


Neurologic Manifestations of Systemic Disease: Sleep Disorders

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Published online: 6 August 2020

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This article is part of the Topical Collection on *Neurologic Manifestations of Systemic Disease*

Keywords Sleep disorders · Sleep manifestations of systemic diseases · Sleep impacts on health · Sleep apnea · Insomnia

Abstract

Purpose of review Sleep is intimately involved in overall health and wellbeing. We provide a comprehensive report on the interplay between systemic diseases and sleep to optimize the outcomes of systemic disorders.

Recent findings Spanning the categories of endocrinologic disorders, metabolic/toxic disturbances, renal, cardiovascular, pulmonary, gastrointestinal, infectious diseases, autoimmune disorders, malignancy, and critical illness, the review highlights the prevalent coexisting pathology of sleep across the spectrum of systemic disorders. Although it is rare that treating a sleep symptom can cure disease, attention to sleep may improve quality of life and may mitigate or improve the underlying disorder. Recent controversies in assessing the cardiovascular relationship with sleep have called into question some of the benefits of treating comorbid sleep disorders, thereby highlighting the need for an ongoing rigorous investigation into how sleep interplays with systemic diseases.

Summary Systemic diseases often have sleep manifestations and this report will help the clinician identify key risk factors linking sleep disorders to systemic diseases so as to optimize the overall care of the patient.

Introduction

All Earth's species maintain a solar 24-h cycle of rest and activity, and disrupting the cycle affects adaptation and homeostasis. Sleep's quotidian "normalness" means that analogous to fish not knowing about water until it is dry, sleep is not commonly thought about until it is disrupted.

For example, about 30% of the adult population complain of transient insomnia, and about 10% experience chronic insomnia that disrupts daytime function [1]. Patients with chronic insomnia experience less work

productivity, more absenteeism, more accidents, and more hospitalizations, leading to direct treatment costs of approximately \$60B annually [2]. Considering the potential widespread reach of comorbid sleep disorders, evaluating sleep in the neurological patient is important.

This review will introduce the accepted organization of sleep disorders, review important features in history taking and evaluation, and survey the systemic diseases that have important comorbidities with particular sleep disorders.

General considerations

Classification of sleep disorders

An abridged listing of sleep disorders from the American Academy of Sleep Medicine (Table 1) provides an overview of the current classification [3].

Insomnia is a chronic dissatisfaction with sleep duration and quality that is associated with daytime dysfunction. Although pharmacologic treatment is often pursued for chronic insomnia management, outcomes are often better addressing underlying factors with the early use of cognitive-behavioral therapy for insomnia (CBT-i) [1].

Sleep-related breathing disorders involve dysfunction of the respiratory system during sleep, usually resulting in daytime hypersomnia. Obstructive sleep apnea (OSA), central sleep apnea (CSA), and respiratory effort related arousals are classified under this category. Treatment options including continuous positive airway pressure (CPAP), positional therapy, mandibular advancement devices, healthy weight loss, and even a novel cranial nerve stimulator which protrudes the tongue forward during sleep [4••].

Central hypersomnias are defined as a primary dysregulation of sleep resulting from dysfunction of the central nervous system that causes daytime hypersomnia. Often treatment addresses the underlying cause and may include use of strategic napping and wake-promoting medications.

Circadian disorders consist of various lesions or external disruptions of the circadian timing system that desynchronize the brain's clock from the external solar light-dark cycle, resulting in hypersomnia or insomnia in a clock-dependent fashion. Treatment of circadian rhythm disorders involves adjusting life around the patient's desired sleep time or augmenting factors that entrain the body's clock.

Parasomnias represent disorders of faulty inhibition of waking behaviors that arise inappropriately during sleep and are divided into those that occur during nonREM sleep, REM sleep, or state transitions. REM sleep behavior disorder is a parasomnia characterized by loss of muscle atonia during REM sleep that usually occurs in patients with neurodegenerative disorders. It is often treated effectively addressing other sleep disturbances and treating with clonazepam or melatonin [5].

Table 1. Abridged classification of the AASM sleep disorders**Insomnia**

Chronic insomnia disorder
Short-term insomnia disorder
Excessive time in bed
Short sleeper

Sleep-related breathing disorders

Obstructive sleep apnea
Central sleep apnea
Sleep-related hypoventilation disorders
Sleep-related hypoxemia disorders

Central disorders of hypersomnolence

Narcolepsy types 1 and 2
Idiopathic hypersomnia
Kleine-Levin syndrome
Hypersomnia due to medical disorder, medication, substance, psychiatric disorder
Insufficient sleep syndrome

Circadian rhythm sleep-wake disorders

Delayed
Advanced
Irregular
Non 24 h
Shift work
Jet lag

Parasomnias

NREM related
Arousal disorders
Confusional arousals
Sleepwalking
Sleep terrors
Sleep-related eating disorder
REM related
REM sleep behavior disorder
Recurrent isolated sleep paralysis
Nightmare disorder
Other
Exploding head syndrome
Sleep-related hallucinations
Enuresis
Sleep talking

Sleep-related movement disorders

Table 1. (Continued)

Restless legs syndrome
Periodic limb movement disorder
Leg cramps
Bruxism
Rhythmic movement disorder
Benign sleep myoclonus of infancy
Propriospinal myoclonus at sleep onset
Normal variants

Sleep-related movement disorders consist of fragmentary, often repetitive body movements that can disrupt sleep or, sometimes worse, disturb the sleep of bed partners. Periodic limb movement disorder (PLMD) and restless legs syndrome (RLS) both fall under this category and are treated with repletion of iron stores and consideration of dopaminergic agonists [6].

Sleep history

A sleep history helps a patient disclose sleep findings and helps the physician organize it into categories of hypersomnia, sleep habits and scheduling, sleep characteristics, environmental issues, and sleep interrupters (Table 2).

The Epworth Sleepiness Scale quantifies the degree of hypersomnia [7]. Most adults require 7–9 h of daily sleep [8] and prefer it organized into either a monophasic, nocturnal schedule or in a biphasic pattern augmented with an afternoon “siesta.” The sleep pattern characterizes the presence and severity of sleep-onset insomnia, sleep maintenance insomnia, or terminal insomnia (insomnia distributed within the last half of the sleep period). “Catch-up” sleep, a phenomenon of prolonged sleep on a free day, is a classic sign of sleep deprivation. Habitual early-phase advances (“morning larks”), late-phase delays (“night owls”), or a chaotic, irregular schedule can be a sign of circadian disorders. One also must inquire about common sleep disruptors including leg movements, snoring, witnessed apneas, and environmental factors.

Diagnostic testing modalities

Sleep diary

The sleep diary, often available through standardized forms or even websites or smartphone apps, consists of 1–2 weeks of self-reported sleep times.

Polysomnography

The overnight polysomnography (PSG) is the gold-standard measurement of sleep architecture, respiratory disorders such as OSA, and parasomnias. In the case of OSA, the unattended (home) sleep study has had an

Table 2. A categorical sleep history**Hypersomnia**

Epworth Sleepiness Scale (7): Considering the last 2 weeks, how likely would you fall asleep while doing each task: not at all (0 points, slight (1), moderate (2), severe (3)). Normal ≤ 9 points

Sitting and reading

Watching TV

Sitting inactive in public (lecture, church, ...)

Car passenger for an hour

Lying down to rest in the afternoon

Sitting conversation

Sitting quietly alone after lunch

Driving, stopped in traffic

Schedule/sleep time

Workday bedtime and out of bedtime

Weekday bedtime and out of bedtime

What is your estimated sleep latency? If > 15 min, what are you doing in bed before you fall asleep?

How often do you awaken at night, and why?

Do you need an alarm clock to awaken in the morning?

How many days of the week do you nap and for how long?

Environment

Do you have a bedroom?

Do you have a bedpartner? TV? Mobile phone or other electronics?

What are you doing right before bedtime?

How much caffeine (coffee/tea/soda pop/energy drinks) and alcohol do you consume and when is the latest intake?

Interrupters

Do you have leg pain or restlessness?

Do you have chronic pain that prevents or interrupts sleep?

Do you have daytime hallucinations or dreams, severe or lucid nightmares, sleep paralysis, or cataplexy?

Do you snore or have witnessed apneas?

increasing role as a diagnostic testing alternative to the traditional in-lab PSG. Concerns of other sleep disorders (or those that may be present comorbidly with probable OSA) require in-lab PSG that can measure sleep architecture and sleep-associated movements.

Multiple sleep latency test

The multiple sleep latency test (MSLT) consists of a series of 5 daytime naps from which sleep onset is calculated. The test, in combination with PSG performed the night before, is the gold standard in measuring hypersomnia, especially in the evaluation of narcolepsy.

Actigraphy

Wrist actigraphy provides measurements of long-term patterns of rest and activity as proxies for sleep and wakefulness. Such patterns can help to corroborate histories of sleep duration and timing.

Personal devices

Popular smartphones and other ambulatory devices with physiological monitoring capabilities may transform the evaluation of sleep. However, a recent comparison of different brands of activity trackers found that sleep-wake measurements varied widely in comparison with sleep diaries or standard PSG [9]. The overall conclusion is that, at the beginning of 2020, wearable devices are not ready for reliable quantification of sleep across individuals. Although serial recordings confined to a single individual may hold some value, these measurements have yet to be validated.

Sleep comorbidities with systemic diseases

Considering the various sleep disorders and diagnostic tools afforded by a good sleep history and sleep testing, understanding the relationship between sleep disorders and systemic diseases has far-reaching implications in optimizing the care of the patient. The following sections will address sleep manifestations of various neurological disorders arising from systemic disease based on organ system.

Endocrine disorders

Thyroid disease

Almost half of the patients with hypothyroidism report at least one sleep complaint such as restless sleep, choking, hypersomnia, or fatigue [10]. OSA is present in approximately 30% [11]. A unique mechanism of airway restriction in hypothyroidism is myxedematous mucoprotein deposition in the airway's soft tissues and dilator muscles even though myxedema can be absent [12]. Larger goiters can also cause OSA by external compression of the airway [13].

On the other side of the thyroid spectrum, hyperthyroidism is most closely associated with insomnia, occurring in 37% of patients [14]. Arousal disorders—specifically, sleep walking—also occur, especially in the setting of thyrotoxicosis [15], proposed to arise from frequent arousals and impairment of attaining slow-wave sleep as the direct result of thyroid hormone.

Beyond the treatment of the specific sleep disorder, sleep problems usually remit following appropriate treatment of the underlying thyroid disorder [15].

Type 2 diabetes mellitus

Sleep disorders affect high proportions of those with type 2 diabetes mellitus (DM): surveys of patients with DM compared with those of controls show a

nearly 2-fold propensity for insomnia, fourfold higher use of sedative-hypnotics, and a 10-fold higher rate of hypersomnolence [16]. OSA is highly prevalent in DM, and many are undiagnosed [17]. Contributors to a multifactorial series of sleep disruptors include periodic limb movements and restless legs syndrome (RLS), diabetic neuropathy, and fluctuations in blood glucose [18].

DM presents an excellent model by which to demonstrate the reciprocal effects of sleep disruption on the primary disease. First, sleep disturbances affect the regulation of the neuroendocrine control of appetite. Sleep deprivation promotes overeating through hyperactivity of orexin system [19] and activates the hypothalamic-pituitary-adrenal system to increase cortisol secretion resulting in impaired glucose tolerance [20, 21]. These multiple mechanisms support clinical observations that untreated OSA may be reason for the ineffective treatment of DM, and that accordingly, treatment with CPAP leads to improvements in glycemic control in some patients [22].

Sex hormones

Sex hormones and gender affect the distribution and susceptibility to a variety of sleep disorders. Men, on the basis of relative airway collapsibility, have approximately a twofold increased risk of OSA compared with women (15–30% in males and 10–15% in females) [23]. A potential side effect in the treatment of hypoandrogenism is the facilitation of OSA given the impact testosterone has on upper airway collapsibility [24].

Testosterone levels may affect the propensity for chronic insomnia. Men with hypoandrogenism demonstrate reduced sleep efficiency, increased nighttime awakenings, and reduced deep sleep compared with the normal-testosterone-level controls, although it is not clear whether these features improve with testosterone therapy [25]. Women experience higher rates of chronic insomnia (risk ratio of 1.41 for women versus men) which becomes even more pronounced in the elderly [26]. Despite sleeping longer, overall sleep quality is often lower in women than men [27].

The distribution of sleep disorders in women varies with reproductive lifespan. Younger women are more susceptible to restless legs syndrome (RLS), mainly on the basis of menses-associated iron-deficiency. During pregnancy, women are at significantly increased risk for the development of RLS with an overall prevalence exceeding 25% of all pregnant patients [28]. Treatment of RLS in pregnancy involves iron supplementation with a goal ferritin level > 50 mcg/l. Often, oral iron repletion is adequate although there are reports of intravenous iron therapy in severe cases of pregnancy-related RLS and iron-deficiency [29]. Pregnancy is also associated with an increased prevalence of OSA (up to 19% of pregnant patients during the third trimester) which is associated with increased risks of complications including gestational hypertension, gestational DM, and pre-eclampsia [30].

Medications

Although not a particular systemic neurological disease, pharmacological effects on sleep form an important aspect of neurological sleep medicine, since many medications that are used by neurologists may affect sleep. Table 3 shows common medications that provoke insomnia, hypersomnolence, respiratory suppression, parasomnias, and RLS/periodic limb movement disorder.

Table 3. Medication classes (and specific examples) that can cause sleep disturbances**Insomnia**

Central nervous system stimulants (methylphenidate, amphetamines, modafinil)

Caffeine

Antidepressants:

Selective serotonergic reuptake inhibitors (fluoxetine, sertraline)

Selective norepinephrine reuptake inhibitors (venlafaxine, duloxetine)

Secondary tricyclic antidepressants (desipramine, nortriptyline)

Cardiovascular

Beta2 agonists (albuterol)

Vasopressors (epinephrine, dopamine)

Corticosteroids

Sympathetic amines (phentermine)

Hypersomnia

Benzodiazepines (alprazolam, diazepam)

Non-benzodiazepine receptor agonists (zolpidem, eszopiclone)

Opioids

H1 antihistamines (diphenhydramine)

Antiepileptic agents (phenytoin, levetiracetam)

Antidepressants

Selective serotonergic reuptake inhibitors (paroxetine, sertraline)

Tertiary tricyclic antidepressants (amitriptyline)

Typical and atypical antipsychotics (haloperidol, olanzapine)

Dopaminergic agonists (ropinirole, carbidopa-levodopa)

Anticholinergic medications

Centrally acting α_2 agonists (clonidine, dexmedetomidine)

Respiratory suppression

Opioids (oxycodone, morphine)

Benzodiazepines (diazepam, clonazepam)

Alcohol

Phenobarbital

Parasomnias

Antidepressants (clomipramine, fluoxetine, citalopram)

Non-benzodiazepine receptor agonists (zolpidem)

Caffeine

Alcohol withdrawal

Restless legs syndrome and periodic limb movements

Selective serotonergic reuptake inhibitors (fluoxetine, mirtazapine)

Antipsychotics (haloperidol, risperidone)

Tricyclic antidepressants (amitriptyline, clomipramine)

Renal disease

Sleep disturbances are highly prevalent in patients with chronic kidney disease (CKD) spanning the broad spectrum of sleep disorders including hypersomnia, insomnia, sleep-related breathing, and RLS.

The prevalence of OSA in CKD ranges from 25 to 70%, rates that are not explained solely by overlapping comorbidities common to both OSA and CKD [31]. The co-occurrence of both CKD and OSA is associated with increased cardiovascular events and all-cause mortality [32–34]. Usually, OSA develops in patients with CKD independent of underlying renal dysfunction, but some evidence shows that CKD can cause or exacerbate OSA and central sleep apnea. Proposed mechanisms for this causal relationship include uremic neuropathy, altered chemosensitivity, and hypervolemia [35]. Accordingly, renal replacement therapy and fluid removal [36] may improve obstructive or central sleep apnea. Conversely, treatment of sleep apnea with PAP may improve renal function in those with borderline renal impairment [37].

RLS is a common and debilitating symptom in patients with CKD, occurring in up to 25% of patients on hemodialysis compared with that in approximately 7% of the general population [38]. Although RLS symptoms generally follow a circadian rhythmicity with increased symptoms occurring at night, RLS symptoms can occur during the long periods of daytime inactivity during hemodialysis [39]. Treatment is primarily focused on ensuring adequate iron stores then considering medical therapy, as per routine care of RLS.

Infectious diseases

Sleep disorders and infectious diseases have few specific associations. In general, acute infection is associated with mild encephalopathy that masquerades as hypersomnolence and fatigue. Pro-inflammatory cytokines are implicated in the development of these constitutional symptoms. Some infections, however, directly affect regulatory centers of the sleep-wake system.

Encephalitis lethargica is a historical, pandemic cause of hypersomnolence of renewed interest since this review is being written in the middle of the COVID-19 pandemic. Also known as Von Economo's encephalitis, it occurred in association with the Spanish flu pandemic of 1918 [40]. An estimated 1 million were affected worldwide. The most common subtype, the somnolent-ophthalmoplegic form, developed after flu-like symptoms of fever and malaise and consisted of subsequent ophthalmoplegia accompanied by long periods of hypersomnia. Despite the appearance of deep sleep, patients could be easily awoken and sometimes maintained memories of activities that had transpired around them while "asleep." This state of acute akinetic pseudosomnolence could be followed by the development of chronic postencephalitic parkinsonism.

The pandemic associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; i.e., COVID-19), occurring during the writing of this review, features evolving literature. The first reports centered on respiratory symptoms. Although the involvement of the nervous system now appears prevalent [41], sleep disorders have yet to be specifically reported. However, the psychological responses to social distancing, change in schedules, and other features of an active pandemic have caused a wave of anxiety and depression, which in turn have been associated with poor sleep quality. For example, a

survey of 1250 Chinese health care workers showed prevalences of depression at 50%, anxiety at 45%, and insomnia at 34% [42].

Postinfectious or postvaccination narcolepsy is rare but is important in developing overall hypotheses in the etiology of idiopathic narcolepsy. In 2009, certain vaccinations in Europe for the H1N1 pandemic caused narcolepsy at a risk of 1:16,000 in pediatric patients [43]. Fortunately, the risk of postvaccination narcolepsy appeared confined to specific vaccine formulations. The incident, however, has led to ongoing research in the immunological etiology of narcolepsy.

African trypanosomiasis, or sleeping sickness, remains important in the developing world. It is a parasitic infection spread by the tsetse fly that is endemic in sub-Saharan Africa. The first symptoms include fever, headaches, and lymphadenopathy. Once the parasite enters the central nervous system, disordered, fragmented sleep ensues often with inversion of the circadian sleep-wake cycle. The World Health Organization outlines treatment with a regimen of antiparasitic medications once symptoms have started [44].

Gastrointestinal system

Non-alcoholic fatty liver disease (NAFLD) consists of idiopathic hepatic steatosis with a prevalence of 17 to 33% of the general population with increased frequency in individuals with obesity or DM [45]. Given these co-associations, OSA is common. Untreated OSA may exacerbate liver injury because of oxidative stress and systemic inflammation [46] and is a risk in conversion from NAFLD to liver fibrosis [47]. Trials with CPAP have shown inconsistent results in markers of liver injury following treatment of OSA [48].

The symptoms of *gastroesophageal reflux disease (GERD)* worsen during sleep, particularly if sleep occurs soon after a meal [49]. The lower esophageal sphincter that normally prevents reflux may be compromised by the increase in thoracic pressure in the setting of the upper airway obstruction [49]. Patients with symptoms of GERD should be screened for OSA, and conversely, interruption of sleep in absence of OSA may improve with treatment with a proton pump inhibitor (PPI) [50] or by simply elevating the head of the bed.

Inflammatory bowel disease (IBD) has bilateral interactions with sleep [51]. Given the relationship between sleep deprivation/fragmentation on cytokine regulation and immune dysfunction, it is hypothesized that poor sleep quality worsens overall symptoms of IBD [52, 53]. Additionally, the pro-inflammatory state disrupts the circadian rhythm [54]. Subjective and objective measurements of sleep quality and timing should be considered in patients with IBD particularly in those who have frequent inflammatory flares despite otherwise adequate management. An algorithmic approach to sleep assessment in IBD patients has been proposed by Canakis et al. [51].

Autoimmune disorders

Systemic lupus erythematosus and rheumatoid arthritis serve as the prototypical diseases of this group of disorders, with a prevalence of sleep disturbances of greater than 50% [55]. The mechanisms of sleep disturbances, as well as the reciprocal relationship in the contribution of poor sleep to worse autoimmune status, are thought to be similar to those described above with IBD [56, 57]. The specific sleep disorders prevalent in this group are OSA and periodic limb

movement disorder (PLMD) (both with greater than 25% prevalence) [58, 59]. As seen above, hypersomnolence and activity-limiting fatigue arise from specific sleep disorders, pain, and medication side effects well as the primary effects of the primary pro-inflammatory status [60, 61]. Often treating the underlying autoimmune disorder improves associated fatigue. However, if sleepiness persists, then evaluating for a comorbid sleep disorder such as obstructive sleep apnea is indicated.

One syndrome with possible autoimmune origins is chronic fatigue syndrome. Sleep disturbances, insomnia, and unrefreshing sleep are common symptoms, yet patients rarely report relief despite appropriate identification and treatment of comorbid sleep disorders [62]. Cognitive-behavioral therapy (CBT) and graded exercise therapy are commonly pursued treatment approaches [62].

Pulmonary

Obstructive lung diseases (most commonly asthma, chronic obstructive pulmonary disease (COPD), and less common disorders such as cystic fibrosis (CF) or bronchiolitis obliterans) may affect nocturnal ventilation. OSA and COPD often overlap given shared body habitus and other mutual risk factors; estimates of comorbid OSA and COPD range from 7 to 66% [63]. Patients with severe COPD treated with nocturnal noninvasive ventilation (NIPPV; a more advanced form of positive airway pressure) experience an absolute risk reduction of 17% of the risk of hospital readmission or death at 12 months, compared with those treated with standard care and without NIPPV [64•].

Insomnia is another common complaint among patients with COPD. Circadian bronchial constriction may cause nocturnal wheezing, dyspnea, or other symptoms of asthma prompting the patient to awaken [65]. In addition, the hyperadrenergic response to beta 2 agonist inhalers used in treatment for acute dyspnea impairs sleep onset (see Table 3).

The growing success in treatments for CF patients means that sleep disorders arising from their intrinsic obstructive lung disease are now coming to the attention of caregivers. Many factors contribute to sleep disruption including chronic cough, frequent infections, abdominal discomfort, reflux, frequent stools, medication side effects, and psychological disease [66]. In addition to sleep disruption, patients with CF are susceptible to hypoventilation that worsens with disease progression. Use of NIPPV in high-risk patients with hypercapnia has been shown to improve physiologic parameters and at times can positively impact symptoms, particularly in patients who have severe disease while awaiting lung transplant [67].

Restrictive lung diseases (defined by a reduced total lung capacity) include those with parenchymal damage such as idiopathic fibrosis, hypersensitivity pneumonitis, or other interstitial pneumonias. Alternatively, lung parenchyma is normal in restrictive diseases such as obesity hypoventilation syndrome, hemi-diaphragm paresis, or neuromuscular disorders (muscular dystrophies, amyotrophic lateral sclerosis). Restrictive lung disease patients, as seen above with obstructive disease patients, are susceptible to nocturnal hypoventilation, subsequent CO₂ retention, and compensatory sleep fragmentation. Use of NIPPV in patients with severe restrictive lung disease (spanning obesity hypoventilation syndrome to muscular dystrophies and ALS) has had positive impacts on survival and quality of life [68, 69].

Cardiac

Over 40% of patients with congestive heart failure (CHF) have comorbid OSA mainly on the basis of mutual risk factors of DM, hypertension, obesity, and older age [70, 71]. In addition, insomnia in those with CHF may arise from a variety of factors including diuretic medications (and subsequent nocturia), positional heart failure symptoms, increased adrenergic status, or psychosocial factors [72]. Treatments addressing comorbid OSA and insomnia improve sleep quality but demonstrate mixed results in terms of long-term cardiovascular outcomes [72, 73].

Patients with acute myocardial infarction (AMI) experience both acute and chronic sleep disorders. Due to the circadian variability of adrenergic hormones and cardiac and systemic vasculature [74], the timings of AMI, sudden cardiac death, and arrhythmia occur with increased frequency at night [75]. Cardiac ischemia may present a series of nocturnal symptoms including paroxysmal dyspnea, chest pain, agitation, or insomnia. Surviving patients are at risk for chronic sleep disorders such as insomnia and sleep-disordered breathing with or without the co-occurrence of anxiety or depression [76].

Retrospective, longitudinal data demonstrate that those with OSA and who are adherent with CPAP experience improved cardiovascular morbidity and mortality over non-adherent patients [77]. However, these findings have not been clearly supported by prospective, randomized trials. The Sleep Apnea cardiovascular Endpoints Trial (SAVE Trial) has called into question the causal link between the treatment of OSA and cardiovascular outcomes. With a mean follow-up of 3.7 years, those randomized to PAP experienced no significant improvements in study endpoints of death from cardiovascular causes, AMI, stroke, and hospitalization for unstable angina, CHF, or transient ischemic attack compared with controls [78••]. Because of possible insufficient CPAP use and because of the lack of main indications for CPAP treatment (such as severe sleepiness), interpretation of the findings of this large trial remains controversial. In practice, these authors often pursue CPAP treatment for patients with OSA and cardiovascular risk factors (even in the absence of sleepiness) at least for a trial period to assess adherence to treatment and to determine if there are subjective and objective improvements to sleep quality.

With a prevalence range of 21–74%, OSA is common in patients with atrial fibrillation and other arrhythmias [79]. Accordingly, the Sleep Heart Health Study showed a two- to fivefold higher risk of arrhythmia in patients with severe OSA compared with that in controls [80]. Retrospective series show that, in patients with atrial fibrillation and untreated OSA, the risk of atrial fibrillation recurrence following cardioversion is 82% compared with 42% in patients who are adherent to CPAP [81]. However, a prospective randomized control trial called retrospective findings into question [82]. Similar in design to the SAVE Trial, patients with atrial fibrillation were randomized to CPAP versus usual therapy from a cohort in which sleepiness was specifically excluded. This small trial (25 total) assessed the primary outcome of time to arrhythmia recurrence. Both arms had recurrence rates of 25%. Although the trial showed that CPAP itself provides no specific benefit to those with atrial fibrillation, the outcomes for treatment of those with both disorders remain unclear.

Although the above studies centered on associations between cardiac disease and OSA, patients with CHF, AMI, and atrial fibrillation experience high rates of

central sleep apnea (CSA) as well, exceeding 35% in patients with mild symptomatic CHF as an example [83]. Cheyne-Stokes respiration, a cyclical form of CSA, results when circulatory impairment perturbs the normal responsiveness in respiratory control resulting in alterations in “the loop gain” in modulating changes in carbon dioxide and oxygen levels in the bloodstream [84], analogous to overly aggressive adjustments to a thermostat in response to changing temperature. The presence of CSA has been considered a marker of increased mortality in patients with CHF, although aims to resolve the treatment of CSA (with CPAP or more advanced modalities) have not clearly demonstrated an improvement in cardiovascular outcomes [85].

Cancer

Estimates of the prevalence of sleep disturbances across cancer patients range widely from 25 to 95% [86, 87]. Insomnia is the most common disorder with prevalence levels ranging from 30 to 50% [86, 88]. Patients with cancer who undergo PSG have shorter total sleep times, longer times in bed, low sleep efficiency, and proportionately less deep sleep than controls [88]. Insomnia in patients with cancer is driven by a multitude of factors including pre-existing socioeconomic and psychiatric disorders, fatigue, age, RLS, pain, and medication effects [86, 89]. Treatment follows that for the general population. Although sedative-hypnotics are most commonly prescribed, no evidence exists for specific pharmacologic interventions for sleep disturbances in this population [90]. Cognitive-behavioral therapy is currently the recommended first-line treatment for chronic insomnia [91]. Because the rarity of trained psychologists makes finding a provider difficult in some circumstances, the electronic delivery of cognitive-behavioral therapy has been sought as an alternative to face-to-face therapy [92, 93].

Critical illness

The bilateral interactions between sleep and critical illness form a rapidly changing area of investigation which is made particularly challenging given the difficulties in measuring sleep in critically ill patients [94, 95]. Lack of sleep—or its encephalopathic analog—may affect outcomes in critical illnesses. For example, a lack of scorable REM sleep correlates with longer ventilator weaning time compared with controls with intact REM [96]. Failure rates on noninvasive ventilation are impacted by sleep continuity [97]. Delirium, a common neurobehavioral syndrome seen in upwards of 80% of patients in the ICU [98, 99], is associated with significantly worse outcomes in the ICU including longer hospital stay and increased mortality [100]. In turn, disrupted circadian rhythms are a strong risk factor for the development of delirium [101].

Ongoing work may establish that the optimization of circadian rhythmicity can directly improve ICU outcomes. The most widespread technique is to provide hospital environments that enable entrainment to a stable circadian rhythm. Exposure to daylight, mitigation of noise, stimulation, and lights during “quiet periods” have been established as good practice in many ICUs [102].

Other investigations have centered on pharmacological interventions. Melatonin, a hormone with important regulatory interactions with the main clock, has been employed to optimize sleep and circadian rhythm in the ICU. However, a small randomized trial of 3 nights therapy with melatonin versus placebo did not alter behavioral sleep or the need for sedation for delirium [103].

Perhaps more promising is the use of dexmedetomidine, a potent selective alpha-2 adrenergic receptor agonist, which provides what appears to be adequate sedation without obliteration of underlying sleep-wake cycles. A prospective study of patients on mechanical ventilation with delirium was randomized to receive dexmedetomidine or placebo in addition to standard medical care [104]. Patients in the treatment arm had a significant increase in the number of ventilator-free hours at 7 days and shorter duration of delirium when compared with the placebo. Although this trial suggests a role for dexmedetomidine in the treatment of delirium in mechanically ventilated ICU patients, those in the treatment arm also required reduced amounts of other sedatives, and therefore, its benefit may be secondary rather than primary. Nevertheless, dexmedetomidine may serve as a less “deliriogenic” sedative agent in the ICU.

Other: *agrypnia excitata*

Some disorders specifically disrupt the thalamic regulation of sleep, present with primary sleep disturbances, and have a variety of systemic or hereditary causes and thus are difficult to classify in our system-based organization used above. *Agrypnia excitata* is a syndrome of unrelenting insomnia, autonomic hyperactivity, agitated delirium, and oneiric stupor (dream-like movements and hallucinations) [105]. Polysomnography of those with *agrypnia excitata* will show the absence of slow-wave sleep and sleep spindles with fluctuating, poorly sustained wake, stage N1, and REM sleep stages. *Fatal familial insomnia* is an autosomal dominant disorder caused by a mutation of the prion protein. Patients experience progressive, subacute dementia, delirium, and insomnia. Treatment is supportive. *Morvan's syndrome* is a rare autoimmune disorder that is caused by antibodies to voltage-gated potassium channels. Patients present with acute onset of insomnia along with myokymia and diaphoresis that progresses at variable rates and usually is fatal without treatment. Most have high levels of immunoglobulin and respond to plasmapheresis. Finally, an unfortunately common syndrome is *delirium tremens* that arises acutely within 48 h of cessation of alcohol in abusers. The onset of ophthalmoparesis and ataxia denotes Wernicke's encephalopathy. Unless prophylactically treated with thiamine and appropriate inhibitory alcohol analogs (such as benzodiazepines), permanent sequelae in the form of hippocampal degeneration may occur (Korsakov's syndrome: profound and permanent anterograde amnesia).

Overall summary

A sleep history is the first step in the evaluation of a patient with systemic disease who presents with “trouble sleeping.” Patients with hypersomnia that is not easily attributable to insufficient sleep should be evaluated with overnight polysomnography, or in certain patients with isolated risk factors for OSA—home sleep testing. The mainstay treatment for OSA is positive airway pressure, especially if underlying systemic disease prevents modification of the underlying risk factors of obesity. Insomnia is best treated with cognitive behavioral therapy that features identification of poor sleep habits, but limited use of sedative-hypnotics can also benefit patients. Sorting out the sleeping environment, whether at home or in the hospital, can improve sleep.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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