater degrees of restlessness, enuresis, and perspiration during sleep than healthy controls [68]. Several reports additionally suggest that obstructive SDB may be associated with increased risk of parasomnias [69, 70].

In contrast to the prominent snoring and restlessness exhibited during the sleep of children with obstructive SDB, children with non-obstructive SDB tend to be quiet sleepers who only occasionally exhibit obvious respiratory symptoms at night. The lack of easily recognizable nighttime symptoms may lead to delays in diagnosis and treatment, particularly if sleepiness or other daytime symptoms are misattributed to other causes.

Children with obstructive SDB frequently exhibit sore throat, dry mouth, headache, or grogginess upon morning waking, although these symptoms are often transient and self-limited. Daytime mouth breathing is frequently seen in children with obstructive SDB, particularly when adenotonsillar hypertrophy is present [68]. Somnolence as a daytime symptom is seldom prominent in younger children unless their underlying SDB is severe [71]. When excessive somnolence is present, it is more often subtle or intermittent and sometimes evident only during sedentary activities such as riding in an automobile.

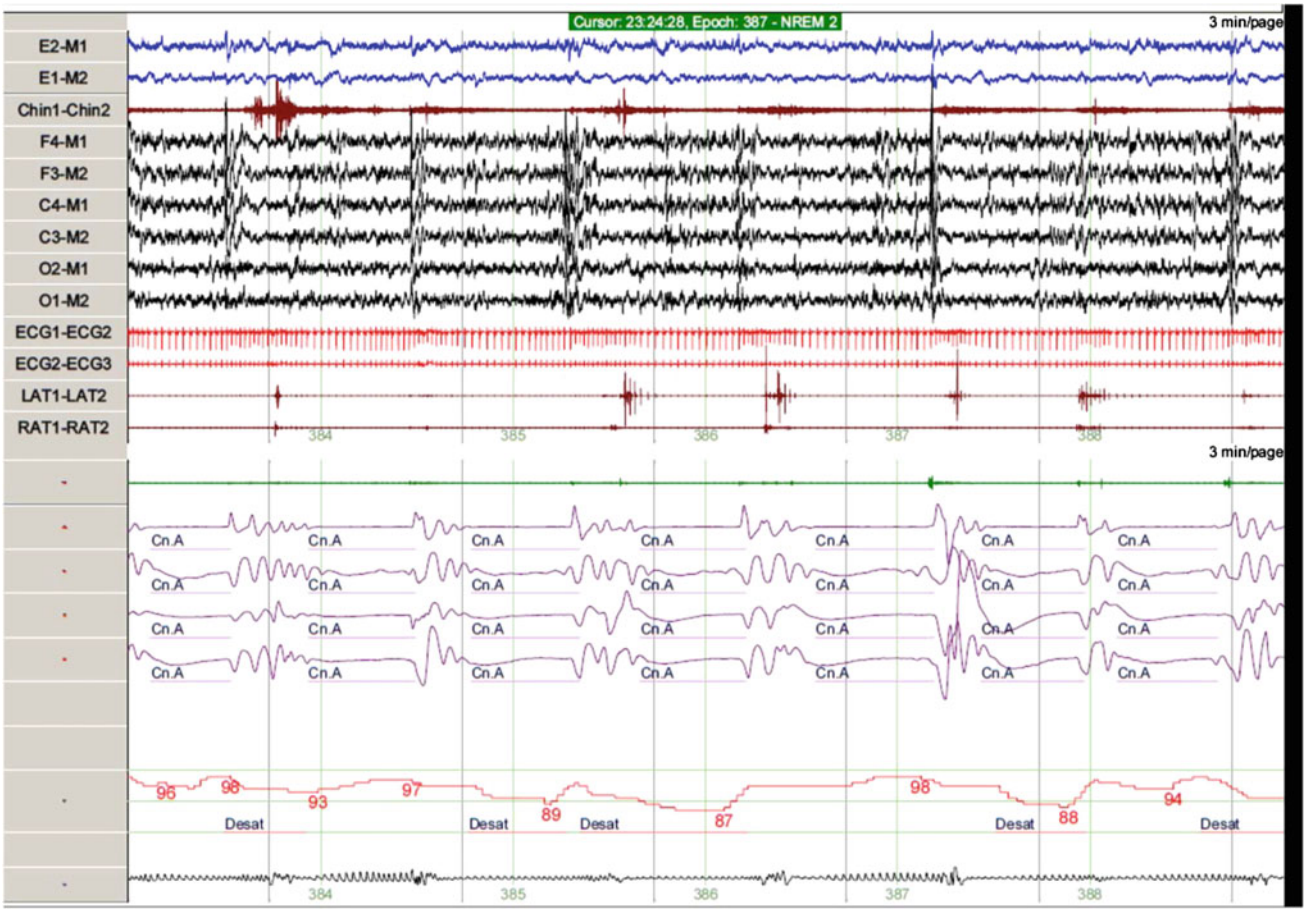

Fig. 52.4 Periodic respiration during stage N2 sleep (60 s epoch). Repetitive, stereotyped central apneas separated by several breaths (NPRE and N/O) are accompanied by cyclical desaturation of SpO_2 from baseline

Neurobehavioral deficits represent the most common and most variable daytime symptoms of childhood SDB. Early reports of childhood OSA, documenting relatively severe cases, identified a high prevalence of school problems, behavioral disturbances, and hyperactivity among affected children [41, 72, 73]. More recent reports have suggested that even less severe varieties of childhood SDB may be associated with the same daytime symptoms. Children with SDB have been reported to have higher rates of parentally reported behavior problems, lower scores on tests of sustained attention, and lower scores on neuropsychometric assessments of executive function [74–77]. Subtle neurocognitive deficits have also been reported for children with primary snoring [54, 76, 77, 78].

There is also compelling evidence that SDB is overrepresented in children with ADHD and learning problems. Snoring was reported to be three times as frequent among children with attention-deficit/hyperactivity disorder (ADHD) compared to non-ADHD controls drawn from general pediatric and child psychiatry clinics, with higher snoring scores being associated with greater levels of inattention and hyperactivity [79]. Among 297 first-grade children performing poorly in school, 54 (18 %) were found to have evidence of nocturnal hypoxemia or hypercapnia during limited, home-based sleep studies [80].

Physical Features Associated with Childhood SDB

The physical examination may be entirely normal in children with SDB, but predisposing anatomic features are often identified in affected children. Adenotonsillar enlargement, which is most common between 2 and 8 years of age, is associated with several physical findings [81]. In addition to visible tonsillar hypertrophy, "adenoid facies"—visible mouth breathing, pinched nose, and elongated facial appearance—is often observed. Narrow and high-arched hard palate, maxillary or mandibular hypoplasia, and macroglossia represent additional physical features which may predispose to SDB.

Table 52.1 Sleep-disordered breathing in children compared to adults

	Children	Adults
Physical characteristics		
Gender	Younger children: sexes equally affected Adolescents: males > females	Primarily males
Peak age	2–8 years	Middle age and older
Body weight	Usually normal, occasionally obese	Most often obese
Upper airway	Adenotonsillar enlargement frequent Redundant soft tissue occasional	Adenotonsillar enlargement occasional Redundant soft tissue frequent
Symptoms during sleep		
Snoring	Frequent, often continuous	Frequent, often interrupted by pauses
Witnessed apnea	Occasional	Frequent
PSG characteristics		
Obstruction	Prolonged partial obstruction > intermittent	Cyclical intermittent obstruction
Sleep architecture	Normal > fragmented	Frequent arousals with sleep fragmentation
Secondary symptoms		
Daytime sleepiness	Most often absent or intermittent	Frequent
Neurobehavioral	Inattention, hyperkinesis, disturbed behavior	Cognitive slowing
Cardiovascular	Hypertension, cor pulmonale	Hypertension, cor pulmonale, stroke

Obesity represents a risk factor for obstructive SDB in children, but this association is less robust in prepubertal children and more common during adolescence. In a group of 22 obese adolescents without sleep complaints, 10 (46 %) were reported to have abnormal PSGs [82]. Daytime sleepiness and AHI for this group both correlated with degree of obesity.

Some children with SDB—particularly infants and young children with severe airway obstruction—may present with decreased growth, low body weight, or failure-to-thrive [83, 84]. Treatment of these children may result in improved growth parameters and insulin-like growth factor 1 levels [85–87].

A variety of medical, genetic, and craniofacial conditions are associated with increased risk for SDB during childhood (Table 52.2). Detailed epidemiologic data are not available for most of these conditions; however, it is estimated that over 30 % of children with Down syndrome may exhibit SDB [88–91].

Secondary Sequelae of Childhood SDB

The long-term effects of childhood SDB are not well understood apart from limited data regarding cardiovascular effects. Reversible cor pulmonale and congestive heart failure have been reported in children with severe SDB [92–94]. In addition, electrocardiographic evidence of heart strain was reported for 3.3 % of 92 children referred for adenotonsillectomy [95]. The frequency with which hypertension affects children with SDB remains uncertain, but obesity and respiratory disturbance index (RDI) were found to be independently associated with increased blood pressure in a large cohort of 6- to 11-year-old children [96].

The public health impact of childhood SDB has also received little scrutiny. The extent to which affected children's neurobehavioral symptoms limit their long-term academic achievement and adult socioeconomic status has not been studied, although the effect is suspected to be substantial for at least some children with SDB. Perhaps the most dramatic evidence illustrating the public health impact of childhood SDB is data reporting substantially higher health care utilization for children with OSA compared to controls, including higher rates for hospitalization, medication use, and emergency department visits [97]. Treatment of OSA children with adenotonsillectomy resulted in a reduction of total annual health care costs by one-third, compared to no change for controls and untreated OSA children [98].

Clinical and Laboratory Assessment of Children with SDB

The assessment of a child with suspected SDB should begin with a detailed history and physical exam as outlined in

Table 52.2 Conditions associated with sleep-disordered breathing (SDB) in children

Craniofacial syndromes associated with maxillary or mandibular hypoplasia
Apert syndrome
Crouzon syndome
Goldenhar syndrome (hemifacial microsomia)
Hallermann-Streiff syndrome
Robin sequence (Pierre Robin syndrome)
Treacher Collins syndrome
Other syndromes with prominent craniofacial involvement
Achondroplasia
Klippel-Feil syndrome
Saethre-Chotzen syndrome
Velocardiofacial syndrome (Shprintzen syndrome)
Conditions associated with macroglossia
Beckwith-Wiedemann syndrome
Down syndrome
Hypothyroidism
Mucopolysaccharide storage disorders (Hunter, Hurler, and Scheie syndromes)
Conditions causing congenital upper airway abnormalities
Cleft palate
Choanal atresia
Fetal warfarin syndrome
Pfeiffer syndrome
Systemic neurological disorders
Structural lesions of the brainstem and medulla (eg, Chiari malformation)
Cranial neuropathies (eg, Fazio-Londe disease)
Neuromuscular disorders (eg, myasthenia gravis, Duchenne muscular dystrophy, myotonic dystrophy
Miscellaneous conditions
Prader–Willi syndrome

Table 52.3. The sleep history must thoroughly screen for the symptoms of SDB already discussed, but also should also include limited assessment for other sleep disorders whose clinical manifestations may mimic those of SDB. The medical history and physical examination should also include screening for other conditions that might cause or predispose toward SDB.

The history and physical examination are often supplemented by other assessment tools that are less expensive and more easily administered than PSG. A variety of standardized questionnaires have been developed with the goal of predicting whether sleepiness or SDB is likely to be present based on the presence and severity of specific symptoms. Questionnaires such as the Epworth Sleepiness Scale and Stanford Sleepiness scale are of limited usefulness in the assessment of children with suspected SDB due to limited validation data for this age-group and because the symptom that these measures assess—sleepiness—is often not obvious in affected children [99, 100]. Several questionnaires have been developed specifically for use in children, and limited validation data have been obtained regarding the use of the Pediatric Sleep Questionnaire and OSA-18 as screening tools for childhood SDB in clinical and research populations, [101–103]. The sensitivity of these tools for detection of SDB in clinical populations may be limited, however [104].

Although audio recordings of a child's snoring have long been recommended as a "$5.00 sleep study," this technique did not reliably distinguish primary snoring from SDB (AHI $\geq$ 5) in a blinded study assessing 29 snoring children [105]. Although home video recordings of a child's sleep are an easy and usually inexpensive supplement to the clinical history during evaluation of a child with suspected SDB, the sensitivity and specificity of this technique have not been rigorously assessed.

Overnight oximetry is not recommended for primary assessment of children with suspected SDB [106]. Although the technique is unobtrusive, inexpensive, and well tolerated by most children, it reliably detects SDB only when arterial

Table 52.3 Clinical assessment of the child with suspected sleep-disordered breathing (SDB)

Sleep history	Snoring: volume, frequency, character, changes over time Mouth breathing Unusual sleeping positions (eg, neck hyperextension, propping on pillows) Restlessness, limb movements Excessive perspiration Night waking: frequency, duration, and patterns Enuresis Symptoms upon waking: grogginess, headache, sore throat, dry mouth Sleep schedule Family history of SDB or other sleep disorders
Daytime symptoms	Mouth breathing Headache Behavior: irritability, distractibility, hyperkinesis, temperamental behavior School: attention, academic performance, decline in grades Sleepiness, especially in sedentary situations (e.g., automobile rides)
Medical history	ENT: adenotonsillar disease, allergic rhinitis, congenital anatomic abnormalities Endocrine: obesity, growth, thyroid disease Cardiovascular: hypertension, congenital heart disease Pulmonary: asthma, other intrinsic lung disease Neurologic: disorders affecting brainstem and cranial nerves or causing muscle weakness Development: developmental delay, infant failure-to-thrive Other: craniofacial disorders, genetic syndromes (eg, Prader–Willi Syndrome, Down Syndrome)
Physical examination	Vital signs: weight, height, body mass index, blood pressure, percentile ranks Oropharynx: tonsillar size, airway patency, palate, dentition, occlusion, tongue Nasopharynx: polyps, septal deviation, airflow, “pinched-nose” appearance Craniofacial: micrognathia, maxillary hypoplasia, occlusion, cleft palate, or other craniofacial syndrome Neck: thyroid, masses, circumference Thorax: cardiac exam, lung auscultation, evidence of scoliosis Neurologic: cranial nerve palsies, evidence of muscular weakness or neuropathy Behavior: attention, hyperkinesis, evidence of irritability or sleepiness Other: mouth breathing, noisy respiration, “adenoid facies”

oxygen desaturation is prominent and does not identify those children whose SDB is characterized primarily by hypercapnia or obstruction without desaturation. Among 210 children with PSG-documented OSA (AHI $\geq$ 1), 120 (57 %) had normal or inconclusive nocturnal oximetry, confirming that normal oximetry cannot be used to rule out SDB in children [107].

Other non-PSG diagnostic tests are used on selective basis for children with suspected SDB, primarily in children with predisposing conditions and children presenting with severe symptoms. Anatomic obstruction of the upper airway is often demonstrable on radiographic or endoscopic assessment [108, 109]. Children suspected to have severe SDB or concurrent cardiorespiratory problems sometimes require chest X-rays, electrocardiogram (ECG), echocardiogram, and formal pulmonary function testing for complete assessment. Children with prominent learning or behavioral problems usually benefit from neuropsychometric testing and age-appropriate behavioral assessment and intervention, even when such symptoms are secondary to SDB.

Polysomnography in Childhood SDB

Laboratory-based PSG represents the most sensitive and reliable tool presently available for the detection and classification of SDB in children. It is also a test that can be easily customized based on the clinical presentation of each patient. For example, 16-lead EEG can be added to standard PSG to provide increased sensitivity for the detection of interictal discharges or nocturnal seizures. Similarly, esophageal pressure monitoring (Pes) is sometimes performed for children felt to be at risk of UARS and other obstructive SDBs associated with prolonged partial airway obstruction.

PSG also has several limitations when used in children. The test itself is lengthy, expensive, and potentially stressful for both children and their parents. Laboratories having substantial experience in performing and interpreting PSG for children are limited in number and sometimes have lengthy waiting lists. Finally, routine PSG is not always sensitive for the detection of prolonged partial airway obstruction (e.g., UARS), but tools such as Pes make the

study more invasive and are not available in all pediatric sleep laboratories.

PSG should be performed when a child's symptoms, medical history, and physical examination suggest significant risk of clinically significant SDB. Isolated snoring—especially when it is only soft and occasional—is seldom a sufficient indication for PSG unless other symptoms or risk factors are also present. Practice guidelines that address respiratory indications for PSG in children have recently been issued by the American Academy of Sleep Medicine [106, 110]. Although it is common for otolaryngologists to perform adenotonsillectomy for suspected SDB without preoperative PSG, the safety and cost-effectiveness of this practice have been vigorously debated [111–113]. In addition, this practice can potentially result in children with noisy respiration, but no clinically significant SDB having surgery for which the overall health benefit is uncertain. Until validated practice guidelines address these issues, the author's practice is to apply the same standards presently used for adults: to obtain a baseline PSG for patients with clinically suspected SDB before decisions are made with respect to treatment.

PSG in children is performed in a manner comparable to adult studies, utilizing frontal, central, and occipital EEG channels, electrooculogram (EOG), and ECG, as well as chin and limb electromyogram (EMG). Respiratory monitoring at minimum includes oral and nasal airflow, chest and abdominal movement, arterial oxygen saturation, and measures of carbon dioxide (end-tidal and/or transcutaneous). Most laboratories use nasal pressure transducers—thought to be sensitive to flow limitation and subtle decrements in flow—to assess nasal airflow, but since many children breathe through their mouths, thermistor, or thermocouple sensors to monitor oral or oral–nasal flow remain necessary as well.

Many sleep laboratories have the capability to supplement standard recording techniques with additional modes of respiratory monitoring when clinically indicated. Pes may be added to improve the sensitivity of PSG for partial airway obstruction and increased work of breathing. Pes is minimally invasive—requiring insertion of a thin catheter through the nasopharynx into the esophagus—but the technique has negligible impact upon children's sleep and is the most sensitive method presently available for the measurement of increased upper airway resistance [114, 115]. Several less invasive techniques for the assessment of partial airway obstruction have been investigated for use in children, including *pulse transit time*, *peripheral arterial tonometry*, *respiratory cycle-related EEG changes*, and *intercostal EMG monitoring*, but none of these techniques are yet available for routine clinical use [116–121].

Scoring of sleep stages, movements, and arousals during pediatric PSG is performed in the same manner used for adult studies. Thirty-second epochs are reviewed and scored manually using standard criteria recently revised by the American Academy of Sleep Medicine [122–124]. Scoring of respiratory events for children differs slightly from that for adults. Whereas scoring of apneas, hypopneas, and respiratory effort-related arousals (RERAs) requires a minimum event duration of 10 s in adult studies, scoring of these events for pediatric studies requires only that the event last at least the duration of 2 missed breaths. This rule permits scoring of brief events in children whose baseline respiratory rate during sleep exceeds 12 breaths per minute.

Standards for interpreting the results of pediatric PSG have evolved over time. Normative PSG data for 50 healthy, asymptomatic children between 1 and 18 years of age were reported in 1992, as summarized in Table 52.4 [125]. Although these data have helped define the statistical limits of normality in healthy children, the point at which abnormal PSG parameters become associated with pathologic symptoms and outcomes has not been precisely determined. An AHI exceeding 5 events per hour is generally considered to be abnormal for adults. Although this threshold had previously been used for the diagnosis of OSA in children, the fact that children frequently demonstrate symptomatic OSA with AHIs below 5 has long suggested that a lower threshold is more appropriate for children [55, 56].

The current *International Classification of Sleep Disorders, Third edition (ICSD-3),* criteria for the diagnosis of pediatric OSA require the presence of one or more scorable obstructive events per hour of sleep or documentation of obstructive hypoventilation in conjunction with other clinical and PSG findings as outlined in Table 52.5 [52]. These revised criteria now permit many children who previously would have been classified as having nocturnal hypoventilation or UARS to be classified as having OSA. Further

Table 52.4 Polysomnographic (PSG) parameters in 50 healthy children aged 1–18 years

PSG parameter	Mean ± SD
Apnea index (events/hour)	0.1 ± 0.5
Minimum SaO_2 (%)	96 ± 2
Desaturations ≥4 % (per hour of total sleep time)	0.3 ± 0.7
Maximum $ETCO_2$ (mm Hg)	46 ± 4
Duration of hypoventilation (ETCO2 > 45 mm Hg) (percentage of total sleep time)	7 ± 19 %

Adapted from Marcus et al. [125]

Table 52.5 ICSD-3 criteria for pediatric obstructive sleep apnea

Criteria A and B must both be satisfied:
A. The presence of one or more of the following symptoms:
1. Snoring
2. Obstructed, labored, or paradoxical respiration during sleep
3. Hyperactivity, disturbed behavior, learning problems, or sleepiness
B. PSG demonstrates one or both of the following findings:
1. One or more obstructive apneas, hypopneas, or mixed apneas per hour of sleepOR
2. The presence of obstructive hypoventilation ($\geq$ 25 % of total sleep time spent with PCO_2 > 50 mm Hg) associated with one or more of the following findings:
a. Snoring
b. Flattening/ flow restriction of the inspiratory nasal pressure waveform
c. Paradoxical thoraco-abdominal effort

Adapted from The International Classification of Sleep Disorders, Third Edition [52]

outcomes-based research remains necessary to better define the thresholds at which abnormal respiratory parameters on PSG become associated with clinically significant sequelae.

ICSD-3 did not specify separate pediatric criteria for non-obstructive forms of hypoventilation, with the partial exception of congenital central hypoventilation syndrome, a genetically mediated condition secondary to mutations of the PHOX2B gene which typically presents during infancy [52]. Current American Academy of Sleep Medicine, PSG, scoring rules define sleep-related hypoventilation for children as consisting of PCO_2 levels exceeding 50 mm Hg for greater than 25 % of total sleep time [123] (Fig. 52.5).

Diagnostic criteria for UARS in children were not addressed in ICSD-3, although proposed criteria have been published elsewhere [55].

Treatment of SDB in Children

Adenotonsillectomy is the most commonly administered treatment for obstructive SDB in children [126]. Although this procedure is thought to be effective in alleviating upper airway obstruction for many symptomatic children, the frequency with which adenotonsillectomy "cures" SDB in children is variable.

Early case series assessing response of childhood OSA to adenotonsillectomy reported surgical cure rates exceeding 70 %; however, these studies were limited by substantial variability in patient selection and frequent use of adult rather than pediatric PSG criteria to define OSA [127, 128].

More recent studies have reported variable and sometimes lower operative success rates. Among one group of 110 children with OSA (AHI > 1, mean AHI 22.3), complete postoperative normalization of the AHI was observed in only 27 subjects (25 %) [129]. In another large cohort of successively seen children with OSA (AHI > 1), 94 of 199 subjects (47 %) demonstrated abnormal polysomnograms postoperatively [130]. Among 397 children with OSA enrolled in a large, randomized, multicenter trial, PSG findings normalized in 79 % of children treated with adenotonsillectomy compared to 46 % of those assigned to watchful waiting and supportive care [131]. These and other studies suggest that children with high Mallampati scores, high preoperative AHI, obesity, or atypical anatomy of the upper airway may be at elevated risk of residual SDB following adenotonsillectomy.

In addition to improvements in obstructive symptoms and PSG parameters, adenotonsillectomy for children with SDB may also be associated with tangible improvements in behavior, school performance, and quality of life measures [132–134]. In one large cohort of children assessed before and after clinically indicated adenotonsillectomy, half of the children having ADHD prior to surgery no longer qualified for the diagnosis when reassessed one year postoperatively [117, 118].

The potential clinical benefits of adenotonsillectomy in children with OSA should be considered with due attention to the possible complications of the procedure. Postoperative hemorrhage may occur in up to 8 % of pediatric patients [135]. Reports documenting the frequency of postoperative respiratory complications range from 0 to 27 % of children, with greatest risk of children who are young (especially less than age 2), exhibit high baseline AHIs, or have associated craniofacial or medical problems [136–138]. Children who fall into these high-risk groups benefit from close or prolonged cardiorespiratory monitoring in the immediate postoperative period.

Follow-up for children treated via adenotonsillectomy should commence with a postoperative clinical assessment. Repeat PSG is usually indicated for children who have residual symptoms postoperatively or whose OSA was severe prior to surgery. Delayed recurrence of SDB following childhood adenotonsillectomy has been reported, with recurrence in 20 of 40 children reassessed one year postoperatively in one report and in 3 of 13 patients reassessed during adolescence in another series [139, 140].

Nasal CPAP (continuous positive airway pressure) represents the most common non-surgical treatment for childhood SDB. Although children with adenotonsillar hypertrophy are most often treated via adenotonsillectomy,

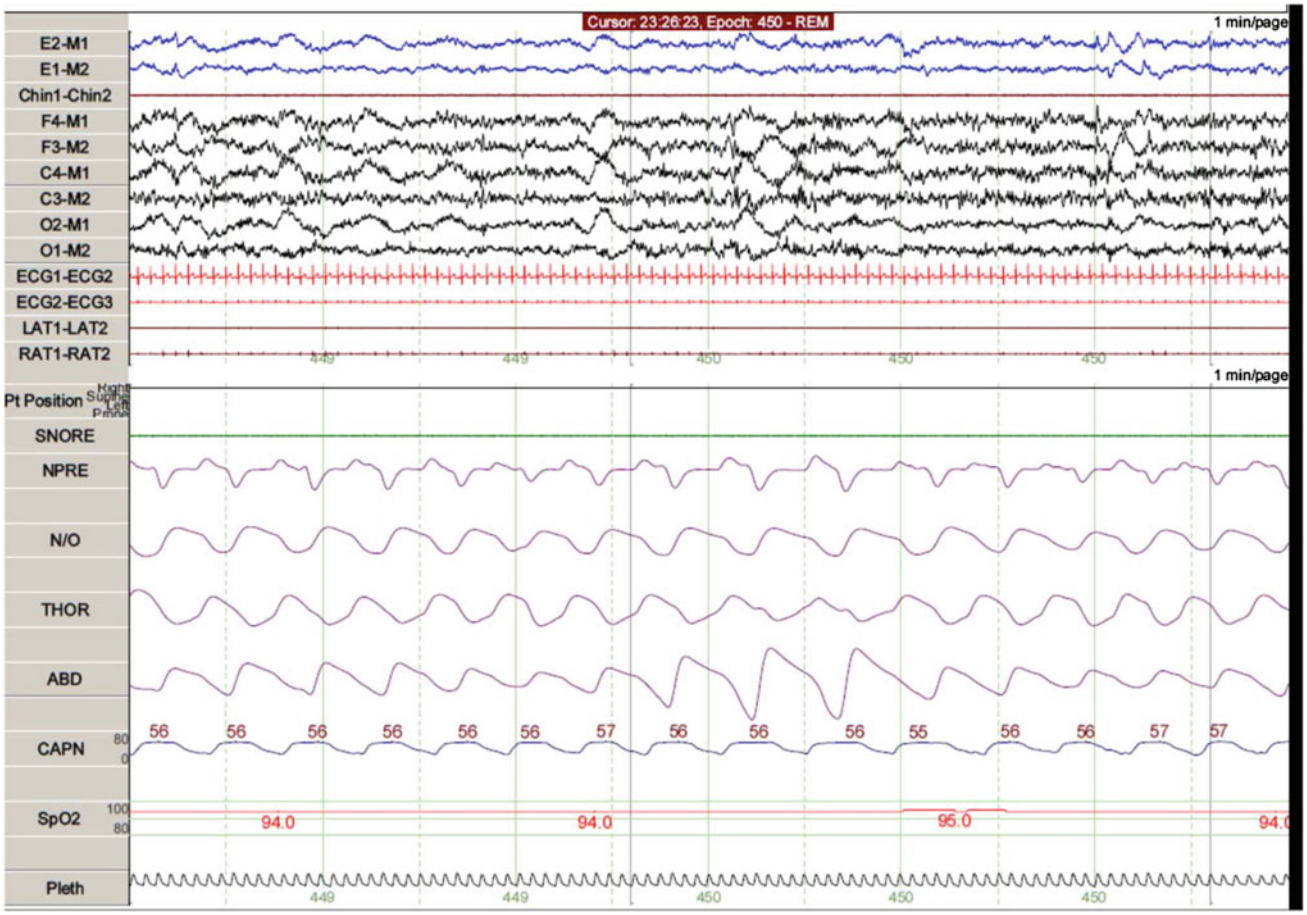

Fig. 52.5 Sleep-related hypoventilation (60 s epoch). Capnography (CAPN) demonstrates persistent elevations of end-tidal CO_2 above 50 mm Hg during REM sleep in the absence of desaturation and scorable respiratory events. Paradoxical respiratory effort is demonstrated in the thoracic (THOR) and abdominal (ABD) effort channels

CPAP represents the most common treatment for children with obstructive disease who are not appropriate candidates for adenotonsillectomy, for children whose obstruction persists despite adenotonsillectomy, and for children having non-obstructive varieties of SDB. CPAP has not been formally approved by the US Food and Drug Administration for use in children weighing less than 30 kg, but is nonetheless generally considered to be a first-line treatment for pediatric SDB, with reports of successful use in hundreds of children [65]. CPAP in children may be customized using a variety of interfaces, including nasal pillows, nasal or oral–nasal masks, and total face masks.

Effective use of CPAP as treatment for obstructive SDB has been reported in children of all ages (Table 52.6), although data are limited regarding long-term compliance and outcomes for the pediatric population. Side effects are generally mild, most often consisting of skin irritation, mask leak, or pressure sores, which are easily remedied by improving mask fit. Nasal dryness or congestion often improves with addition of a heated humidifier. Central apnea may occasionally complicate treatment with CPAP, particularly at higher pressure settings. Serious side effects are uncommon, but isolated cases of pneumothorax have been reported in children with concomitant neuromuscular disorders [141, 142]. Mid-face hypoplasia has been also been reported as a rare complication of long-term therapy [102, 103].

A child's compliance with the use of CPAP is influenced by several important factors. Disabled children who are unable to easily remove the CPAP mask will sometimes tolerate nasal CPAP once acclimated. Typically developing children and adolescents who are old enough to understand and accept the need for CPAP are also likely to achieve consistent long-term use. Compliance is most challenging for younger or disabled children who are able to remove their mask independently, for typically developing children who actively resist CPAP use, and for families who are

Table 52.6 Major pediatric reports assessing CPAP in the treatment of sleep-disordered breathing

Study	Population	Successful use	Effective pressures
[161]	94 patients Age: infants to 19 years OSA: PSG-documented, not otherwise defined	Successful: 86 % Unsuccessful: 1 % Non-compliant: 13 %	Median 8 cm H_2O (range 4–20 cm H_2O)
[162]	74 patients Age: infants 2–12 months SBD: AHI > 5 or abnormal Pes	Successful: 97 % Unsuccessful: 3 %	Not reported
[163]	80 patients Age: 12 days to 15 years (mean 5.7 ± 0.5 y) SDB: AHI generally >10	Successful: 86 % Unsuccessful: 14 %	Mean 7.9 ± 3.2 cm H_2O (range 4–16 cm H_2O)
[164]	24 patients Age: infants 1–51 weeks OSA: obstructive and mixed apnea index >5	Successful: 75 % Unsuccessful: 25 %	Range 4–6 cm H_2O
[165]	18 patients Age: children <2 years SDB: Average AHI 12.8 ± 20	Successful: 78 % Unsuccessful: 22 %	Mean 7.6 cm H_2O (range 6–11 cm H_2O)
[143]	66 patients Age: infants to 19 years SDB: Obstructive apnea index ≥5 or desaturation index (10 s < 90 %) ≥4	Successful: 67 % Unsuccessful: 33 %	Mean 8.5 ± 3.2 cm H_2O (range 4–16 cm H_2O)
[166]	79 patients Age: 6 months to 18 years OSA: AHI > 1	Successful: 82 % Unsuccessful: 18 %	Mean 6.8 ± 1.9 cm H_2O
[167]	29 patients Age: 2–16 years OSA: Obstructive AHI ≥ 5, SpO_2 nadir ≤85 %, or hypoventilation	Successful: 72 % Unsuccessful: 28 %	CPAP: mean 8 ± 3 cm H_2O BiPAP: inspiratory mean 11 ± 4 cm H_2O, expiratory mean 5 ± 3 cm H_2O
[168]	27 patients Age: 7–19 years OSA: AHI ≥ 5 or abnormal SaO_2/$ETCO_2$	Adherent: 70 % Non-adherent: 30 %	Mean 8.8 ± 2.1 cm H_2O
[169]	13 obese adolescents Age: 10–16 years OSA: mean obstructive AHI 9.3 (non-adherent), 10.0 (adherent)	Adherent: 46 % Non-adherent: 54 %	CPAP: mean 10.0 ± 2.7 cm H_2O (non-adherent); 9.2 ± 2.2 cm H_2O (adherent)
[170]	56 children, primarily obese Age: 2–16 years OSA: PSG-documented, mean AHI 19 ± 16	CPAP used ≥50 % of nights during first month, mean duration of nightly use 3 ± 3 h	CPAP: mean 8 ± 2 cm H_2O; BiPAP: mean 13 ± 3/7 ± 2 cm H_2O

unable to consistently incorporate CPAP into their child's bedtime routine. Sustained parental effort or age-appropriate desensitization programs with experienced providers can sometimes help these children achieve consistent use [143].

Data regarding use of CPAP for treatment of non-obstructive SDB are extremely limited, addressing small numbers of patients. Standard or bilevel CPAP may be effective in the treatment of hypoventilation, with most reports focusing on children with CCHS [144–146].

Alternative Surgical Treatments for Childhood SDB

Other surgical treatments besides adenotonsillectomy are only occasionally performed in children. **Septoplasty** and **turbinectomy** can sometimes alleviate non-adenoidal nasal obstruction. **Uvulopalatopharyngoplasty** (UPPP) is sometimes performed for children with low-lying soft palates or redundant lateral pharyngeal tissue. Despite reports of

clinical improvement in several small series of children treated with UPPP, efficacy as determined by PSG measures is not well established for the procedure [147, 148]. Soft tissue procedures such as **lingual tonsillectomy** and lingual reduction surgery have not been formally studied in children. **Radiofrequency ablation** procedures involving the tongue base and soft palate are rarely undertaken in children. Ablation procedures entail risk of potential complications including abscess, neuralgia, and mucosal sloughing [149].

For children having significant micrognathia, maxillary hypoplasia, or other craniofacial deformity, skeletal surgeries have the potential to improve upper airway obstruction. Mandibular reconstruction techniques used in children include **distraction osteogenesis** and, for older children, **mandibular advancement** via sagittal osteotomy [150]. For children with maxillary hypoplasia, **Lefort advancement** procedures can correct cosmetic deformity and sometimes alleviate nasopharyngeal obstruction. These procedures should only be considered in the context of significant skeletal deformity, since effectiveness for the purpose of treating childhood SDB has not been rigorously assessed.

Tracheostomy for treatment of childhood SDB is performed only when the underlying condition is severe and refractory to conventional therapy. The procedure is highly effective in alleviating upper airway obstruction but carries significant trade-offs in the form of ongoing stoma care, increased risk of infection or bacterial colonization involving the respiratory tract, and adverse impact upon overall quality of life [151, 152]. Because of these trade-offs, aggressive use of CPAP and skeletal or soft tissue surgery has been advocated to reduce reliance upon tracheostomy [153].

Alternative Medical Treatments for Childhood SDB

Supplemental oxygen has a limited role in the treatment of childhood SDB and is used most often for children who have failed first-line therapies or who have underlying pulmonary disease [154]. A randomized, double-blind study assessing the response of children with OSA to oxygen at one liter per minute reported modest improvements in oxygen saturation but no change in the frequency or severity of apnea [53]. In addition, two of 23 patients became significantly hypercapnic with treatment, consistent with the premise that some children may rely upon hypoxic respiratory drive during sleep to maintain adequate ventilation [65]. For this reason, and also because many varieties of SDB disrupt sleep and produce secondary symptoms even in the absence of hypoxemia, this therapy should be used cautiously and with due recognition of its limitations.

Respiratory stimulants are used frequently in the treatment of apnea of infancy but are seldom used and largely unstudied outside of this context. Methylxanthine agents—most frequently theophylline and caffeine—produce short-term improvement of infant apnea and reduce the need for mechanical ventilation, but their impact upon long-term outcome is unknown [155]. Acetazolamide is occasionally used for the treatment of central sleep apnea in children as well, although optimal dosing and long-term effectiveness have not been established [156].

Oral appliances are seldom used for the treatment of childhood SDB due to concerns that this therapy could result in orthodontic problems. **Positional therapy**—affixing a small ball to the back of patients' pajamas or nightclothes to prevent them from comfortably assuming a supine position—is sometimes recommended for children with OSA when obstructive symptoms are problematic primarily in that position. Although this technique has been reported to improve the AHI for adults with OSA, no pediatric trials have been undertaken [157].

Some reports suggest that the use of **nasal steroids** may be associated with improvements in the AHI for children with obstructive SDB. Trials of budesonide in children with OSA reported improvement of mean AHI from 5.2 to 3.2 following 4 weeks of treatment in one uncontrolled series and reduction in AHI from 8.4 to 1.2 following 6 weeks of treatment in another [158, 159]. In a randomized, placebo-controlled trial, 6 weeks of treatment using fluticasone propionate was associated with reduction in the obstructive AHI from 10.7 to 5.8 for children with OSA versus an increase in the placebo group. Because the post-treatment AHIs in these reports are often still abnormal as determined by current pediatric criteria for the diagnosis of OSA (AHI $\geq$ 1), and because no long-term studies have been performed, nasal steroids cannot yet be routinely recommended as a primary treatment for children with SDB. **Systemic steroids** have been found to be ineffective in treating OSA in children with adenotonsillar hypertrophy [160].

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Sleep and Sleep Disorders in Women

53

Helen S. Driver and Eileen P. Sloan

The Menstrual Cycle and the Effects on Sleep

Hormonal and Sleep-Related Changes Across the Menstrual Cycle

Cyclical changes in four reproductive hormones—luteinizing hormone (LH), follicle-stimulating hormone (FSH), estrogen, and progesterone—and in body temperature occur in a normal, ovulatory menstrual cycle. The cycle lasts 28 days on average (Fig. 53.1) but may range from 25 to 35 days. When menstruation starts (day 1), levels of all four key reproductive hormones are low. As FSH and estrogen rise, ovarian follicles develop and mature. This follicular phase precedes ovulation and may vary in length. LH peaks about 16 h prior to ovulation, and the appearance of LH in urine is a reliable marker of ovulation. At ovulation, an oocyte is released from the follicle. The corpus luteum then evolves from the ruptured follicle and secretes progesterone and estrogen during the luteal phase. If ovulation occurs, body temperature, measured at the same time every morning, increases by about 0.4 °C; this effect is mediated by progesterone [1–3]. In the absence of pregnancy, about 7 days after ovulation, the corpus luteum degenerates and hormone production begins to decline. The luteal phase lasts 14–16 days. Most negative menstrual symptoms are experienced as hormone concentrations decline toward the end of the luteal phase and during the first days of menstruation.

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Subjective Reports of Sleep Across the Menstrual Cycle

Normally, subjective sleep quality is reduced both premenstrually and at menstruation [4–6]. Retrospective surveys have found that 16–32 % of women report increased fatigue, difficulty in concentrating, or lethargy in the premenstrual period [1, 7–9]. A telephone survey of 514 women for the National Sleep Foundation (NSF) in 1998 found that approximately 70 % of women report that their sleep is adversely affected on average 2½ days every month by menstrual symptoms such as cramps, bloating, tender breasts, and headaches [10].

Increased sleep disturbance around menstruation has been confirmed in some, but not all, prospective studies [4–6]. In a study of 32 women who kept daily diaries across two menstrual cycles, although there was no change in sleep duration in the late luteal compared to the mid-follicular phase, sleep disturbances increased, with poorer sleep quality. In the premenstrual period, sleep onset was delayed and there was an increased number of awakenings [5]. In contrast, there was no change in sleep quality or sleep duration in 30 young women with normal menstrual cycles [6]. In our study based on daily self-reports across one menstrual cycle, ovulation was confirmed in 26 young women without significant menstrual-associated complaints, sleep quality was reduced in the 3–6 premenstrual days and during the first 4 days of menstruation [4]. These studies, and other reviews [1, 7–9], highlight the challenges

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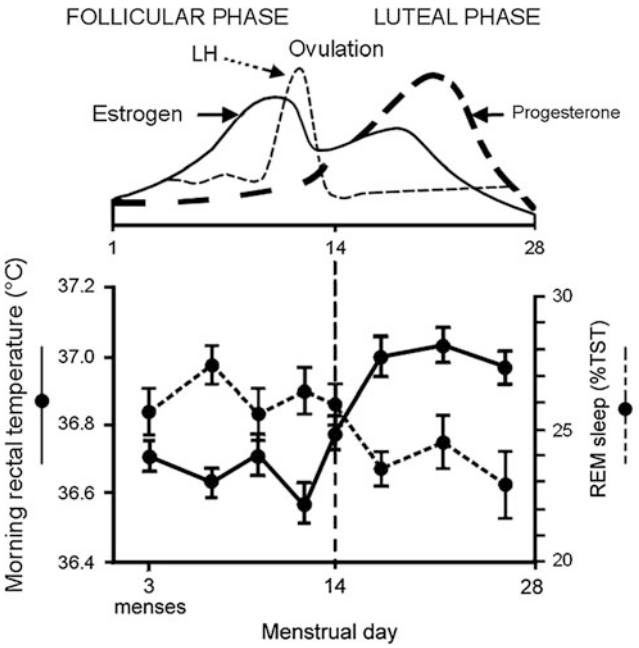

Fig. 53.1 Menstrual cycle changes across a 28-day ovulatory cycle. The day menstruation begins is generally considered the first day of the menstrual cycle, and ovulation occurs around day 14. *Top* The profile for luteinizing hormone (*LH*), which peaks before ovulation (*dotted line*), and the ovarian hormones estrogen and progesterone. *Bottom* Morning core body temperature (*solid line*, axis on the *left*) and REM sleep as a percentage of total sleep time (TST; *dashed line*, axis on the *right*) (Modified from Driver et al. [2] and Driver and Baker [1])

inherent in studying menstrual cycle effects, including variability in cycle length, the presence of ovulation, individual and cycle-to-cycle differences, changes with age, and the frequency of data sampling. Given the cyclical, though modest, reduction in sleep quality around the time of menstruation in women without sleep complaints, assessment of insomnia in naturally cycling women should consider the temporal relationship of sleep complaints and the phase of the menstrual cycle.

Polysomnographic Studies Across the Menstrual Cycle

Early laboratory studies were based on small sample sizes, usually in young women (<30 years of age), with heterogeneous groups including those with affective symptoms or those taking oral contraceptives (OCs), often without verification that ovulation had occurred [1, 7, 9]. Two studies addressed these issues [2, 11] by conducting more frequent recordings, at 3 nights per week [11] and every other night [2], in nonsymptomatic good sleepers with verified ovulatory cycles. These polysomnographic (PSG) studies included spectral analysis of the sleep electroencephalogram (EEG) and core body temperature measurements. Both studies revealed an increase in sleep spindle frequency [2, 11] in the mid- to late-luteal phase compared with the follicular phase. This effect on sleep spindles was reflected in a menstrual-associated variation in stage 2 sleep (higher in the luteal phase). Increased stage 2 sleep in the luteal phase compared to the follicular phase was also reported by Shechter and colleagues [12] who recorded sleep every third night in the laboratory in five healthy women and seven women with premenstrual dysphoric disorder (PMDD). This luteal phase increase in stage 2 and sleep spindle power may represent an interaction between endogenous progesterone metabolites and γ-aminobutyric acid (GABA) type A membrane receptors [2]. However, in a group of 16 healthy women and 18 women with severe premenstrual syndrome (PMS), Baker et al. [13] found no correlation between EEG sigma (12 to <15 Hz) power (i.e., sleep spindle frequency) and progesterone based on one night laboratory recording in the mid-follicular and the late-luteal phase.

No significant effect of menstrual cycle phase on slow-wave sleep (SWS, now N3) [2, 11–14] or EEG slow-wave spectral activity [2] has been reported suggesting that sleep homeostatic mechanisms are not altered by menstrual phase. With the higher nocturnal temperature of the luteal phase, rapid eye movement (REM) sleep is slightly reduced [2, 3, 14] particularly in the early-luteal compared to the early-follicular phase [12], with shorter REM sleep episodes in the first 3–4 cycles if not the whole night [13, 15]. No significant menstrual phase effect on sleep latency or sleep efficiency based on PSG has been reported. The few controlled PSG studies in young women with no menstrual-associated complaints show that sleep across the menstrual cycle is remarkably stable, aside from variation in sleep spindles and subjectively disturbed sleep in the premenstrual and menstrual periods [1–4, 7–9, 11].

Oral Contraceptives and Their Effect on Sleep

OCs are used by approximately 100 million women worldwide [16, 17], yet few studies have examined their effects on sleep. Studies are complicated by different levels of synthetic estrogen and progestin within the various OCs, which are available as monophasic and triphasic pills [16, 17]. OCs contain synthetic estrogen and/or progestin that prevent ovulation by suppressing endogenous reproductive hormones. While the progestin is responsible for the contraceptive effects, the estrogen component is included for cycle control, and ethinyl estradiol is a potent suppressor of pituitary gonadotropins. Side effects are reported by about half of the women who start taking OCs [17]. Among the most commonly reported are weight gain, painful periods, swollen legs, and heavy menstrual bleeding; a change in sleep is not a commonly reported side effect [16, 17].

Women taking monophasic combination OCs, which provide the same dosage of hormones through the entire 21-day active cycle followed by 7 days of inactive placebo, had persistently raised body temperatures when taking either the active OC or the placebo [3]. This increase in temperature with OCs has also been reported in a study of circadian rhythms during 24 h of sleep deprivation with 8 women in the follicular phase, 9 in the luteal phase, and 8 who were taking OCs (pseudo-luteal phase) in an environment free of time cues using a modified constant routine procedure [18]. There was also an increase in melatonin levels in the OC group when compared to the women studied in the follicular phase [18]. Women taking OCs had significantly more stage 2 sleep in the active phase of the OC compared to the placebo, and more stage 2 compared to the naturally cycling women in both menstrual cycle phases [3]. OC users also had less SWS than naturally cycling women in the luteal phase [3]. A reduction in SWS with OC use was reported based on an archival analysis that compared women diagnosed with major depressive disorder and healthy controls, although menstrual phase or type of contraceptive was not controlled [19]. Reduced REM latency has also been reported in healthy women taking OCs [19], but OC use does not affect sleep efficiency [3, 19] or subjective sleep quality [3].

On balance, because OC effects on sleep appear modest, for women with premenstrual and menstrual symptoms as described in the next sections, attenuation of pain and mood symptoms by OCs may improve sleep.

Premenstrual-Related Effects on Sleep: Premenstrual Syndrome and Premenstrual Dysphoric Disorder

Starting from puberty and lasting until menopause, women are at twice the lifetime risk of developing major depression as are men [20, 21]. Approximately 60 % of women experience mild premenstrual symptoms, referred to as premenstrual syndrome (PMS), but for 3–8 % of women, the cyclical pattern of symptoms is severe enough to be diagnosed as premenstrual dysphoric disorder (PMDD) [21]. Common symptoms that occur in the last week of the luteal phase and lessen after the onset of menstruation include irritability/anger, anxiety/tension, depression and mood swings, change in appetite, bloating, weight gain, fatigue, and problems with sleep [22]. Complicating the comparison of studies of sleep in premenstrual mood disturbance is the fact that definitions and severity of symptoms vary considerably as do the duration of symptoms [21, 23, 24]. Sleep disturbances include problems falling or staying asleep, hypersomnia, unpleasant dreams, wakening during the night, failure to wake at the expected time, and tiredness in the morning. Women with PMS perceive their sleep to be poor in the symptomatic phase with a decline in subjective ratings of sleep quality [13], with more unpleasant dreams [25]. These women report tossing and turning, frequent awakenings, and taking a long time to fall back asleep after an awakening during the night. Perhaps as a consequence of the disturbed sleep, or reflecting an underlying need for more sleep, women with severe PMS have increased daytime sleepiness [25–29]. Subjectively poorer sleep quality in women with severe PMS has been related to anxiety indicating the relationship of mood with sleep quality ratings [13].

Laboratory studies in symptomatic women have yielded conflicting findings, and only a small number of women have been studied [24]. There are reports of significantly more stage 2 sleep [14, 27] and less SWS [14] or more SWS [2, 12] and less REM sleep [27] compared to asymptomatic women in both phases of the menstrual cycle. Other studies show no objective change in sleep [28]. The finding of increased SWS (N3) in women with PMS/PMDD compared to controls while sleep efficiency was unaltered has been associated with psychological state [2] and with reduced nocturnal melatonin secretion [12] suggesting changes in homeostatic and circadian processes.

Women with increased severity of premenstrual symptoms have been found to have an increase in luteal phase daytime sleepiness [5]. In a study by Lamarche et al. [29], 10 women with significant emotional/behavioral premenstrual symptoms when compared with 9 women with minimal symptoms (mean age 26 years) were more sleepy and less alert in the late luteal phase than in the follicular phase. No menstrual phase change in sleepiness was found in the women with minimal symptoms. Women with more severe symptoms were significantly sleepier and less alert than women with minimal symptoms during the late luteal phase but not the follicular phase of the cycle. Using a midafternoon 40-min nap intervention, there were no group differences in sleep-onset latency, with both groups falling asleep within an average of 7 min. The short sleep-onset latency found for both groups of women suggests a high sleep need during the late luteal phase regardless of symptom severity, but may also be indicative of chronic sleep restriction in this age group.

Changes in nocturnal temperature rhythms and melatonin secretion suggest that women with PMDD have underlying circadian rhythm abnormalities that could impact sleep [20]. As reviewed by Baker et al. [24] in the symptomatic (luteal) phase, women with PMDD tend to have higher nocturnal temperatures and decreased melatonin secretion than normal controls; compared to their follicular phase, women with PMDD have delayed and decreased melatonin secretion. Therapeutic mood benefit has been reported by Parry et al. [30] from 1 night of partial sleep deprivation (4 h of sleep,

either 9:00 P.M. to 1:00 A.M. or 3:00 A.M. to 7:00 A.M.), with further improvements reported after a subsequent recovery night of sleep (11:00 P.M. to 7:00 A.M.). Initial findings indicate that appropriately timed light therapy may be a treatment strategy for PMDD, reducing depression, irritability, and physical premenstrual symptoms compared to a placebo condition. Thirty minutes of light therapy in the evening for 2 weeks during the luteal phase resulted in a significant improvement in premenstrual symptoms in women with PMS compared to baseline levels [31]. Larger trials with light therapy in this population are needed.

Painful Menstrual Conditions: Dysmenorrhea and Endometriosis

As many as 50 % of women suffer from dysmenorrhea and experience extremely painful cramps during menstruation, the pain is very severe in approximately 10–25 % of women [24, 32]. Similarly, women with endometriosis—who have misplaced uterine (endometrial) tissue in the abdominal and pelvic area—suffer extreme menstrual pain. Not surprisingly, these women report poorer sleep quality and higher anxiety during menstruation compared to symptom-free women.

Baker et al. [33] found that dysmenorrheic women had more disturbed sleep and subjective sleepiness than controls. Their sleep efficiency was reduced when experiencing menstrual pain, with increased wakefulness, movement, and stage 1 sleep compared with pain-free phases of their cycle. In a subsequent study of 10 women with primary dysmenorrhea, when experiencing menstrual pain, sleep efficiency was reduced with less REM sleep, and more stage 1 sleep during the night compared with a pain-free mid-follicular phase of their menstrual cycle [34]. Women with dysmenorrhea (like those with PMS/PMDD) had decreased REM sleep and increased core temperature during the luteal and menstrual phases compared to normal controls. Although progesterone concentrations in the luteal phase were similar to those in asymptomatic women, dysmenorrheic women had elevated morning estrogen levels in the follicular and luteal phase and higher prolactin levels in the luteal phase [21, 33]. Prostaglandins have been implicated as the mediators of the pain of primary dysmenorrhea, with the most common pharmacologic treatment for dysmenorrhea being nonsteroidal anti-inflammatory drugs (NSAID) [35]. Indeed, when dysmenorrheic pain was treated with the NSAID diclofenac potassium, given as two doses of 50 mg during the day and a 50 mg dose in the evening before bedtime, menstrual pain was attenuated and both objective and subjective sleep quality was restored with increased sleep efficiency and REM sleep compared to placebo [34].

Fibromyalgia (FM) and Functional Somatic Syndromes

Fibromyalgia is more common in women than in men, as are the other chronically widespread and regional painful, multi-symptom syndromes: irritable bowel syndrome, chronic pelvic pain, low back pain, temporomandibular joint disorder, and tension-type headache [36]. These conditions are sometimes referred to as functional somatic syndromes when pain hypersensitivity and stress-immune dysregulation are evident with emotional arousal and physiologic activation but no clear pathologic indicators [36]. With FM, painful regions and tender points have been associated with poorer sleep and increased alpha EEG [36, 37]. Complaints of pain and insomnia are more prevalent in women than in men, though little is known about the physiologic and behavioral mechanisms involved [37]. In chronic pain conditions, objective PSG measures show lighter and less consolidated sleep, possibly with more arousals, but no specific marker aside from a characteristic alpha EEG (7.5- to 11-Hz) intrusion into non-REM delta sleep (alpha-delta sleep, ADS); in patients with fibromyalgia, ADS was first described in 1975 by Moldofsky and colleagues [38]. However, not all studies have found differences in objectively measured sleep parameters. A recent study of female adolescents (n = 10, aged 16 years) with juvenile primary fibromyalgia syndrome revealed poorer sleep efficiency, more arousals/awakenings, and more ADS (70.3 % of total SWS versus 21.9 % SWS) than controls [39]. In the adolescent women, completion of a multidisciplinary pain treatment program over approximately 4 weeks that included intensive exercise therapy, improved pain, disability, and subjective sleep quality, but neither ADS nor other objective measurements of sleep quality changed after treatment [39]. Combining data from two randomized placebo-controlled double-blind trials of pregabalin (Lyrica®) for the management of FM in adults (n = 748 and 745, 95 % females, mean age 50 years), in addition to pain relief, improvements in subjective sleep quality and the severity of sleep disturbance compared to placebo showed clinically important differences [40].

Fibromyalgia has also been associated with a high prevalence of inspiratory flow limitation [41]. Conceivably, cortical arousability in response to increased upper airway resistance (UAR) may be reflected as increased EEG frequency and sleep fragmentation, causing more somatic

symptoms than those more commonly associated with obstructive sleep apnea (OSA), namely excessive daytime sleepiness and snoring.

Polycystic Ovarian Syndrome

Women with polycystic ovary syndrome (PCOS), a condition of irregular or anovulatory menstrual cycles, increased androgen production, and metabolic consequences related to insulin resistance and weight gain [42, 43], are more likely to develop OSA [42–46]. Sleep apnea is described in more detail in the next section on sleep-disordered breathing (SDB).

Four percent to 10 % of women of reproductive age may suffer from PCOS [42–47]. About half of these women are overweight [48] with metabolic-related disorders and visceral obesity [47]. Approximately 15 % of obese normal women have OSA [49], but in obese women with PCOS, the incidence of OSA is markedly increased at 41–58 % [42] interestingly their body mass index (BMI) itself does not correlate with their OSA severity [43–45]. In obese women with PCOS, fat distribution follows a male pattern, with increased waist-to-hip ratio [45, 46]. However, in adolescent girls (15 years) with PCOS (n = 31) compared with healthy obese girls without PCOS (n = 19) neither group had significant OSA although total sleep time (TST), percentage of REM sleep, and sleep efficiency were lower in the girls with PCOS [47]. Symptoms of PCOS usually begin in adolescence and perhaps OSA develops in a subgroup of females over time along with worsening insulin resistance. A relationship of OSA severity with waist-to-hip ratio, elevated serum testosterone [44], and higher fasting insulin levels [45] indicates the contribution of androgenization and insulin resistance to the higher prevalence of OSA in women with PCOS [42, 46].

Sleep-Disordered Breathing in Women

The range of SDB includes snoring, the upper airway resistance syndrome (UARS), OSA, and the obesity-hypoventilation syndrome (OHS) as well as central sleep apnea (CSA) and periodic breathing (Cheyne–Stokes respiration). Women with SDB may report snoring less frequently than men [50] but they report more fatigue [51] and nonspecific complaints [52, 53]. Young premenopausal women (<30 years) in particular more often present with these nonclassical symptoms of OSA such as insomnia and depression, as well as cranio-facial findings [54]. One study found that women were more likely than men to be treated for depression and have hypothyroidism at the time of diagnosis [55]. As reviewed by Banno and Kryger [56], women with a diagnosis of OSA had higher obesity and comorbid psychiatric conditions and received more antidepressants, hypnotics, and anxiolytics before OSA diagnosis, compared to men with OSA matched for age, BMI, and apnea-hypopnea index (AHI) [57].

The prevalence of CSA in women and OSA in premenopausal women is quite low, with women showing about half the prevalence of OSA as men, although this discrepancy declines in postmenopausal women [58–60]. More recent large cohort studies in the general population, coupled with changes in technology (e.g., more accurate airflow measurement via nasal cannula pressure transducers than with thermocouples), the increase in obesity with higher prevalence in women than men [48], and the referral bias in favor of men [55], indicate that OSA is more common in women than previously recognized. An association between lighter sleep (more high-frequency EEG beta) that is more fragmented and of lower sleep efficiency with the metabolic syndrome was reported in a group of 368 midlife women (age 46–57 years) enrolled in the SWAN study [61]. Sleep-disordered breathing, as measured by a clinical cutoff score AHI $\geq$ 15, and lower sleep efficiency were found to be independent correlates of the metabolic syndrome and were independent of race and menopausal status [61].

There is evidence that upper airway resistance (UAR) during sleep is higher in men [62], and the male airway is more collapsible than in women. Premenopausally, women are protected from developing sleep apnea. Indeed, there is a menstrual phase effect on UAR, with UAR being lower during the luteal phase than in the follicular phase [63], possibly related to progesterone effects. A number of other factors may contribute to the gender differences in SDB, such as differences in anatomy, upper airway collapsibility, the arousal response to increased inspiratory resistance, and ventilatory control [62, 63]. The clinical effect of lower airway resistance and less collapsibility in women is apparent in PSG differences: Women with OSA have more hypopneas than frank apneas with a shorter duration of apneas than in men [64], and lower apnea severity in the luteal versus follicular phase [65]. Women with OSA tend to have a clustering of respiratory events during REM sleep [66, 67], the frequency of which is related to BMI in both men and women [67]. The magnitude of the increase in blood pressure after apnea termination compared with immediately prior to apnea termination was higher during the luteal phase than during the follicular phase, despite lower OSA severity in the luteal phase [65]. The augmented luteal phase pressor response to apneas may effectively be enhancing the arousal response due to a combination of centrally mediated and peripheral sympathetic responses [65]. The arousal response in UARS to airflow limitation results in daytime sleepiness due to fragmented sleep [52]. Excessive sleepiness is a key presenting complaint for OSA. However, in women with recently

diagnosed OSA, insomnia was more likely to be a presenting complaint than it was in men [55, 68].

Clinically there is the potential that in some women, polysomnographically significant SDB may manifest in the follicular phase and could be missed by a diagnostic study in the luteal phase. Menstrual-related variability in the severity of sleep apnea may require a corresponding adjustment in management, such as varying the pressure requirement of continuous positive airway pressure (CPAP) therapy as could be achieved using long-term auto-adjusting positive airway pressure (APAP).

Sleep Disorders Associated with the Menstrual Cycle

There is very limited research on premenstrual sleep disorders, and its inclusion is based on isolated case reports. Three forms of "menstrual-associated" sleep disorders—premenstrual insomnia, premenstrual hypersomnia, and menopausal insomnia—were listed under the category of Proposed Sleep Disorders in the revised International Classification of Sleep Disorders (ICSD) published in 1997 [69]. In the second edition of the ICSD from 2005 [70], the only two disorders carried over were menstrual-related hypersomnia and menopausal insomnia. The third edition of the ICSD published in 2014 eliminated these as separate categories and listed menstrual-related hypersomnia as menstrual-related Kleine-Levin Syndrome (see Chap. 27).

Difficulty falling asleep or staying asleep, usually in the week before menstruation (premenstrual insomnia), should be distinguished from PMS and PMDD. Insomnia as the only premenstrual symptom is not considered sufficient to receive a diagnosis of PMS. Premenstrual hypersomnia occurring periodically around menses, preceding and into the early-follicular phase, has been successfully treated with hormonal treatment (conjugated estrogen or oral contraceptives) [71]. In another case of periodic hypersomnia, prolactin was elevated but did not respond to hormone replacement therapy and was symptomatically treated with methylphenidate [72].

Sleep During Pregnancy

Sleep disruption during pregnancy is a common and multifaceted problem [73, 74]. Contributing factors include hormonal changes, fetal movement, bladder distention, gastrointestinal discomfort, vomiting, and temperature fluctuations. There are significant changes in sleep architecture, and primary sleep disorders such as OSA and restless legs syndrome (RLS) may be more common. Most women accommodate to the changes in sleep, but for a proportion of them, the disruption will prove problematic and may result in medical and psychiatric complications.

Subjective Changes in Sleep

A large percentage (66–94 %) of women note alterations in their sleep during pregnancy [75–77]. During the first trimester, subjective sleep quality decreases and the number of nocturnal awakenings increases. Daytime sleepiness is more problematic. During the second trimester, women report that sleep normalizes, although 19 % of women continue to experience difficulties at this stage [77]. By the third trimester, women experience worsening insomnia, increased daytime sleepiness, and decreased alertness [76]. Reasons cited for the increased sleep disturbances were mainly urinary frequency, backache, fetal movement, abdominal discomfort, leg cramps, and heartburn. A survey of sleep disruption across pregnancy found that 97 % of women identified themselves as having disrupted sleep, while a third felt they had a "sleep disorder" [78]. The latter group may be biologically or psychologically more vulnerable to the detrimental effects of disrupted sleep. Factors such as a prior history of a psychiatric disorder, lack of a social support network, poor coping skills, and difficulty adjusting to the impending role of motherhood are likely important in this regard.

The 1998 NSF survey found that 79 % of women reported that their sleep was, or had been, disturbed during pregnancy [10]. Women who were currently pregnant or had been pregnant recently were more likely to report frequent insomnia (64 %) when compared to premenopausal or menopausal women. Of the women reporting sleep disturbance during pregnancy, 70 % reported that it interfered with daily functioning on at least a few days per month. It is unclear for what proportion it represented a *serious* problem. There are limitations to this survey, such as the fact that not all women were pregnant at the time of reporting and were hence providing retrospective accounts of their sleep during pregnancy, but it does shed light on the extent of subjective sleep disruption during pregnancy. The NSF 2007 "Sleep in America" telephone poll of 1003 women included 150 pregnant (second trimester, $n = 47$; third trimester, $n = 91$) and 151 postpartum women [79]. More pregnant women (84 %) experienced insomnia symptoms at least a few nights a week, compared to 67 % of the overall group. In response to whether they were getting a good night's sleep at least a few nights a week, 82 % of pregnant women felt they were doing so before their current pregnancy, compared to 60 % who felt this to be the case during their ongoing pregnancy. More women in their second trimester (72 %) said they got a good night's sleep at least a few nights a week than those in their third trimester (54 %). Reasons for sleep disturbance were to go to the bathroom (92 % in the third trimester and 75 % in the second trimester), and pain in their back, neck, or joints (66 and 47 % of third and second trimester women,

respectively). Two other reasons for disturbed sleep in the third trimester are leg cramps (54 %) and heartburn (51 %).

Objective Changes in Sleep

Pregnancy has a significant impact on sleep architecture and on the quantity and quality of sleep. Several excellent reviews [9, 80–82] show that the findings are not fully consistent and that more research into the changes in sleep architecture that accompany pregnancy is necessary. However, there is consensus that there is a "lightening" of sleep as pregnancy progresses, with a decrease in sleep efficiency, decreased total sleep time, increased wakefulness after sleep onset, and decreased REM sleep. Most studies show a decrease in SWS, especially in the third trimester [83, 84]. One study reports an *increase* in SWS from early to late pregnancy [85]. This last finding may relate to the fact that only primiparous women were included, while the other studies included both primiparous and multiparous subjects. The sleep of these two groups of women appears to differ; exactly in what way remains to be determined. According to one study, multiparous women have lower sleep efficiency at all time points across pregnancy [84]. Immediately postpartum, primiparous women have lower sleep efficiency, but at 3 months postpartum, their sleep had improved but did not revert to its prepregnancy baseline. This finding would suggest that pregnancy and childrearing has a prolonged impact on sleep architecture. Another study, following women's sleep using actigraphy during pregnancy and at 1 and 6 weeks postpartum, reported that primiparous women have lower sleep efficiency in general during pregnancy and postpartum, when they also had fewer sleep episodes than their multiparous counterparts [86]. Again, the discrepancy in findings could be secondary to varying assessment techniques (PSG, actigraphy) and relatively small sample sizes.

Primary Sleep Disorders Associated with Pregnancy

The risk for OSA increases substantially with obesity [48, 87] but the prevalence with the weight gain during pregnancy is unclear. Changes in respiratory physiology during pregnancy, such as decreased functional residual capacity [88], changes in the airway mucosa [89], and hyperventilation with increased sensitivity to CO_2 [90], may predispose to obstructive or central apneic events. Some investigators have found no decrease in nocturnal arterial oxygen saturation during pregnancy [91, 92]. Others, however, report significantly more nocturnal desaturation in pregnant women compared with controls [93, 94]. Hypertension in the mother at the time of birth and lower Apgar scores in the infant are significantly more common in women who reported snoring during pregnancy as compared to nonsnorers [95]. A large (n = 1091) prospective study of pregnant women suggests that severe snoring in the third trimester is a significant risk factor for fetal growth restriction and preterm birth [96]. A number of case series, using small numbers and relying on clinical examination rather than PSG, indicate that OSA may be associated with intrauterine growth retardation, especially if other complications such as maternal obesity and diabetes mellitus are present [97]. The control of partial upper airway obstruction and snoring using nasal CPAP in women with preeclampsia has been shown to decrease blood pressure significantly [98]. Edwards and Sullivan [99] have reviewed the risks and treatment options of SDB during pregnancy and with preeclampsia.

Restless legs syndrome (RLS) and periodic limb movements in sleep (PLMS) increase during pregnancy [81, 100]. Women cite restless legs as a common cause of sleep disruption during pregnancy [74]. Complaints of leg cramps during waking in the middle of the night should raise the possibility of RLS-PLMS, especially if the woman is experiencing daytime sleepiness or fatigue.

Risks Associated with Sleep Disruption During Pregnancy

The role of sleep disturbance in the development of psychiatric illness is a grave concern. Patients with persistent insomnia are at significant risk for developing depression [101]. This holds true even when there is a medical cause, such as sleep apnea, for the insomnia. Women with sleep disruption during pregnancy and in the weeks postpartum may be at higher risk for depressive symptoms during pregnancy [76] and for postpartum mood disorders, especially where there is a previous history of mental illness [102, 103]. Parity may play a role in this regard. One study which compared sleep and mood in primiparous women and multiparas noted that both parameters were better in the latter group [104].

Sleep disruption often heralds the onset of a manic or hypomanic episode among patients in the general population who suffer from bipolar illness [105, 106]. The risk of new-onset mania or recurrence of a preexisting illness during the postpartum period is significant. Women with a history of bipolar affective disorder (BAD) have a twofold increase in risk for symptom exacerbation during the immediate postpartum period. Furthermore, women with a prior history of BAD have a sevenfold increase in risk for a psychiatric admission in the puerperum when compared with nonpostpartum and nonpregnant women [107]. Even fathers with BAD are at increased risk of relapse in the postpartum period [108]. This suggests that the sleep disruption associated with

caring for a neonate may play an important role in the development or recurrence of postpartum psychiatric illness. The challenge for the clinician is to identify those women for whom sleep loss, an inevitable part of childbearing, will have serious consequences.

Patients with insomnia often resort to the use of alcohol and over-the-counter remedies. The NSF report [10] found that 7 % of pregnant women used over-the-counter medications and 7 % used alcohol at some point in the pregnancy to help them sleep, while 4 % used prescription medications for this purpose. The use of such sleep aids during pregnancy could have significant consequences for the developing fetus.

Research is being carried out on the impact of pregnancy-related sleep complaints and inflammatory markers. A study by Okun et al. [109] on 19 women during mid- and late-trimester pregnancy examined subjective sleep reports and the levels of circulating (naturally occurring) and secreted (experimentally stimulated peripheral blood mononuclear cells) interleukin-6 (IL-6). Complaints of shorter sleep duration and poor sleep efficiency at both stages of pregnancy were associated with higher levels of stimulated IL-6; while in late pregnancy, sleep complaints were also associated with higher levels of circulating IL-6. The implications of these findings for maternal well-being and fetal development remain to be determined.

Management of Pregnancy-Related Sleep Disruption

Significant sleep disruption during pregnancy is likely underreported by women. Hence, it is imperative that the primary caregiver inquire about it and determine to what extent it warrants further assessment and intervention. Potential medical causes should be considered (e.g., medications, thyroid problems, psychiatric illness) and treated where appropriate. Primary sleep disorders such as OSA and RLS/PLMS should be ruled out.

Significant respiratory disturbance can be treated with CPAP, which has been shown to be safe during pregnancy [97, 98]. Milder respiratory disturbances may respond to conservative measures such as positional therapy.

There is a relationship between low serum ferritin levels and RLS/PLMS. Iron supplementation should be instituted where this is the case. Conservative measures such as reducing caffeine intake or wearing supportive stockings should be implemented. The use of any form of medication during pregnancy must be approached with caution, and the patient must be made fully aware of the risks and benefits. Pregnant women are not included in drug trials, and the safety of many medications during pregnancy has not been determined. The safety of certain medications used to treat RLS/PLMS (e.g., pramipexole, gabapentin, ropinirole) is unknown. The benzodiazepine clonazepam carries concern about possible teratogenicity when used in the first trimester. However, judicious use in the second and third trimesters may be warranted. There is a risk of "floppy baby syndrome" if used close to the time of delivery, and the patient should be educated accordingly. Some patients with RLS/PLMS respond well to opioids such as codeine and oxycodone, and there is no evidence of teratogenicity, although there is a risk of a withdrawal syndrome or respiratory depression in the neonate.

During the postpartum period, the sleep of women with a history of a mood disorder must be protected since a recurrence at this time can have disastrous consequences for both mother and infant [106]. Prolongation of the hospital stay to enable the new mother to recover from the impact of labor and birth may be beneficial. The patient's partner and other family members should be encouraged to play an active role in nocturnal feeding.

Where no primary cause for the sleep disruption can be determined, nonpharmacologic treatments should be the primary intervention. Attention to sleep hygiene factors, such as a regular sleep–wake schedule, avoiding caffeinated beverages, reducing the amount of fluids consumed in the evening, and ensuring the temperature in the bedroom is comfortable, should be highlighted. There are no data concerning the efficacy of cognitive and behavioral techniques, such as cognitive behavioral therapy or stimulus control therapy, for insomnia during pregnancy. However, given that they are efficacious for insomnia in general, we would expect that they would be beneficial when applied during pregnancy.

The majority of women are likely to resist the use of sleeping medications, but where insomnia is having a severe effect, the use of a sleep aid may be warranted. The antihistamine dimenhydrinate has not been associated with fetal effects in animal studies. The nonbenzodiazapine hypnotics, zopiclone, zaleplon, and zolpidem, all considered Class C drugs by the America Academy of Pediatrics (AAP), should be limited during pregnancy until more data are available. A study of pregnancy outcome in 40 women exposed to zopiclone during the first trimester did not find an increase in the rate of major malformations when compared with a nonexposed group [110]. A population-based study in Taiwan compared the rates of adverse pregnancy outcomes (preterm delivery, small for gestation age, low birth weight infants) in a large number of women who were exposed to zolpidem during pregnancy with those in women who were not exposed. All adverse outcomes were significantly higher in the exposed group but the rate of *major congenital malformations* did not differ between the 2 groups [111]. There are many potential confounding factors that could not be accounted for (e.g., adherence with the medication, other medical or psychiatric factors, social factors such as

smoking, alcohol use, and nutrition status of the mother) but these data highlight the need to use this class of medications during pregnancy with caution.

The antidepressant trazodone may be beneficial for reducing sleep-onset latency and improving sleep quality in depressed patients [112]. The AAP stated that data are too limited to provide a recommendation on the use of this and other sedating antidepressants, such as mirtazapine and nefazadone (not available in Canada), during pregnancy [113]. No difference in pregnancy outcome (including rate of major malformations and gestational age at birth) has been found between patients taking nefazadone and trazodone during the first trimester when compared with women taking other nonteratogenic antidepressants or other nonteratogenic drugs (e.g., sumatriptin, dextromethorphan), matched for age, smoking, and alcohol use [114]. Both antidepressant groups, however, had a trend toward a higher rate of spontaneous abortion, although the difference was not statistically significant. The tricyclic antidepressant amitriptyline has considerable sedating properties, does not appear to have teratogenic effects, and is considered safe for use in pregnancy [113].

Benzodiazepines are frequently used to treat insomnia in the general population. The AAP [113] recommends that their use be limited during pregnancy since they can induce sedation, withdrawal signs (including restlessness, hypertonia, irritability, seizures, and abdominal distention), and floppy baby syndrome (muscular hypotonia, low Apgar scores, neurologic depression) in the neonate, effects that can last for up to 3 months. Hence, when benzodiazepines are used, they should be slowly tapered over a number of weeks prior to delivery. Use during the first trimester should be avoided if possible because of concerns about congenital malformations such as cleft palate [115]. However, no congenital defects have been associated with lorazepam or alprazolam [113]. Use of the former is preferred since it lacks active metabolites and is less likely to be associated with a withdrawal syndrome in the neonate.

Menopause and the Climacteric

Changes in menstrual cycle frequency and menstrual flow reflect the changing hormone milieu in the perimenopausal period. Menstrual cycle length decreases from 28 days for women in their 20 s to 26 days for women in their 40 s [116]. Between the ages of 45 and 55 years, production of estrogen and progesterone decreases, FSH levels increase, and menstrual cycles become irregular [116]. This transition occurs over a few years (mean 3.8 years) prior to the last menstrual period. There is no definitive way to distinguish transient amenorrhea from menopausal amenorrhea, and generally menopause is only confirmed when menstrual periods have stopped for a year (average age 51 years) [117]. The term *climacteric* is used to refer to the transition period (usually 7–10 years) preceding the last menses when ovarian function decreases, and afterward, when women experience hormonally induced physical and/or psychological changes [116].

Sleep Disturbance and Climacteric Symptoms

Women of any age are more likely than men to report dissatisfaction with their sleep and to experience daytime consequences. Insomnia is more prevalent in women than men [118] and this gender disparity increases with age [119]. Comparing the sex difference in the prevalence of insomnia among young adults (15–30 years), middle-aged (31–64 years), and elderly ($\geq$ 65 years), the overall relative risk (RR) for females compared to males increased from 1.28 in young adults to 1.46 in middle age and 1.73 in elderly [119]. In a Canadian survey of 2000 adults, by Morin and colleagues, 15.6 % of women and 11 % of men met all the criteria for insomnia showing that women have 1.5 times (95 % Confidence Interval: 1.15–1.95) the risk of presenting with insomnia syndrome than men [120]. This gender disparity increases with age—the female:male ratio of insomnia symptoms after 45 years of age is 1.7:1 [121]. There is evidence that the higher prevalence of affective disorders among women contributes toward their insomnia symptoms. Data from 148,938 postmenopausal women who were enrolled in the Women's Health Initiative study revealed that the strongest independent risk factors for sleep disturbance were depression, somatic symptoms, lower emotional well-being, and restlessness [122].

Menopause is often cited as the underlying cause for the gender disparity in sleep complaints in middle-aged individuals. Complaints of sleep disruption are higher in perimenopausal than in premenopausal women [121, 123, 124]. Sleep disturbances include waking at night (the most common problem) [124], waking early, and difficulty falling asleep [123]. Trouble sleeping has been associated with more depressive symptoms, vasomotor symptoms, mood swings, higher levels of stress, tension and anxiety, and palpitations, particularly during perimenopause [116, 123–127]. Furthermore, midlife women with disturbed sleep were found to have a twofold increase in menopausal symptoms [124].

Other menopausal symptoms that can be disruptive to sleep either directly or indirectly include weight gain, vaginal dryness and irritation, and urinary problems. Nocturia in postmenopausal women is reportedly improved with estrogen therapy [128]. However, as in men, the prevalence of nocturia increases with age (9 % in women <39 years old to 51 % of women $\geq$ 80 years old) [128], and OSA can

increase nocturnal diuresis through increased atrial natriuretic peptide production. Thus, aside from menopausal symptoms disturbing sleep, underlying chronic physical conditions or sleep disorders should also be considered.

The terms *hot flush, hot flash*, and *vasomotor symptoms* are used to describe the same phenomenon. Nocturnal hot flashes (also called night sweats) that can soak bedclothes, followed by chills as the body cools down, lead to sleep disruption [23, 129]. Vasomotor symptoms, including night sweats and hot flashes, are the primary reason for women to seek treatment at the time of menopause [130]. Up to 85 % of women experience hot flashes [116, 127, 129], with variation depending on ethnicity and culture [127, 129]. In a large (n = 14,906) multisite, multiethnic study in the USA of women's health across the nation (SWAN), the population group with the lowest incidence of night sweats were Japanese women at 9 % and the highest was African women at 32 % [131]. A further analysis from the SWAN study found that 38 % of all women reported subjective difficulty sleeping; the incidence was lowest in Japanese women (28 %) and highest in Caucasian women (40 %), and difficulty sleeping was associated with hot flashes [129]. In the SWAN study, an odds ratio for sleep problems in women with vasomotor symptoms was 2.0 compared to asymptomatic women. Furthermore, in a smaller study (n = 63) based on healthy women who had undergone hysterectomy, those with subjectively impaired sleep had more hot flashes and palpitations as well as mood-related symptoms (anxiety, depression, mood instability, memory problems) [132]. A study of 15 perimenopausal women who reported increased awakenings and dissatisfaction with sleep quality showed an increased number and duration of arousals and more movement activity on wrist actigraphy compared to 13 age-matched premenopausal controls [125].

Interestingly, PSG studies do not consistently show worse sleep quality peri- and postmenopausally than premenopausally [126, 132–136], or an association with climacteric vasomotor, somatic, or mood symptoms [132, 134, 135]. Although no significant differences in sleep were apparent, for 39 symptomatic versus 32 nonsymptomatic women, there was a trend toward lower sleep efficiency [133]. Young et al. [134] compared objective sleep data from a single night in 589 women of known menopausal status but, despite postmenopausal women reporting more dissatisfaction with their sleep than premenopausal women, PSG sleep efficiency was not lower in peri- and postmenopausal women. Indeed, the proportion of SWS was higher in postmenopause than premenopause. A study by Freedman and Roehrs [135] also found that 12 symptomatic versus 8 asymptomatic postmenopausal women and 11 premenopausal women did not have more sleep disturbance. Clearly there is a disconnect between objective and subjective sleep that merits further investigation.

Potential factors contributing to the disparity between subjective dissatisfaction with sleep and objective measures include (1) the severity of climacteric symptoms and the presence of hot flashes during the sleep recording, (2) effects on sleep microstructure—arousals, alpha EEG intrusion [37], and EEG cyclic alternating pattern (CAPS) [136]—rather than macrostructure, and (3) sympathetic activation. The association of hot flashes with subjectively poorer sleep suggests that they should be monitored during PSG studies. One study that used skin conductance to monitor hot flashes in women with nightly complaints of sweating found that after 4 weeks of conjugated estrogens (0.625 mg), there was a reduction in hot flashes associated with polysomnographically documented reduced CAPS rate and improved sleep efficiency [136]. Similarly, when monitoring hot flashes in breast cancer survivors with insomnia (n = 24), more sleep disruption and wake time around the time of hot flashes was observed; sleep efficiency was lower on nights with than on nights without hot flashes [137]. However, no association of sleep disturbance around the time of hot flashes measured by skin conductance has been found [135].

Hormone and Estrogen Replacement Therapy: A Role for Improving Sleep?

Vasomotor symptoms are reduced with estrogen alone (estrogen replacement therapy, ERT) [136, 138, 139] or in combination with progesterone therapy (hormone replacement therapy, HRT) [140–143], but in laboratory studies, they have not been found consistently to improve sleep. Findings from three studies highlight these inconsistencies. Polo-Kantola et al. [138] reported subjective sleep improvement with transdermal estrogen preparations compared with placebo (n = 70), associated with reduced hot flashes and sweating, but estrogen was no better than placebo in terms of sleep on PSG. Antonijevic et al. [144] in contrast found reduced wakefulness and increased REM sleep with an estradiol patch (n = 11). In a third study, an HRT with estrogen (Premarin 0.625 mg) and two different progesterone preparations—either micronized progesterone (Prometrium 200 mg) (n = 10), which gives rise to sedative metabolites, or medroxyprogesterone (Provera 5 mg) (n = 11)—showed improved sleep efficiency with micronized progesterone [143]. Despite the sleep improvement, daytime vigilance was unchanged with the micronized progesterone, whereas it improved with medroxyprogesterone. Overall, most studies of HRT on sleep show favorable effects including improved subjective sleep quality and reduced sleep fragmentation and wake on PSG [145, 146].

Clearly, more detailed studies of the effects of HRT are needed before firm conclusions can be drawn regarding their effects on sleep.

For those women whose menopausal symptoms and sleep may be alleviated on hormone therapy, safety concerns with HRT from the Women's Health Initiative (WHI) [139] posed a dilemma [130]. The large (n = 16,608), randomized, placebo-controlled WHI trial on the effect of conjugated equine estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) revealed increased risks for stroke, venous thromboembolism, coronary heart disease, and breast cancer [139]. These risks have been subsequently confirmed in other clinical trials that used a variety of estrogen and progestin products [147]. Given the fear of adverse events, over 50 % of women stop therapy after 1 year [148]. However, in the WHI trial, the average age of women at enrollment was 63 years (range 50–79), and women with severe menopausal symptoms were excluded, yet symptom relief is the reason most women initiate HRT. The choice of whether to use hormone therapy or not is a balance between age, symptoms, current quality of life, and potential risk [130, 149].

Subsequent analysis of health-related quality of life in nonsymptomatic women from the WHI trial [150] showed there was only a small and not clinically meaningful reduction in sleep disturbance in the first year that was not evident after 3 years. In contrast, from the Heart and Estrogen/Progestin Replacement Study (HERS)—another large (n = 2763) randomized, placebo-controlled trial of the same hormone concentrations as the WHI trial—women who experienced hot flushes had improved mental health and depressive symptoms [151]. Thus, the effects of HRT on quality of life appear to depend on the presence of menopausal symptoms with negative effects in women without vasomotor symptoms and improvements in women with vasomotor symptoms [151]. For women who experience significant disruptive menopausal symptoms, the smallest effective dose of estrogen may serve a useful short-term role in symptom management [147, 149, 152]. Family history and potential risk of disease should be taken into account when considering HRT for relief from disturbed sleep [130, 146, 147, 152].

Alternatives to Hormone Replacement Therapy for Sleep Disruption

With a decrease in HRT prescriptions since July 2002, there has been an increase in prescriptions of serotonergic antidepressants [153]. Some antidepressants that block the release of serotonin and norepinephrine (e.g., fluoxetine, paroxetine, venlafaxine) have been reported to alleviate climacteric symptoms [153, 154]. Norepinephrine and serotonin have a central role in the pathophysiology of hot flashes [149]; clonidine, an α_2-adrenergic agonist, has also been found to alleviate climacteric symptoms and accordingly related sleep problems.

An age-related decline in melatonin secretion occurs between 17 and 45 years in premenopausal women, with an increase during perimenopause (46–50 years), and a decline postmenopause [155]. In the first 15 years of postmenopause, there is a steep decline in melatonin, followed by a more gradual decline. The timing of melatonin secretion is also advanced in postmenopausal compared with premenopausal women [156]. Melatonin has chronobiotic (circadian effect) and hypnotic properties. Exogenous melatonin, as well as a controlled-release formulation of 2 mg melatonin Circadin®, and the melatonin agonist Ramelteon have been reported to promote sleep onset and improve sleep quality in middle-aged and elderly insomniacs [157].

Given the safety concerns related to hormone therapy, many women seek alternative therapies to relieve sleep disturbances. Hot flashes occur more frequently in warmer than cooler environments [127]; reducing ambient temperature (to 16–19 °C) may provide relief from hot flashes and sleep disruption [142, 149].

A telephone survey of 866 women on the use of eight alternative therapies to manage menopause symptoms found that 76 % of women had used at least one type of alternative therapy [158]. Women who experienced trouble sleeping were more likely to use alternative therapies such as dietary soy and stress management. Soy isoflavones are estrogen-like substances that have been investigated as an alternative therapy to relieve menopausal symptoms but have not been found consistently to have an appreciable effect [159].

Valerian is commonly used as a sleep aid and has been tested with conflicting results in small groups of older individuals. For example, Taibi et al. [160] found no improvement in sleep in 16 older women (69 years) who took 300 mg concentrated valerian extract for 2 weeks compared with placebo. Whereas Taavoni et al. [161] found that 50 menopausal women (aged 50–60 years) given 160 mg valerian with 80 mg lemon balm for one month improved subjective sleep quality (based on the Pittsburg Sleep Quality Index, PSQI) compared to a placebo control group. A meta-analysis of 18 RCTs of valerian (300–600 mg/d) suggested that it improves subjective sleep quality based on yes/no responses [162].

Though not well studied, black cohosh (a root extract from a North American perennial plant) may relieve hot flash symptoms, and gabapentin (a GABA analog) has been found to have a favorable effect compared to placebo [154] but concerns have been raised about liver toxicity [see 163]. Linseed (flaxseed) extract as well as Mediterranean pine bark extract have been reported to reduce vasomotor symptoms [163]. The hop-flavonoid (the hop flower is an ingredient in

beer) 8-prenylnaringenin, a stronger estrogen than soy isoflavones, has been studied in two RCTs for effectiveness in reducing vasomotor symptoms with conflicting findings suggesting no advantage over placebo [163]. Hypnotic drugs such as zolpidem (10 mg) in women with menopause-related insomnia ($n = 141$) reduced wake after sleep onset and improved subjective sleep quality [164].

Chronic heavy smoking in adulthood is a significant risk factor for insomnia. Compared with nonsmokers, midlife women who were chronic heavy smoker were more likely to report insomnia at mean age 65 (Adjusted OR = 2.76; 95 % CI = 1.10–6.92) [165]. However, women who quit smoking in midlife (43–48 years) by the age of 65 years did not have any more insomnia symptoms that a nonsmoking group.

Yoga has been found to improve insomnia severity scores and menopausal symptoms after 4 months of practice in 15 postmenopausal women not taking hormone therapy compared to passive stretching and a wait-control group [166]. Consistently high physical activity rated as sports/exercise (e.g., participation in recreational activity or sports) for 6 years preceding assessment has been associated with better sleep efficiency on PSG and better PSQI scores in 339 midlife women (mean age 52 years) in the SWAN study [167]. In menopausal women (mean age 54 years) with vasomotor symptoms, nonsupervised aerobic training four times per week for 50 min for 6 months improved subjective sleep quality and vasomotor symptoms in a group of 73 women compared with a control group of 76 women [168]. Thus, a more active lifestyle is recommended to improve sleep disruption in menopause.

Sleep-Disordered Breathing in the Menopause

Menopause increases the risk of SDB by three to four times, even after adjusting for known risk factors such as age and BMI, compared to premenopausal women [59, 169]. Increased age, hormone-related changes, and weight gain—including a change in fat distribution [116] with more visceral adiposity—are all contributing factors for increased OSA. Older, overweight women with high blood pressure, insomnia, disturbed sleep, or "fatigue" should be considered at high risk for having OSA.

Progesterone is a respiratory stimulant and, in women receiving HRT, the prevalence of OSA and SDB was found to be lower than women not taking HRT [59]. This finding needs to be confirmed in larger clinical trials. The prevalence of moderate-to-severe OSA in women in the Sleep Heart Health Study ($n = 2994$, age ≥ 50 years) among women using hormone replacement (either ERT or HRT) was half the prevalence in nonusers [170]. The reduction in SDB (estimated odds ratio, 0.55) for hormone users corresponded to the predicted effect of reducing BMI by 6.8 kg/m^2 [170]. Before recommending menopausal hormone replacement to treat apnea in women, however, many other factors need to be considered. The focus should instead be on using standard therapy such as weight loss, CPAP, an oral appliance, or positional therapy (side sleep) for milder OSA.

Other Factors Influencing Sleep During Menopause

The secretion of other endogenous hormones, such as thyrotropin, decreases with age: 25 % of postmenopausal women show clinical or subclinical thyroid disease, which often causes symptoms similar to those of the climacteric [149]. The cause of sleep problems around menopause is not always evident and possibly is multifactorial. Factors aside from menopause—such as systemic diseases, medications, depressed mood, stress, behavioral or cognitive factors, social and family situations, pain, and aging-associated increases in RLS and PLMS—may explain, or contribute to, decreases in sleep quality.

Conclusion

The changing hormone profile across the reproductive life of a woman, from puberty through the reproductive period to the postmenopausal years, has a significant influence on sleep. Abrupt changes in, or withdrawal of, female hormones may lead to sleep disruption. During pregnancy, however, multiple factors contribute to sleep disruption, and these will vary according to the stage of pregnancy. Certain sleep disorders such as OSA and RLS are influenced by stage of menstrual cycle or life cycle. This chapter has highlighted the impact of the reproductive and menstrual cycles on sleep. It is imperative that sleep clinicians take these factors into account when working with women. Women should be encouraged to track whether there is a cyclical change in their symptoms in association with hormone changes or if the symptom changes are due to age-related changes in hormonal profile.

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Sleep, Violence, and Forensic Implications

54

Michel A. Cramer Bornemann and Carlos H. Schenck

Introduction

Increasingly, sleep medicine practitioners are asked to render formal opinions in a court of law regarding criminal allegations pertaining to violent or injurious behaviors arising from the sleep period. Automatic behaviors (automatisms) resulting in acts that may result in illegal behaviors have been described in many different conditions. Those automatisms arising from wakefulness are reasonably well understood. Recent advances in sleep medicine have made it apparent that some complex behaviors, occasionally resulting in forensic science implications, are exquisitely state dependent, meaning that they occur exclusively, or predominately, during the sleep period.

Case Examples

Two sleep forensics court cases involving sexual assault, one resulting in acquittal and the other resulting in a guilty verdict, will now be presented.

Acts done by a person asleep cannot be criminal, there being no consciousness [1].

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Case 1

As reported by The Copenhagen Post and Associated Press on April 10, 2013, Danish legal history was made on that date when a sexual assault charge (i.e., molestation form of rape) for the first time resulted in acquittal by use of the "Sexsomnia Defense"—which is in regard to a NREM Parasomnia formally referred to as Sleep-related Abnormal Sexual Behavior. The Glostrup District Court cleared a 32-year-old man of "sex crime charges." Two years previously, in 2011, the man had fondled two 17-year-old females while they were sleeping in his suburban Copenhagen apartment after a party in 2011. (This raises the question about any use, and extent of any use, of alcohol by the accused during the party.) The girls awoke and stopped the man, and later reported him to police. The defendant said he had no recollection of what happened, as he claims to have been asleep.

"It is the first time that someone has been acquitted under these circumstances in Denmark," the man's lawyer, Andro Vrlic, stated. "The defendant had always claimed that he was asleep when the incident took place, but he was charged by police who did not believe his explanation."

> According to his explanation, he did not know that there was anything wrong with him," the prosecutor, Martin von Bülow, told Ekstra Bladet. "But when former girlfriends told him that they had experienced something similar while he slept, he sought out a sleep specialist [who tested him].

The man was subsequently studied in a sleep laboratory, and the conclusions were pronounced in court during the trial to support the diagnosis of Sleep-related Abnormal Sexual Behavior—but the details of the sleep laboratory findings were not disclosed to the public and were sealed in the court records. However, an expert for the defense testified in regard to the sleep laboratory findings: "It's not something that can be faked."

Von Bülow added that the testimony from the girls supported the man's claim that he was asleep when he touched one and made sexual motions against the other. He added

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that given that the man's defense was supported both by the victims and by experts in court, he was not surprised by the acquittal.

One of the authors of this chapter (CHS) was interviewed by a Danish journalist, Nola Grace Gaardmand, shortly after the court ruling, who then published two related articles about this case (**see Add Reference Addendum** [103, 104]). Ms. Gaardmand provided more details about the case after interviewing the defendant's attorney.

The accused previously had dated the older sister of one of the 17-year-old girls, and after they terminated their relationship subsequently remained close friends over the years. Furthermore, the man and the younger sister were "kind-of like family, like an older brother–younger sister relationship," the lawyer explained. She had just moved to Copenhagen and was staying in a guest-room at his apartment until she found her own place; on the night of the assault, she happened to have a girlfriend stay over with her for that night. They slept together in a separate bedroom from the accused. According to the girls' lawyer, there were no lingering ill sentiments among any of them (the two girls, and the older sister [ex-girlfriend of the accused]) after the sexual assault and trial, and the man and the older sister (i.e., the man's ex-girlfriend) apparently have remained good friends.

Comments: The court testimony of previous recurrent episodes of Sleep-related Abnormal Sexual Behavior provided by the former girlfriend of the accused, with whom he had remained friends for years, considering themselves as "family" together with the younger sister of the former girlfriend (and sexual assault victim), was strong supportive evidence presented in favor of the "Sexsomnia Defense." The sleep laboratory evaluation reportedly provided additional strong support to sustain the argument in favor of the "Sexsomnia Defense," as acknowledged by the presiding judge. However, since details of this testing were not made available to the public, it remains indeterminate whether this was a legitimate, science-based finding that would be critically upheld after peer review consensus among experts in the fields of sleep medicine and sleep forensics. Finally, in regard to the party held at the apartment of the accused on the night of the sexual assault, the possible use, and extent of any use, any possible role of alcohol consumption in the sexual assault remains indeterminate. This could possibly have been a troublesome, confounding factor, which may contaminate the case and has been addressed carefully in the peer-reviewed literature (**see Add Reference Addendum** [104, 105]).

Case 2

This pertains to a court case in rural western Norway involving a 42-year-old married man, with acknowledged marital problems, who sexually assaulted a 12-year-old girl who was spending the night with his 12-year-old daughter at the family home. (The sleep medicine expert Stale Pallesen, PhD, from Bergen, Norway, informally consulted with one of the authors of this chapter [CHS] prior to rendering his opinion in court.) On the night in question, the accused and his wife drove from their home at 8 PM to visit friends, but did not consume any alcohol. They returned home at 12:30 AM. The accused had previously sustained significant physical injuries, and regularly struggled with persistent pain, for which he was prescribed codeine, paracetamol, and gabapentin, which he took nightly for the week leading up to the sexual assault. On the night of the assault, he also took some methotrimeprazine.

His wife then went to bed and fell asleep in their second floor bedroom; she had left the bedroom window open, creating a chill that the accused found uncomfortable in tandem with his pain. He decided to sleep on a couch on the first floor, as he subsequently claimed. He fell asleep in approximately 30 min. At 3 AM, he gradually awakened and found himself in a separate room, lying on the same mattress as the 12-year-old girl who was visiting his daughter. He was lying behind her with an erect penis pressed against her. According to her court statement, he tried to pry his hands between her thighs, which she attempted to keep tightly together. However, she believed that his fingers might have penetrated between her vaginal labia. She estimated that the incident lasted approximately 15 min, and she was too frightened to scream. Her friend (daughter of the accused) was sleeping 3 ft. away in her own bed—but she suffered from deafness. After the victim repeatedly tried to pull away, the assault suddenly ceased. The man looked at the girl, and believed she was asleep, and so he decided that "no good would come of it" were he to subsequently report what had transpired. He then went to the kitchen to drink some water, noticed the time of 3:15 AM, and then went to join his wife in their bed on the second floor. He slept until 10–11 AM.

The following day the girl told her parents about the incident, and the police was notified. At trial, he was eventually convicted of sexual assault, a decision which was then appealed whereby Dr. Stale Pallesen then consequently became involved as a court expert (not an expert hired by either the Defense or the Prosecution, a highly desired impartial forensic expert role that is not often available in the USA).

Although the patient and his wife subsequently were divorced, she testified that he had engaged in sexualized behaviors which apparently arose from sleep with her about 1–2 nights weekly during their 15-year marriage. However, the sexual behavior was limited to fondling and never penile penetration. She would typically push him away, which would immediately abort the "sexsomnia" episode. He had

previously been married and his first wife never recalled any such sexualized behavior in the midst of sleep on his part.

The accused had infrequent episodes of sleepwalking during childhood, including a cousin (with whom he shared a bedroom) who had observed at least one such episode. However, there had been no reported sleepwalking during adolescence or that which persisted into adulthood.

The accused lost his appeal, and his conviction was upheld. The role of the sleep forensics expert (as with all forensic experts in Norway) was to determine whether there was a greater or lesser probability than 50 % that the accused had engaged in the behavior for which he was claiming as his defense. In this case, the sleep medicine expert (Dr. Pallesen), after his informal consultation with one of the authors (CHS), gave the opinion of less than 50 % probability that a Sleep-related Abnormal Sexual Behavior had occurred, mainly for three reasons: first, the accused had not engaged in sleepwalking since childhood; second, the accused sought out his victim, which is quite rare in sleepwalking; (**see Add Reference Addendum** [107]) and third, in the preponderance of published cases on Sleep-related Abnormal Sexual Behavior, the sexual behaviors during sleep occurred in the context of confusional arousals with the individual remaining in bed, and in only a small percent of cases did sleepwalking proceed to culminate in a Sleep-related Abnormal Sexual Behavior (**see Add Reference Addendum** [108]).

Neurophysiology of Sleep-Related Violence

The State-Dependent Nature of Violence

The concept that sleep is simply the passive absence of wakefulness is no longer tenable. Not only is sleep an active rather than passive process; it is now clear that sleep comprises two completely different states: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Therefore, our lives are spent in three entirely different states of being: wakefulness, REM sleep, and NREM sleep. Studies have indicated that bizarre behavioral syndromes can occur as a result of the incomplete declaration or rapid oscillation of these states [2, 3]. Although the automatic behaviors of some "mixed states" are relatively benign (i.e., shoplifting in narcolepsy) [4], others may be associated with violent behaviors.

The fact that violent or injurious behaviors may arise in the absence of conscious wakefulness and without conscious awareness raises the crucial question of how such complex behavior can occur. Examination of extensive animal experimental studies provides preliminary answers. The widely held concept that the brain stem and other more "primitive" neural structures primarily participate in elemental/vegetative rather than behavioral activities is inaccurate. There are overwhelming data documenting that extremely complex emotional and motor behaviors can originate from these more primitive structures—without involvement of "higher" neural structures such as the prefrontal cortex [5–11].

Sleep-Related Disorders Associated with Violence

Violent sleep-related behaviors have been reviewed in the context of automatized behavior in general. There are well-documented cases of (1) somnambulistic homicide, attempted homicide, and suicide; (2) murders and other crimes with sleep drunkenness (confusional arousals); and (3) sleep terrors/sleepwalking with potential violence/injury. A wide variety of disorders may result in sleep-related violence [12, 13]. Conditions associated with sleep period-related violence are listed in Table 54.1. These conveniently fall into two major categories: neurologic and psychiatric.

Neurologic Conditions Associated with Violent Behaviors

Extrapolating from animal data to the human condition, it has been shown that structural lesions at multiple levels of the nervous system may result in wakeful violence [14–17]. The animal studies provide insights into violent behaviors in the disorders of arousal, REM sleep behavior disorder (RBD), and sleep-related seizures.

Disorders of Arousal (Confusional Arousals, Sleepwalking, Sleep Terrors)

The disorders of arousal comprise a spectrum ranging from confusional arousals (sleep drunkenness) to sleepwalking to sleep terrors [18]. Although there is usually amnesia for the event, vivid dream-like mentation may be experienced and reported [19]. Contrary to popular opinion, these disorders may actually begin in adulthood and are most often *not* associated with psychopathology [19]. The commonly held belief that sleepwalking and sleep terrors are always benign is erroneous: The accompanying behaviors may be violent, resulting in considerable injury to the individual or others, or damage to the environment.

Febrile illness, prior sleep deprivation, emotional stress, and the inadvertent interaction from those who may be sleeping in close proximity may serve to trigger disorders of arousal in susceptible individuals [20–22]. Sleep deprivation is well known to result in confusion, disorientation, and hallucinatory phenomena [23]. Medications such as

Table 54.1 Conditions associated with sleep-related violent behavior

Neurologic sleep disorders
• Disorders of arousal (confusional arousals [sleep drunkenness], sleepwalking, sleep terrors)[a]
– REM sleep behavior disorder[a]
– Nocturnal seizures[a]
– Automatic behavior
i Narcolepsy and idiopathic hypersomnia
ii Sleep apnea
iii Sleep deprivation (including jetlag)
Psychiatric sleep disorders
• Psychogenic dissociative states (may arise exclusively from sleep)
– Fugues
– Multiple personality disorder
– Psychogenic amnesia
• Malingering
• Munchausen syndrome by proxy

[a]Obstructive sleep apnea may mimic or trigger these episodes

sedative-hypnotics, neuroleptics, minor tranquilizers, stimulants, and antihistamines, often in combination with each other or with alcohol, may also play a role [18].

Confusional arousals (also termed *sleep drunkenness*) occur during the transition between sleep and wakefulness and represent a disturbance of cognition and attention despite the motor behavior of wakefulness, resulting in complex behavior without conscious awareness [24–26]. These may be potentiated by prior sleep deprivation or the ingestion of sedative-hypnotics before sleep onset [27]. These episodes of "automatic behavior" occur in the setting of chronic sleep deprivation or other conditions associated with state admixture. Examples of such behaviors cover a broad spectrum including sleep eating, sleep driving, and sleep texting, to cite but a few. In one unusual case, even shoplifting has been reported during a period of automatic behavior in an individual with narcolepsy [4, 28, 29] (**see Add Reference Addendum** [109]).

Numerous associations exist between obstructive sleep apnea (OSA) and confusional arousals. Patients suffering from OSA may experience frequent arousals that may serve to trigger arousal-induced precipitous motor activity [30]. Therefore, the observed clinical behavior—a confusional arousal—is actually the result of another underlying primary sleep disorder, OSA. Guilleminault and Silvestri have made the following observations [30]:

It is well known that adult patients with OSA syndrome may engage in nocturnal wandering during sleep. These patients frequently demonstrate yelling and screaming during sleep, as well as confusion, disorientation, and sleepwalking. The nocturnal hypoxia and the repetitive sleep disruptions secondary to the OSA syndrome readily explain these symptoms.

This is another example of why overnight polysomnographic (PSG) studies with extensive physiologic monitoring are mandatory in the evaluation of problematic motor parasomnias. Disorders of arousal may also be precipitated by inadequate or incomplete treatment of sleep apnea with nasal continuous positive airway pressure [31, 32].

To remind us that apparently criminal acts without conscious awareness occurring during sleep drunkenness (formerly termed *somnolentia*) are not a recently described condition, dramatic cases were described in a classic book on sleep well over a century ago. The author's conclusion regarding sleep drunkenness was: "It is a natural phenomenon, to which all are liable" [33]. Treatment of the disorders of arousal includes both pharmacologic (benzodiazepines and tricyclic antidepressants) and behavioral (hypnosis) approaches [34].

The behavioral similarities between documented sleepwalking and sleep terrors violence in humans and "sham rage," as exhibited in the "hypothalamic savage" syndrome, are striking [35]. Although it has been assumed that the "sham rage" animal preparations are "awake," there is some suggestion that similar preparations are behaviorally awake and yet (partially) physiologically asleep, with apparent "hallucinatory" behavior possibly representing cross interference of REM sleep dream mentation into wakefulness, dissociated from other REM state markers [36].

The neural bases of aggression and rage in the cat have been reviewed, indicating that there is clearly an anatomic basis for some forms of violent behavior [37]. The prosencephalic system may serve to control and promulgate, rather than initiate, behaviors originating from deeper structures [10]. In humans, during confusional arousals (sleep drunkenness), which can result in confusion or aggression, there is clear electroencephalographic (EEG) evidence of rapid oscillations between wakefulness and sleep [26, 38]. It may be that such behaviors occurring in states other than wakefulness are the expression of motor/affective activity generated by lower structures—unmonitored and unmodified by the cortex. As sleep is a very active process coupled with the generators or effectors of many components of both REM and NREM sleep that reside in the brain stem and other

"lower" centers, it is not surprising that, during sleep, prominent motoric and affective behaviors do occur given the close neuroanatomic real estate in which these reside.

Some very dramatic cases have been tried in a court of law to utilize confusional arousals as an explanation for an alleged criminal offense. This avenue for potential acquittal has been popularly referred to as the "Sleepwalking Defense." In one, the "Parks" case in Canada, the defendant drove alone 23 km across town, entered the home of his in-laws, killed his mother-in-law, and attempted to kill his father-in-law. Somnambulism was the legal defense, and he was acquitted [39]. In another, the "Butler, PA" case, a confusional arousal attributed to underlying OSA was offered as a criminal defense for a man who fatally shot his wife during his usual sleeping hours. He was found guilty [40]. In a highly publicized homicide case out of Phoenix, Arizona, a man stabbed his wife 44 times then left her body in the backyard pool. This case was particularly curious as both the prosecution and the defense were each able to secure the services of well-respected notable sleep medicine experts that offered sharply contrasting opposing opinions. He was found guilty of 1st Degree Murder and continues to serve his life sentence in prison without chance for parole [41].

Inappropriate sexual behaviors during the sleep state, presumably the results of an admixture of wakefulness and sleep, have been well described [42–51]. The "*Sleepwalking Defense*" has been well-received by defense attorneys and has been successfully applied in the USA in cases of purported "*Sexsomnia*" resulting in a complete acquittal, as in *State of Oregon v. James Kirchner* (**see Add Reference Addendum** [110]). Cramer Bornemann presented at SLEEP 2014 (the annual meeting of the Affiliated Professional Sleep Societies) in Minneapolis, Minnesota that over 33 % of the more than 260 forensics cases submitted between 2006 and 2013 for formal medico-legal review to a sleep forensics consulting consortium were associated with charges of sexual assault for which a Sleep-related Abnormal Sexual Behavior was considered (**see Add Reference Addendum** [111]). Furthermore, recurrent sexually oriented hypnagogic hallucinations experienced by patients with narcolepsy may be so vivid and convincing to the victim that they may serve as false accusations [52]. Despite the broad clinical acceptance of this condition and some success in the court of law, many in the legal community remain skeptical over the legitimacy of "Sexsomnia" as demonstrated by a recent update put forth by the National Center for the Prosecution of Child Abuse entitled "*Overcoming the Sleep Disorder Defense*" (**see Add Reference Addendum** [112]).

Sleep talking has also been addressed by the legal system; it is interesting to ponder whether utterances made during sleep are admissible in court [53].

Specific incidents of violence associated with disorders of arousal include [13]

1. Somnambulistic homicide and attempted homicide
2. Murders and other crimes during sleep drunkenness, including sleep apnea and narcolepsy
3. Suicide or suicide attempts [54, 55]
4. Violence/injury during sleep terrors or sleepwalking; these episodes may be drug-induced.

Violent sleep behaviors may result in post-traumatic stress disorder in the spouse or bed partner [56].

Other, very important factors beyond the scope of this chapter include (1) the known effect of genetics on violence and (2) the well-demonstrated effects of environmental and social factors upon the structure and function of the nervous system [57]. (In one study of 31 individuals awaiting trial or sentencing for murder, none was neurologically or psychiatrically normal [15].) The plasticity of the nervous system is greater than previously thought [58, 59]. These factors are undoubtedly operant in both wakeful and sleep-related violence.

REM Sleep Behavior Disorder

RBD represents an experiment of nature, predicted in 1965 by animal experiments [60] and more recently identified in humans [61]. Normally, during REM sleep, there is active paralysis of all somatic muscles (sparing the diaphragm and eye movement muscles). In RBD, there is the absence of REM sleep atonia, which permits the "acting out" of dreams, often with dramatic and violent or injurious behaviors. The oneiric (dream) behavior demonstrated by cats with bilateral peri-locus coeruleus lesions and by humans with spontaneously occurring RBD clearly arises from and continues to occur *during* REM sleep. These oneiric behaviors displayed by patients with RBD are often misdiagnosed as manifestations of a seizure or psychiatric disorder. Longitudinal research studies tracking RBD have revealed a compelling association between this condition and the eventual development of any of a number of chronic neurodegenerative disorders, most notably the synucleinopathies (Parkinson's disease, multiple system atrophy (Shy-Drager syndrome), and dementia with Lewy body disease). RBD may be the first manifestation of these conditions and may precede any other manifestation of the underlying neurodegenerative process by more than 10 years [62, 144] (**see Add Reference Addendum** [113, 114]). The overwhelming male predominance (90 %) of RBD raises interesting questions about the relationship of sexual hormones to aggression and violence [63, 64]. The violent and injurious nature of RBD behaviors has been extensively reviewed

elsewhere [62]. Treatment with clonazepam is highly effective [62].

As with the disorders of arousal, underlying sleep apnea may simulate RBD, again underscoring the necessity for thorough formal PSG evaluation of all bothersome complex behaviors arising during the sleep period [65].

Nocturnal Seizures

The association between seizures and violence has long been debated. It is plain that, on occasion, seizures may result in violent, murderous, or injurious behaviors [2, 66]. Of particular note is the frantic and elaborate nocturnal motor activity that may result from seizures originating in the orbital, mesial, or prefrontal region [67]. "Episodic nocturnal wanderings," a condition clinically indistinguishable from other forms of sleep-related motor activity such as complex sleepwalking, but that is responsive to anticonvulsant therapy, has also been described [68–70]. Aggression and violence may be seen pre-ictally, ictally, and postictally. The postictal violence is often induced or perpetuated by the good intentions of bystanders trying to "calm" the patient following a seizure [71]. As with disorders of arousal, OSA may masquerade as nocturnal seizures [72–74].

Psychiatric Conditions

Psychogenic Dissociative States

Waking dissociative states may result in violence [75]. It is now apparent that dissociative disorders may arise exclusively or predominately from the sleep period [2, 76]. Virtually all patients with nocturnal dissociative disorders evaluated at our center were victims of repeated physical and/or sexual abuse beginning in childhood [77].

Malingering

Although relatively uncommon in a clinical sleep medicine setting, malingering must also be considered in cases of apparent sleep-related violence In contrast, malingering is not uncommon in criminal proceedings and should be strongly suspected if: (i) the case is presented in a medico-legal context or has potential criminal implications, (ii) marked discrepancy between reported symptoms and objective findings, (iii) lack of cooperation with evaluation, and (iv) the presence of Anti-Social Personality Disorder (**see Add Reference Addendum** [115, 116]). Additionally, malingering should be distinguished from Factitious as well as somatoform disorders. In cases involving sleep-related violence, opportunistic malingering would appear to be the most relevant subtype of this condition with its potential for exploiting a naturally occurring event or preexisting condition. Our center has recently seen a young adult male who developed progressively violent behaviors, apparently arising from sleep, directed exclusively at his wife. This behavior included beating her and chasing her with a hammer. Following extensive neurologic, psychiatric, and PSG evaluation, it was determined that this behavior represented malingering.

Munchausen Syndrome by Proxy

In this syndrome, a child is reported to have apparently medically serious symptoms that, in fact, are induced by an adult—usually a caregiver, often a parent. The use of surreptitious video monitoring in sleep disorder centers during sleep (with the parent present) has documented the true etiology for reported sleep apnea and other unusual nocturnal spells [78–80].

Medicolegal Evaluation

Clinical and Laboratory Evaluation of Waking and Sleep Violence

The history of complex, violent, or potentially injurious motor behavior arising from the sleep period should suggest the possibility of one of the previously mentioned conditions. Our sleep forensics consulting consortium experience with over 300 adult cases of sleep-related injury/violence has repeatedly indicated that clinical differentiation, without PSG study, among RBD, disorders of arousal, sleep apnea, and sleep-related psychogenic dissociative states and other psychiatric conditions may be impossible [13]. It is likely that violence arising from the sleep period is more frequent than previously assumed.

The legal implications of automatic behavior have been discussed and debated in both the medical and legal literature [1, 81–83]. As with nonsleep automatisms, the identification of a specific underlying organic or psychiatric sleep violence condition does not establish causality for any given deed as the two are not temporally linked.

These conditions are diagnosable, and most are treatable. Clinical evaluation should include a complete review of sleep/wake complaints from both the victim and bed partner (if available). This should be followed by a thorough general physical, neurologic, and psychiatric examination. The diagnosis may only be suspected clinically. Extensive polygraphic study employing a full EEG montage, electromyographic monitoring of all four extremities, and continuous audiovisual recording is mandatory for correct diagnosis in atypical cases; and clinical and laboratory evaluations are best performed by experienced clinicians [13].

Establishing the diagnosis of nocturnal seizures may be extremely difficult, as the motor activity associated with the spell often obscures the EEG pattern. Further, there may be no scalp-EEG manifestation of the seizure activity. Numerous well-documented cases of scalp electrode EEG-negative but depth electrode EEG-positive electrical seizure activity or video-documented clinical seizure activity have been reported [84–86]. Another possible explanation for "scalp electrode EEG-negative" seizures is that some seizures manifest electrically with only generalized low-voltage fast activity, not followed by postictal slowing [87]. Such activity arising from EEG-recorded sleep may be misinterpreted as an "arousal," rather than as electrical seizure activity. Seizure activity arising in the limbic system may spread to other more "primitive" structures, with resultant clinical behaviors, without EEG involvement of the neocortex [9]. The treatment of nocturnal seizures is similar to that of diurnal seizures. The previously mentioned difficulties in evaluating nocturnal seizures (obscuring of the record by movement artifact, the absence of surface EEG abnormality or electrical seizure activity, lack of postictal slowing, misinterpretation of electrical seizure activity as an "arousal") emphasize the necessity of extensive, in-person laboratory monitoring. (Scantily channeled "ambulatory" EEG monitoring has led to the misdiagnosis of functional psychiatric disease in a number of our patients subsequently demonstrated to have bona fide nocturnal seizures.) If the history or physical examination suggests underlying neurologic disease, further studies such as magnetic resonance imaging or computed tomography scanning of the brain, multimodal (visual, auditory, and somatosensory) evoked potentials, and/or formal neuropsychometric evaluation are indicated.

While it is often possible to state that a given violent act may conceivably have arisen from the sleep period or from a mixed state of wakefulness and sleep, it is usually impossible to prove that a given incident did, in fact, represent a sleep-related phenomenon. To assist in the determination of the putative role of an underlying sleep disorder in a specific violent act, we have proposed guidelines, modified from Bonkalo (sleepwalking) [21], Walker (epilepsy) [88], and Glasgow (automatism in general) [89] and formulated from our clinical experience [2]:

1. There should be reason by history to suspect a *bona fide* sleep disorder. Similar episodes, with benign or morbid outcome, should have occurred previously. (It must be remembered that disorders of arousal may begin in adulthood.)
2. The duration of the action is usually brief (seconds), though action of longer duration (minutes) does not necessarily exclude a sleep disorder or a sleep-related behavior.
3. The behavior is usually abrupt, immediate, impulsive, and senseless—without apparent motivation. Although ostensibly purposeful, it is completely inappropriate to the total situation, out of (waking) character for the individual, and without evidence of premeditation.
4. The victim is someone who merely happened to be present, usually in proximity, and who may have been the stimulus for the arousal. Sleepwalkers rarely, if ever, seek out victims (**see Add Reference Addendum** [107])
5. Immediately following return of consciousness, there is perplexity or horror, without attempt to escape, conceal, or cover up the action. There is evidence of lack of awareness on the part of the individual during the event.
6. There is usually some degree of amnesia for the event; however, this amnesia need not be complete.
7. Sleep is an analgesic state. The sensory pathway for pain for the most part is considered "off-line" during sleep. Consequently, pain associated with acts committed during disorders of arousal may not be perceived until awakening after the event.
8. In the case of sleep terrors/sleepwalking or sleep inertia, the act:

   A. May occur upon awakening (rarely immediately upon falling asleep)—usually at least 1 h after sleep onset
   B. Occurs upon attempts to awaken the subject
   C. Has been potentiated by sedative-hypnotic administration or prior sleep deprivation
9. Polysomnographic studies performed "after the fact" are of absolutely no value in determining whether a parasomnia accounted for the remote act in question. Even capturing a parasomnia event during a sleep would indicate behavior at the time of the recording, not remotely. Furthermore, there is no scientific basis for attempting to replicate conditions surrounding the event in question (sleep deprivation, alcohol, or other substance ingestion) during a sleep study. Provocation tests to trigger parasomnias by any intoxicants or mind-altering agents would appear to be ethically challenged until well-controlled validated research studies have been performed.
10. Voluntary intoxication by alcohol over the legal limit, or other illicit mind-altering intoxicants, precludes the sleepwalking defense.
11. Lastly, the violent criminal allegation cannot be better explained by another mental disorder, medical condition, or substance use. This last guideline is also in accordance with the diagnostic guidelines for parasomnias as set forth in the most recent International Classification of Sleep Disorders 3rd edition (ICSD-3).

Sleep forensics has been defined as the application of the principles and tools of neuroscience as applied to Somnology and Sleep Medicine that have been widely accepted under international scientific peer review to the investigation in understanding unusual, irrational, and/or bizarre human behaviors associated with alleged criminal behavior which is to undergo further examination in a conflict resolution legal atmosphere and/or courtroom. The proposition that sleep disorders may be a legitimate defense in cases of violence arising from the sleep period has been met understandably with much skepticism [90] (**see Add Reference Addendum** [112]). For credibility, evaluations of such complex cases are best performed in experienced sleep disorders centers with interpretation by a veteran clinical polysomnographer. Due to the complex nature of many of these disorders, a multidisciplinary approach is highly recommended.

One fortunate, and unexplained, fact is that nocturnal sleep-related violence is seldom a recurrent phenomenon [90]. Very rarely, recurrence is reported, and possibly could be termed a "noninsane automatism." Thorough evaluation, effective treatment, and longitudinal clinical management are mandatory before the patient can be regarded as no longer a menace to society [91]. In other cases, clear precipitating events can be identified and must be avoided to be exonerated from legal culpability. This concept has led to the proposal of two new forensic categories: (1) "parasomnia with continuing danger as a noninsane automatism" and (2) "(intermittent) state-dependent continuing danger" [91].

Legal and Forensic Medicine Evaluation

With the identification of ever-increasing causes, manifestations, and consequences of sleep-related violence comes an opportunity for neurologists and sleep medicine specialists to educate the general public and practicing clinicians as to the occurrence and nature of such behaviors, and about their successful treatment. More important, the onus is on the sleep medicine professional to educate and assist the legal profession in cases of sleep-related violence that result in forensic medicine issues. This often presents difficult ethical problems, as most "expert witnesses" are retained by either the defense or the prosecution, leading to the tendency for expert witnesses to become advocates or partisans for either one side or the other. Historically, this has been fertile ground for the appearance of "junk science" in the courtroom [92]—from Bendectin to triazolam to breast implants. Junk science leads to junk justice, and altered standards of care [93]. Recently, much attention has been paid to the existence and prevalence of junk science in the courtroom, with recommendations to minimize its occurrence. Prior to accepting any given case, the sleep professional should familiarize him/herself with this most important issue. A good starting point is the highly informative book, *Galileo's Revenge: Junk Science in the Courtroom* [92]. There is some hope that the judicial system is paying more attention to the process of authentic science and may move to accept only valid scientific evidence [94, 95]. To address the problem of junk science in the courtroom, many professional societies are calling for, and some have developed guidelines for, expert witness qualifications and testimony. Similarly, the American Sleep Disorders Association (the American Academy of Sleep Medicine) and the American Academy of Neurology have adopted their own guidelines, which include [96, 97]:

A. Expert witness qualifications:
   1. Must have a current, valid, unrestricted medical ,or psychology license.
   2. Must be a Diplomat of the American Board of Sleep Medicine or have passed the American Board of Internal Medicine specialty examination in sleep medicine.
   3. Membership in the Sleep Research Society is strongly encouraged.
   4. Must be a recognized resource within the sleep medicine community and should have been actively involved in clinical practice in a manner consistent with the requirement of the criminal case at the time of the event.
   5. Given the essential position of *mens rea* in criminal law and the pivotal role of levels of consciousness must have significant direct experience in either neurology and/or neuroscience.

B. Guidelines for expert testimony:
   1. The practitioner must be impartial: The ultimate test for accuracy and impartiality is a willingness to prepare testimony that could be presented unchanged for use by either the plaintiff or the defendant.
   2. Fees should relate to time and effort, not be contingent upon the outcome of the claim. Fees should not exceed 20 % of the practitioner's annual income.
   3. The practitioner should be willing to submit such testimony for peer review.
   4. To establish consistency, the practitioner should make records from his or her previous expert witness testimony available to the attorneys and expert witnesses of both parties.
   5. The practitioner must not become a partisan or advocate in the legal proceeding.

Familiarizing oneself with these guidelines may be helpful in a given case, as the expert witnesses for each side should be held to the same standards [98].

The current legal system unfortunately must consider a parasomnia case strictly in terms of choosing between "insane" or "noninsane" automatism. Such a choice results in two very different consequences for the accused: either commitment to a mental hospital for an indefinite period of time if "insane" or acquittal without any mandated medical consultation or follow-up, or without any stipulated deterrent concerning a recurrence of the behavior with criminal charges that was induced by a recurrence of the high-risk behavior. One reasonable approach in dealing with these automatisms from a legal standpoint would be to add a category of acquittal that allowed for innocence based on lack of guilt consequent to set diagnoses—specific illnesses that could be categorized by a group of subspecialty clinicians in consultation with the legal profession [99]. Another suggestion has been a two-stage trial, which would first establish who committed the act and then deal separately with the issue of culpability. The first part would be held before a jury; the second would be held in front of a judge with medical advisors present [100].

Forensic Sleep Medicine Experts as Impartial Friends of the Court (Amicus Curae)

One infrequently used tactic to improve scientific testimony is to use a court-appointed "impartial expert" [92]. When approached to testify, volunteering to serve as a court-appointed expert, rather than one appointed by either the prosecution or defense, may encourage this practice. Other proposed measures include the development of a specific section in scientific journals dedicated to expert witness testimony extracted from public documents with request for opinions and consensus statements from appropriate specialists, or the development of a library of circulating expert testimony that could be used to discredit irresponsible "professional witnesses" [92]. Good science is determined not by the credentials of the expert witness, but rather by scientific consensus [93].

Summary and Directions for the Future

It is abundantly clear that violence may occur during any one of the three states of being. That which occurs during REM or NREM sleep may have occurred without conscious awareness and may be due to one of a number of completely different disorders. Violent behaviors during sleep may result in events that have forensic science implications. The apparent suicide (e.g., leaping to death from a third-story window), assault, or murder (e.g., molestation, strangulation, stabbing, shooting) may be the unintentional, nonculpable but catastrophic result of disorders of arousal, sleep-related seizures, RBD, or psychogenic dissociative states. The majority of these conditions are diagnosable and, more important, are treatable. The social and legal implications are obvious.

The fields of neurology and sleep medicine must pursue further productive study and discourse and request adequate funding to objectively study the following important questions: What is the true prevalence of these disorders? How are they best and most accurately diagnosed? How can the usually present prodromes be taken seriously? Why the male predominance in many? How can they best be treated or, better yet, prevented? Are "social stressors" truly more prevalent in this population? What is the best way to deal with forensic science issues? What to do with the offender? What is the likelihood of recurrence? Is such behavior a sane or an insane automatism? [101]. How to protect the potential victim?

More research, both basic science and clinical, is urgently needed to further identify and elaborate upon the components of both waking and sleep-related violence, with particular emphasis upon neurobiologic, neuroplastic, genetic, and socioenvironmental factors [15, 16, 102]. The study of violence and aggression will be greatly enhanced by close cooperation among clinicians, basic science researchers, and social scientists.

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General Principle of Treatment of Sleep Dysfunction and Pharmacology of Drugs Used in Sleep Disorders

55

Jaime M. Monti

Abbreviations

AASM	American Academy of Sleep Medicine
BZD	Benzodiazepine
CNS	Central nervous system
EEG	Electroencephalogram
EMG	Electromyogram
GABA	Gamma-aminobutyric acid
GAD	Generalized anxiety disorder
LPS	Latency to persistent sleep
MCH	Melanin-concentrating hormone
MDD	Major depressive disorder
MOTN	Middle of the night
NREMS	Non-REM sleep
REMS	REM sleep
SE	Sleep efficiency
SOL	Sleep onset latency
SWS	Slow-wave sleep
TST	Total sleep time
W	Wakefulness
WASO	Wake time after sleep onset

Introduction

Sleep is closely related to every facet of daily life. In this respect, disturbed sleep affects not only our health and well-being but also our quality of life. Dement and Kleitman [1] and Rechtschaffen and Kales [2] provided a description of sleep cycles and a classification system of sleep stages that comprise a waking state, four non-rapid eye movement sleep (NREMS) stages, and rapid eye movement sleep (REMS). Accordingly, the young adult was found to spend 20–28 % of a night's sleep (7–8 h) in REMS, 4–5 % in stage 1 (S1), 46–50 % in stage 2 (S2), 6–8 % in stage 3 (S3), and 10–16 % in stage 4 (S4). Agnew et al. [3] studied the sequence in which one sleep stage appeared after another during NREMS. When NREMS started deepening, a progression of only one stage at a time (from S1 to S4) was usually observed. When sleep was moving out of S4 sleep, stage-by-stage changes were also observed. However, comparatively higher amounts of abrupt shifts were evident. REMS follows a course independent of the NREMS stages. The first REM period appears about 90 min after falling asleep. NREMS preceding the first dream period distinctively shows large amounts of slow-wave sleep (SWS: S3 + S4). During a typical 8-h sleeping night, five to six REM periods occur at intervals of 80–100 min, with the duration of each period generally increasing over the night. Stage 4 sleep and REMS are differentially distributed during the night. Stage 4 sleep predominates during the early part of the night and REMS in the latter part. In 2007, the American Academy of Sleep Medicine (AASM) introduced a new

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guideline for terminology, recording method, and scoring rules for sleep-related phenomena [4]. In the AASM classification, S1, S2, and S3 + S4 are referred to as N1, N2, and N3, respectively. NREMS and REMS latency, total sleep time, and sleep efficiency (SE) are not affected by the new scoring criteria, whereas wake time after sleep onset (WASO) is increased significantly. With respect to sleep architecture, light sleep (S1 vs. N1) and SWS or deep sleep (S3 + S4 vs. N3) are significantly increased, while intermediate sleep (S2 vs. N2) is reduced. The diagnostic criteria of sleep disturbances according to the International Classification of Sleep Disorders (ICSD-2) [5] do not depend on sleep laboratory findings (ICSD-3 [see Chap. 27] published in 2014 retains the same principle), which tend to indicate that the former would not be influenced directly by the AASM classification [6]. Sleep stages reported in polysomnographic studies that included either untreated or medicated patients with a diagnosis of primary or comorbid insomnia are mostly based on the sleep scoring rules and terminology developed by Rechtschaffen and Kales [2].

Electrographic activity of the rat, a species currently used in preclinical studies, has been assigned to the following categories based on the waveform: wakefulness (W) [low-voltage fast waves in frontal cortex, a mixed theta rhythm (4–7 Hz) in occipital cortex and relatively high electromyographic (EMG) activity]; light sleep [high-voltage slow cortical waves interrupted by low-voltage fast electroencephalographic (EEG) activity]; SWS (continuous high-amplitude slow frontal and occipital waves combined with a reduced EMG); and REMS (low-voltage fast frontal waves, a regular theta rhythm in the occipital cortex and a silent EMG except for occasional myoclonic twitchings).

Neurotransmitters and Circulating Factors Involved in the Regulation of Sleep and Wakefulness

Our present knowledge on the neurotransmitters and somnogens involved in the regulation of the behavioral state has helped to understand the mechanism of action of substances currently administered for the treatment of insomnia in man and to the development of new compounds with an improved therapeutic profile.

Wake-Promoting Structures and Neurotransmitters

The central nervous system (CNS) structures involved in the promotion of the waking state are located in the brainstem, hypothalamus, and basal forebrain (BFB). The nuclei found in the brainstem include the dorsal raphe nucleus (DRN) synthesizing serotonin (5-HT); locus coeruleus (LC) synthesizing norepinephrine (NE); ventral tegmental area (VTA), substantia nigra pars compacta (SNc) and ventral periaqueductal gray (vPAG) containing dopamine (DA); and laterodorsal and pedunculopontine tegmental nuclei (LDT/PPT) containing acetylcholine (ACh). The structures found in the hypothalamus comprise the tuberomammillary nucleus (TMN) and the posterior lateral hypothalamus around the fornix where histamine (HA)- and orexin (OX)-containing cells are located, respectively. The cholinergic and glutamatergic neurons of the BFB involved in the regulation of W have been characterized mainly in the diagonal band of Broca, substantia innominata, and medial septal area [7, 8]. Most of the neuroanatomical structures included in the arousal system show, in addition, a great variety of neuropeptide-containing neurons as well as γ-aminobutyric acid (GABA)-ergic cells. The monoamine-, acetylcholine-, and glutamate-containing neurons that participate in the regulation of W give rise to mainly ascending projections to (1) the thalamus (dorsal route) which in turn projects to the cerebral cortex and (2) the BFB (ventral route) where cells in turn project to the cerebral cortex and hippocampus. The DA-containing neurons of the VTA and SNc project to the basal ganglia and the prefrontal cortex, whereas those corresponding to the vPAG project predominantly to the BFB and midline thalamus. Furthermore, OX-containing cells carry projections to the entire forebrain and brainstem arousal systems [9]. Of note, isolated activation of each of the arousal systems already provokes W. However, under normal conditions, they all participate in the occurrence of behavioral and EEG arousal. This is partly related to the interconnections of most W-promoting structures. Additionally, the systems that foster W inhibit neural structures located in the brainstem and hypothalamus that promote and/or induce NREMS (light sleep + SWS in laboratory animals) and REMS [10].

NREM Sleep-Promoting Structures and Neurotransmitters

Neurons of the preoptic area and adjacent BFB constitute the NREMS-inducing system. NREMS active neurons of the preoptic area and BFB contain GABA and galanin, and project to brainstem and hypothalamic areas involved in the promotion of W [11]. Somnogens including adenosine (formed inside cells or extracellularly by the breakdown of adenosine nucleotides), prostaglandin D2 (produced by lipocalin-type prostaglandin synthase which is mainly present in the leptomeninges, choroid plexus, and oligodendrocytes, and released in the cerebrospinal fluid), nitric oxide

(NO) (synthesized at central sites mainly from L-arginine by neuronal NO synthase), and cytokines (interleukin-1 and tumor necrosis factor-α) promote also sleep, mainly NREM sleep, in laboratory animals and man [12–15].

REM Sleep-Promoting Structures and Neurotransmitters

Cholinergic (REM-on) neurons of the LDT/PPT have been identified as promoting REMS. Moreover, the subcoeruleus nucleus has been proposed as the critical area for REMS generation in the cat. Its equivalent in the rat and mouse is called the sublaterodorsal nucleus. It should be mentioned that the parabrachial area, nucleus pontis oralis, and nucleus pontis caudalis contribute also to the occurrence of a number of REMS signs [16]. The REMS induction regions include predominantly glutamatergic and GABAergic neurons. More recently, melanin-concentrating hormone (MCH) neurons located in the lateral hypothalamus and zona incerta have been proposed to participate also in the regulation of sleep, including NREMS and REMS [17]. With respect to the prospective role of GABAergic neurons in the regulation of REMS, the updated reciprocal interaction model [18] proposes that during REMS, REM-on cholinergic LDT/PPT neurons excite pontine reticular formation REM-on GABAergic cells which in turn inhibit REM-off monoaminergic neurons.

Role of Neurotransmitter Systems in the Regulation of the Behavioral State: Experimental Approaches

Strategies aimed at determining the role of neurotransmitter systems in the regulation of sleep and W have included electrophysiological, genetic, neurochemical, and neuropharmacological approaches.

During quiet W, 5-HT, NE, HA, and OX neurons fire in a slow and regular fashion. During active W, the neuronal activity shows a significant increase. As the animal enters NREMS, the mean discharge rate shows a progressive reduction, and during REMS, there is a further decrease or even a cessation of neuronal activity.

Mutant mice that do not express 5-HT1A or 5-HT1B receptor exhibit greater amounts of REMS than their wild-type counterparts. A similar outcome has been described in dopamine-β-hydroxylase and histidine decarboxylase (the enzymes responsible for converting DA to NE and histidine to HA, respectively)-deficient mice, or following the systemic administration of the neurotoxin DSP-4, which selectively lesions the NE neurons. Moreover, systemic injection of α-fluoromethylhistidine, a highly specific, irreversible inhibitor of histidine decarboxylase, induces a significant reduction of W, while NREMS and REMS are increased. Orexin knockout mice show severe sleepiness and are unable to maintain long periods of W during the dark phase. With respect to the dopaminergic system, behavioral arousal is impaired in D1 and D2 receptor-deficient mice, whereas it is facilitated in mutant mice lacking functional D3 receptor (Table 55.1).

Sleep and W have been studied in MCH knockout mice. The knockout animals sleep less during the light and the dark phase of the light/dark cycle under basal conditions. An increase of W and a reduction of SWS have been described in MCHR1 receptor knockout mice, which agrees with the proposed role of MCH in the regulation of the behavioral state [19].

Systemic or i.c.v. injection of full agonists of postsynaptic 5-HT1A, 5-HT1B, 5-HT2B, 5-HT2C, 5-HT3, 5-HT6, and 5-HT7 receptor; the selective NE α1 receptor agonist methoxamine or the NE reuptake inhibitors amphetamine and cocaine; the relatively selective HA H1 receptor agonist 2-thiazolylethylamine; the selective DA D1 receptor agonist SKF 38393; or the neuropeptide OX consistently increase W and reduce SWS and REMS in laboratory animals. In contrast, the DA D2 receptor agonists apomorphine, bromocriptine, or quinpirole produce biphasic effects, such that low doses decrease W and augment sleep, while large doses induce the opposite effects in the rat (Table 55.1).

A series of pharmacological studies have provided further evidence for the involvement of ACh in the regulation of W and REMS. Thus, systemic administration of the muscarinic receptor agonists pilocarpine and arecoline evokes a characteristic cortical arousal which is reduced by atropine, while microinjection of the broad-spectrum cholinergic agonist carbachol or the anticholinesterase agents physostigmine and neostigmine into the medial pontine reticular formation induces a long-lasting REMS-like state in the cat (Table 55.1).

The actions of GABA in the CNS are mediated by three different classes of receptors denominated GABA-A, GABA-B, and GABA-C receptors. The GABA-A receptor predominates at central sites. GABAergic neurons comprise many functionally different subgroups, as evident in recorded cells in the BFB, hypothalamus, and brainstem. As mentioned before, a majority of sleep-active cells of the preoptic area contain GABA, and project to the BFB and to brainstem and hypothalamic areas involved in the promotion of W. BFB GABAergic neurons have been shown to be involved in the occurrence of W; in this respect, they target inhibitory interneurons and through disinhibition activate pyramidal cells. BFB GABAergic cells have been proposed

Table 55.1 The role of monoamines, orexin, and acetylcholine in the regulation of wakefulness in laboratory animals

	W	SWS	REMS
Serotonin			
– Electrophysiological approach			
Discharge rates during the sleep–wake cycle	High	Low	Lowest
– Genetic approach			
Mutant mice that do not express 5-HT_{1A} or 5-HT_{1B} receptor	n.s.	n.s.	+
– Neuropharmacological approach			
Systemic or i.c.v. administration of full agonists of postsynaptic 5-$HT_{1A/1B}$, 5-$HT_{2A/2B/2C}$, 5-HT_3, 5-HT_6, and 5-HT_7 receptor	+	−	−
Norepinephrine			
– Electrophysiological approach			
Discharge rates during the sleep–wake cycle	High	Low	Lowest
– Genetic and neurochemical approaches			
Dopamine-β-hydroxylase-deficient mice Systemic injection of the neurotoxin DSP-4	n.s. n.s.	n.s. n.s.	+ +
– Neuropharmacological approach			
Systemic administration of NE reuptake inhibitors (cocaine, amphetamine) or α_1-receptor agonist methoxamine	+	−	−
Histamine			
– Electrophysiological approach			
Discharge rates during the sleep–wake cycle	High	Low	Lowest
– Genetic and neurochemical approach			
Histidine decarboxylase knockout mice	n.s.	n.s.	+
Mutant mice that do not express H_1 receptor	Fewer brief awakenings and a shorter SWS latency		
Systemic injection of the synthesis inhibitor α-fluoromethylhistidine	−	+	+
− **Neuropharmacological approach**			
I.c.v. injection of the H_1 receptor agonist 2-thiazolethylamine Systemic administration of the H_1 receptor antagonists mepyramine, diphenhydramine, and promethazine	+ −	− +	− −
Orexin			
– Electrophysiological approach			
Discharge rates during the sleep–wake cycle	High	Low	Lowest
– Genetic approach			
Orexin knockout mice	Severe sleepiness; do not maintain long periods of W during the dark phase		
– Neuropharmacological approach			
I.c.v. administration of orexin Injection of the orexin receptor antagonist almorexant	+ −	− +	− +
Dopamine			
– Electrophysiological approach			
Discharge rates during the sleep–wake cycle	Change in temporal pattern that manifests in the VTA as an increase in burst firing during W and REMS		
– Genetic and neurochemical approaches			
Dopamine D_1 and D_2 receptor deficient mice	Impairment of behavioral arousal		
Systemic administration of the neurotoxin MPTP	n.s.	−	−

(continued)

Table 55.1 (continued)

	W	SWS	REMS
– Neuropharmacological approach			
Systemic injection of the D_1 receptor agonist SKF 38393	+	−	−
Systemic injection of the D_2 receptor agonist bromocriptine			
– Presynaptic effect	−	+	n.s./−
– Postsynaptic effect	+	−	−
Systemic injection of the D_2 receptor antagonist haloperidol	−	+	−
Acetylcholine			
– Electrophysiological approach			
Discharge rates during the sleep–wake cycle (LDT/PPT nuclei)	High (W-on)	Low	High (REM-on)
– Neurochemical approach			
I.c.v administration of the choline uptake inhibitor hemicholinium-3	−	n.s.	−
– Neuropharmacological approach			
Systemic administration of the muscarinic receptor agonists pilocarpine and arecoline	+	−	−
Medial pontine reticular formation injection of physostigmine and neostigmine	n.s.	n.s.	+

W wakefulness; *SWS* slow-wave sleep; *REMS* REM sleep; *I.c.v.* intracerebro-ventricular; *VTA* ventral tegmental area; *n.s.* non-significant; + significant increase; − significant reduction

to contribute also to the modulation of REMS via descending projections that induce direct inhibition of REMS-regulatory neurons located in the brainstem.

Of note, the GABA-A receptor is the site of action of several hypnotic drugs, including the benzodiazepine (BZD) (midazolam, temazepam), cyclopyrrolone (zopiclone, eszopiclone), imidazopyridine (zolpidem), and pyrazolopyrimidine (zaleplon) derivatives where they behave as allosteric modulators.

The injection of MCH into the left lateral ventricle of the rat at the beginning of the dark phase induced a significant and dose-dependent increase in REMS during the first 2 h of the recording period. Microinjection of MCH into the nucleus pontis oralis, DRN, LC, and BFB (horizontal limb of the diagonal band of Broca) produced also a marked increase in REMS in the cat and the rat, respectively [19].

Melatonin is synthesized in great measure in the pineal gland and released in close association with the increase in sleep propensity (night in primates and man). The finding that systemic administration of melatonin to laboratory animals reduces sleep onset latency and increases SWS supports the proposal that it is involved in the regulation of sleep. The sleep-promoting and sleep–wake rhythm-regulating effects of melatonin are related to the activation of MT1 and MT2 receptors expressed by cells located in the suprachiasmatic nucleus of the hypothalamus [20]. Ramelteon is a melatonin MT1/MT2 agonist that acts predominantly on the suprachiasmatic nucleus and is effective in reducing sleep latency in laboratory animals and man.

Insomnia: Diagnostic Criteria

Insomnia is characterized by one or more of the following: difficulty falling asleep (sleep latency of more than 30 min), insufficient sleep (total sleep time of less than 5.5–6 h), numerous nocturnal awakenings, early morning awakenings with inability to resume sleep, or non-restorative sleep. Common daytime complaints include somnolence, fatigue, irritability, and difficulty concentrating and performing everyday tasks. Because insomnia is associated with reduction in attention span, affected individuals can often be impulsive and experience impaired judgment, and thus are at an increased risk for having injuries at home or work, or involvement in accidents while driving.

The ICSD-2 [5] considers severity criteria as a guide to be applied in conjunction with the consideration of the patient's clinical status. Mild insomnia refers to complaints of an insufficient amount of sleep almost every night or of not feeling rested the following day. Moderate and severe insomnia refers to complaints of experiencing an insufficient amount of sleep every night or of not being rested after the impaired sleep episode, accompanied by moderate and severe impairment of social and/or occupational functioning, respectively. The duration of insomnia has been considered also an important guide to its evaluation and treatment. Individuals with transient insomnia are normal sleepers who experience an acute stress for a few days which disrupts their sleep. Short-term insomnia is usually associated with situational stress. This type of insomnia may last up to 3 weeks.

However, in some cases, short-term insomnia may progress into a chronic condition. Conventionally, long-term or chronic insomnia has been considered to be that which lasts for at least 21–30 nights. Usually, it persists for months or years, and its onset may or may not be associated with an identifiable stressor.

The ICSD-2 [5] has classified chronic insomnia in adult patients as primary or secondary. The term secondary insomnia has been replaced recently by comorbid insomnia, because during some instances, the sleep disturbance can show as a separate complaint and require a treatment different from that of the comorbid condition. When there is no other diagnosable condition directly associated with the chronic insomnia, it is diagnosed as primary insomnia. If the insomnia is precipitated or aggravated by a psychiatric or neurological disease, a general medical condition, another sleep disorder, a disturbance of circadian rhythm, or the direct effects of a medication or a substance of abuse, then the other disorder is termed primary and the insomnia comorbid. The ICSD-3 abandoned classifying insomnia into subtypes and instead retained a global view and classified insomnia into chronic, short-term and other insomnia disorders (see Chap. 27). The ICSD-3 also eliminated the severity criteria.

The prevalence of chronic insomnia has been shown to vary between 10 and 15 % of the adult population. It is higher in older adults, and in this group, women prevail significantly. Moreover, depression or anxiety disorders have been diagnosed in 40 % of patients with chronic insomnia [21, 22]. The determinants of comorbid insomnia and induced subjective and objective sleep changes are presented in Tables 55.2, 55.3, 55.4, and 55.5.

Treatment of Primary and Comorbid Insomnia

Any strategy to the effective management of primary and comorbid insomnia should appropriately combine both pharmacological and non-pharmacological measures. In patients with comorbid insomnia, the underlying disorder needs to be assessed and treated appropriately [23]. Several classes of medications have been prescribed as hypnotics over the years, including the BZD receptor agonists (either benzodiazepinic or non-benzodiazepinic agents); melatonin and the melatonin agonist ramelteon; and the tricyclic antidepressant doxepin. The BZD hypnotics (midazolam, triazolam, temazepam, flunitrazepam, flurazepam, quazepam) were introduced in the 1970s and rapidly increased in popularity because of their efficacy and relative safety compared with barbiturates, carbamates, chloral derivatives, and methaqualone. However, the occurrence of adverse events including somnolence, dizziness and fatigue, the contingency of rebound insomnia following the withdrawal of short- and intermediate-acting derivatives, the risk of falls

Table 55.2 Determinants of comorbid insomnia: mental disorders

Determinants of comorbid insomnia	Subjective sleep changes	Objective sleep changes
– **Depressive disorder** (lifetime prevalence of 16.2 %)	Difficulty falling asleep, fragmented sleep, disturbing dreams, early morning awakening, decreased amount of sleep, being tired during the day. Similar findings during bipolar depression	Increased W and reduced sleep efficiency; SOL is increased, while SWS and TST are reduced; REMS latency is shortened, and the duration of the first REM period is augmented
– **Anxiety disorders** Generalized anxiety disorder (lifetime prevalence of 6 %)	Difficulty falling asleep and staying asleep, early morning awakening	Increased SOL and WASO; reduced TST and sleep efficiency; less S2 sleep and SWS
Panic disorder (lifetime prevalence of 2–3 %)	Difficulty falling asleep and staying asleep; panic attacks can occur during sleep	Longer SOL and increased WASO; reduction in TST and SWS; increase of W. Sleep panic attacks are NREMS-related events, usually emerging from late S2 sleep or early S3 sleep
Obsessive–compulsive disorder (lifetime prevalence of 7–8 %)	Disturbed sleep continuity	Increased number of awakenings; decreased TST
Post-traumatic stress disorder (lifetime prevalence of 7–8 %)	Difficulty falling and staying asleep, early morning awakening	Anxiety arousals; REMS-related nightmares
– **Schizophrenia** (lifetime prevalence of 1 %)	Sleep induction and sleep maintenance are altered; total sleeplessness is frequently observed in patients with psychotic agitation	S2 sleep latency and WASO are increased; the majority of studies indicate that S4 sleep and REMS latency are reduced, whereas REMS duration tends to remain unmodified

REMS rapid eye movement sleep; *SE* sleep efficiency; *SOL* sleep onset latency; *SWS* slow-wave sleep; *TST* total sleep time; *W* wakefulness

Table 55.3 Determinants of comorbid insomnia: neurological diseases

Determinants of comorbid insomnia	Subjective sleep changes	Objective sleep changes
– **Alzheimer disease** (prevalence of sleep disturbances of 25–50 %)	Difficulty falling and staying asleep. The 24-h sleep–wake pattern can be disrupted to the point that patients spend as much as 30–40 % of their time in bed awake, and numerous daytime hours napping	Increased duration and frequency of awakenings and of S1 sleep; reduced SWS and REMS and lower sleep efficiency; EEG slowing during W and REMS
– **Parkinson disease** [prevalence of sleep disorders increases with age (1 % in patients aged 65–69 years old to 5 % among patients 80–84 years old)]	Difficulty falling and staying asleep. Factors that compromise sleep in these patients include tremor, akinesia, akathisia, PLM, painful dystonia, REMS behavioral disorder, nocturia, depression, and medications	Frequent awakenings; decrease in SWS and REMS; reduced sleep efficiency
– **Epilepsy** (about 25 % of patients with epilepsy have seizures during sleep)	Epileptic episodes may cause hypnic jerks, recurrent dreams, nightmares, or numerous arousals that may result in EDS or paroxismal awakenings and a complaint of insomnia	
– **Ischemic stroke**	Insomnia or hypersomnia and sleep-disordered breathing are often seen in patients who have an ischemic stroke	
– **Headache**	The headache can awaken the patient during the night. The attack may have the clinical features of a migraine, a cluster headache, or a chronic paroxismal hemicranea	

EDS excessive daytime sleepiness; *PLM* periodic limb movements; *REMS* rapid eye movement sleep

Table 55.4 Determinants of comorbid insomnia: medical conditions

Determinants of comorbid insomnia	Subjective and objective sleep changes
– Cardiovascular diseases	Congestive heart failure, hypertension, angina pectoris, and myocardial infarction are capable of disturbing sleep. Patients with ventricular insufficiency or mixed cardiopathy have more difficulty falling asleep, wake up more often, and have more daytime sleepiness as compared to normal subjects. In patients with acute or chronic coronary heart disease symptoms, sleep may be altered by angina, factors related to a myocardial infarction, antiarhythmic, and antihypertensive medication or the occurrence of anxiety and depression
– Respiratory disorders	Disturbances of sleep in COPD patients comprise increased SOL, frequent awakenings, increased WASO, and reduced TST. Moreover, obesity and menopausia are aggravating factors in the development of the sleep disturbance. Obstructive sleep apnea may coexist with COPD and contribute to the sleep-related symptoms Patients with nocturnal asthma awaken with dyspnea, wheezing, and cough. Attacks tend to develop mainly during S2 sleep or REMS and follow a random distribution. Patients complain of early awakenings, difficulty in maintaining sleep, daytime fatigue, and EDS
– Gastrointestinal disorders	The burning discomfort or pain in the chest during gastroesophageal reflux induces a fragmentation of sleep that can lead to a complaint of insomnia The pain of peptic ulcer disease can occur at night, producing arousal and awakenings that disturb sleep
– Renal diseases	Patients with end-stage renal disease complain very frequently of difficulty falling asleep, awakening in the middle of the night, restless legs, and EDS
– Endocrine diseases	Central sleep apnea is extremely common in patients with acromegaly. EDS is frequently observed in patients with hypothyroidism. Polysomnographic studies in these patients have shown that SOL and sleep continuity are not modified, while SWS is significantly reduced Usually, patients with asymptomatic hyperthyroidism do not complain of disturbed sleep. In contrast, most patients with thyrotoxicosis complain of insomnia characterized by an increase in the latency to sleep onset and frequent awakenings during the night Obstructive sleep apnea has been reported in patients with diabetic autonomic neuropathy. Apneic episodes have been noted mainly in type 1 patients. However, it was not a constant findings Insomnia is one of the somatic symptoms described in postmenopausal women. The sleep disturbance associated with menopause manifests as a sleep initiation and maintenance insomnia. The sleep complaints are mainly related to hot flashes, sweating, headaches, anxiety, depression, and sleep-disordered breathing

(continued)

Table 55.4 (continued)

Determinants of comorbid insomnia	Subjective and objective sleep changes
– Neoplastic diseases	Sleep disturbance is a frequent complaint among patients with neoplastic diseases Available evidence tends to indicate that between 30 and 50 % of cancer patients complain of difficulties initiating and/or maintaining sleep. In this respect, patients with breast and lung cancer seem more likely to have an insomnia complaint. In addition, environmental factors related to hospitalization, and oncologic treatments tend to aggravate the sleep disturbance
– HIV infection	Daytime fatigue and lethargy are common findings during the acute or preserum conversion phase of the disease. However, sleep disruption does not seem to be a major issue. In contrast, sleep complaints are frequently present during chronic infection with HIV. In these patients, SOL, TST, and S1 sleep are increased, whereas S2 sleep is reduced. There are also subjective complaints of non-restorative sleep. Medications used to treat HIV further disrupt sleep in these patients
– Rheumatic disorders	Disturbed sleep and daytime fatigue are frequent findings in patients with rheumatoid arthritis. There is a strong association between pain and the disruption of sleep referred by these patients. Sleep is also disturbed in other rheumatoid diseases, including lupus erythematosus, Sjögrens syndrome, osteoarthritis, and low back pain Fybromyalgia is associated in more that 75 % of patients with sleep disturbance and related daytime symptoms such as fatigue and morning stiffness. The non-restorative sleep depends mainly on the presence of pain. GAD and depression further add to the disruption of sleep

COPD chronic obstructive pulmonary disease; *EDS* excessive daytime sleepiness; *GAD* generalized anxiety disorder; *SOL* sleep onset latency; *SWS* slow-wave sleep; *TST* total sleep time; *WASO* wake time after sleep onset

Table 55.5 Determinants of comorbid insomnia: substance-induced sleep disorders

Determinants of comorbid insomnia	Subjective and objective sleep changes
– Methylated xantines	Caffeine behaves as a CNS stimulant. Acute or chronic use of caffeine-containing beverages or medications increases SOL, WASO, and the number of awakenings, whereas SWS is suppressed. These effects are more evident in patients with primary insomnia or anxiety disorders
– Nicotine	The rewarding actions of nicotine include alertness, improved cognitive functioning, and reduction in craving for cigarettes. SOL is frequently enhanced in smokers compared to non-smokers
– Antiepileptic drugs	Phenobarbital decreases SOL and improves sleep continuity during short-term administration to patients with epilepsy. In contrast, REMS is suppressed. At therapeutic doses, gabapentin improves sleep continuity in epileptic patients, while valproate only slightly affects sleep continuity. In contrast, vigabatrin and tiagabine do not significantly modify sleep variables. Carbamazepine has been shown to shorten SOL and to improve sleep continuity, whereas phenytoin increases S1 and S2 sleep and suppresses SWS. Lamotrigine administration has been associated with reduced SWS duration
– Antihypertensive agents	Several β-adrenoceptor antagonists are available for clinical use. At clinical doses, propranolol may cause visual perceptual disorders, vivid dreams, and occasional insomnia. Pindolol has been reported to increase TST and to reduce REMS percentage. In addition, the compound augments the incidence of recalled awakenings and dreams. Atenolol slightly decreases REMS as compared to baseline values. When given to normal subjects, the α2-adrenoceptor agonist clonidine strikingly reduced the duration of REMS. In contrast, sleep changes have not been reported during the administration of calcium antagonists to man
– Corticosteroids	There is increasing recognition of direct effects of corticosteroids on the CNS, including effects on sleep and mood. Polysomnographic studies have shown that dexamethasone given by oral route exerts a disrupting effect on sleep characterized by increased W and S1 sleep and reduced time spent in REMS. Changes of SWS were inconsistent

Substance-induced sleep disorders
SOL sleep onset latency; *TST* total sleep time; *WASO* wake time after sleep onset

and cognitive decline in elderly patients, the occasional loss of efficacy, and the development of physical dependence led to a decrease in their use in the recent years. The clinical need for medications that did not have these side effects was an important factor leading to the development of zolpidem, zopiclone, eszopiclone, zaleplon, ramelteon, and low-dose doxepin.

Melatonin is available in the USA as a nutritional supplement in doses generally between 1 and 5 mg. However, the formulations are not regulated by the Food and Drug

Administration (FDA) with respect to quality and quantity. A long-acting prescription formulation (prolonged-release melatonin 2 mg) was approved by the European Medicines Evaluation Agency (EU-EMEA) in 2007 for the treatment of primary insomnia in patients aged 55 years and over.

Sedating antihistamines including chlorpheniramine and diphenhydramine are used in a number of countries as sleep aids. However, sedating antihistamines are compared unfavorably with zopidem, zopiclone, eszopiclone, and zaleplon because they produce acute tolerance, residual daytime sedation, diminished cognitive function, and other adverse effects, including dry mouth, blurred vision, urinary retention, constipation, and risk of increased intraocular pressure [24]. As an exception, low-dose doxepin is devoid of the above-mentioned side effects.

Preclinical Pharmacology of BZD and Non-BZD Hypnotics

The BZD hypnotics induce a sedative effect with doses that are similar or greater than those producing anticonvulsant or myorelaxant effects. Preclinical studies have shown zolpidem to exhibit also sedative, anticonvulsant, and myorelaxant activities. However, in contrast to the BZDs, zolpidem is more potent in suppressing locomotor activity (sedative effect) than pentylenetetrazol convulsions (anticonvulsant activity) and rotarod performance (muscle relaxation) in rats. In relation to the effects of zolpidem on sleep, a spectral analysis of sleep EEG in curarized rats revealed that its power density in SWS is predominantly increased in the low-frequency band (1.0–4.0 Hz). Moreover, in freely moving animals, zolpidem has been found to augment the duration of SWS and to reduce W. On the other hand, variable results have been reported in regard to REMS, such that an increase and a reduction in the behavioral state have been described in rats recorded during the light period [25].

Preclinical studies have shown zopiclone to exhibit sedative–hypnotic, anticonvulsant, myorelaxant, anti-aggressive, and anticonflict activities. With regard to the sedative–hypnotic activity, zopiclone decreases locomotor activity, reduces W, and increases SWS in the rat. Spectral analysis of the electrocorticogram after zopiclone administration has shown an increase in power density in the 2.0–4.0 Hz (delta) and the 12.0–16.0 Hz (beta) bands in the rat. Eszopiclone, the dextrorotatory enantiomer of racemic zopiclone, shares the sedative–hypnotic properties of zopiclone [26].

Zaleplon has been shown to reduce locomotor activity and to produce motor deficits in the rotarod and grid tests in the rat. In addition, the pyrazolopyrimidine derivative blocked electroshock-, pentylenetetrazole-, and isoniazid-induced convulsions. Zaleplon increased SWS and the relative EEG power density in the delta frequency band of rats prepared for chronic sleep recordings. REMS values showed no significant changes [27].

The sleep-promoting action of ramelteon has been studied on daytime and nighttime sleep in rats, cats, and monkeys. Systemic injection of ramelteon exerted a sleep-promoting effect in the rat characterized by a reduction in SWS latency and a short-lasting increase in SWS duration [28]. Ramelteon given by the oral route to freely moving cats significantly reduced W and increased SWS and REMS, while sleep latency was not modified. Exogenous melatonin was about 10 times less potent than ramelteon [29]. Oral administration of ramelteon significantly shortened sleep onset latency (SOL) and increased total sleep time (TST) in freely moving monkeys (*Macaca fascicularis*); the effect of melatonin was limited to a reduction in latency to sleep onset. Neither ramelteon nor melatonin affected the EEG spectra or the general behavior of the monkeys [30]. Compared with placebo, ramelteon had no effect on learning and memory, motor performance, and rewarding properties in rats and mice. Moreover, ramelteon showed neither a positive reinforcing effect nor produced BZD-like discriminative stimulus effects on tasks used to determine abuse potential and dependence in monkeys [31].

The basic actions of doxepin, a tricyclic antidepressant, are similar to those of other compounds of the group, including imipramine and amitryptiline. Doxepin inhibits the reuptake of 5-HT and NE. Additionally, the compound behaves as an antagonist of histaminergic (H_1), cholinergic (M_1), and noradrenergic (α_1) receptors [32].

Mechanism of Action of BZD and Non-BZD Hypnotics

γ-Aminobutyric acid is the most important inhibitory neurotransmitter in the mammalian brain and localizes to approximately 30 % of CNS synapses. The majority of GABA-A receptors consists of α, β, and γ subunits, which contain multiple isoforms or variants: α_1–α_6, β_1–β_3, and γ_1–γ_3. Zolpidem, zopiclone, eszopiclone, and zaleplon share with the BZDs the property of bindings to α subunits of the GABA-A receptor/chloride channel complex, however, with a decisive difference in selectivity concerning the subtypes. The sedative–hypnotic activity of BZDs is dependent on the integrity of the α_1 subtype. On the other hand, the anxiolytic, anticonvulsant, myorelaxant, ataxic, and withdrawal effects depend upon their predominant affinity for the α_2- and α_3-containing receptors. Similar to the BZD hypnotics, zolpidem and zaleplon bind at the GABA-A receptor, yet, unlike BZDs, they have more selectivity for the α_1 subtype. Zopiclone and eszopiclone have been proposed to bind at all GABA-A subtypes. Notwithstanding this, the mechanism of action of the cyclopyrrolone derivatives may not be identical

to that of the BZD hypnotics. In other words, the cyclopyrrolone derivatives might have more selectivity for certain subunits of the GABA-A receptor. This could tentatively explain the difference in effects on sleep architecture and the lower incidence of adverse events during their administration to patients with insomnia [26].

Melatonin receptors have been classified as MT1, MT2, and MT3. The former two receptors belong to the family of G-protein-coupled receptors linked to the inhibition of adenylate cyclase and have been detected in the suprachiasmatic nucleus (SCN), while MT3 is a melatonin-sensitive form of quinone reductase 2. MT1 mediates the inhibition of neuronal firing in the SCN by melatonin, while MT2 is involved in the coordination of mammalian circadian rhythms. Ramelteon is a highly selective MT1/MT2 agonist. Compared to melatonin, it shows a sixfold higher affinity for the human MT1 and a threefold higher binding potency for the human MT2. Of note, ramelteon has no affinity for GABAergic, monoaminergic, cholinergic, and opioid receptors [33, 34].

Low-dose doxepin acts as a selective HA H_1 antagonist. At the doses approved for insomnia treatment, pharmacological effects related to NE and 5-HT reuptake inhibition, and α_1 adrenergic and M_1 cholinergic blockade are not evident.

Pharmacokinetics of BZD and Non-BZD Hypnotics in Healthy Adults and Populations at Risk

Hypnotic drugs approved by governmental agencies for the treatment of primary and comorbid insomnia differ significantly in pharmacokinetic properties, including elimination half-life ($t_{1/2}$) and the presence of active metabolites. On the other hand, the majority of them have in common short absorption and distribution times. As a result, in most circumstances, they induce sleep rapidly. According to their elimination, half-life hypnotics can be divided into short-, intermediate-, or long-acting derivatives. The BZD hypnotics midazolam and triazolam, together with zolpidem, zopiclone, eszopiclone, zaleplon, and ramelteon, are short-acting derivatives. The BZDs flunitrazepam and temazepam, and low-dose doxepin are intermediate-acting hypnotics, whereas flurazepam is a long-acting derivative (Table 55.6). BZD hypnotics are rapidly absorbed after oral administration, and peak plasma concentrations are attained in 0.3–1.0 h. Metabolism takes place in the liver, and biotransformation products often have hypnotic activity (Table 55.6). For BZDs, the mechanisms of inactivation comprise hydroxylation, methylation, oxidation, and conjugation to form glucuronides. A reduced clearance and an increased $t_{1/2}$ of the BZD hypnotics have been reported in patients of 65 years and older. Furthermore, hepatic disease leads to impaired removal of these drugs from the body. The clearance of oxidatively metabolized BZDs (triazolam, flunitrazepam, flurazepam) is much more affected than those that undergo glucuronidation (temazepam). Renal failure can also affect the pharmacokinetics of BZD hypnotics. The reduction in plasma binding frequently associated with renal disease is the major causative factor in this type of patient. This results in an increase in the unbound fraction of the drug in plasma. The clearance of BZD hypnotics that are metabolized by glucuronidation is also affected in renal disease.

Zolpidem immediate-release (IR) is rapidly absorbed and extensively distributed to body tissues including the brain. Bioavailability is reported to be in the range of 70 %. A large fraction is bound to plasma protein (92.5 %), independently of concentrations between 40 and 790 ng/ml. After administration of a single therapeutic dose of 10 mg zolpidem IR to healthy adults, peak plasma concentrations (T_{max}) are attained in 60 min, (range 45–90 min) and the mean $t_{1/2}$ amounts to about 2.4 h [35] (Table 55.6).

Table 55.6 Pharmacokinetic parameters for benzodiazepine and nonbenzodiazepine hypnotics

Drugs	$t_{1/2}$ (h)	T_{max} (h)	Time to onset	Active metabolite(s)
Short-acting agents				
Midazolam	1.2–2.5	0.3	15–30	No
Triazolam	2.1–6.0	1.0	15–30	No
Zopiclone	3.5–6.0	0.5–2.0	15–30	*N*-oxide derivative
Eszopiclone	5.0–7.0	1.0	15–30	*N*-oxide derivative
Zolpidem	2.0–2.5	1.0	30	No
Zaleplon	1.0	1.0	15–30	No
Ramelteon	1.0–2.0	0.5–1.5	15–30	Hydroxylated derivative (M-II)
Intermediate-acting agents				
Temazepam	10.0–20.0	1.0–1.5	45–60	No
Flunitrazepam	9.0–31.0	1.0	20–30	7-amino derivative *N*-demethyl derivative
Doxepin	20.0	2.0–6.0	30–45	No
Long-acting agent				
Flurazepam	40.0–150.0	1.0	30–60	Hydroxyethylflurazepam

Zolpidem extended-release (ER) in its 12.5 mg formulation consists of a coated two-layer tablet. The primary release comprising about 60 % of the content is as fast as that of zolpidem IR 10 mg, and the rise in plasma concentration within the first 30 min does not differ from the IR values. Between 45 and 120 min, plasma levels are very similar in healthy subjects, but the ER formulation leads to a subsequently higher concentration over more than 6.0 h.

Sublingual zolpidem (SL) for middle-of the-night awakening shows a duration of action of approximately 4 h at the available dosages of 3.5 and 1.75 mg.

Zolpidem is metabolized in the liver by a number of cytochrome P450 isoenzymes, but predominantly CYP3A4, to inactive metabolites. The major routes of metabolism are oxidation and hydroxylation. After oral administration, zolpidem metabolites are largely excreted in the urine.

The metabolic clearance of zolpidem is reduced in elderly patients, aged 65 years and older, resulting in increases in maximum plasma concentration (C_{max}), area under the concentration curve (AUC) and $t_{1/2}$, the latter amounting to approximately 2.9 h. Thus, a reduction in the initial dose from 10 to 5 mg in the elderly is recommended. These changes largely reflect an age-related decrease in hepatic metabolism. The clearance of zolpidem from the body is also impaired in patients with severe hepatic insufficiency, thus requiring dose reduction. On the other hand, the clearance of the hypnotic drug is not altered in patients with compromised renal function.

Zopiclone is available as a racemic mixture. Zopiclone 7.5 mg administered at nighttime is rapidly absorbed. It has a bioavailability of approximately 75 %, a T_{max} of 0.5–2.0 h, and a C_{max} of 1.6 h. The compound undergoes oxidation to the *N*-oxide metabolite, which is pharmacologically active, and demethylation to the inactive *N*-demethyl-zopiclone. The $t_{1/2}$ of zopiclone and its active metabolite ranges from 3.5 to 6 h (Table 55.6).

Eszopiclone, the dextrorotatory enantiomer of racemic zopiclone, is currently used for the treatment of insomnia. (S)-zopiclone is responsible for the hypnotic effect of zopiclone, whereas the (R)-isomer has no hypnotic properties. Eszopiclone is rapidly absorbed and extensively distributed to body tissues including the brain. It is weakly bound to plasma protein (52–59 %). Moreover, its T_{max} is attained 1.0–1.6 h after a single therapeutic dose of 3 mg, and the $t_{1/2}$ amounts to approximately 6.0 h. Eszopiclone is metabolized in the liver to form (S)-zopiclone-*N*-oxide and (S)-*N*-demethyl zopiclone. In vitro studies have shown that CYP3A4 and CYP2E1 are the major enzymes involved in eszopiclone metabolism. After oral administration, eszopiclone is excreted in the urine, primarily as metabolites (Table 55.6). The metabolic clearance of eszopiclone is reduced in elderly subjects, aged 65 years and older, resulting in increases in C_{max} and $t_{1/2}$, the latter amounting to approximately 9.0 h. The removal of eszopiclone from the body is also impaired in patients with severe hepatic insufficiency, thus requiring dose reduction. On the other hand, the clearance of the compound is not altered in patients with renal insufficiency. Thus, based on the available evidence, a reduction in the initial dose of eszopiclone is recommended in elderly subjects and patients with severe hepatic insufficiency [36].

Zaleplon is rapidly and almost completely absorbed following the oral administration of a 10 mg dose. The compound undergoes significant first-pass hepatic metabolism after absorption. As a result, its bioavailability amounts to only 30 %. The derivative attains maximum plasma concentration in approximately 1.0 h and has a $t_{1/2}$ of 1.0 h. Zaleplon is primarily metabolized by aldehyde oxidase, and all of its metabolites are pharmacologically inactive (Table 55.6). The pharmacokinetics of zaleplon in elderly patients, including those over 75 years of age, is not significantly different from that in young healthy subjects. The clearance of zaleplon is reduced in cirrhotic patients, leading to a marked increase in C_{max} and AUC. Thus, the hypnotic drug should not be administered to patients with severe hepatic impairment. The pharmacokinetics of the compound is not altered in patients with mild-to-moderate renal insufficiency [37].

Ramelteon is absorbed rapidly with peak plasma concentrations occurring at 45 min (range 30–90 min) after oral administration. Its absolute oral bioavailability is only 1.8 % due to extensive first-pass metabolism. Protein binding of ramelteon is approximately 82 % in human serum. The metabolism of ramelteon consists primarily of oxidation to hydroxyl and carbonyl derivatives, with secondary metabolism producing glucuronide conjugates. CYP1A2 is the major enzyme involved in the hepatic metabolism of ramelteon. M-II is the major metabolite of ramelteon and contributes to the pharmacological effects of the parent drug. The $t_{1/2}$ of ramelteon is in the range of 1–2 h, while that of M-II is 2–4 h (Table 55.6). Ramelteon clearance is significantly reduced in elderly versus young subjects, and $t_{1/2}$ significantly increased. The ramelteon exposure parameters (C_{max}, AUC) are increased in patients with mild-to-moderate hepatic impairment. To date, the derivative has not been evaluated in patients with severe hepatic impairment. The pharmacokinetics of ramelteon has been studied also in patients with mild-to-severe renal impairment; no effect on C_{max} or AUC of the parent drug or M-II was detected in any of the treatment groups. Furthermore, mild-to-moderate obstructive sleep apnea and chronic obstructive pulmonary disease (COPD) were not exacerbated by the compound [38, 39].

Doxepin is rapidly absorbed following the oral administration of 1, 3, and 6 mg doses. It undergoes first-pass metabolism and is extensively protein bound (up to 95 %). The compound attains maximum plasma concentration in 2.0–6.0 h and has a $t_{1/2}$ of 20.0 h (range 10.0–30.0 h).

Doxepin is metabolized in the liver to form *N*-demethyl doxepin, and CYP2C19 and CYP2D6 are the major enzymes involved in its hepatic metabolism (Table 55.6). The metabolic clearance of doxepin is decreased in elderly subjects [40].

The Effects of BZD and Non-BZD Hypnotics in Patients with Primary Insomnia and Comorbid Insomnia

The main findings obtained with drugs used for the treatment of insomnia are based on questionnaires (subjective self-evaluation) and on objective measures obtained by polysomnography. The efficacy end points used in many studies included SOL, latency to persistent sleep (LPS), WASO, the number of awakenings, TST, SE, quality of sleep, fatigue, daytime sleepiness, cognitive impairment, mood disturbance, impaired work function, and impaired interpersonal function.

Benzodiazepine Hypnotics

The sleep induced by BZD hypnotics, including midazolam, triazolam, temazepam, flunitrazepam, quazepam, and flurazepam in patients with chronic primary insomnia, is characterized by a shortened SOL, decreased number of nocturnal awakenings, reduced time spent awake, increase in S2 sleep, consistent reduction in SWS (S3 + S4), dose-dependent suppression of REMS, and improvement in the subjective quality of sleep when compared with no treatment [41, 42]. Clinical and polysomnographic studies of triazolam 0.5 mg, temazepam 30 mg, and flurazepam 30 mg per night have found improvement in sleep over 4–5 weeks [43, 44]. The commonly reported adverse effects of BZD hypnotics are drowsiness, tiredness, dysarthria, ataxia, depression, and anterograde amnesia. Memory impairment and rebound insomnia have been reported more often with BZDs that have short half-life, such as triazolam and midazolam. Daytime functioning can be negatively affected, as evidenced by the effects on measures of psychomotor performance in patients taking a long-acting BZD such as flurazepam. Increased daytime sleepiness as quantified by the multiple sleep latency test can occur (Table 55.7). The elderly are particularly susceptible to the adverse effects of BZDs, due to the age-related alterations in pharmacokinetics as a result of changes in hepatic metabolism and renal excretion [45].

Non-benzodiazepine Hypnotics

Zolpidem

The therapeutic efficacy of zolpidem formulations has been investigated in a number of studies with either evening or middle-of-the-night dosing. Outcome measures in such studies have employed objective measures obtained in the sleep laboratory as well as subjective ratings of improved sleep.

Zolpidem Immediate-Release in Patients with Chronic Primary Insomnia

Considerable research attention has been given to the suitability of zolpidem IR for chronic insomnia. In this respect, the effectiveness of zolpidem IR has been assessed in 13 studies involving outpatients and inpatients who have not been taking hypnotic medication prior to the study for periods ranging from 4 to 30 nights. Zolpidem IR was administered for the extent of time ranging from 7 to 35 nights. Six of the studies used polysomnography and either a single-blind or double-blind experimental design to evaluate the effect of the medication on sleep variables in patients with a diagnosis of chronic primary insomnia. Results with zolpidem IR 10 mg indicate that the compound is capable of reducing SOL and WASO, and, with certain qualifications, can augment TST and SE. The number of nocturnal awakenings was not significantly modified. The predominant reduction in WASO during the first part of the night and the absence of an effect on the number of nocturnal awakenings could be related to zolpidem's short elimination half-life. This could also explain the inconsistencies observed in supporting sleep maintenance. However, the subjective feeling of being more refreshed on awakening, as reported by many patients, should not be underrated, even when not supported by objective measures. With respect to sleep architecture, zolpidem tended to increase S2 sleep, whereas SWS (S3 + S4), REMS latency, and REMS in min or as percentage of TST were not significantly modified (Table 55.7) [25, 46].

Spectral analysis in patients with moderate-to-severe chronic primary insomnia under treatment with 10 mg zolpidem IR for 15 nights showed only moderate effects. Power density of SWS was significantly increased in the delta (0.25–1.0 Hz) band only during the first two-hour interval, during both short and intermediate-term treatments. In contrast to BZD hypnotics, zolpidem did not suppress low-frequency EEG activity in patients with a sleep disorder [47].

Table 55.7 Effects of hypnotic drugs on sleep variables in patients with chronic primary insomnia: benzodiazepine and non-benzodiazepine GABA-A receptor allosteric agonists

Variable	Benzodiazepines	Zolpidem	Zopiclone–Eszopiclone	Zaleplon
Sleep induction				
– Sleep onset latency	Decrease	Decrease	Decrease	Decrease
Sleep maintenance				
Number of awakenings	Decrease	No change (IR) Decrease (ER)	Decrease	Variable effects
– Wake time after sleep onset	Decrease	Decrease (IR) Decrease (ER)	Decrease	No change
– Total sleep time	Increase	Inconsistent (IR) Increase (ER) Increase (SL)	Increase	Variable effects
Subjective measure of sleep				
– Sleep quality	Improved	Improved (IR, ER, SL)	Improved	Variable effects
Sleep architecture				
– Stage 2 sleep – Slow-wave sleep – REM sleep	Increase Decrease Decrease	Increase No change No change	Increase No change No change	Variable effects Variable effects Variable effects
Adverse events	Drowsiness Tiredness Dysarthria Ataxia Anterograde amnesia Depression	Zolpidem IR/ER Headache Drowsiness Dizziness Nausea Diarrhea Myalgia Bizarre behaviors	Bitter taste Headache Dyspepsia Pain Diarrhea Dry mouth Dizziness	Asthenia Dizziness Somnolence
Dosage (mg/night—adult/elderly)	Midazolam: 15/7.5 Triazolam: 0.25/0.125 Temazepam: 30-15/15-7.5 Flunitrazepam: 1/0.5 Flurazepam 30/15	IR: 10/5 ER: 12.5/6.25 SL: 3.50/1.75	Zopiclone: 7.5/3.5 Eszopiclone: 3/2	10/5

ER extended-release; *IR* immediate-release; *SL* sublingual

Sublingual Low-Dose Zolpidem

A low-dose sublingual formulation of zolpidem IR has been developed to be administered following the middle-of-the-night (MOTN) awakenings in patients with sleep maintenance difficulties. In a study that included middle-aged patients with a diagnosis of chronic primary insomnia, the administration of sublingual zolpidem 3.5 or 1.75 mg for 2 consecutive nights after MOTN awakenings significantly reduced latency to return to sleep and increased TST and sleep quality in comparison with placebo. The increase in TST was limited to the first 2 h following the scheduled MOTN awakening. Subject-reported estimates of sleep variables paralleled the polysomnographic findings. The hypnotic medication was well tolerated [48].

The efficacy and safety of 3.5 mg sublingual zolpidem as needed were evaluated during 28 nights in middle-aged patients with insomnia characterized by difficulty returning to sleep after MOTN awakenings. The response to the hypnotic medication was confirmed on the basis of subjective measures. Sublingual zolpidem decreased SOL over the 28-night treatment period compared with placebo. In addition, there was an improvement of sleep quality and morning sleepiness/alertness scores [49].

The long-term use of hypnotic drugs has been generally discouraged on the grounds of risk of rebound insomnia, withdrawal reactions, and/or dependence. Although this recommendation is mainly relevant to the BZDs, it has nevertheless been extended to many of the recently introduced non-BZD hypnotics. Concerning zolpidem, evidence from accumulated clinical practice and controlled studies tends to indicate that long-term treatment of insomnia with the medication is efficacious and safe. More recent studies with zolpidem ER over 6 months support this conclusion (see below).

Non-nightly Administration of Zolpidem Immediate-Release

Non-nightly zolpidem administration has been proposed as an alternative option to nightly drug intake. Administration of 10 mg zolpidem IR for 5 nights followed by 2 nights of placebo per week for 2 weeks induced an improvement of sleep that was comparable to nightly zolpidem treatment in patients with chronic insomnia [50]. Rebound insomnia did not occur on the nights during which zolpidem was substituted by a placebo. Similar improvements in sleep quality were observed when the 2 placebo nights per week were randomly assigned. More recently, zolpidem IR 10 mg or placebo was administered for 12 weeks to patients with a diagnosis of chronic primary insomnia. The patients were instructed to take no fewer than 3 and no more than 5 pills per weeks. Patients receiving zolpidem exhibited an improvement of sleep induction and maintenance that persisted over time. There was no evidence of either rebound insomnia or dose escalation [51]. Thus, the currently available data suggest that long-term non-nightly administration of zolpidem 10 mg for patients with chronic primary insomnia is an effective alternative to its continued nightly use.

Zolpidem Extended-Release in Patients with Chronic Primary Insomnia

Zolpidem ER 12.5 mg has been administered in several placebo-controlled studies to patients with chronic primary insomnia. In middle-aged patients treated nightly for 3 weeks, polysomnographic and subjective measures revealed significant improvements in sleep quality, in particular with respect to LPS, WASO during the first 6 h of sleep, and SE, as well as self-reported SOL, WASO, the number of awakenings, and TST [52]. In another study comprising insomnia patients, based on self-ratings, subjective SOL, WASO, the number of awakenings, and sleep quality were improved at a significant level [53]. In conclusion, the available data tend to indicate that zolpidem ER is effective for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance [54].

Zolpidem Immediate-Release and Extended-Release in Patients with Comorbid Insomnia

In the study by Joffe et al. [55], breast cancer patients, who had hot flashes in association with nocturnal awakenings and were receiving venlafaxine 75 mg, were randomized to double-blind treatment with zolpidem IR 10 mg or placebo for 5 weeks. Augmentation of venlafaxine with zolpidem IR significantly improved sleep and quality of life in the breast cancer women.

The effect of zolpidem ER has been demonstrated also in patients with comorbid insomnia and major depressive disorder (MDD) or generalized anxiety disorder (GAD), in either case with concurrent escitalopram therapy. In a multicenter study, adult MDD patients received open-label escitalopram (10 mg/day) and were randomized to concomitant zolpidem ER 12.5 mg/night or placebo for 8 weeks (phase I). Responders continued 16 weeks of double-blind treatment (phase II). Significant improvements were observed during phase I in SOL, WASO, TST, and sleep quality, and some measures of sleep-related next-day functioning. Depressive symptoms remained unchanged. During phase II improvements in the zolpidem, ER/escitalopram group were restricted to an increase in TST [56]. Another phase I and phase II trials in MDD patients treated with zolpidem ER in combination with escitalopram showed likewise improvements of sleep impact [57].

In a multicenter double-blind study that included GAD patients treated with either zolpidem ER/escitalopram or placebo/escitalopram, there were significant improvements in SOL, WASO, TST, SE, next-day morning energy, morning concentration, and sleep impact on daily activities in the patients receiving the hypnotic medication. There was no substantial change in the psychiatric symptoms [58].

Safety and Adverse Effects of Zolpidem

The safety profile of zolpidem IR and ER is very similar. The most commonly observed adverse events associated with the use of zolpidem IR are headache, drowsiness, dizziness, nausea, diarrhea, and myalgia, but these complaints occur only with moderate frequency. Rebound insomnia is not evident after discontinuation of the hypnotic agent [44]. Of interest, in a double-blind, placebo-controlled, clinical trial, it was found that 12 months of nightly zolpidem IR 10 mg did not lead to dose escalation in non-elderly primary insomniacs [59]. The nature of adverse events reported in adult patients receiving zolpidem IR 10 mg was similar to that described by elderly patients being given zolpidem IR 5 mg [60]. The most frequently observed adverse events in adults and elderly patients treated with zolpidem ER at daily doses of 12.5 and 6.25 mg, respectively, were next-day somnolence, headache, and dizziness [61, 46]. Precautions have to be considered and require surveillance in patients with hepatic impairment, respiratory diseases (especially obstructive sleep apnea syndrome and COPD), pregnancy, or concomitant use of other CNS depressants.

Several case reports have described behavioral changes caused by zolpidem, including the occurrence of bizarre behaviors, agitation, and sleep-related complex behaviors, such as sleep eating, sleep walking, sleep conversations, sleep driving, and sleep shopping, frequently with amnesia for the event [62]. With these exceptions, the general and overwhelming impression remains that zolpidem, whether IR or ER, is a remarkably safe hypnotic, having few adverse effects in conjunction with considerable efficacy relative to other options in sleep medicine, especially in comparison with BZDs.

Zopiclone and Eszopiclone

Zopiclone and Eszopiclone in Patients with Chronic Primary Insomnia

Zopiclone is effective in inducing and maintaining sleep in patients with chronic primary insomnia. The increase in TST is related to greater amounts of S2 sleep.

In adult and elderly patients with insomnia, zopiclone 7.5 and 3.5 mg increased, decreased, or had no effect on S3 sleep and S4 sleep as percentage of TST. No significant change has been observed in REMS duration as a percentage of TST, although REMS latency may be delayed. No development of tolerance has been described in studies of zolpiclone that lasted up to 4 weeks [63, 64].

Non-elderly and elderly patients with chronic primary insomnia and comorbid insomnia have been included in the studies that assessed the efficacy and safety of eszopiclone. However, to date much of the published information on the effect of eszopiclone on sleep variables has been gathered from studies that included subjects with chronic primary insomnia.

The effects of eszopiclone 3 mg or a placebo have been evaluated in non-elderly patients with moderate primary insomnia during 44 nights. SOL and WASO showed a significant decrease after eszopiclone relative to placebo, while TST and SE were enhanced. Tolerance did not develop during the eszopiclone 3 mg administration period. With respect to sleep architecture, the inferred increase in NREMS was coupled with significantly higher levels of S2 sleep, whereas S3 sleep and S4 sleep were not significantly different between 3 mg eszopiclone and placebo. A similar outcome was observed in relation to time spent in REMS. Subjective evaluation was correlated with the sleep laboratory findings. Accordingly, eszopiclone 3 mg improved subjective ratings of the perceived ease of getting to sleep, the duration of sleep, and the quality and depth of sleep [65].

The use of eszopiclone to improve sleep over a longer period of time has been evaluated also in middle-aged subjects suffering from chronic primary insomnia [66]. The study was conducted according to a double-blind, placebo-controlled design with randomization. The efficacy of eszopiclone 3 mg and a placebo was assessed once a week during 6 months using an interactive voice response system. Eszopiclone significantly reduced SOL, WASO, the number of nocturnal awakenings per night, and the number of nocturnal awakenings per week. TST was increased compared with baseline at the end of the first week and through months 1 to 6. Sleep quality, daytime ability to function, alertness, and physical well-being also improved significantly.

The safety of eszopiclone during an additional 6-month period was evaluated by Roth et al. [67] in the patients originally included in the study by Krystal et al. [66]. The sustained improvement in sleep and daytime functioning reported in the previous study during the double-blind phase of the investigation was confirmed during the second 6-month, open-label, phase of the study. There was no evidence of tolerance.

The effects of eszopiclone administration have been assessed also in elderly patients with chronic primary insomnia. These were randomized, double-blind, placebo-controlled studies. In a 2-week study, patients were given either eszopiclone 1 mg or 2 mg or placebo nightly. Efficacy was assessed using an interactive voice response system. Eszopiclone 2 mg was effective in reducing SOL, WASO, and the number of awakenings, while TST was increased. Additionally, sleep quality and depth, daytime alertness, and quality of life were improved compared with placebo [68]. In another chronic primary insomnia study where patients received also eszopiclone 2 mg or placebo for 2 weeks, efficacy was assessed by means of polysomnography and patients' reports. Eszopiclone administration significantly reduced LPS and WASO, whereas TST and SE showed significant increments. S2 sleep was significantly augmented, whereas S1 sleep, SWS (S3 + S4), and REMS in min were not modified. Subjective evaluation was relatively well correlated with the sleep laboratory findings [69] (Table 55.7).

In conclusion, during the active treatment period eszopiclone improved sleep induction and maintenance compared with placebo in middle-aged and elderly patients with chronic primary insomnia.

Eszopiclone in Patients with Comorbid Insomnia

Insomnia related to depression may be alleviated by treating the underlying mood disorder with antidepressant drugs. However, this is not always the case since a stimulant effect may appear during treatment. This is particularly true with the selective serotonin reuptake inhibitors, which according to pharmacoEEG studies behave as activating antidepressants.

The disruption of sleep continuity is more pronounced after fluoxetine administration compared with other SSRIs [70].

The effect of adding eszopiclone to fluoxetine was evaluated in non-elderly patients who met DSM-IV criteria for MDD and comorbid insomnia. Patients who had been receiving fluoxetine (dose range 20–40 mg/day) were randomized to receive either eszopiclone 3 mg or placebo double-blind for 8 weeks. Patients' self-reports of various sleep parameters, daytime functioning, and depressive symptoms were obtained with an interactive voice recording system. Sleep induction, sleep maintenance, and daytime function showed a significant improvement in the patients in the eszopiclone plus fluoxetine group compared with the placebo plus fluoxetine group during the 8-week treatment period. In addition, scores in the Hamilton Depression-17 Rating Scale were significantly lower at week 4 and week 8 [71].

Pollack et al. [72] determined the efficacy of eszopiclone combined with escitalopram in treating insomnia comorbid with GAD. The double-blind, placebo-controlled study included adult patients meeting DSM-IV-TR criteria. Subjects received escitalopram 10 mg and were randomized to receive also either eszopiclone 3 mg or placebo nightly for 8 weeks. The association of eszopiclone with escitalopram resulted in significantly improved sleep variables (SOL, WASO, the number of awakenings, TST), daytime functioning (alertness, ability to function and to concentrate, and physical well-being), and anxiety (Hamilton Anxiety Scale response). There was no evidence of tolerance. Moreover, rebound insomnia did not show after eszopiclone withdrawal.

In another randomized controlled study, Soares et al. [73] evaluated the efficacy of 3 mg of eszopiclone for the treatment of insomnia in perimenopausal and early postmenopausal women. The study concluded with the finding that eszopiclone significantly improved many sleep characteristics (sleep induction, maintenance, duration, quality, and next-day functioning). The study showed also a positive impact on the mood, quality of life, and other subjective menopausal-related symptoms in post-menopausal women with insomnia.

Adverse Events of Eszopiclone

The most commonly reported side effects in non-elderly and elderly patients who received zopiclone (7.5/3.5 mg) or eszopiclone (3/2 mg) were unpleasant or bitter taste, headache, dyspepsia, pain, diarrhea, dry mouth, dizziness, and accidental injury. There is no evidence of an addicting potential of eszopiclone in individuals without known history of drug abuse.

Zaleplon

Zaleplon in Patients with Chronic Primary Insomnia

A number of placebo-controlled trials have determined the efficacy of zaleplon in improving sleep in non-elderly patients with chronic primary insomnia.

Walsh et al. [74] evaluated the efficacy of zaleplon 10 mg during 5-week administration in adult patients with primary insomnia. Polysomnographic data and subjective measures showed that zaleplon significantly decreased LPS relative to placebo during all 5 weeks. No consistent effects on WASO, TST, or the number of awakenings were seen with the hypnotic drug. Furthermore, zaleplon administration induced inconsistent changes of sleep architecture, including S2 sleep, SWS (S3 + S4), and REMS.

In an outpatient study of adults with primary insomnia, the subjects were given zaleplon, 5 mg, 10 mg, and 20 mg, or placebo during 4 weeks. Zaleplon 5 mg significantly reduced the subjectively reported SOL over the first 3 weeks of treatment, and for zaleplon 10 and 20 mg over all 4 weeks. The number of awakenings during the night was not significantly affected by the medication [75].

Using a similar protocol, Fry et al. [76] reproduced the findings by Elie et al. [75] with respect to subjective sleep latency. In addition, zaleplon 20 mg significantly, but variably, improved subjective TST, the number of awakenings and sleep quality.

The efficacy and safety of zaleplon 5 and 10 mg were investigated also in elderly patients with chronic insomnia. Sleep induction and sleep maintenance were assessed by using morning questionnaires completed during baseline nights, double-blind treatment nights, and after discontinuation of the hypnotic medication. The 10 mg zaleplon dose induced better subjective sleep onset during both weeks of the study, while zaleplon 5 mg decreased sleep latency only during the second treatment week. TST was significantly increased with zaleplon 5 mg during the whole treatment period and with zaleplon 10 mg during week 1 [77]. Similar effects on subjective sleep latency were obtained by Hedner et al. [78], following the administration of zaleplon 5 and 10 mg over a period of 2 weeks to elderly patients with primary insomnia. Moreover, zaleplon 10 mg increased TST and reduced the number of awakenings during the first treatment week.

Adverse Events of Zaleplon

Evening administration of zaleplon 5 and 10 mg to non-elderly and elderly patients was associated with minimal next-day residual sedation and impairment. Of note, the

effectiveness of zaleplon 10 mg was maintained over 6–12 months of use, and weak or no rebound insomnia occurred upon discontinuation of the medication [79] (Table 55.7).

In conclusion, available evidence tends to indicate that zaleplon is suitable for the treatment of primary insomnia associated with sleep onset difficulty.

Ramelteon

Ramelteon in Patients with Chronic Primary Insomnia

A number of studies have investigated the effects of ramelteon in adult and elderly patients with chronic primary insomnia.

In a randomized, double-blind, placebo-controlled trial, Erman et al. [80] evaluated the use of ramelteon at doses ranging from 4 mg to 32 mg in adult subjects with chronic primary insomnia. Patients received all 5 treatments, with a washout period of 5–12 days between treatments. In this study, all doses of ramelteon resulted in a statistically significant reduction in SOL and increase in TST as quantified by polysomnography.

Zammit et al. [81] conducted a 35-night double-blind, randomized study to evaluate the efficacy of ramelteon 8, 16 mg, and placebo in adult patients with primary insomnia. Compared with the placebo group, ramelteon 8 and 16 mg significantly reduced polysomnographically recorded SOL throughout the treatment period. Patient-reported sleep latency was significantly reduced with ramelteon 8 mg at weeks 1, 3, and 5, and ramelteon 16 mg at weeks 1 and 3. In addition, both ramelteon doses significantly increased TST and improved SE at week 1. The number of awakenings, WASO, and sleep architecture were not significantly modified by the hypnotic drug. Rebound insomnia and withdrawal effects were not evident following discontinuation of the medication.

In the randomized, double-blind, placebo-controlled study by Mayer et al. [82], efficacy and safety of ramelteon 8 mg administered nightly for 6 months was evaluated in adult patients with chronic primary insomnia by using polysomnography and a post-sleep questionnaire. Ramelteon 8 mg significantly decreased LPS at week 1 and months 1, 3, 5, and 6. A significant increase in TST was detected at week 1 only. Furthermore, the compound induced a small but significant increase in S2 sleep and reduction of SWS (S3 + S4) compared with placebo at each time point. REMS values remained unchanged along the study. Subjective sleep latency was reduced at week 1, month 1, and month 5. In contrast, subjective WASO, the number of awakenings, TST, and sleep quality showed no significant differences compared to placebo.

The efficacy and safety of ramelteon were assessed also in elderly patients with chronic primary insomnia. To this purpose, ramelteon 4 and 8 mg, and placebo were administered in 3 consecutive phases for 2 consecutive nights. Sleep was quantified via polysomnography and a postsleep questionnaire. Ramelteon 4 mg and 8 mg significantly decreased LPS and augmented TST and SE. Reductions in subjective sleep latency were reported with ramelteon 4 mg only [83].

In a randomized double-blind placebo-controlled study involving elderly patients with insomnia, ramelteon in doses of either 4 or 8 mg was given at night for 5 weeks. The long-term nightly effect of ramelteon was evaluated using a sleep diary [84]. Sleep latency for both ramelteon doses was significantly reduced from the first week onwards and became increasingly more pronounced until week 5. These findings were similar for both dosage regimens of the medication. TST was significantly increased in the 4 mg group for the week 1 and week 3 assessments. There were no significant differences in the number of awakenings and quality of sleep (Table 55.8).

Ramelteon in Patients with Comorbid Insomnia

The effect of ramelteon 8 mg was evaluated in peri- and postmenopausal women with insomnia by DeFronzo Dobkin et al. [85]. This was an open-label trial where patients completed sleep-wake diaries on a daily basis for six weeks. Patients reported significant improvements in SOL, TST, SE, quality of life, and mood during ramelteon administration. There was no evidence of tolerance or rebound insomnia after cessation of the treatment.

The effect of ramelteon for insomnia was examined in adults with GAD partially responsive to a selective serotonin reuptake inhibitor or a serotonin–norepinephrine reuptake inhibitor. Patients were given openly ramelteon 8 mg at bedtime for 10 weeks. As a result, they reported falling asleep faster and sleeping longer during the treatment period [86].

Gooneratne et al. [87] evaluated in a randomized, double-blind, placebo-controlled study, the effectiveness of ramelteon for insomnia symptoms in older adults with obstructive sleep apnea. Patients received ramelteon 8 mg or placebo for 4 weeks. Ramelteon administration was associated with a significant reduction in SOL as measured by polysomnography. However, no change was observed in subjective SOL or SE. Of note, the apnea–hypopnea index showed no statistically significant changes during the administration of the hypnotic drug.

Table 55.8 Effects of hypnotic drugs on sleep variables in patients with chronic primary insomnia: ramelteon (melatonin MT1 and MT2 receptor agonist) and low-dose doxepin (histamine H1 receptor antagonist)

Variable	Ramelteon	Doxepin
Sleep induction		
– Sleep onset latency	Decrease	No change or decrease
Sleep maintenance		
Number of awakenings – Wake time after sleep onset – Total sleep time	No change No change Small increase	Decrease Decrease Increase
Subjective measure of sleep		
– Sleep quality	No change or small improvement	Improved
Sleep architecture		
Stage 2 sleep Slow-wave sleep REM sleep	Increase Decrease No change	Increase No change No change or decrease
Adverse events	Somnolence Headache Dizziness Fatigue	Somnolence
Dosage (mg/night—adult/elderly)	8	6/3

Safety and Adverse Effects of Ramelteon

Generally, the incidence of side effects resulting from the continued use of ramelteon was not significantly different from that of placebo. The most commonly reported symptoms were somnolence, headache, dizziness, fatigue, and nausea. In addition, ramelteon was well tolerated and without significant cognitive, memory, or psychomotor effects.

Doxepin

Doxepin in Patients with Chronic Primary Insomnia

The effectiveness of low-dose doxepin in adult and elderly patients with chronic primary insomnia has been evaluated in 5 studies.

In an outpatient study of adults with chronic primary insomnia, the subjects were randomly assigned to one of four sequences of 1, 3, and 6 mg of doxepin, and placebo. The efficacy of doxepin was evaluated across 2 nights for each dose using polysomnography and patient reports. All 3 doses significantly improved WASO, TST, and SE. In addition, the doxepin 6 mg dose reduced subjective SOL. There was a significant increase in min of S2 sleep after the whole range of doses administered, whereas REMS percentage was reduced at the 3 and 6 mg dose. Values corresponding to SWS (S3 + S4) remained unchanged [88].

The efficacy of doxepin 3 and 6 mg in adults with chronic primary insomnia was confirmed in a placebo-controlled 5-week trial. Doxepin 3 mg and 6 mg improved WASO and TST on nights 1, 15, and 29 in polysomnographic sleep recordings. LPS was decreased only on night 1. Doxepin improved also early morning awakenings and SE in the last quarter of the night. There was no evidence of rebound insomnia after discontinuation of the medication [89].

Scharf et al. [90] determined the efficacy and safety of doxepin 1, 3 mg, and 6 mg in elderly patients with chronic primary insomnia. Each treatment period consisted of 2 polysomnographic assessment nights. All 3 doxepin doses significantly increased WASO, TST, and SE versus placebo. The 6 mg dose induced also a significant reduction in SOL. Subjective sleep maintenance was also improved.

A 12-week sleep laboratory trial of elderly chronic insomnia subjects assessed the long-term efficacy of doxepin with a comparison of 1 mg and 3 mg doses with placebo. Doxepin 3 mg significantly decreased WASO and augmented TST and SE during weeks 1, 4, and 12. In addition, the medication improved patient-reported SOL, TST, and sleep quality. Regarding doxepin 1 mg, sleep maintenance was also improved at several time points [91].

A 4-week outpatient study of doxepin was performed in elderly chronic primary insomnia subjects. The participants were randomly divided into groups dosed with nightly doxepin 6 mg or placebo. Efficacy was assessed using patient reports and clinician ratings. Doxepin 6 mg reduced WASO and increased TST and sleep quality during the treatment period. SOL was not modified [92] (Table 55.7).

Safety and Adverse Effects of Doxepin

The clinical efficacy trials described above have monitored potential adverse effects of doxepin. All 3 doxepin doses had side effect profiles comparable to placebo. There was no evidence of next-day sedation, memory impairment, anticholinergic effects, or rebound insomnia.

It can be concluded that the administration of low-dose doxepin improves sleep, including SE in the last quarter of the night, in adult and elderly patients with chronic primary insomnia as measured by polysomnography and patient self-report.

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Sleep and Alternative Medicine: I

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Divya Gupta

Introduction

In the year 2000, the World Health Organization (WHO) defined Traditional Medicine (TM) as "the sum-total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or note, used in the maintenance of health as well as in the prevention, diagnosis, and improvement or treatment of physical and mental illness" [1]. Complementary and alternative medicine (CAM) is often used interchangeably with TM [2]. Complementary medicine refers to medicine given as a complement to conventional therapies, whereas alternative medicine is that which is given in lieu of conventional therapy [3].

CAM includes a large and diverse set of systems of diagnosis, treatment, and prevention based on philosophies and techniques other than those used in conventional Western medicine, often derived from traditions of medical practice used in other (non-Western) cultures. Such practices may be described as alternative that exists as a body separate from and as a replacement for conventional Western medicine, or complementary, that is, used in addition to conventional Western practice. CAM is characterized by its focus on the whole person as a unique individual, on the energy of the body and its influence on health and disease, on the healing power of nature and the mobilization of the body's own resources to heal itself, and on the treatment of the underlying causes, rather than symptoms of disease. Many of the techniques used are subject to controversy and have not been validated by randomized double-blind, placebo controlled studies, thus setting CAM apart from conventional (allopathic) medicine. Congress in 1992 established an office of Alternative Medicine within the National Institutes of Health (NIH) to evaluate alternative therapies. In 1994, Congress exempted these remedies from regulation by Federal Drug Administration (FDA). Randomized controlled trials (RCTs) using these alternative products so far have not generated rich scientific data. Marcia Angell and Jerome Kassirer, editors of the New England Journal of Medicine, noted in an editorial [4] in 1998: "There cannot be two kinds of medicine—conventional and alternative. There is only medicine that has been adequately tested and medicine that has not, medicine that works, and medicine that may or may not work."

Rationale: Many prescription medications and over-the-counter sleep aids are widely advertised and used for sleep disorders; most have side effects and are intended for short-term use. These treatment options have less side effects such as tolerance (lowering of effectiveness following chronic use), rebound of sleep disturbance (sleep problems that develop after stopping a sleep aid), decrease in slow-wave, and REM sleep. Sometimes they treat multiple diseases.

Problems

Persons using alternative therapies should always tell their doctors what, how much, and how often they are taking them. Some of them, especially herbal preparations interact with prescription medications.

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Also, potency of the preparation may vary from brand to brand and from batch to batch within the same brand. Hence, clinical effect may vary from patient to patient, or may fluctuate in the same patient over time.

There are limited studies in the literature for evidence based CAM in sleep disorders regarding efficacy of alternative treatments. Since there are no randomized controlled trials, dose regulation and side effect data are lacking. In fact, some side effects may be unknown. Such preparations are best avoided during pregnancy and lactation.

Since the preparations are outside the regulation of oversight organizations such as the US Food and Drug Administration (FDA), the ingredients and production process may introduce contaminants or toxic substances into the preparations that have not been inspected or tested.

Placebo and Nocebo Effects

Placebo effect, also called the **placebo** response is a remarkable phenomenon in which a **placebo**—a fake treatment, an inactive substance such as sugar, distilled water, or saline solution—can sometimes improve a patient's condition simply because the person has the expectation that it will be helpful.

Nocebo effect: Negative suggestion can induce symptoms of illness [5]. Nocebo effects are the adverse events that occur during sham treatment or the result of negative expectations. While the positive counterpart—the placebo effect—has been intensively studied in recent years, the scientific literature contains few studies on nocebo phenomena.

Description and classification of CAM therapies: CAM therapies are broadly classified into the following five categories [6]:

1. Biologically based therapies (e.g., herbal medicines);
2. Manipulative and body-based methods (e.g., chiropractic, massage and acupuncture);
3. Alternative medical systems (e.g., Chinese Traditional Medicine [TCM] and ayurvedic medicine);
4. Mind–body interventions (e.g., meditation, hypnosis, and prayer);
5. Energy therapies (e.g., Reiki).

1. **Biologically based therapies**: These use substances found in nature.

Herbal Preparations are popularly used for insomnia.

Aromatherapy is the use of fragrant plant extracts and essential oils in massage or baths. The use of essential oils of bergamot, lavender, basil, chamomile, neroli, marjoram, or rose helps reduce stress. Preliminary research showed some sleep inducing effects, but more studies are needed. The herb Chamomile is commonly used as bedtime tea, but scientific evidence of its effectiveness is lacking. Likewise, the herb Kava has been used for insomnia. FDA has issued a warning that kava supplements have been linked to a risk of severe liver damage. Valerian is the most popular herbal supplement used for sleep problems in USA. It has also been used for nervousness, trembling, headaches, heart palpitations, gastrointestinal spasms and distress, epileptic seizures, and attention-deficit hyperactive disorder [7, 9]. Like any other herbal product scientific evidence is not sufficient to support its use. Studies by Taavoni et al. [7] in menopausal women showed that Valerian/lemon balm may assist in reducing symptoms of sleep disorder during the menopause (Table 56.1). German government has approved certain herbs (valerian, hops, and lemon balm) for the relief of sleep problems. A recent meta-analysis reviewing the efficacy and safety of Chinese herbal medicine (CHM) for subjects with insomnia showed that CHM alone was more effective than placebo by reducing Pittsburg Sleep Quality Index scores. However, there was no significant difference between CHM and placebo as far as the frequency of adverse events [8].

Other herbal remedies that are helpful in relieving insomnia include [23]:

- catnip (*Nepeta cataria*): poor sleep
- chrysanthemum (*Chrysanthemum morifolium*): insomnia
- hops (*Humulus lupulus*): overactive mind
- lime blossom (*Tilia cordata*): anxiety
- linden (*Tilia* species): anxiety
- oats (*Avena sativa*): poor sleep and nervous exhaustion
- passionflower (*Passiflora incarnata*): anxiety and muscle cramps
- skullcap (*Scutellaria lateriflora*): nervous tension
- squawvine (*Mitchella repens*): insomnia
- St. John's wort (*Hypericum perforatum*): depression
- vervain (*Verbena officinalis*): nervous tension, sleep apnea

Dietary supplements such as Vitamins B_6, B_{12}, and D, and Calcium and magnesium may also be helpful.

Melatonin is a naturally occurring hormone associated with sleep. According to a recent randomized controlled study, melatonin supplements may help improve sleep in people with high blood pressure (hypertension) who take beta-blockers [10]. Beta-blockers are prescribed to treat a number of health problems and are the most commonly prescribed class of drugs for hypertension. However, frequent side effects of these drugs are difficulty sleeping and daytime fatigue, which may result from their suppression of

Table 56.1 List of sleep symptoms and biological therapy used

Symptoms	CAM
Nervousness, trembling, headaches, heart palpitations, gastrointestinal spasms and distress, epileptic seizures, and attention-deficit hyperactive disorder, during menopause	Valerian
Nervous tension	Skull cap, valerian
Depression	St. John's wort
Sleep apnea	Vervain
Anxiety	Passion flower, lime blossom, linden, arsenicum
Nervous exhaustion	Oats
Overactive mind	Hops
Muscle cramps	Passion flower
During menopause	Valerian, lemon balm
HTN on beta–blockers	Melatonin
Jet lag	Melatonin
Hysteria	Dragon bones, magnetite
Alcohol or substance-related sleeplessness	Nux Vomica
Emotional upset	*Ignatia*
Mental stress, aches, and pains	Passiflora
Talking and laughing during sleep	Lycopodium
Pain	Acupuncture, acupressure, reflexology, chiropractic, biofeedback
Mental stress	Yoga, tai chi, exercise, biofeedback
Muscle tension	Massage, biofeedback, yoga
Circadian rhythm disorders	Melatonin, light/dark therapy

melatonin; a hormone that promotes sleep. Since beta-blockers are taken typically for life in these patients, melatonin supplements would be highly beneficial [11, 12]. However, larger effects of melatonin are observed in patients whose sleep problems are caused by a circadian rhythm abnormality (disruption of the body's internal "clock") and may be helpful in decreasing sleep disturbance caused by jet lag. Dietary supplements containing melatonin "precursors"—**L-tryptophan** and 5-hydroxytryptophan (**5-HTP**)—are also used as sleep aids. (The amino acid L-tryptophan is converted to 5-HTP, which is converted to serotonin and then melatonin.) However, these supplements have not been proven effective in treating insomnia, and there are concerns that they may be linked to eosinophilia–myalgia syndrome (EMS), a complex and debilitating systemic condition with multiple symptoms including severe muscle pain.

Practitioners of traditional Chinese medicine usually treat insomnia as a symptom of excess yang (positive) energy. Either magnetite or "dragon bones" are recommended for insomnia associated with hysteria or fear.

Dietary factors: It has been proved that intake of some nutrients is associated with sleep problems [13]. Those nutrients include alpha-carotene, selenium, dodecanoic acid, calcium and hexadecanoic acid, salt (OR = 1.19), butanoic acid, carbohydrate, vitamin D, lycopene, hexanoic acid, vitamin C (OR = 0.92), cholesterol, moisture, theobromine, and potassium. Avoiding taking these nutrients in excess may be beneficial. Some naturopaths recommend Vitamins B_6, B_{12}, and D for the relief of insomnia. Calcium and magnesium are natural sedatives, which help to explain the traditional folk recommendation of drinking a glass of warm milk at bedtime. Tryptophan may relieve insomnia; as turkey is high in tryptophan, a turkey sandwich as a bedtime snack may be helpful. Melatonin is widely used to induce sleep although adequate studies of its effectiveness are lacking [14].

2. **Manipulative and Body-Based Methods** based on manipulation and/or movement of one or more parts of the body.

Acupuncture is a traditional Chinese medicine which is shown to have improved the sleep quality. This procedure involves the insertion of very fine needles sometimes in combination with electrical stimulus or with heat produced by burning specific herbs into the skin at specific acupuncture points in order to influence the functioning of the body [15, 16].

Acupressure: Acupressure involves stimulating the same points as in acupuncture, but by using finger pressure rather than inserting needles. Acupressure is used in various disorders and painful conditions. The pressure points on both heels, the base of the head, forehead part in between the eyebrows, and on the inner side of the wrists can be used to relieve sleeplessness. It can be performed by lay people and so it is easily and economically accessible. Acupressure therapy can also be used to improve fatigue, stress, and sexual dysfunction and to enhance the immune system.

Reflexology: Reflexology is a form of touch therapy in which pain is relieved by stimulating certain pressure points on the feet and hands. Reflexologists work from maps of certain pressure points that are located on the hands and feet. These pressure points are believed to connect directly through the nervous system, affecting the body's organs and glands. The reflexologist manipulates the pressure points according to specific techniques of reflexology therapy. By means of this touch therapy, any part of the body that is the source of pain, illness, or potential debility can be strengthened through the application of pressure at the respective foot or hand location. The use of the reflexology points for the diaphragm, pancreas, ovary/testicle, pituitary, parathyroid, thyroid, and adrenal gland helps to relieve insomnia. However there is no clear evidence of its role in insomnia [17].

Chiropractic is also a kind of holistic medicine. Chiropractic is derived from Greek words meaning done by hand. It is grounded in the principle that the body can heal itself when the skeletal system is correctly aligned and the nervous system is functioning properly. To achieve this, the practitioner uses his or her hands or an adjusting tool to perform specific manipulations of the vertebrae. Chiropractic care includes adjustments, massage, and physical therapy that can all be beneficial to aid with sleep problems. Spinal manipulation can reduce stress upon the nervous system, thus allowing relaxation. Further studies are needed to prove its efficacy as minimal evidence is available [18].

Exercise: Physical activity [19] has been shown to have beneficial effects on sleep in the general population. Results of the study by Andrews et al. [19] in patients with chronic pain suggest engagement in high intensity activity and high fluctuations in activity is associated with poorer sleep at night; hence, activity modulation may be a key treatment strategy to address sleep complaints in individuals with chronic pain. Regular exercise [20, 21] deepens sleep in young adults with or without sleep disorders.

Massage. Therapeutic massage can relieve the muscular tension associated with chronic insomnia.

3. **Alternative medical system**: This mode of treatment is used in place of conventional medicine which includes ayurvedic medicine, homeopathy, naturopathy, and traditional Chinese Medicine (TCM). **Ayurvedic medicine** [22] is a practice of holistic medicine from India that is based on bringing humans into harmony with nature. It provides guidance regarding diet and lifestyle, to enhance health and improve disease. Therapies include diet, herbal, visual, and audio therapies, aroma therapy, and meditation. Ayurvedic treatments for insomnia or nightmares include scalp and soles massage with essential oils such as sesame, brahmi, a warm bath, or a nutmeg paste applied to the forehead. Tranquility tea (jatamansi, brahmi, ginkgo, and licorice root), and yoga are also found to be helpful. Sleep apnea is treated by avoiding sleeping on the back, using a humidifier for ambient air, and using nose drops with warm brahmi ghee (clarified butter) [23].

Homeopathy is a system for treating disease based on the administration of minute doses of a drug that in massive amounts produces symptoms in healthy persons similar to those of the disease. Homeopathic remedies are chosen according to the specific causes of insomnia [24–26]). They may include: *Nux vomica* (alcohol or substance-related sleeplessness), *Ignatia* (emotional upset), *Arsenicum* (anxiety), *Passiflora* (mental stress, aches, and pains), and *Lycopodium* (talking and laughing during sleep).

4. **Mind–body interventions**:

Progressive muscle relaxation is a therapy in which the therapist instructs patients to contract and release different muscle groups. Studies suggest that relaxation techniques may help people with insomnia, although, the effects appear to be short lived. Cognitive forms [27] of relaxation such as **Meditation** have slightly better results than somatic forms such as progressive muscle relaxation. Regular meditation practice can counteract emotional stress. Several studies have shown that regular meditation practice either alone or part of yoga practice results in higher blood levels of melatonin. **Yoga** is a mind–body approach that has components of meditation, breathing, and postures. Preliminary studies [28, 29] suggest Yoga can promote relaxation by releasing muscular tension and improve quality of sleep. When these forms of relaxation are combined with other components of cognitive-behavioral therapy (e.g., sleep restriction and stimulus control), lasting improvements in sleep have been observed.

Music therapy uses music prescribed in a skilled manner by a music therapist. Wang et al. [30] found that Music has significant impact in improving sleep quality of patients with acute and chronic sleep disorders. For chronic sleep disorders, music showed a cumulative dose effect and a treatment

duration of more than three weeks is required to assess its effectiveness. There is scientific evidence that music therapy can have sleep benefits for older adults and children [31, 32].

Biofeedback, or applied psycho-physiological feedback, is a patient-guided treatment that teaches an individual to control muscle tension, pain, body temperature, brain waves, and other bodily functions, and processes through relaxation, visualization, and other cognitive control techniques. The name biofeedback refers to the active physiological monitoring of biological signals (such as electromyography activity) that are fed back, or returned, to the patient in real time in order for the patient to develop techniques of manipulating them. This technique can help in improvising quality of sleep by promoting relaxation.

Tai chi is a Chinese exercise system that uses slow, smooth body movements to achieve a state of relaxation of both body and mind, thus strengthening cardiovascular and immune systems [33, 34]. Recent studies have shown that it improves sleep quality in older adults and in patients with heart failure who experience insomnia and impaired breathing during sleep. It is not yet proven as to which component of tai chi meditation, relaxation or physical activity, is responsible for its beneficial effects on sleep.

Visualization may also help to promote relaxation.

5. **Energy Therapies**

Light/dark therapy involves making the bedroom very dark at night and exposing the patient to early morning sunlight (or a light box). It also helps to treat depression. Bright Light Therapy is used to manage circadian rhythm disorders such as delayed sleep phase syndrome (DSPS), a condition which shifts the normal sleeping pattern outside what is considered the social norm. Treatment with true green light can balance the nervous system and may relieve insomnia. Low-energy emission therapy (LEET) is a clinically proven treatment for chronic insomnia [35–37]. LEET treatment involves delivering electromagnetic fields through a mouthpiece.

Neural therapy is a modified form of acupuncture with local anesthetic injections.

Naturopathic medicine is a multimodal therapy including diet, herbs, nutritional supplements, homeopathy, physical medicine, and counseling. It emphasizes prevention, treatment, and optimal health through the use of therapeutic methods and substances that encourage individuals' inherent self-healing process. It has been used for treatment of insomnia in adults as well as children [38].

CAM and Insomnia: Insomnia is a disorder of sleep initiation or maintenance difficulties or unrefreshing sleep. Research on CAM and insomnia has produced promising results for some CAM therapies. However, evidence of effectiveness is still limited for most therapies, and additional research is needed. This section summarizes what is known about some of the CAM approaches that people use for insomnia.

Herbs

Aromatherapy using essential oils from herbs such as lavender or chamomile is a popular sleep aid; preliminary research suggests some sleep-inducing effects, but more studies are needed. The herb **chamomile** is commonly used as a bedtime tea, but scientific evidence of its effectiveness for insomnia is lacking.

The herb **kava** has been used for insomnia, but there is no evidence of its efficacy. The US FDA has issued a warning that kava supplements have been linked to a risk of severe liver damage.

The Herbal supplement **valerian** is one of the most popular CAM therapies for insomnia. Several studies suggest that valerian (for up to 4-to-6 weeks) can improve the quality of sleep and slightly reduce the time it takes to fall asleep. However, not all of the evidence is positive. One systematic review of the research concluded that although valerian is commonly used as a sleep aid, the scientific evidence does not support its efficacy for insomnia [39]. Researchers have concluded that valerian appears to be safe at recommended doses for short-term use. Some "sleep formula" products combine valerian with other herbs such as **hops, lavender, lemon balm,** and **skullcap**. Although many of these other herbs have sedative properties, there is no reliable evidence that they improve insomnia or that combination products are more effective than valerian alone [39, 40].

The findings of a Chinese study in mice suggest that treatment with Wen-Dan Decoction, a formula of traditional Chinese medicine, may improve sleep deprivation-induced negative emotions by regulating orexin-A and leptin expression [41].

Recently, a study in Bangladesh, evaluating sedative and hypnotic effect of the ethanolic extract of whole plants of *Scoparia dulcis* (EESD) in mice, showed significantly decreased induction time to sleep and prolonged the duration of sleeping, induced by thiopental sodium [42].

The seeds of *Ziziphus mauritiana* Lam are popularly used as a sedative and hypnotic drug in China, and Southeast Asia. A study from Thailand correlated the hypnotic effect of these seeds with the contents of total phenolics and total flavonoids in the extract and assessed weight-based doses effective in mice [43].

Si Ni San freeze-dried powder is a traditional Chinese medicine, consisting of four herbs that are bupleurum, white

peony, immature bitter orange, and licorice. A Chinese study in rats showed that it extended the total sleep time and prolonged slow wave sleep (SWS) and REM sleep for both insomniac and normal rats [44].

Melatonin and Related Supplements

Like valerian, melatonin supplements are widely used and researched for insomnia. A 2013 evaluation of the results of 19 studies concluded that melatonin may help people with insomnia fall asleep faster, sleep longer, and sleep better, but the effect of melatonin is small compared to that of other treatments for insomnia. Greater effects are observed in patients with circadian rhythm sleep disorders. Studies of melatonin in children with sleep problems suggest that it may be helpful, both in healthy children and in those with conditions such as autism or attention-deficit hyperactivity disorder. However, both the number of studies and the number of children who participated in the studies are small, and all of the studies tested melatonin only for short periods of time [46].

Melatonin supplements appear to be relatively safe for short-term use, although the use of melatonin was linked to bad moods in elderly people (most of whom had dementia) in one study. The long-term safety of melatonin supplements has not been established.

Dietary supplements containing substances that can be changed into melatonin in the body—L-tryptophan and 5-HTP—have been researched as sleep aids.

Dietary supplements containing melatonin "precursors"—**L-tryptophan** and **5-HTP**—are also used as sleep aids. The amino acid L-tryptophan is converted to 5-HTP, which is converted to serotonin and then to melatonin. Studies of L-tryptophan supplements as an insomnia treatment have had inconsistent results, and the effects of 5-HTP supplements on insomnia have not been established. Also, there are concerns that they may be linked to eosinophilia–myalgia syndrome (EMS), a complex and debilitating systemic condition with multiple symptoms including severe muscle pain.

Other CAM Approaches

Traditional Chinese medicine commonly uses **acupuncture** to treat insomnia. A review of available studies found some evidence of benefits, but many studies had design flaws that make it difficult to draw firm conclusions. According to a Chinese study, differential activation patterns of functional MRI in sleep-deprived brain may explain the restoring effects of acupuncture [45]. A randomized control trial done in China to study efficacy of acupuncture for primary insomnia found that verum acupuncture appeared to be more effective in increasing sleep quality and daytime functioning than sham acupuncture and estazolam [47]. A recent study of acupuncture for residual insomnia associated with major depressive disorders (MDD) showed that the efficacy is similar to that of placebo acupuncture raising doubts about the value of acupuncture in the treatment of residual insomnia in MDD [48]. Of note, in a small trial placebo acupuncture significantly reduced insomnia severity index (ISI) score in 18 respondents out of 86 participants (those with primary insomnia and residual insomnia in MDD) [49]. A Taiwanese study suggests that low level laser stimulation at the palm, might be conducive to falling into sleep in patients with sleep problems [50] based on EEG changes in subjects with closed eyes.

Studies suggest that **relaxation** techniques may help people with insomnia, although the effects appear to be short-lived. Cognitive forms of relaxation (such as **meditation**) have had slightly better results than somatic forms (such as progressive muscle relaxation) [51, 52]. Preliminary studies suggest that **yoga** may also improve sleep quality. In addition, when these forms of relaxation are combined with other components of cognitive-behavioral therapy (e.g., sleep restriction and stimulus control), lasting improvements in sleep have been observed. Again, additional research is needed in these areas.

Chinese health Qigong exercise, characterized by eight simple, slow, and relaxing movements, each of which can enhance the function of certain organs or parts of the body according to Chinese medicine theory [53]. "Baduanjin" Qigong is easy to learn and less physically or cognitively demanding. A study in Hong Kong has found that the number of Qigong lessons attended and the amount of Qigong self-practice were significantly associated with sleep, fatigue, anxiety, and depressive symptom improvement, and may be helpful to treat chronic fatigue syndrome type of illness [53].

CAM and Other Sleep Disorders

Snoring and Obstructive Sleep Apnea: Sleep apnea is a sleep disorder characterized by pauses in breathing or instances of shallow or infrequent breathing during sleep. In obstructive sleep apnea, there is effort to breathe but reduced airflow due to upper airway collapse in sleep. In central sleep apnea, there are pauses in effort to breathe as well as in airflow, and it can occur in the setting of stroke, trauma, and heart failure. In a survey study, approximately 60 % patients with a diagnosis of Obstructive Sleep Apnea/ Hypopnoea Syndrome (***OSAHS***) reported previous or current use, and interest in future use, of CAM; 20 % reported having used CAM specifically for improving sleep. This serves as a reminder for sleep medicine providers to inquire about CAM use and underscores the need to conduct future studies of

CAM in patients with OSAHS [54]. In this study, CAM included biological treatments such as melatonin and other CAM techniques but excluded use of nasal strips and throat sprays.

Alternative therapies may help treat sleep apnea caused by allergies. Homeopathy and nutrition are most likely to have a positive effect. While some manufacturers promote supplements for weight loss, none of these products have been proven to work as well as eating less and exercising more [55].

Nutrition and Supplements [56]

- Diet—It is recommended to avoid mucus-producing foods (such as bananas). Aerobic exercise, as tolerated, along with a healthy diet will help to reduce weight. Diet should include a balanced mix of fruits and vegetables, healthier fats such as olive oil, whole grains, and low fat dairy products.
- Use of Chromium may be beneficial in building lean muscle mass but large doses can cause renal damage.

Homeopathy

This is based on the principle that "like cures like" e.g., an allergy medicine may contain a minute dose (very, very dilute) of allergen which causes mild allergic reaction (e.g., runny nose). Few studies are available regarding its efficacy. It may be helpful as an adjunctive therapy. Providers determine a person's constitutional type including physical, emotional, and intellectual parameters to assess the appropriate therapy. Some of the substances that have been reported to be beneficial include *Arsenicum album*, *Lachesis* (for morning depression), *Opium*, *Sambucus (for feeling of suffocation)*, *Spongia (for chest tightness),* and *Sulfur* (for heat intolerance).

Acupuncture

Some evidence suggests that a type of acupuncture called auriculotherapy acupoint pressure may help treat sleep apnea.

Acupuncture has also been examined in small studies, as a treatment of sleep apnea.

In one study published in 2009 [57], for instance, researchers assigned 30 people with obstructive sleep apnea to treatment with three to five acupuncture sessions per week. After 30 sessions, the patients showed significant improvements in factors such as hypoxia. An earlier study of 26 patients with obstructive sleep apnea found that those assigned to 10 weeks of weekly acupuncture treatment had greater relief of sleep apnea-related respiratory problems (compared to those who received no treatment [58]) possibly, by strengthening of the genioglossus muscle, to reduce airway blockage in sleep, but others have questioned that claim. Acupuncture also appeared to reduce inflammation in the genioglossus.

Efficacy of external and internal nasal dilators, nasal lubricants, oral dietary supplements, and magnetic therapy (magnetic pillows and mattresses) has not been proven [59].

CAM and Parasomnias: **Parasomnias** are a category of sleep disorders that involve abnormal movements, behaviors, emotions, perceptions, dreams, and autonomic nervous system activity, that occur while falling asleep, during sleep, in between sleep stages, or during arousal from sleep. CAM therapies that may be more frequently used for parasomnias include acupuncture, homeopathy, herbs and supplements, aromatherapy, timed awakenings, and hypnosis. There are very few clinical studies utilizing CAM therapies for parasomnias. However, the following observations can be made: Treatment of nocturnal enuresis has the most supportive evidence with clinical studies advocating the use of acupuncture, homeopathy (homotoxicology), and hypnosis. Overall, hypnosis proves to be the most versatile for treatment of parasomnias with clinical studies supporting its use in nocturnal enuresis, sleepwalking, night terrors, and nightmares.

The most often mentioned alternative approach to bedwetting, or enuresis, is chiropractic manipulation of spine. **Chiropractic care** for nocturnal enuresis treats the bladder through manipulation of the lower spine and pelvis. Since the nerve supply to the muscles, which control urinary emptying, are connected to the brain through the spinal cord, it is believed that aligning the spine will correct any slow messaging or incomplete signals between the brain and the bladder. **Hypnosis** is another option for parents seeking non-invasive methods of treatment for bedwetting. The hypnotist works with the subconscious brain to make positive connections with the conscious goal of awakening to visit the toilet in the night. Instead of using negative reinforcements from an alarm system, the child is trained through self-hypnosis and visual imaging to respond to physical symptoms of a filling bladder before an accident. This method emphasizes relaxation, self-control, and independence. The National Kidney Foundation reports that children who can benefit from this treatment usually show improvement within four to six sessions, but they caution that more studies are needed to determine its true effectiveness. There are other methods which are less popular such as acupuncture, touch therapy, acupressure, shiatsu, reflexology, and homeotherapy.

Scheduled awakenings work well for children who have sleep terrors or sleep walking at the same time almost every night. However, this treatment can take 2–4 weeks, and parent must be consistent every night for it to be effective. Scheduled awakenings should occur 15–30 min before the child typically has his/her first event of the night. Child is gently aroused with a light touch or a soft verbal prompt. Once he/she arouses (i.e., opens eyes, changes positions, and/or says that he/she is awake), allow the child to return to sleep [60].

Narcolepsy and CAM: Narcolepsy is a disorder of excessive daytime sleepiness with symptoms of REM-related phenomena, the most specific of which is cataplexy (episodes of sudden loss of muscle tone, focal or generalized, without loss of consciousness) that is usually triggered by emotions such as laughter and excitement.

Web-based sources [61] have described the beneficial role of nutrients such as tryptophan, amino acids, minerals, and vitamins. However, data regarding their efficacy is not available. Avoiding allergy-producing foods, such as dairy and gluten, is also advised.

Circadian rhythm sleep disorders and CAM: Circadian rhythm Sleep disorders are caused by alteration of the circadian time keeping system (internal clock), its entrainment mechanisms (to light dark cycle) or misalignment of the endogenous circadian rhythm and external environment. People with circadian rhythm disorders respond well with behavioral therapy such as chronotherapy, bright light therapy, and melatonin supplements. Chronotherapy consists of gradually shifting the sleep time in accordance with your desired schedule. For example, if you have trouble getting to sleep at your desired bedtime, you would delay your bedtime by a few hours each night until you reach your desired bedtime hour. The reverse would be true if you are falling asleep earlier than your desired bedtime; you would then advance your bedtime by a few hours each night until the desired bedtime is achieved. Once your desired bedtime has been established, you must adhere to this schedule on a regular basis.

Enhancing environmental cues: Keep a dark and quiet room during sleep and a well-lit room upon awakening. Avoid bright light exposure in the evening and enforce regular hours for eating and other activities.

Bright light therapy [62]: Circadian rhythm sleep disorders are characterized by asynchrony in the patient's internal clock or time-keeping system, with the external environment, for example, the patient's wake–sleep pattern may be misaligned from the environmental light–dark cycle. This may result in symptoms of insomnia, fatigue, and psychomotor slowing. Exposure to bright light at the appropriate time of the day stimulates the retinal-hypothalamic pathway and helps to synchronize the person's internal clock and wake–sleep times to the environmental time. This will help to achieve restorative sleep and improve daytime energy and alertness levels. Blue light is most effective and the direction of shift of the patient's internal clock depends on the time during the internal circadian cycle that the light exposure is received. Luminescence of 2500–10,000 lux is required to be effective, and morning exposure helps phase advance sleep onset in Delayed Sleep Phase Syndrome. Evening exposure helps to delay sleep onset in Advanced Sleep Phase syndrome, by suppressing night-time release of melatonin. Light therapy is also used for entrainment in non-24 h sleep wake syndrome in sighted individuals, and for adaptation to shift work and jet lag. However, chronic exposure to bright light may impose oxidative stress on the light receptor cells in the retina.

Melatonin (described above).

Restless Legs Syndrome (RLS) and CAM

RLS is a sleep-related neurological movement disorder with an urge to move the legs with or without uncomfortable sensation at bedtime, or after prolonged inactivity, that is partially relieved by stretching or moving the legs and is worse or exclusively present in the evenings, at least in the early stage of illness. Research indicates that the needle-based traditional Chinese therapy known as acupuncture may help relieve restless leg syndrome. Recently, a Japanese study evaluated the effects of acupuncture in patients with RLS by actigraphic recordings and found that standard acupuncture might improve the abnormal leg activity in RLS patients, and thus is a potentially suitable integrative treatment for long-term use [63].

In a 2007 study, scientists found that receiving massage therapy that targets the lower body could help ward off restless leg syndrome symptoms for several weeks. Managing your stress may help stave off restless leg syndrome symptoms, so make sure to include a stress-reducing practice (such as deep breathing or meditation) in your everyday routine. Since maintaining sufficient levels of calcium and magnesium is thought to keep muscles and nerves functioning properly, taking a daily multivitamin/multimineral may help restless legs syndrome symptoms (there is, however, no scientific study to support this). In many cases, low levels of iron can result in restless leg syndrome. However, since too much iron can be toxic to the body, iron supplements should not be used without first consulting with the physician. Certain foods such as beans, dark green leafy vegetables, nuts, and seeds are rich in iron. Applying a warm or cold compress to the affected area, or alternating hot and cold therapy, may soothe restless legs syndrome symptoms. Exercise (in moderation and not heavy) may benefit restless leg syndrome as well.

Table 56.2 Differences between conventional and alternative medicine

Criterion	Conventional medicine	Alternative medicine
Definition of health	Normal function (a specific disease or dysfunction is not present)	Intactness of the mind, body and spirit and optimal balance in between them
Definition of illness	Disease based: Dysfunction of organs or metabolic processes	Symptom and individual based: Imbalance between mind, body and spirit
Concept of life force	Life processes involve physical and metabolic events	A nonphysical life force integrates mind and body, and interconnects all living beings, and is the essence of health
Understanding of consciousness	Results only from physical processes in the brain	Not limited to the brain only; it can exert healing effects on the body
Method of treatment	External interventions (e.g., drugs, surgical procedures, radiation therapy etc.)	Support and strengthen the patient's intrinsic capability for self-healing

Calf muscle vibration pad [64] provides 30 min of vibratory counter stimulation, gradually ramping down and shutting off without waking the patient. Results from two randomized controlled trials indicated that the device was superior to placebo pads for improving sleep quality in patients with primary RLS.

Bega and Malkani [65] recently reviewed the role of various alternative therapies in RLS and concluded that high-quality randomized controlled trials are warranted to support and verify the data presented.

Interaction of CAM therapies with conventional/Allopathic medicine and differences are listed in Table 56.2 [66].

Safety of CAM treatment relies on history of use for millennia without seemingly causing harm. Evidence for safety of most of the treatments is not based on rigorously controlled scientific trials or studies. Therefore, it is important to keep in mind some safety considerations such as:

- Avoid use of an alternative approach to treat a medical emergency or life-threatening disorder for which effective conventional treatments exist (e.g., pneumonia, hypertensive urgency, thyroid storm)
- There can be toxic effects from certain herbal preparations (e.g., pyrrolizidine and kava can cause liver damage and aristolochia can affect the kidneys)
- Harmful contaminants may be present in herbal preparations (e.g., heavy metal may be present in some Chinese and Ayurvedic preparations; other drugs may be inter-mixed in some Chinese herbs)
- CAM therapies may interact with each other (e.g., herbal preparations and other dietary supplements) and with other drugs (e.g., induction of cytochrome P-450 [CYP3A4] enzymes by St. John's wort, resulting in reduced activity of antiretroviral medications. Elmer et al have reported risk of bleeding due to use of ginkgo, garlic, or ginseng together with aspirin, warfarin, ticlopidine, or pentoxifylline [67])
- There is potential for injury to the body or organs by physical manipulation (e.g., inappropriate spinal manipulation could damage nerves or spinal cord in predisposed patients or cause internal bleeding in patients with bleeding disorders)

Safety alerts about harmful dietary supplements are available at the FDA web site [68]. FDA regulations require that manufacturing processes should assure the quality and safety of supplements.

To help reduce risk of injury or complications due to physical manipulations, patients should look for providers who have credentials from accredited training programs and have a professional license.

Points to Consider for Selecting Complementary Health Approaches for Sleep Problems [69]

- Patient should discuss with their health care providers about the complementary health approach they are considering and ask any questions they may have. It is important that patient discuss their sleep-related symptoms with their health care providers before trying any complementary health product or practice. Because trouble sleeping can be an indication of a more serious condition, and because some prescription and over-the-counter drugs can contribute to sleep problems.
- Patient should exercise caution about using any sleep product—prescription medications, over-the-counter medications, dietary supplements, or homeopathic

remedies. They should find out about potential side effects and any risks from long-term use or various combining products.

- Patients should remember that "natural" does not always mean safe. For example, kava products can cause serious harm to the liver. Also, a manufacturer's use of the term "standardized" (or "verified" or "certified") does not necessarily guarantee product quality or consistency. Natural products can cause health problems if not used correctly. The health care providers that the patient sees about his/her sleep problems can advise him/her.
- If a woman is pregnant, nursing a child, or considering giving a child a dietary supplement or other natural health product, it is especially important for her to consult with her (or her child's) health care provider.
- Also, patients who are considering a practitioner-provided complementary health practice, should check with their insurer to see if the services will be covered and ask a trusted source (such as the health care provider or a nearby hospital or medical school) to recommend a practitioner.
- Patient should inform their health care providers about any complementary health approaches that they use so that the providers have a full picture of what the patient does to manage their health. This will help ensure coordinated and safe care. National Center for Complementary and Integrative Health (***NCCIH***) has a Time to Talk campaign that gives tips about talking with one's health care providers about complementary health approaches.

Acknowledgments Anitha Nimma M.B.B.S.

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Approach to Sleep Disorders in the Traditional School of Indian Medicine: Alternative Medicine II

57

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Introduction

Ayurveda is a reflection of anatomical, physiological, psychological, pathological, and therapeutic views, expressed in the *Vedas* (meaning "*sacred knowledge*" or "*wisdom*"), *Upanishads* (which means the "inner or mystic teaching") and *Smritis* (means "that which is remembered"). The literal meaning of the word *Upanishad* is "sitting in front of" (i.e., sitting at the master's feet and receiving instructions). This refers to the practice of disciples gathering before Vedic seer-sages (*rishis*) for discussions on religious concepts, experiences, and revelations of Hinduism, such as the Universe (world or infinite), Soul (or *Brahman*), and the Universal Self (or *Atman* or *purusha* or pure awareness) [1]. The *Upanishads*, which embody the experiences of the sages, date back well before the age of Buddha, some 2500 years ago [1–3]. Sleep, consciousness, and dreaming have been dealt with in detail in the *Upanishads.* These scriptures mentioned about sleep, both with and without dream, much before the modern scientific world described REM and non-REM sleep [4, 5].

The meaning of the term *Ayurveda* is knowledge of life [6–8]. Though the word *Ayurveda* sounds as if it is related to the *Vedic* period, it originated much later. According to traditional Indian religious belief, Brahma, the creator, also provided the knowledge contained in Ayurveda. Ayurveda in its original form is not available now, but most of its contents are revealed in the *Samhitas* (encyclopedias) written by *Acharyas* Charaka and Sushruta in about 1000 BC [9–11]. Along with these encyclopedias, *Astangasangraha* and *Astangahrdayasamhita,* written much later (may be about 500 or 600 AD) by *Acharya* Vagbhata, are the most important classical writings in Ayurveda. In Ayurvedic literature, the three factors, i.e., *Ahara* (diet), *Nidra* (sleep), and *Brahmacharya* (celibacy), are mentioned as the three *Upastambhas* (supporting sub-pillars) which play an important role in maintaining good health [12]. *Acharya* Charaka called sleep *Bhootadaatri,* meaning supporter of being [13]. *Acharya* Sushruta considered sleep as *Vaishnavimaaya* (i.e., which provides nourishment to the living body and maintains the health) [14]. He has included sleep-related disorders in the list of serious morbidities [15].

Ayurvedic Concept of *Dhatus* (*Doshas*) and Sleep

Ayurvedic medical traditions have a unique understanding of physiology, pathogenesis, pharmacology, and pharmaceuticals which are different from modern Western biomedicine. According to Ayurveda, when *Pancha Mahabhootas* (five basic elements of nature) are impregnated by *Atma* (the life element), the living human being is created. The five basic elements of nature are *Prithvi* (Earth), *Jala* (Water), *Teja* (Fire), *Vayu* (Wind), and *Aakasha* (Ether). From these five basic elements of nature are formed the three *Dhatus* (basic factors), namely *Vata, Pitta,* and *Kapha*. These *Dhatus* decide the status of the health of an individual. All these terminologies cannot be appropriately translated into any other language, as they do not have equivalent terms in modern physics, physiology, and medicine. This unique concept of psychophysiological body types forms the cardinal principle in the Ayurvedic approach to health. So, it is essential to mention about this concept here as Ayurvedic physicians believe that sleep disturbances (like all other health problems) are caused by the deviations in these *Dhatus*. In recent years, some attempts have been made to validate the concept of *Dhatus* [16–19].

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Dhatus determine our physical composition or constitution of our body. Thus, they decide the physical and mental peculiarities with which each of us is born. When these basic factors are in equilibrium, or in their natural state, they provide the individual with strength, happiness, and long life. On the other hand, if these *Dhatus* are aggravated or deranged, they bring about health problems. For example, increase in *Kapha* can cause *nidradhikya* (excessive sleep), and *asvapna* (sleeplessness) can result from increase in *Vata*. Children sleep more because they have predominance of *Kapha* [20].

Ayurvedic Concepts About Sleep Types and Factors Modifying It

According to Ayurvedic texts, sleep is a natural urge and suppression of it will lead to several physiological and psychological problems [21]. *Acharya* Charaka has dealt with sleep and sleep disorders in great detail in his *Samhita,* and it gives details about his approach to sleep problems [22]. According to *Charaka Samhita,* "When the mind gets tired, when the senses get dulled and incapable, the man goes to sleep."

Acharya Charaka has stated that happiness and sorrow, growth and wasting of body mass, strength and weakness, virility and impotence, knowledge and ignorance, and existence of life and its cessation depend on the quality of one's *Nidra* (sleep). The *Charaka Samhita* goes on to say that as happiness and longevity are dependent on proper sleep, its deficiency as well as its excess will result in just the opposite. According to him, *Nidra* gives *Pushti* (Anabolic effect) and *Jagarana* (vigil) produces *Karshana* (Catabolic effect) of the body. There is also emphasis on diet regimentation for getting proper sleep.

Sleeping during daytime is advocated only for very young children, weak, tired, and those suffering from various diseases. During summer season (when the night becomes shorter), some sleep during the day can be indulged in by all. Although any comfortable position of the body may be regarded as suitable for sleep, sleeping on one's right side (*daksirasana*) is considered the most favorable position for sleep. According to them, sleeping in sitting posture does not produce any harm. Roughness in the body is caused by keeping awake at night. Obesity and emaciation are specially mentioned as two conditions caused by improper sleep and diet. *Acharya* Charaka has classified sleep into six, laying emphasis on causative factors (see Box 57.1) [23], whereas *Sushruta Samhita* classified sleep into three categories (see Box 57.2) [24] and *Acharya* Vagbhata has classified sleep into seven types (see Box 57.3) [25].

Box 57.1: Classification of Sleep into Six types according to causative factors (Acharya Charaka, c 1000 BC)

- *Tamobhava*—caused by *tama* (mental perplexity).
- *Slesmasamudbhava*—caused by vitiated (phlegm).
- *Manah-sarir srama saambha*—caused by mental exertion.
- *Agantuki*—indicative of bad prognosis leading to imminent death.
- *Vyadhi-anuvartini*—caused as a complication of diseases such as fever.
- *Ratri-swabhava prabhava*—caused by night during light dark cycle.

Box 57.2. Sushruta Samhita Classification of Sleep (c 1000 BC)

- *Tamsi*—when sense organs get filled with *Kapha* and are dominated by *tamoguna* (mental perplexity), *tamsik* sleep is produced.
  - *Swabhaviki*—this is the normal sleep.
  - *Vaikariki*—if there is any disturbance to mind and body, normal sleep does not occur. But the sleep that occurs in such a situation is called *vaikariki nidra* (modified sleep).

Box 57.3. Seven Types of Sleep (*Acharya* Vagbhata, c 500–600 AD)

- *Kalaswabhawaj*—it is the normal sleep that occurs at night.
- *Amayaja*—it is the sleep that is produced due to some disease.
- By fatigue of *mana*—sleep produced by mental fatigue.
- By fatigue of *sharer*—sleep produced by physical fatigue.
- *Shleshmaprabhavaj*—it is produced due to predominance of *Kapha dosha*.
- *Agantuka*—this is the type of sleep resulting from trauma.
- *Tamobhava*—it is produced by predominance of *tamoguna.*

According to *Acharya* Vagbhata, diseases, purgation, emesis, fear, anxiety, anger, smoking, blood-letting, fasting, uncomfortable bed, irregular sleep pattern, and old age are considered as causes of insomnia. According to *Acharya*

Charaka, there are four causes for the disturbance in sleep [26]. They are as follows:

- Differences in *Dhatus* (basic factors) that constitute the body. A person having predominance of *Vata* shows shorter duration of sleep, whereas those with *Kapha* predominance have longer sleep.
- Age-related change in sleep is also explained in terms of changes in *Dhatus.*

Predominance of *Kapha Dosha* produces more sleep in children, whereas *Vata Dosha* brings about diminished sleep during old age.

- Excessive exercise or work and nighttime work cause disturbances in the sleep.
- Disturbances in sleep produced by other diseases are also explained on the basis of deviations in *Dhatus*.

As can be seen from above descriptions, good sleep is that which occurs at night. It is described as that which "nurses all the living beings." The sleep which is caused by *Tamas* is considered as "the root cause of sinful acts." It is interesting to note that insomnia has been classified by *Acharya* Charaka as primary (*Pranashta*) and secondary (*Nimitta*).

Ayurvedic Concept of Dreams and *Dhatus*

Charaka Samhita also deals at length with the theories of dream. Not only *Acharya* Charaka but also *Acharya* Sushruta and *Acharya* Vagbhata did believe that dreams are produced when the vital equilibrium between the three *Dhatus* is disturbed. It may be noted that *Acharya* Charaka had recognized the lack of meaning in most of our dreams. At the same time, he and *Acharya* Vagbhata had mentioned about seven types of dreams that are significant [27–29] (see Box 57.4).

Box 57.4. Types of Dreams (Acharya Vagbhata, c 500–600 AD)

- Objects seen earlier (*Dr'shta*).
- Things which we have heard earlier (*S'r'uta*).
- Past experience (*Anubhoota*).
- Wish fulfillment (*Praar'tita*).
- Imagination (*Kalpita*).
- Premonition (*Bhaavika*).
- Morbid things (*Dhoshaja*).

Acharya Sushruta had devoted one complete chapter on the analysis of dreams. He considered them as omens. According to him, a favorable or unfavorable termination of a disease could be predicted from the dreams. Curiously enough, in many places in the ancient literature it is mentioned that dreams are produced by "*Svapnavha nadi*" (sleep/dream center). According to *Sushruta Samhita*, ten "*nadis*" (nerve centers) control the various functions of the body. Man goes to sleep by using two of them, and with the help of two others, he wakes up [30].

Treatments for Sleep Disorders in Ayurveda

There is a great similarity in the approach to sleep disorders in different *Samhitas.*

In due course of time, several later writers on Ayurveda have also added their wisdom in treating sleep disorders. Treatment of insomnia (*anidra*) is described more extensively than hypersomnia (*nidradhikya*) in Ayurvedic literature. Hypersomnia is considered a disorder due to increased *Kapha.* Apart from many causative factors, decreased *Kapha* can also produce insomnia. As per Ayurveda, disease is nothing but the distortion of natural order of the body. Holistic approach in Ayurveda in the management of sleep disorders involves avoidance of causative factors. So a relaxation technique, along with other therapies, is the mainstay in the treatment for insomnia. Ensuring happiness and encouraging activities which please the mind are considered part of the management of sleeplessness.

Ayurveda stresses on the importance of purification of the body (*panchakarma*) for treatment of many disorders, including sleep disorders. Many of these purification procedures are aimed at giving physical and mental relaxation to the patient. Mental relaxation is given a lot of importance in the management of sleep disorders, especially insomnia. Some of the Ayurvedic treatments for both *anidra* (insomnia) and *nidradhikya* (hypersomnia) are aimed at purification of the body. Thus, the approach to both these diseases may be identical at times. Some treatments would require purification of the body before other corrective measures are taken. In addition, treatment for the same disorder in two different individuals may also differ, depending on the *Dhatus* that are predominant in him or her. The efficiency of the treatment will also depend on the ability of the physician to recognize the *Dhatus* predominant in the patient. Clinical assessment of the patient is done on the basis of a prolonged interview with the patient (or patient's relatives) and some physical examination of the patient.

During clinical examination, the parameters used by the Ayurvedic physician for evaluation of sleep disorder may differ from those employed in modern medicine. Parameters used by them include assessment of drowsiness and yawning, which have obvious bearing on sleep, but it also includes parameters which may not be so obviously related to sleep such as malaise, fatigue, inertness, headache, lack of

concentration, loss of memory, poor sensory perception, indigestion, constipation, weight gain or loss, and even skin luster [31]. Recently, some research studies have been undertaken to evaluate the efficacy of various Ayurvedic treatments in many Indian universities, devoted to indigenous system of medicine. Many of these studies were part of the thesis work of postgraduates. Unfortunately, in none of them was sleep assessed on the basis of polysomnographic studies. They have employed their own clinical assessment based on Ayurvedic principles, in addition to sleep diaries maintained by the patient, for assessment of sleep. Because of these deficiencies, the results of many of these studies have not been published in standard medical journals. Ayurvedic physicians believe that polysomnographic assessment is not of much significance, if it cannot reflect correctly the patient's own feeling about his sleep. Without disputing their concern about the patient's satisfaction in any treatment, we have to accept that if Ayurvedic medical therapies are to be considered as viable stand-alone or adjuvant treatments for sleep disorders, future researchers will have to use acceptable methodology, including appropriate sample sizes, adequate controls, and appropriate statistical analysis, in addition to any other technique that they may use to assess sleep [32].

In most traditional medical interventions, complex treatment methods such as individualized diagnosis, herbal medications, and other procedures are employed [33].

There is an emphasis on maximizing the body's innate ability to heal itself and a "whole systems" approach, wherein the physical, mental, and spiritual attributes of a patient are emphasized, rather than a focus on the disease as in conventional modern medicine. Many of the studies undertaken in Indian universities on sleep disorders have also employed combination of procedures such as herbal medicine, diet regulation, and lifestyle regimens. This also makes it difficult to attribute the effect of treatment to any one of the procedures. The very nature of traditional medicine itself poses several problems in designing a research study that is acceptable in standard journals [34]. Choosing traditional medicine as a therapy could itself be considered as a criterion for exclusion. Selecting a suitable placebo, and alternate intervention, and masking and blinding are also very difficult. Selecting a sham treatment, which is identical to the Ayurvedic procedure, is also not easy.

Different approaches to sleep disorders in Ayurvedic medicine include prayer, yoga, physical procedures, sleep hygiene (including psychological manipulation), drug administration, and diet regulations. Apart from the herbal formulations mentioned in classical literatures, there are also formulations in the market such as *Insomrid* and *Tagara Kwatha* for insomnia, which are not part of classical herbal formulations.

Physical Procedures

Exercise

Exercise as a treatment is suggested for both insomnia and hypersomnia. The type of exercise that is suggested depends on the constitution and age of the patient. Though walking and exercise in the sun are suggested, patients are always instructed to avoid too much exposure to sun. Modern physicians do advise exercises such as jogging, bicycling, and aerobics. The effect of exercise on sleep is something that has been studied extensively using modern scientific techniques, including polysomnography [35–38]. Though these investigations were not done to validate Ayurvedic approach to sleep problems, the inferences drawn from these studies do support the traditional beliefs.

Letting Oil Drip on Head

This procedure called *Shirodhara* is a form of Ayurvedic therapy that involves pouring liquids gently over the forehead. This is one of the most commonly used procedures for sleep disorders. This is also a procedure employed for cleansing of the body (*panchakarma*) according to Ayurvedic concepts. Though this procedure is primarily used for insomnia, it is also recommended for hypersomnia. The name *Shirodhara* comes from the Sanskrit words *shiro* (head) and *dhara* (flow). The liquids used in *Shirodhara* depend on what is being treated, but can include oil, milk, buttermilk, coconut water, or even plain water. It is very commonly used in modern spas for relaxation. A clinical study conducted for evaluation of *Shirodhara* with milk has claimed significant improvement in insomnia [39]. Sleep diary and clinical assessment based on Ayurvedic principles were the methods used for evaluation of the treatment. It is claimed that *Apamargadi Vati,* a decoction containing *Apamarga* (*Achyranthes aspera*), *Kokilaksha* (*Asteracantha Longifolia*), *Kakajangha* (*Peristrophe Paniculata*), and *Bakuchi* (*Psoralea coryifolia*), given in *Shirodhara* provided 89.5 % improvement in sleep quality and 95.3 % relief in mood [40]. A more recent study of *Shirodhara* with *Brahmi* (*Bacopa monnieri*) oil, which evaluated insomnia using patient's self-report questionnaire, also claimed beneficial effect [31].

Making Medicated Oil Stand Over the Scalp for a Prescribed Period of Time

This procedure (*Shirobasti*), which is also meant to purify the body (*Panchakarma*), is another widely used treatment for sleep disorders. During the procedure, warm oil is retained at a level of one inch above the head for around 30 min. It is preferably applied on a clean shaved head. A leather belt is tied around the head, and the sides are sealed with black gram paste to retain oil. This is followed

by gentle massage over back, shoulder, neck, head, and mandible. *Shirobasti* is normally given for seven days and can be repeated if required. Studies in two postgraduate theses on clinical evaluation of *Shirobasti* on patients of insomnia were conducted at two Ayurvedic medical colleges at Rajiv Gandhi University of Health Sciences, Bangalore, India. These studies, which were carried out using sleep diary and clinical assessment based on Ayurvedic principles, have also claimed improvement in insomnia [41].

Application of Medicinal Paste on the Head

Shiro lepa (application of paste on the head) is another form of therapy in which pastes of various medicinal powders and herbs are applied on the scalp. After that, the scalp is covered and tied with certain leaves. This procedure is supposed to allow the herbs to act on the scalp and nourish the head. The most common paste that is used in *Shiro lepa* therapy is *Amalika* (*Emblica officinalis*) and buttermilk. This technique is supposed to help in the treatment of insomnia by reducing tension.

Herbal Face Pack

Application of paste on face (*Mukhalepam*) is an Ayurvedic treatment, which is more or less like the modern facial treatment. The herbs to be used for making the paste are carefully chosen after studying the skin type of the person. This is very important because if the ingredients are not accurate, there will not be any desired effect from the *Mukhalepam* therapy.

Anointing, Massage, and Bath

In simple anointing (*Utsadana*), the medicine mixed with oil or water in a paste form is applied over the body with gentle friction by an expert hand before bath. Application of *til* oil (gingelly oil) and sour fermented drink called *kanjika* on the head, legs, and heels is supposed to produce sleep. *Kanjika* (Indian functional food, also abbreviated as *Kanji*) is a dish in which lactic fermentation is the terminal step in food processing. It is considered suitable even for vegans as it is prepared from raw material of plant origin and devoid of dairy product. Application of paste prepared from *nilotpala* (*Nymphaea stellata*) and seeds of *Sigru* (*Moringa oleifera*) and *Naga kesara* (*Mesua ferrea*) prevents excessive sleep [6].

There is enough evidence to show that sleep can be induced in adults and children by body massage [42–44]. Various types of massages are employed in treatment of sleep disorders in *Ayurveda*. In *Abhyanga* massage, medicated oil is applied all over the body with pressure. The efficiency of the treatment depends on the expertise of the person giving the massage. The type of oil and the ingredients added to the oil depend on the *dosha* of the individual [45, 46].

Whole-body massage using light pressure (*Samvahana*) promotes circulation and helps the patient to relax. The word *Samvahana* denotes the massage technique which predominantly involves long sweeping and soft stroking motions to activate the so-called energy channels (*Nadis*) of the body. The gentle massage using warm organic herbal oils is performed by one or two therapists working in unison. It is claimed to have a soothing and balancing effect and is performed on patients of insomnia caused by excess *Pitta* and *Vata*.

Massage of the feet (*Padabhyanga*) is considered very important in Ayurveda as stimulation of the nerves terminating in the feet helps in restoring health. The vital point (*marma*) in the feet when massaged balances the *Dosha,* and it is very helpful for people with insomnia.

Bath (*Snana*) has been suggested as a practice for inducing sleep. *Snana* is given to the patient at the end of anointing procedures and body massage. Daily bath is an essential part of Ayurvedic medical advice for healthy living. Usually a bath is taken after the application of prescribed medicated oil on the head and body. Warm water, boiled with herbs, is preferred for bath. However, the water should be cooled to a comfortable level before the bath. Green gram powder and herbal shampoos are part of a complete herbal bath. Herbal bath is believed to soothe the body and soul to regain the lost grace and harmony of a person's bio-balance, and to produce deep sleep. The valerian root is one of the commonest herbs added to the bath water to promote sleep [47]. Exposing the body to steam from the boiling herbal water was also in practice. Modern Ayurvedic therapists use steam bath tents to expose the body to steam from the boiling herbal water. The advocated time for bath is morning or just before the sunset. Having a bath at noon is not considered ideal. Bathing immediately after taking food is not advised.

Tying Herbs on the Head (Hair Lock)

It is claimed in classical literature that when roots of *Apamarga, Kokilaksha, Kakajangha,* and *Bakuchi* are tied onto the lock of hair on the head, it could induce sleep. Putting flowers and fragrant leaves on the hair has been a practice by women in ancient India. In olden days, even men used to have long hair or keep a tuft of hair on top of the shaven head.

Harita Samhita mentions about a mixture of *Kantakaridwaya* (*Solanum xanthocarpum*), *Vasa* (*Adhatoda vasica*), *Kakamachi* (*Solanum nigrum Linn*), *Punarnava* (*Boerhavia diffusa*), and *Vartakimoola* (*Solanum melongena*) which can be used in the above-mentioned manner.

Kaka jangha (*Peristrophe bicalyculata*) is a flowering plant in the family of *Acanthaceae*, native to warm temperate-to-tropical regions of Asia. Root of *kaka jangha* tied onto the head is believed to produce sleep.

Herbal Medication

There are descriptions of about 700 medicinal plants, 64 preparations from mineral sources, and 57 preparations based on animal sources in classical Ayurvedic literature [48]. Indian Council for Medical Research has published several volumes on Indian Medicinal Plants [49]. Central Council for Research in Ayurveda and *Siddha* (*CCRAS*), Govt. of India, has a database on medicinal plants used in Ayurveda [50, 51]. Though medicinal plants are found throughout India, the natural habitat of many of the herbs mentioned in Ayurveda is in the Himalayan range. The Himalayan kingdom of Nepal is home to about 700 species of medicinal plants, about 250 of which are endemic to the country. Medicinal plants are one of the important export items from this country. Indian Western Ghats with its species diversity is a treasure house for about 700 medicinal plants. It is also believed that the potency of many of the herbs depends on their source of collection [52–56]. Not only the place from where it is collected but also the way it is collected and stored is considered important for their potency in treatment [52–56]. Many experts believe that the active principles extracted from these herbs cannot be as effective as the herbal plant itself [52–56]. Botanic Gardens Conservation International believes that many of the medicinal plants are at risk from over-collection and deforestation [57]. Coupled with this, their short life span makes their availability difficult. Unfortunately, only a few researches were conducted on the herbs mentioned in *Ayurveda*. Therefore, before they disappear from their source of supply, there is an urgent need for initiating proper studies of their phytochemical and pharmacological properties.

A list of herbs that have been reported to have sedative activity and those that have alerting property is given in Box 57.5 [58].

Box 57.5. List of herbs showing sedative and CNS stimulant properties

Sedative herbs		Stimulant herbs
Acorus calamus Linn	*Erythrina indica* Lam	*Aconitum ferox* Wall[b]
Actaea racemosa (Linn) Nutt	*Euphorbia hirta* Linn	*Alstonia venenata*
Alangium begoniaefolium (Roxb)	*Ferula sumbul*	*Anamirta cocculus* (Linn)
Alstonia scholaris (Linn)	*Fumaria officinalis* Linn	*Bassia longifolia* Koen
Anacardium occidentale Linn	*Garcinia mangostana* Linn	*Camellia sinensis* (Linn)
Anemone obtusiloba	*Humulus lupulus* Linn	*Cinnamomum zeylanicum*[c]
Anthemis nobilis Linn	*Hyoscyamus niger* Linn	*Coffea arabica* Linn
Apium graveolens	*Jasminum officinale* Linn	*Cyperus scariosus*
Areca catechu Linn	*Lactuca virosa* Linn	*Eryngium caeruleum* Bieb
Artemisia capillaris	*Lavandula angustifolia* Mill	*Heracleum candicans* Wall
Avena sativa Linn	*Leonurus cardiaca* Linn	*Ilex paraguariensis*
Atropa acuminata Royle ex Lindl	*Leucas lavandulaefolia* Rees	*Panax pseudoginseng* Wall[a]
Azadirachta indica	*Marsilea minuta* Linn	*Piper longum* Linn[d]
Bacopa monnieri (Linn) Wettst	*Melia azedarach* Linn	*Rivea corymbosa*
Berberis vulgaris Linn	*Melilotus officinalis* Linn	*Rosmarinus officinalis* Linn
Blumea balsamifera DC	*Melissa officinalis* Linn	*Selenicereus grandiflorus*
Boswellia serrata Roxb	*Myristica fragrans* Houtt	*Strychnos ignatii* Bergius
Butea superba Roxb	*Nardostachys jatamansi* DC	*Strychnos nux-vomica* Linn
Calendula officinalis Linn	*Nelumbo nucifera* Gaertn	*Taraxacum officinale*
Calophyllum inophyllum Linn	*Nepeta hindostana* (Roth)	*Theobroma cacao* Linn
Cannabis sativa Linn	*Nyctanthes arbor-tristis* Linn	
Canscora decussata Schult	*Origanum majorana* Linn	
Capparis zeylanica Linn	*Panax pseudoginseng* Wall[a]	
Cardiospermum halicacabum Linn	*Papaver somniferum* Linn	

(continued)

Sedative herbs		Stimulant herbs
Carthamus tinctorius Linn	*Passiflora incarnata* Linn	
Cassia fistula Linn	*Perilla frutescens* (Linn)	
Catharanthus roseus (Linn)	*Phaseolus trilobus*	
Cedrus deodara (Roxb)	*Piper longum* Linn	
Celastrus paniculatus Willd	*Piper nigrum* Linn	
Centella asiatica (Linn)	*Pongamia pinnata* (Linn)	
Cichorium intybus Linn	*Prunus amygdalus*	
Cinnamomum camphora (Linn)	*Rauvolfia serpentine*	
Cissus quadrangula Linn	*Scutellaria galericulata* Linn	
Citrus maxima (Burm)	*Selinum vaginatum*	
Clerodendrum phlomidis Linn	*Sida rhombifolia* Linn	
Clitoria ternatea Linn	*Sonchus arvensis* Linn	
Cochlospermum gossypium	*Stephania glabra* Miers	
Convolvulus pluricaulis Choisy	*Strobilanthes callosus* Nees	
Cymbopogon citratus (DC) Stapf	*Valeriana officinalis* Linn	
Cyperus rotundus Linn	*Waltheria indica* Linn	
Datura stramonium Linn	*Withania somnifera* (Linn)	
Delphinium denudatum Wall	*Xylosma longifolium* Clos	
Eclipta alba (Linn) Hassk	*Ziziphus jujuba* Mill	
Elaeocarpus ganitrus Roxb		

Latin names of the herbs are given in the alphabetical order in the table
[a]Ginsenosides Rb and Rc are "diols," while Rg is a "triol" ("triol" group is arousing; "diol" is sedative)
[b]Roots possess depressant activity, but after mitigation in cow's milk for 2–3 days, they exhibit stimulant activity
[c]At high doses
[d]Piperine is a CNS stimulant

Though Box 57.5 gives a long list, some of the herbs that are commonly suggested for treatment of insomnia by Ayurvedic physicians in India are *Bijapoora* (*Citrus medica Linn*), *Kakajangha* (*Peristrophe Paniculata*), *Apamarga* (*Achyranthes aspera*), *Kokilaksha* (*Asteracantha Longifolia*), *Kantakaridwaya* (*Solanum xanthocarpum*), *Vasa* (*Adhatoda vasica*), *Kakamachi* (*Solanum nigrum linn*), *Punarnava* (*Boerhavia diffusa*), and *Vrntaka* (*Solanum melongeva*).

Jeevaneeya Mahakashaya is a group of drugs that is given great importance in the original classics of Ayurveda. *Jeevaneeya Mahakashaya* means a group of substances that are extremely beneficial for life. The ten herbal drugs mentioned in *Jeevaneeya Mahakashaya* are *Jeevaka, Rhshabhaka, Meda Madhura, Mahameda, Kakoli, Ksheerakakoli, Mudgaparni, Mashaparni, Jeevanti*, and *Madhuka*. The drugs of this *Mahakashaya* have not been evaluated scientifically till date, though they are believed to be beneficial to sleep [59]. Decoction of *Jeevaneeya* group of drugs is administered with milk and ghee (melted butter), as per tradition. Herbs such as *Acorus calamus* (*Vacha*), *Papaver somniferum* (*Ahiphena*), and *Rauwolfia serpentina* (*Sarpagandha*) are used infrequently as it is believed that they have other effects. Ayurvedic drugs are given either orally or applied onto the skin. External application is given as much importance as oral medication. External application can vary from anointing to using it with body massage and bath. External application can be on the head or throughout the body. Application of herbal drugs on the head is one of the preferred treatments in sleep medicine. *Valerian* (*Tagara*), *Piper longum* (*Pippalimoola*), *Citrus medica linn* (*Bijapooraka*), *Withania somnifera* (*Ashwagandha*), *Acorus calamus* (*Vacha*), and *Acorus gramineus* (*Bhutanashini*) are some of the herbs where some kind of scientific evaluation for their use in sleep medicine is ongoing.

Valerian (*Tagara*)

The herb *Tagara* (known as Indian *Valerian* or *Valeriana wallichi*) is a perennial herb, found in plenty all over India, Pakistan, and Afghanistan. It is considered an important medicinal herb and is mentioned in all scriptures of Ayurveda. *Valerian* is one Asian herb which has been studied rather extensively using randomized placebo-controlled trials, mostly outside India [60]. There is a mild subjective improvement in sleep, especially when used for two weeks or more, though objective testing had shown less consistent results. One study has reported an increase in slow-wave sleep after consumption of this herb [61].

Root of *Piper longum* (*Pippalimoola*)

Root of *Pippalimoola* is usually administered with jaggery (*Guda Pippalimoola*). According to traditional belief, the powder of *Pippalimoola* boiled with *Guda* can be used as linctus to cure even chronic sleeplessness. Beneficial effects of this preparation on patients of insomnia are mentioned in a thesis submitted to a health university in Mysore (India) in 2010. The study showed that the administration of *Guda Pippalimoola* along with practice of yoga and diet regimentation gave the most beneficial effect. Though administration of *Guda Pippalimoola* with yoga was also beneficial to some extent, diet regimen alone did not show any positive effect. Sleep was not assessed on the basis of polysomnography in this study [62].

Citrus medica Linn (*Bijapooraka*)

Bijapooraka is an important plant of mentioned in *Materia Medica of Ayurveda*. Though its various parts are widely used to treat many ailments in traditional system of medicine, the powder of *Bijapooraka* leaves is used with honey to treat insomnia [63]. The leaf of *Bijapooraka* contains lysigenous cavities with the presence of oil globules, calcium oxalate crystals, paracytic stomata, and incomplete ring of sclerenchyma [64].

Withania somnifera (*Ashwagandha*)

Ashwagandha is a shrub cultivated in India and North America whose roots have been used for thousands of years by Ayurvedic practitioners as a folk remedy. *Ashwagandha* is consumed in various forms. In traditional medicine, its powder is mixed with sugar and ghee for consumption. In experimental animals, systemic application of the defined extract from *Ashwagandha* led to slightly enhanced acetylcholine esterase activity in the lateral septum and *globus pallidus*, whereas in the vertical diagonal band acetylcholine esterase activity was reduced [65]. Oral administration of *Ashwagandha* (100 mg/kg) prevented the rise in lipid peroxidation in stress-induced rabbits and mice [66]. In a clinical study, 18 apparently healthy volunteers received *Ashwagandha* capsules (aqueous extract, 8:1) daily in two divided doses with increase in daily dosage every 10 days for 30 days (750 mg/day × 10 days, 1000 mg/day × 10 days, 1250 mg/day × 10 days). Six subjects reported improvement in quality of sleep [67]. The most useful action of *Ashwagandha* is to reduce stress and perhaps indirectly aid in sleep.

Acorus calamus Linn. (Araceae)

Araceae, commonly known as "sweet flag" or "calamus," is a semiaquatic, perennial, aromatic herb with creeping rhizomes. The plant is found in the northern temperate and subtropical regions of Asia, North America, and Europe [68]. *Araceae* rhizome and its constituents, particularly alpha- and beta-asarone, possess a wide range of pharmacological activities such as sedative, CNS depressant, behavior-modifying, anticonvulsant, acetylcholinesterase-inhibitory, memory-enhancing, anti-inflammatory, antioxidant, antispasmodic, cardiovascular, hypolipidemic, immunosuppressive, cytoprotective, antidiarrheal, antimicrobial, anthelmintic, insecticidal, adulticidal, diuretic, genotoxic, and mutagenic activities [58, 68]. Roots and rhizomes of *Araceae* prolong the behaviorally assessed "sleeping time" of mice and rats when used with pentobarbital, hexobarbital, and ethanol [69, 70]. The essential oil and alcoholic and aqueous extracts showed depressant action on normotensive mongrel dogs [71]. The hypnotic potentiating action has been claimed to be mediated through serotonin and catecholamines [72]. Alpha-asarone, one of the active principles of *Araceae*, potentiated the pentobarbital-induced-sleeping time periods by two- to threefold [73]. Assessment of sleep using electrophysiological signal has shown that alpha-asarone could induce sleep and decrease in body temperature in rats [74].

Acorus gramineus (Bhutanashini)

Acorus gramineus is an evergreen perennial herb which is native to Japan and occasionally seen in Sikkim [58]. Rhizome of this herb (0.5–5.0 g/kg) dose-dependently decreased the locomotor activity and increased the pentobarbital-induced "sleeping time" [75].

Polyherbal Preparations

Loknath Ras is an Ayurvedic medicine in tablet or powder form. Active ingredients of it are *Kajjali, Abhrak Bhasma, Tamra Bhasma, Laugh Bhasma*, and *Kapardak Bhasma*. This medicine contains heavy metal ingredients, and hence should only be taken under strict medical supervision. It is traditionally administered along with long pepper, honey, jaggery, *Haritaki* (*Chebulic myrobalan*), cow's urine, cumin seeds, etc. It is administered with *Cannabis* (*Bhang*) powder and honey at night for treating insomnia [76].

A polyherbal preparation of *Nardostachys jatamansi, Rauwolfia serpentina*, and *Tinospora cordifolia* is found to be effective in the treatment of insomnia, as it reduces wakefulness and increases total sleep in patients subjected to polysomnographic analysis [77]. A soup containing *Sali parni* (*Orygza sativa*), *Bala* (*Sida Cordifolia*), *Eranda* (*Ricnus communis*), *Yava* (*Solanum melongeva*), and *Mudga Parni* (*Phaseolus mungo*) is also given to induce sleep [6].

Sleeping Environment and Psychological Factors

Comfortable bed, safe home environment, and sleeping time are given importance in Ayurvedic texts. Patients of insomnia and hypersomnia are advised to avoid daytime

sleep. Pleasant smell, sound, touch, or anything that is pleasurable, and gives a sense of satisfaction, is considered good for proper sleep. Having good fragrance in the bedroom and listening to some agreeable music are some of the suggestions given for inducing sleep. There are studies which support these ideas [78–83]. One is also advised to think about things that are pleasant and desirable when going to bed to get good sleep. Though celibacy is mentioned as one of the three pillars supporting good health, a good bed partner is also recommended for having good sleep.

Diet Regulations

Dietary advice always forms part of any Ayurvedic treatment. Consuming milk, rice with curd, alcohol, and meat soup are some of the most common suggestions given for getting good sleep [6, 8]. Other diets suitable for patients of insomnia are creamy or oily food, milk of buffalo, milk product, wheat, dough preparations, sugar, sugar cane, grape, meat of boar, jaggery, fish, curd, black gram, and soup of pulses. It is believed that these dietary substances will control the causative factor, i.e., aggravated *Vata*. The patient is supposed to get the sleep when *Vata* is controlled.

As excessive sleep is believed to be due to the dominance of *Kapha*, diets that cause *Kapha* depression such as spicy or hot foods and light soups are prescribed for them. *Kapha*-pacifying diets include fruits such as apples and pears. Grains such as barley, buckwheat, millet, and corn are also suggested for them. Honey is the only sweetener recommended for *Kapha*-dominant people. They are advised to minimize oils, fats, wheat, rice, cold food, sweets, nuts, rich desserts, red meat, and most dairy products. The use of so-called heating herbs such as ginger, pepper, and turmeric is encouraged. Drinking ginger tea is considered good.

Yoga and Meditation

Ayurvedic physicians do recommend yogic exercises and meditation to improve the sleep quality. Several research studies have shown that yogic practice and meditation are effective in improving sleep of all age groups. Readers can get more details of these practices on sleep from other references [84–90].

Prayer

Ayurveda does recognize prayer as one form of treatment. The goddess of sleep *Nidra devi* is invoked to grant sleep to the patient suffering from insomnia [6]. The following *mantra* (prayer) should be chanted to get sleep: "*Om shuddhe yu yogini maha nidre svaha*." Along with it, white *tila* (sacred powder) is put on the body of the patient. Patient is expected to get sleep through this procedure.

Summary

There is growing public interest in complementary and alternative medicine for the treatment of sleep disorders [91]. Though Ayurvedic literature claims great efficacy and potency for treatment of sleep disorders, there are no comprehensive studies done to validate these claims. Though there are some systematic studies on some alternative systems of medicines such as acupuncture, acupressure, yoga, tai chi, massage, and aromatherapy, there is a definite need to look into the claims of Ayurvedic medicines for the treatment of sleep disorders.

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Sleep in Extreme Environment

58

Sudhansu Chokroverty

General Introduction

Following centuries of neglect in understanding sleep and its disorders, twentieth century has witnessed a spectacular growth in the science and practice of sleep medicine. We know a great deal about sleep and its disorders under natural conditions in temperate climates, but sleep scientists have largely neglected what happens to sleep health under extreme environmental conditions. Man is an adventurous and curiosity-seeking animal and thirsty to know the unknown. Hence, there is a natural eagerness to know what is there in the outer space, in the polar regions, at high altitude, in deep down the ocean, and in other extreme environment. It is, therefore, important for sleep scientists to expand their curiosity to understand the impact of extreme environmental conditions on human sleep and how those effects on sleep impact health of the individual [1]. This is the first step, and the next step will be to understand the pathophysiological, preventive, and therapeutic aspects of sleep disorders in these extreme environments.

Sleep in Extreme Environment

Webster's dictionary defines environment as the conditions, circumstances, or objects by which one is surrounded. Environmental conditions could sometimes be extreme, e.g., exotic climates such as in tropical (extreme heat) or polar (extreme cold or high latitudes) regions or other extreme situations such as high altitudes (mountain climbers), deep-sea diving (underwater activity), or space travel (microgravity).

The importance of environment was recognized since the days of Hippocrates [2]

> …… Whoever wishes to pursue properly the science of medicine must proceed thus. First …. Consider what effects each season of the year can produce… the hot winds and the cold… the properties of the water. The soil too, whether bare and dry or wooded and watered, hollow and hot or high and cold.
>
> *Hippocrates, Airs, Waters, Places*

In this chapter, I will briefly describe sleep and its impact on health in certain extreme situations, e.g., space travel, polar regions, mountain climbers, deep-sea divers, and tropical extremely hot climates.

Sleep in Space Travel

There is a lack of adequate data including objective and subjective investigations about sleep in space travel in a large number of subjects with sufficient long-term follow-up of collection of these data [1, 3]. Despite this limitation, sufficient data are available as derived from various space missions, simulated space environmental, and a few experimental studies to succinctly summarize these findings in this section [3]. Travel in outer space takes place in an environment of microgravity. Gravity (G) is defined as a force governing motion (or oscillation) throughout the universe. G-force is responsible for holding us to the ground and keeping the moon in orbit around the Earth. Microgravity is synonymous with weightlessness or very weak force of gravity (not necessarily zero gravity), which is responsible for astronauts floating in the spacecraft. The question is often asked whether microgravity is responsible for sleep loss in the astronauts. We will examine the factors (see further on) responsible for sleep disruption in spaceflight.

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Summary of Sleep Dysfuction in Space

Sleep alteration in astronauts during space flight mission (preflight, intra-flight, and post-flight periods) may result directly from sleep dysfunction and other non-sleep comorbidities which may affect sleep indirectly. Sleep [1, 3, 4–6] disruption and fatigue are common complaints among astronauts and cosmonauts [1, 2, 4–16]. Sleep duration during microgravity environment in space flight (intra-flight sleep duration) is usually 1.5 h less than during the control period on Earth. Sleep architecture shows reduced slow wave (SWS) and rapid eye movement (REM) sleep, decreased sleep efficiency (SE), and increased arousals. The preflight sleep is also disturbed because of anxiety and apprehension, and work demand resulting from the preparation of the mission. Sleep dysfunction persists for some time in the post-flight period as a result of cumulative sleep debt. Sleep disruption causes fatigue, impaired concentration, and performance. At least 50 % of the astronauts have used hypnotic medication without necessarily improving the quality and quantity of sleep, suggesting that microgravity environment itself is somehow responsible for sleep disruption.

An unexpected and a notable feature, so far remaining inexplicable, is the observation by Elliott et al. [17] that microgravity improves sleep-disordered breathing events, reduces time spent snoring, and decreases arousals. Their group [18] also noted a reduction in the human ventilatory response to hypoxia but not hypercapnia for sleep disruption. Elliott and co-investigators [17] performed PSG recordings in five healthy astronauts before spaceflight, during a 16- or 9-day space shuttle mission, and shortly after return to Earth. They noted that microgravity was associated with 55 % reduction in apnea–hypopnea index (AHI). These observations highlight the importance of gravity playing a key role in upper airway resistance and obstruction (ventilatory mechanics) as well as chemoreceptor function, and arousals during sleep. One suggestion [19] for reduced sleep duration during spaceflight is consolidated and efficient sleep without much sleep fragmentation due to reduction in upper airway resistance and arousals.

Literature Review

Stampi [5] in 1994 critically reviewed research in the last three decades on sleep and circadian rhythms in space. He also enumerated factors (see further on) responsible for sleep dysfunction in space and countermeasures for optimal performance by the astronauts. Later in 2005, Mallis and DeRoshia [6] succinctly summarized circadian rhythms, sleep, and performance in space citing several factors (see Section "Pathophysiology and Factors Responsible for Sleep Dysfunction in Spaceflight") responsible for such sleep dysfunction. There is no information on sleep and circadian rhythms in most of the early manned spaceflights [5] as these were too short for attempting to sleep (e.g., Yuri Gagarin in Vostok-1 April 1, 1961; American astronaut John Glenn and others in Mercury Project, 1961–1963). The first person to sleep in space was the Soviet Cosmonaut Titov during Vostok-2 mission, August 1961 [6]. The first American astronaut to sleep in space was Gordon Cooper, May 1963 [6]. The first EEG of sleep in space was recorded from astronaut Borman during Gemini-7 mission [20]. The result of first polysomnographic (PSG) study, recorded during 1988–1989 MIR mission, was recorded by Gundel et al. [21] in 2001. Earlier Gundel et al. [10] performed polygraphic and body temperature recordings from one astronaut in space for eight days and during a baseline period preceding the mission. They found that the circadian rhythm of body temperature and alertness were delayed compared with baseline data making a phase shift or transition to a free-running rhythm. Sleep duration was shorter and more disturbed than baseline, and sleep structure showed less REM sleep with redistribution of SWS. The alterations in sleep quality and quantity resulted in post-flight fatigue. Monk et al. [11] reported sleep and circadian rhythms in 1998 in four orbiting astronauts during STS-78 mission. Next year, Monk and co-investigators [22] reported the results of PSG and actigraphic measurements from the same four male orbiting astronauts. They found a good correlation between actigraphic and PSG findings in terms of sleep duration and SE.

Putcha et al. [7] (1999) reported about sleep medication use among the astronauts. The authors reviewed 79 space shuttle missions and noted that 45 % of astronauts consistently used medication for sleep disturbance. Temazepam, zolpidem, triazolam, and flurazepam were the most commonly used sleeping medications [3]. Medications were also used for space motion sickness by 47 % of the astronauts. Their findings confirmed the results of Newberg et al. [23] as well as those of Santy and co-investigatiors [15]. The field-based research data since 2003 from the National Aeronautics and Space Administration (NASA) Task Book continued to document sleep quality and quantity using actigraphy to determine the effects of short-term and long-term space missions on sleep, circadian disruption, and performance decrement. These data should help develop countermeasures to manage sleep disruption and performance in future space missions.

Buguet [1] while reviewing sleep under extreme environment stated that between 1961 and 2007 more than 400 US and a few Russian astronauts have traveled in space. The first sleep recording (sleep state was determined from EEG data) in space was obtained during the 14 day Gemini-7 mission in December 1965 [20]. Sleep was disturbed in the narrow cabin caused by sitting posture, noise, rapid

90–120-min light–dark cycle in the orbital flight (although window covering was used), emotional factor, demand of work, and other factors (see further on). However, in the Apollo II mission [24], sleep was better but crew fatigue was significant due to large circadian shifts, noise, and discomfort from space suits. During the Skylab program in 1973 and 1974 [16], PSG recordings and subjective sleep assessment showed short sleep duration in space with excessive awakenings. During spaceflight, there is circadian dysrhythmia which may cause advancement of body temperature phase, and body temperature was higher in space than on Earth. After identifying contributing factors for sleep disruption, NASA has introduced countermeasures to improve sleep (see further on).

In a recent observational study, Barger et al. [8] obtained data from 64 astronauts participating in 80 space shuttle missions and 21 astronauts on 13 International space stations (ISS) between 2001 and 2011 involving both inflight experiments and ISS expeditions. Sleep was recorded objectively by wrist actigraphy (for two weeks) and subjectively by daily sleep logs. Data were collected three months and 11 days before launch, and for seven days on return to Earth. Sleep deficiency was prevalent in both preflight and intra-flight missions. More than 50 % of the crew members took sleeping medication (commonly zolpidem during inflight missions), but the hypnotic intake (which was pervasive) did not make a significant difference in objectively measured sleep duration. This raises a fundamental question [9] whether spaceflight reduces the need for sleep or whether it reduces the ability to sleep and not sleep need. Basner and Dinges [9] suggested that neurobehavioral performance measurement in space is needed to answer this question.

Zavalko et al. [25] studied the effects of long-term isolation on night sleep during international ground simulation of an interplanetary manned flight—"Mars-500." The PSG recordings of six men before, four times, during, and after 520 days of confinement showed decreased SE and increased sleep latency (SL) during the isolation period, whereas two weeks after the landing simulation nights with low SE significantly decreased.

Wolfe and Rummel [26] as well as Nicogossian et al. [27] reported the adverse effects of microgravity on bodily functions and suggested possible countermeasures. Wolfe and Rummel [26] described fluid shifts with decreased plasma volume causing cardiovascular deconditioning and orthostatic intolerance. Exercise is mentioned as one countermeasure, but may not be feasible on a long mission. In 1992, Nicogossian and co-investigators [27] mentioned that long-duration space mission will become commonplace in not too distant future and prolonged expose to microgravity will result in altered bodily functions. Environmental health, radiation hazards, physical deconditioning, bone loss (due to negative calcium balance), and muscle wasting are some of the concerns in such missions. Biological effects of radiation remain the most serious unknown adverse events which may increase the risk of cancer in the long term.

Jennings et al. [28] mentioned about space motion sickness which may affect up to 73 % of crew members in the first 2–3 days of the flight, and this will have adverse consequences on the astronauts' sleep indirectly. Intramuscular promethazine has been found to be the most effective pharmacologic management for space motion sickness. Such motion sickness may reappear (characterized by nausea, vomiting, and incoordination) on returning to Earth due to readaptation difficulty.

Pathophysiology and Factors Responsible for Sleep Dysfunction in Spaceflight

Box 58.1. Factors Affecting Sleep in Space

- Noise
- Anxiety and stress
- Excitement of space travel
- Fear of life-threatening risk and fear of death
- Work demand
- Slam shifts (irregular sleep–wake schedule)
- Rapid oscillations (90–120 min) of light–dark cycles
- Excessive environmental light
- Circadian rhythm disturbances
- Sleeping conditions and posture (including confinement to sleeping bags and sleeping vertically)
- Small crowded space inside spacecraft
- Uncomfortable temperature inside spacecraft (often too cold but sometimes too warm)
- Motion sickness and medication used for this
- Rostral fluid shift with facial swelling
- Obscuration of vision with increased intraocular pressure
- Low back pain

Several factors are responsible for sleep disruption which is prevalent in space missions [1, 3, 5, 6] (Box 58.1) that may impair performance and attention during spaceflight.

i. **Microgravity** itself can impair sleep quality as a result of the following six subfactors:
   1. There is a rostral fluid shift with diminution of plasma volume causing swelling of the upper body and face (Fig. 58.1) and orthostatic intolerance;

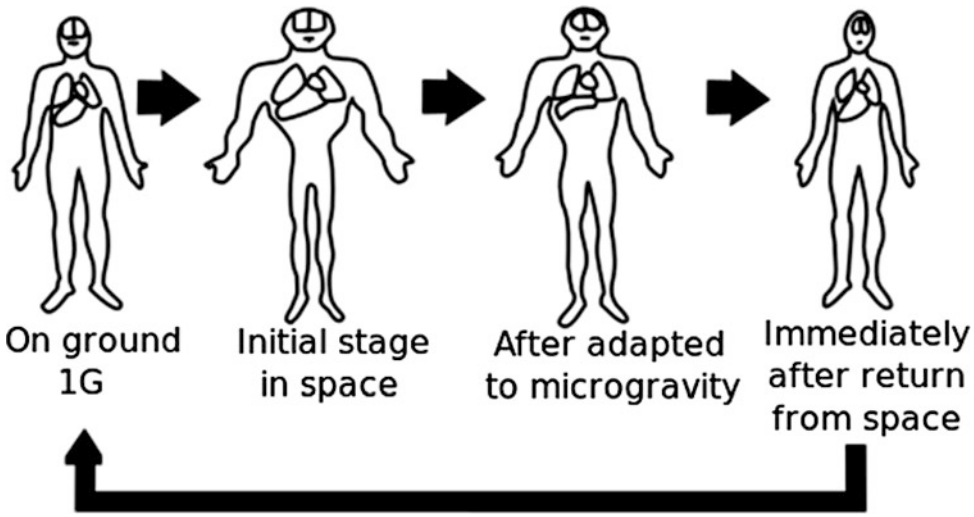

Fig. 58.1 Effects of microgravity on fluid redistribution of upper trunk and face in the first few days in space (From the Internet domain of nasa.gov website)

2. Low back pain due to osteoporosis associated with mineral (calcium) loss;
3. The absence of body pressure associated with "floating" feeling in the spacecraft;
4. Lack of sufficient motor activity reducing sleep quality;
5. Discomfort from the space suits; and
6. Space motion sickness in the first two days of mission (characterized by malaise, drowsiness, and illusion of position and motion) [23, 29] can be a problem compounded by the effects of medication used to treat it (e.g., intramuscular promethazine) causing drowsiness, alteration of alertness, and sleep loss.

ii. **Noise**

The background noise within a spacecraft may reduce sleep quality. This noise may be produced by fans and other life support system, pumps, electrical engines, and frequent communications with ground mission control.

iii. **Psychological Factors**

Excitement of spaceflight, fear of death, or fear of life-threatening failure of the mission, stress and demand for mission work, unfamiliar environment, monotony and feeling of confinement within a closed space, and prolonged isolation causing visual and auditory hallucinations all of which can cause considerable sleep disruption.

iv. **Sleeping Medication**

This is used by about 50 % of astronauts as a short-term solution which may have a negative effect on performance.

v. **Circadian Dysrhthmia**

It has clearly been demonstrated that there are circadian rhythm changes during spaceflight (i.e., mismatch between the body's internal clock and the geophysical environment as a result of rapid oscillations during light–dark cycles). While orbiting the Earth, the astronauts experience 90-minute light–dark cycle (i.e., 16 sunsets per day) disrupting the body's intrinsic circadian rhythm.

vi. **Space Environment**

Excessively low temperature and occasional excessively high cabin temperature as well as excessive environmental light disturb sleep quality. There are other environment factors identified as contributing to sleep loss (e.g., spacecraft vibration, cosmic radiation, increased CO_2 levels).

vii. **Sleeping Condition and Posture**

Confinement to sleeping bags, sleeping vertically and small crowded space inside spacecraft are not conducive to sleep (Fig. 58.2).

viii. **Post-Flight Fatigue**

The cause of this is not known, but most likely results from severely compromised post-flight adaptation to gravity for several days after returning to the Earth after an extended space mission and cumulative sleep loss in space [19].

ix. **Miscellaneous Other Factors**

a. Thinning of the muscle mass from inactivity (not using to overcome gravity).

Fig. 58.2 Sleeping positions of four crew members of the STS-112 on the middeck of the space shuttle Atlantis (From the Internet domain of nasa.gov website)

b. Obscuration of vision and other eyesight problems (e.g., cataract) are noted after long space mission in men. Many astronauts also experience sudden phosphenes or light flashes [30] often noted before sleep with a sense of motion. It was noted in 47 out of 59 respondents in a survey, and some thought that light flashes disturbed their sleep.
c. Cosmic radiation effect. It is not known whether there is a cosmic radiation effect in space mission posing as a risk factor for the development of cancer in the future.
d. Some astronauts are more sensitive to sleep loss in space than on Earth. This susceptibility is dependent on individual characteristics (e.g., circadian chronotype, gender, and genetic susceptibility), which must be considered in pathophysiological mechanism and in designing individual treatment strategy.

Countermeasures and Therapy

Several lines of treatment and countermeasures have been suggested and tried to treat sleep disruption in space and its adverse effects, but further research is needed to optimize sleep and performance in spaceflight missions.

i. **Exercise**

Strenuous exercise as a countermeasure to prevent muscle atrophy and cardiovascular deconditioning was employed on Soviet spaceflights in the past [6, 31]. However, strenuous exercise can have adverse effects on sleep and mood [32]. On the other hand, timely performed exercise has shown to induce phase shifts in the melatonin circadian rhythm [6, 33, 34]: Phase advances were induced by late afternoon or early evening exercise, whereas late evening exercise induced phase delays. Timed exposure to exercise sessions could be used as countermeasures to facilitate adaptation of circadian rhythms in space missions [6, 33, 35].

ii. **An understanding of circadian physiology** is essential to treat circadian dysrhythmia of the astronauts. Effective countermeasures to promote sleep in space include [1, 5, 6, 8, 13, 36–38] modifications of sleep–wake schedule including scheduled naps, strategically timed exposure of bright light of specific wavelength, intensity, color and duration, intermittently or continuously as well as behavioral strategies including sleep hygiene measures. Another suggested strategy [38, 39] is to replace the adult monophasic sleep pattern by polyphasic patterns of childhood (ultrashort sleep schedule) which has shown to decrease total sleep requirement without impairing performance levels.
iii. **A comprehensive management approach** should include education about sleep, sleep–wake schedule, following a common sense sleep hygiene measures as well as scheduling policies and procedures, and employment of specific fatigue countermeasures, and remedies including fatigue training workshops [40, 41].
iv. **Pharmacologic strategy** using melatonin (0.3 mg) [13] and sleeping medications [1, 8] to improve sleep duration and shorten sleep latency has not been very effective.

Intramuscular phenothiazine has been successfully used to treat space motion sickness [6], but may cause drowsiness and impaired performance in space crews.

v. **Other measures to improve sleep** and performance in space mission crews include use of earplugs to minimize noise, window shades in space ships to protect crews from exposure to bright light, use of sleep-restraint bags attached to the wall (Fig. 58.2) in any position (vertical or horizontal) [1, 42], psychological services to the astronauts and their families, and mental monitoring to minimize external stressors.

vi. The other suggestion for improving sleep, fatigue, and performance skill is acquisition of a strong coping mechanism to handle extreme environment—which shows considerable individual variation. This requires the development of high physiological, psychological, and social coping skills [1, 43].

Sleep at High Attitude

Climbing to high altitude (e.g., mountaineers at about 3000 meters above the sea level) exposes human to extreme environmental condition as a result of low barometric pressure associated with hypoxemia (hypobaric hypoxia) causing profound physiological changes in the body [1, 3]. The adverse consequences include periodic breathing and altered sleep–wake rhythms depending on individual susceptibility, speed of ascent, and the actual altitude reached. Those with pre-existing obstructive sleep apnea (OSA) show exacerbation of sleep-related breathing events. Altitude-related illnesses that have major impact on sleep include acute mountain sickness, chronic mountain sickness (Monge's disease), as well as high-altitude pulmonary and cerebral edema [3]. Gradual ascent to altitude promoting acclimatization as a preventive measure and pharmacotherapy for sleep disturbances have been found to be useful in several clinical studies. The readers are referred to Chap. 33 for further details.

Sleep in the Polar Regions

Studies are very limited to make a firm conclusion about sleep and its disorders in the polar regions. Most of these came from Josephine Arendt and her group [44–51] as well as from Buguet and his group [52–54], and Palinkas and co-investigators [55, 56] (these authors mainly dealt with psychological–psychiatric aspects and sleep). A symposium in 1973 gave comprehensive overview of Polar Human Biology published as proceedings [57].

i. It is extremely cold in the polar regions (Arctic 60°N and above; Antarctic 60°S and below), and people are deprived of natural sunlight in winter but have continuous daylight in the summer ("the midnight sun") months (October to March in the Antarctic and April to September in the Arctic). There is no permanent human population at 60°s in Antarctica, which does not belong to any country, and has no government. There is a transient sparse population of scientists and researchers at several scientific bases (about 1000 population in winter and up to 4000 in summer). On the other hand, permanent human population north of 60° N in the Arctic amounts to over four million including indigenous people ("The Inuit"). The arctic region is governed by several nations—USA (Alaska), Russia (Siberia), Canada, Denmark (Greenland), Iceland, Norway, Sweden, and Finland.

ii. There are reports of sleep problems in the polar regions. Because of deprivation of natural sunlight in winter, there is a delay in circadian rhythm in the evening, including melatonin rhythm with delayed sleep onset, decrements in SE, sleep duration, and quality associated with fatigue and tiredness in the morning [44–50]. A few people desynchronize with free-running rhythm showing their intrinsic circadian period longer than 24 h. Timed exposure of light (blue-enriched light appears to be more effective than standard white light) on awakening in the morning combined with exogenous melatonin intake in the evening plus wearing sunglasses in the evening helps restore normal phase and sleep.

iii. Palinkas and co-investigators [55, 56, 58] reported on psychological and psychiatric problems associated with sleep disturbance as a result of long periods of isolation and confinement in the polar regions. A small percentage of people on polar expeditions suffer from mood and sleep disorders [55, 58]. These authors examined sleep (self-reported) and mood measured by profile of mood states (POMS) in 91 American men and women who spent the 1991 Austral (refers to Southern Hemisphere) Winter (March to October) at three different research stations in Antarctica [56]. They made the observation that mood changes were preceded by changes in sleep characteristics.

iv. Sleep in the polar regions was documented objectively by PSG study in the early 1970s in small and limited studies, but more comprehensive PSG evaluations were made later by Buguet et al. [53, 54] and other investigators [59]. PSG recordings [53, 54] in subjects sleeping in unheated tents in sleeping bags showed that SWS was preserved in the first half of the night as in neutral condition.

There were numerous awakenings due to midnight hypothermia (rectal temperature = 34.9 °C). Thermoregulatory shivering and body movements disappeared during REM sleep. REM sleep episodes were shorter in the cold compared with thermoneutral condition resulting in REM sleep deprivation. In a later PSG study of eight individual, Buguet et al. [52] concluded that they could not draw a statistical conclusion as sleep patterns between individuals showed considerable variation.

Bhattacharyya et al. [59] performed PSG study in six members of the Indian expedition team during their winter stay at Maitri, the permanent research station of Indian Antarctica (70°S). PSG findings included reduced sleep duration, SE, and SWS during the winter months. This study showed a prevailing general trend of sleep disturbance among overwintering members in a modern Antarctic station.

v. Joern et al. [60] studied long-term sleep patterns in summer campaigners in South Pole Station (90° south and at 2804-m altitude) by PSG recordings which showed a loss of SWS in all subjects and REM sleep in the oldest subject (50 years old) which was thought to be related to altitude [1]. Long-term sleep patterns were also studied by PSG recordings in four Antartic winterers at South Pole Station (temperature of −78 °C) [61]. In Antarctica, sleep duration was same, but sleep latency was longer than in the USA and SWS decreased, and even disappeared, and REM sleep decreased during the winter. These changes were thought to be due to altitude. Similar findings (decreased SWS and REM sleep) were also noted at the Halley Station (built by the British Antarctic Survey in 1955) in 10 winterers for 38 nights using an Oxford Holter System [62]. SWS and REM sleep increased in summer, and the changes were most likely related to daylight variations.

vi. **An important observation** has been made regarding polar insomnia including midwinter insomnia in the Arctic and the Antarctic continents [44, 46, 63–65]. Midwinter insomnia (delayed sleep onset) has been noted in a large survey in Tromso, a Norwegian City north of the Arctic cycle [64], and the frequency increased with increasing age. This finding of delayed sleep onset along with early morning awakening during winter was confirmed in a recent prospective study [65] using sleep diary and questionnaire in a sample of 162 young adults across three seasons (September, December, and March) in Tromso, Norway at 69°N.

vii. There is no clear evidence for increasing prevalence of seasonal affective depression (SAD), but there is some evidence for subsyndromal SAD (low mood) in polar regions [44, 56, 58, 66].

Arendt [44] suggested that it is important to define the optimal conditions for maintaining circadian phase in the Arctic and Antarctic regions for good quality sleep. The treatment of choice is properly timed light exposure and melatonin treatment. However, uncertainties remain regarding exact duration and spectral composition of light, as well as the dose and timing of melatonin.

Sleep in Hot Tropical Climate

There are some limited data from Buguet and his group on sleep behavior using PSG recording from 34 African students and six French military expatriates living in Niamey (Niger) [dry tropical climate], as well as 11 African subjects in the city of Abidjan, and 17 African volunteers from remote villages 400 km north of Abidjan (hot and humid conditions). The findings under laboratory conditions in hot day tropical climate in Niamey included increased amount of SWS (more in the hot than in the cool season) which was proportional to the environmental heat, increased Stage N1, and nighttime awakenings in both the Caucasian and African groups [67, 68]. In contrast, sleeping under warm humid conditions in Abidjan region did not cause changes noted in the hot and dry climatic condition in Niger [1, 67, 68]. Sleep, however, remained unstable with numerous interruptions, but SWS did not increase in the Abidjan subjects. Buguet's group [69] also made a questionnaire-based sleep behavior study in Africans and Europeans living in the Ivory Coast of Africa during "hot-dry" (n = 53) and "cool-dry" (n = 88) season. There were no major seasonal variations except for an increased number of awakenings during the hot season. Same questionnaire was used in Abidjan on 78 medical students [69]. The Abidjan subjects adopted shorter sleep duration compared with Niamey (Niger) students without any effect on sleep quality. Another questionnaire-based study in Nigerian undergraduates [70] showed no essential difference in night sleep duration from that in Western countries except for more frequent intra-night awakenings and increased duration of afternoon nap in the Nigerian students.

Sleep and Deep-Sea Diving

There are very limited data available for a meaningful conclusion on sleep patterns in professional divers at different depths and breathing compressed air with different concentrations of nitrogen–oxygen (N2-02) and helium–oxygen (He-02) [1, 71–79]. Many of these studies were undertaken under simulated conditions in hyperbaric facilities. PSG recordings revealed alterations of normal sleep patterns (e.g., prolonged SL, decreased sleep durations, SE, and SWS as well as increased awakenings and fatigue) irrespective of the

breathing mixture. There was worsening of sleep changes with increasing depth, and these alterations were also dependent upon the speed of the compression pressure (descent) and decompression (ascent). These sleep changes were thought to be related to a lack of physical activity and confinement to a closed environment. There was no recovery sleep during the post-dive period.

Conclusion

The future of sleep medicine lies in understanding various factors responsible for deterioration of sleep in these extreme environmental situations, acclimatization, and adaptation to those extreme environments, and in findings appropriate countermeasures and optimal treatment for sleep dysfunction [80]. This knowledge is particularly important for space medicine as man's curiosity to know the unknown and to explore the outer space (particularly the Mars mission) is incessant.

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Erratum to: Sleep Disorders Medicine

Sudhansu Chokroverty

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In the original version of the book, the following corrections have to be incorporated: In Cover page, wrongly included "Extra Online" text has to be removed. In Chapter 24, missing copyrights for the below figure captions have to be included. Figures 24.5, 24.22, 24.26, 24.27 and 24.29: Copyrighted to Raman K. Malhotra, MD. Figures 24.1, 24.3, 24.6, 24.7, 24.8, 24.10, 24.12, 24.13, 24.14, 24.16, 24.17, 24.18, 24.19, 24.20, 24.21, 24.23, 24.24, 24.25, 24.28 and 24.30: Copyrighted to Alon Y. Avidan, MD, MPH. The erratum book has been updated with the changes.

The updated online version of the book can be found at
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Epilogue

This book is primarily directed at sleep clinicians with heavy emphasis on clinical aspects of sleep medicine including diagnosis, differential diagnosis, and laboratory procedures to confirm clinical diagnosis as well as treatment. In order to have a critical depth of such knowledge, sleep clinicians must have sufficient knowledge about basic science aspects without delving into greater depth of molecular, cellular, biological and neurochemical aspects of basic science of sleep. These clinicians also must be acquainted with various technical aspects of sleep recording including instrumentation and statistical principles without going into complex details of electronics and statistics. This is exactly what this edition of the book attempts to do and whether I have achieved these goals will be determined by the readers.

We have come a long way in our quest for knowledge in sleep medicine from the ancient Babylonian, Assyrian, Egyptian, Indian and Chinese civilizations (circa 4000–5000 BC) to Hippocrates (circa 460–370 BC) and contemporary sleep medicine which is still evolving.

Considering the pace of growth of sleep medicine, I would like to conclude this book by summarizing my thoughts in this epilogue on areas where there may be future developments of sleep medicine: (1) Increasing application of telemedicine (telemetric transmission and monitoring of data) [currently in its infancy] in diagnosis, therapy and follow-up because of rapidly improving information and communication technology (ICT); (2) Improvement of technical aspects of home sleep apnea testing (HSAT) including incorporation of home video recording so that its indications will expand to include some or all that are now considered contraindications. This will encourage increasing use of HSAT for patient comfort and convenience and better reimbursement; (3) Study of sleep in extreme environment (see Chap. 58) as these situations will be increasingly encountered; (4) Improved software for computerized scoring of sleep and other physiological characteristics, thus eliminating inconvenience and saving cost of manual scoring; (5) Recording of many physiological characteristics throughout the day and night for days to weeks using improved smart phones (of course it has its dangers of both false positive and false negative data); (6) New understanding of insomnia along with development of better hypnotic medication and improved cognitive behavioral therapy (CBT); (7) Emerging treatment of narcolepsy which will include immunotherapy, hypocretin agonists, gene therapy, and stem cell transplantation; (8) Development of pharmacotherapy and better non-invasive treatment devices for obstructive sleep apnea (OSA) including oral appliances; (9) Finding a specific biomarker(s) in REM behavior disorder (RBD) and neuroprotective therapy to prevent its progression to neurodegenerative diseases; (10) Better treatment of circadian rhythm sleep disorder using bright light therapy of a particular wavelength, intensity, color and duration, and better exogenous melatonin, melatonin receptor agonists or other drugs to entrain the body's rhythms.

The woods are lovely, dark and deep,
But I have promises to keep,
And miles to go before I sleep,
And miles to go before I sleep.

Robert Frost, "Stopping by Woods on a Snowy Evening" (last stanza), 1923

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Note: Page numbers followed by *b*, *f*, and *t* indicate boxes, figures, and tables, respectively

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