

Nonrestorative Sleep, Musculoskeletal Pain, Fatigue in Rheumatic Disorders, and Allied Syndromes: A Historical Perspective

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Introduction

The idea that the sleeping–waking brain is intimately related to complaints of unrefreshing sleep, musculoskeletal pain, fatigue, and suffering is not a novel notion. Its origins are found in the remote past. Over the millennia, its origins and significance have been immersed in religious beliefs in evil thoughts or sinful human behavior with special opportunities for redemption through rituals performed by healers, by sacrifice, or by prayer. Consequently, medical attempts have evaded our understanding. Even to this day, rheumatologists, who are often asked to assess and manage such afflicted patients, say that they have no relevance to their focus of interest in people with discernible objective evidence for arthritic or immunological disease pathology. Even though such patients search for understanding and help with their affliction and suffering, they may face rejection by physicians or exploitation by remedies that do not improve their sleep or cure them of their bodily complaints. This matter of despair and hopelessness is clearly and simply described in *Ecclesiastes* 2:23, “All their days their work is grief and pain; even at night their minds do not rest. This too is meaningless.” Despite *Ecclesiastes*, a pessimistic perspective on the troubles of mankind, this chapter focuses on our efforts to bring scientific understanding to how the physiology of sleeping–waking brain allows us to better understand the origins and management of their widespread pain, suffering, and disability.

Such people have acquired a variety of diagnostic labels by various medical disciplines, as though a mere diagnosis provides both understanding and treatment. At the turn of the

last century, such people were given the label, “fibrositis” by an English neurologist, William Gower. He believed that the basis of his patients’ painful limbs and backs were the result of inflammation of fibrous tissue. When systematic studies of infectious or disease pathology could not be verified, the term became a wastebasket diagnosis used by rheumatologists to differentiate these patients from those with similar symptoms but having objective evidence for disease pathology. Other medical specialists, to whom such afflicted people would visit, applied explanations that relate to their specialty’s focus of interest. See Table 48.1 for such a list of health-care specialist providers, their areas of interest, and diagnostic labels that are provided to such patients.

The medical field becomes more complicated when such symptoms are found in patients with a known disease. Even though the disease is successfully treated by well-established disease-modifying substances, they may remain chronically ill with unrefreshing sleep, widespread pain, tenderness, chronic fatigue, and psychological distress. These features often occur in patients with systemic lupus erythematosus and rheumatoid arthritis. Without the objective evidence for arthritic, neuroendocrine, or immunological disease pathology, the community of rheumatologists abandoned the term of ill-understood “fibrositis” and adopted the now-popular descriptive diagnosis, “fibromyalgia” (FM) or “fibromyalgia syndrome” (FMS). The formalization of criteria for the diagnosis approved by the American College of Rheumatology in 1991 [1] permitted epidemiological studies to determine the prevalence of the syndrome. Subsequently, approximately 2% of the US population (3.4% women, 0.5% men) were found to be affected [2]. Those with the diffuse musculoskeletal pains and debilitating fatigue in five European countries (France, Germany, Italy, Portugal, and Spain) affected 2.9% of the population (3.6% women and 2.1% men) [3], making this rheumatic disorder the second most common rheumatic ailment after osteoarthritis.

About the same time, infectious disease experts noted that pain and fatigue symptoms prevailed long after an acute infectious disease had past. They variously diagnosed such

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patients as having a post-infectious or post-viral syndrome, myalgic encephalomyelitis (ME), and Epstein virus syndrome. Where a sporadic cluster of such mysterious ailments appeared, diagnostic labels were attributed to geographic locations, e.g., in 1934, Los Angeles County Hospital disease also known at the time as “atypical poliomyelitis”; in 1948–1949, Akureyri disease (also called Iceland disease); and in 1955, London’s Royal Free (Hospital) disease, which subsequently was thought to be a form of mass hysteria. The absence of any verifiable evidence for any specific infectious agent or inflammatory disease pathology proved perplexing for infectious disease specialists. The lack of objective evidence for a specific virus or specific infectious disease led to a committee of advisory experts to the US Centre for Disease Control to formalize criteria. The current diagnosis, chronic fatigue syndrome (CFS), came into existence [4]. This vague descriptive label emerged in 1994 much to the chagrin of affected American patients who advocate for special recognition by government health agencies for their preferred term “chronic immune deficiency syndrome.” In the UK, the label chronic infectious neuromyasthenia encephalitis is preferred. Often, there is an overlap among the variable clinical criteria adopted by committees of the various medical disciplines so that some authors have referred to such patients as coming under an umbrella of a cluster of overlapping ailments (see Table 48.1). The overriding common feature is the absence of any known clinical features of disease or signs of any abnormalities in any radiological, hematological, histological, chemical, metabolic, or immunological tests. Nevertheless, the hunt for a viral etiology persists with the most current being the 1990 report in *Science* on the prevalence of a retrovirus, xenotropic murine leukemia virus-related virus (XMRV) finding in more than 60% of the patients with CFS. Two years of several scientific reports of failures to replicate the initial findings led to a formal retraction by this journal

in November 2011 [5]. A viral etiology, however, remains relevant in selected populations with post-febrile persistent chronic fatigue and diffuse myalgia. For example, following an outbreak in Toronto of severe acute respiratory syndrome (SARS), those who had survived and had no residual respiratory disease 1–3 years later had persistent diffuse myalgia, disabling fatigue, weakness with unrefreshing sleep, and anomalous increased sleep EEG alpha and the EEG sleep cyclical alternating pattern (CAP) in non-REM sleep. The possibility that the SARS coronavirus, which is known to enter the brain during the acute phase, may have a continuing adverse influence on the sleeping waking brain with associated physical and behavioral symptoms [6].

In the absence of medical disease, these people with ill-understood poor sleep quality, chronic pain, and fatigue tend to be cast into the dark chasm of vague psychiatric labels. The psychiatric diagnostic labels have changed over the course of five revisions of the American Psychiatric Association (APA) *Diagnostic and Statistical Manual of Mental Disorders* (DSM). They range from neurasthenia and hysterical conversion disorder to somatoform pain disorder, somatization disorder, and now the DSM-5 feckless diagnosis, “somatic symptom disorder” [7]. This chain of psychiatric labels represents a history of collective transient agreements by generations of US psychiatric committees that have applied some form of presumed scientific explanations to bodily complaints and sickness where there is no satisfactory medical or psychological explanation. Now, most of these earlier psychiatric diagnoses have been abandoned, in favor of an empirical, presumably less controversial, descriptive label. As seen in Table 48.1, the diagnostic labels adopted by various groups of health specialists are afflicted with similar scientific explanatory dilemmas.

In the prescientific evolution of knowledge, such people and their ailments were given various religious or spiritual

Table 48.1 Medical specialties and their diagnoses of patients with chronic widespread pain, fatigue, unrefreshing sleep, psychological distress, and no medical pathology

Health specialists	Symptom interest, no pathology	Diagnosis
Rheumatologists	Pain, mobility, fatigue	Fibromyalgia
Physiatrists	Pain, mobility, fatigue	Regional pain
Orthopedists	Pain, mobility, fatigue	Chronic pain syndrome
Chiropractors	Pain, mobility, fatigue	Faulty spinal alignment
Infectious disease allergists and environment medicine	Fatigue, pain Hypersensitivities	Myalgic encephalomyelitis, CFS Multiple chemical sensitivity, SBS
Psychiatrists/psychologists	Behavior, mood, cognition	Somatoform or mood disorder
Neurologists	Headache, fatigue, behavior	Tension headache
Gynecologists	Abdominal and pelvic pain	Chronic pelvic pain, dyspareunia
Gastroenterologists	Abdominal pain, GI disorder, fatigue	Irritable bowel syndrome
Urologists	Urinary tract pain and frequency	Interstitial cystitis/irritable bladder
Dentists	Jaw pain with movement	TMJ disorder
Cardiologists	Chest pain, fatigue	Atypical chest pain

GI gastrointestinal, CFS chronic fatigue syndrome, SBS sick building syndrome, TMJ temporomandibular joint

explanations. Remedies stem from particular prayers, rituals, and/or special natural remedies. In non-Western societies, the systems of beliefs, their respective special names, and remedial methods are deemed to be features of culture-bound syndromes. For example, *hwa-byung*, a Korean folk illness is characterized by insomnia, pains, fatigue, weakness, gastrointestinal symptoms, and emotional distress. Chinese patients who have sleep difficulties, headaches, various pains, fatigue, and sexual dysfunction are termed *shenjing shuairuo*. Their society's belief is that the affected people's vital essence is being lost and life threatening. In the Indian society, the term is *dhat*, where Hindus have a similar belief in the dangers to self of the loss of essential sexual fluids. In Latin-American societies, such frightened and emotionally distressed people with similar sleep and somatic symptoms are considered to be afflicted with *susto* or "soul loss." Even now in the Western society, where there is no clear medical understanding of the cause or treatment of such ill-defined symptoms, these culture-bound belief systems and methods for treating these illnesses continue to prevail in our societies. Hence, there is a large industry of purveyors of herbal substances, acupuncture, moxibustion procedures, and useless remedies of various vitamins and minerals. Where there is a lack of faith in medical explanations, there is the hope that nontraditional methods would remedy the mysterious rheumatic symptoms.

Rather than focusing on traditional rheumatic interests in joints, connective tissue, and muscles, current interest has shifted to the central nervous system as the source of hypersensitivity with application of pressure to various predesignated regions of the body and pain behavior that are readily observed by rheumatologists in examining their patients' musculoskeletal system. Based upon experimental evidence, Moldofsky proposed the hypothesis that the sleeping/waking brain is integral to the somatic and behavioral symptoms of these ill-understood painful, fatiguing, distressing, and often disabling chronic illnesses [8]. This hypothesis gives rise to the following questions:

1. How does the sleeping–waking brain connect to these poorly understood somatic and behavioral symptoms?
2. Does an understanding of the disturbances in the sleeping/waking brain favorably influence the management of these suffering patients?

This chapter reviews advances in our scientific understanding of how the sleeping–waking brain is intimately connected to the widespread musculoskeletal pain, fatigue, and psychologically distressing symptoms of previously presumed to be unexplained medical illnesses, which have led to the current advances in their management.

Review of EEG Sleep, Pain, and Fatigue

The pioneering work of Moldofsky and colleagues yielded two critically important findings with regard to the relationship of sleep to widespread musculoskeletal pain and fatigue in rheumatological patients without known medical disease:

- 1) EEG sleep is disturbed in more than 90% of FM patients who report persistently poor sleep quality and impaired quality of life [9, 10].
- 2) Experimental sleep disturbance in healthy individuals can induce FM-like musculoskeletal pain and tenderness [11]. Manifestations of disturbed sleep typically comprise the experience of light and unrefreshing sleep, nocturnal restlessness with frequent awakenings, and at times, sleep-related loud snoring and breathing problems, or periodic involuntary leg movements. Typically, there is a variation in the diurnal pattern of symptoms. Upon awakening from their poor quality of sleep, patients usually experience generalized muscular stiffness, diffuse pain, and profound fatigue, which are unchanged or even increased compared to the previous evening. They report improvement in symptoms with improved energy from late morning to mid-afternoon; then, thereafter there is a downhill course in symptoms as the day progresses. The narrower the period of improvement, the more disabled is the patient. On the rare occasion, they might achieve a restful night of sleep and improved symptoms on the following day. Indeed, unrefreshing or nonrestorative sleep is closely correlated to the widespread pain and tender points in FM while psychological distress is not [12]. FM subjects with light unrefreshing sleep have diurnal impairment in speed of performance on complex cognitive tasks, which are accompanied by sleepiness, fatigue, and negative mood. Such psychological impairment could account for the functional disabilities that are encountered in a work environment and in social behavior. There may be an associated predisposition to emotional hypersensitivity resulting from distrust and insecure attachment in their personality, which is shown to be associated with the alpha-EEG anomaly during sleep [13].

These disabling behavioral symptoms are commonly associated with disturbances in the physiology of sleep [8, 9]. How these FM symptoms are linked to the subjective poor sleep quality and objective PSG measures continues to be of considerable interest in determining the pathophysiology of this illness. Early on, aspects of anomalous changes in EEG sleep physiology were identified in FM patients that were considered to be consistent with subjective poor quality of sleep. Nocturnal polysomnography (PSG) shows a prominent EEG alpha frequency (8–12 Hz) rhythm in the central EEG regions during stages 2 and slow-wave sleep (SWS) NREM sleep (see Fig. 48.1) but less frequently in patients with severely diminished or absent delta SWS [8]. As Hauri and Hawkins had noticed this alpha EEG anomaly to

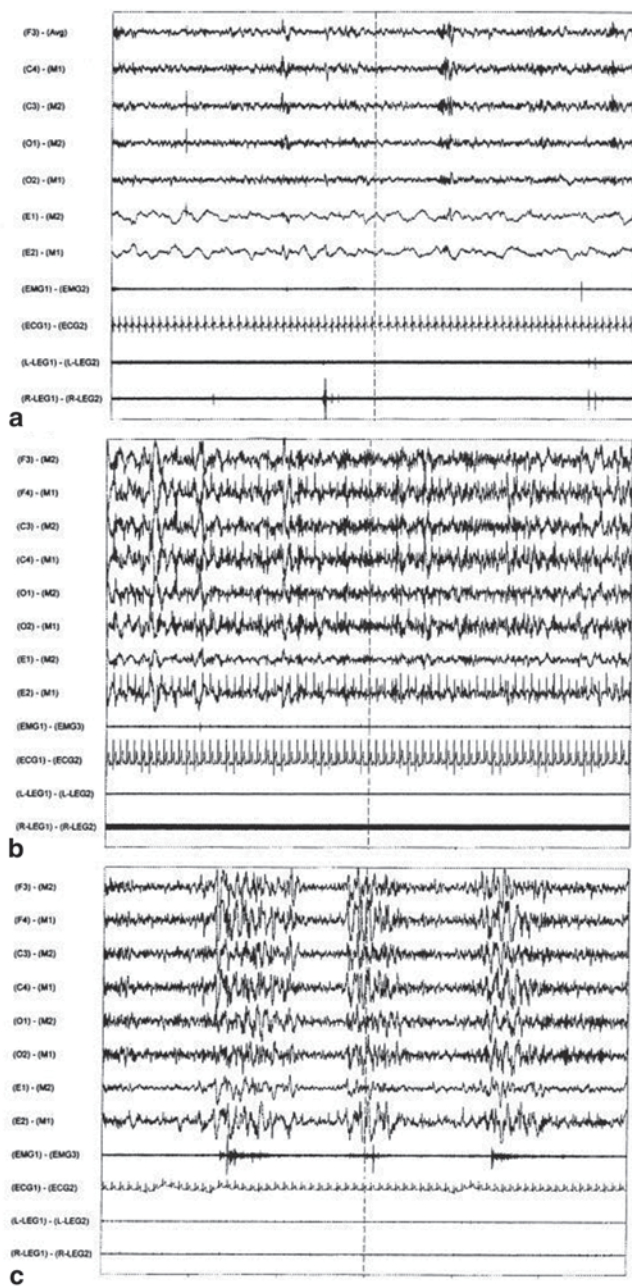


Fig. 48.1 Examples of 60-s stage 2 non-REM sleep EEG and electromyography (EMG) and electrocardiographic (EKG) recordings. **a** Normal, **b** α -EEG sleep, **c**. Cyclic alternating pattern (CAP) sleep EEG: subtype CAP A3 with periodic bursts of polyphasic EEG and coincident bursts of submental EMG activity. REM rapid eye movement, EEG electroencephalogram. (From [24] *The Journal of Rheumatology* 38:10; 2011)

coincide with the delta frequency ($0-4$ Hz) slow waves of SWS, they coined the term alpha-delta sleep, which they described in a small group of not depressed psychiatric patients with poorly understood illness who complained of chronic,

somatic malaise, and fatigue [14]. Subsequently, Moldofsky and colleagues reported this anomaly in patients with so-called fibrositis [11], later considered by rheumatologists to be a wastebasket diagnosis because of the lack of replicated evidence of presumed inflammation of fibrous tissue. Subsequently, the symptoms were relabeled as FM or FMS. This anomalous alpha EEG sleep is seen predominantly in the frontal-central brain area in contrast to the alpha EEG frequency occurring in quiet wakefulness that is localized in the occipital region [15, 16]. Subsequently, reports of this anomalous increased alpha EEG activity in NREM sleep were reported in FM patients [8, 17–21]. Patients with FMS, however, are heterogeneous with respect to exhibiting the alpha anomaly [21]. This alpha activity in NREM sleep is not specific to FM, since it occurs in patients with other painful rheumatic diseases. Moreover, it is described to occur in patients with primary insomnia [22]. As EEG alpha-like rhythm is associated with mentation [16, 18], alpha occurring in NREM sleep may represent a vigilant arousal state that interferes with bodily restorative functions [8]. This abnormal EEG sleep feature may account for a common aspect of impaired sleep quality with symptoms of light sleep and sleep mentation with external environmental awareness and internal self-awareness of subjective discomfort. This sense of vigilance is shown to be associated with an underlying faulty personality characteristic in such people with the prominent alpha EEG sleep anomaly and physical illness which stems from a faulty interactional pattern of childhood personality development. In formal personality testing of such people with the alpha EEG sleep anomaly, most of whom have FMS, they show a pattern of overall distrust and insecurity in interpersonal relationships. Consequently, this pervasive sense of insecurity and distrust, which are ingrained in their personalities, is thought to make them difficult to accept any medical therapeutic effort that results in perpetuation of chronic physical illness behavior [13].

A second physiological component of impaired sleep quality is thought to be a specific EEG pattern that contributes to unstable or nonrestorative sleep, a major diagnostic feature of FMS and CFS. This objective physiological feature in the sleep EEG sleep comprises a high frequency of the CAP. The CAP phenomenon occurs variably throughout NREM sleep characterized by a frequency of approximately 20–30 cycles per second (see Fig. 48.1). The specific type of CAP is reported to reflect a measure of relative stable-unstable sleep. In patients with FMS and CFS where unstable or nonrestorative sleep is commonly reported, there is an increase of CAP activity. The sleep EEG dominant rhythm of CAP A1 and no significant ancillary increase in autonomic or peripheral EMG activity, as seen in CAP A2 and increased in CAP A3, is associated with sleep stability that

is commonly found in young asymptomatic healthy people. In the subgroup CAP A2 and CAP A3, there is physiological evidence for progressive increases in sleep instability [23–25]. This high amount of CAP correlates with the severity of pain as measured by the number of tender points in FMS [23]. The EEG CAP A2 and especially CAP A3 are associated with pathological sleep characterized by physiological evidence of motor and autonomic nervous system abnormalities, e.g., periodic limb movement (PLM) and sleep apnea disorders [24, 26]. Such clinically significant periodic PSG sleep disorders are found in a large sample of US patients with FMS. In this multicenter PSG study of more than 200 FMS patients, 94% were female, with a mean body mass index of about 30 who had FMS for more than 5 years. Approximately 15% had moderate to severe apnea–hypopnea respiratory index and 20% had PLM disorder [24]. Their sedentary behavior with resultant weight gain and obesity may have promoted the sleep apnea disorder and the coincident CAP A2 and A3 EEG unstable and nonrestorative sleep.

Another feature of sleep EEG disturbance, which is reported in FMS, is a decrease in stage 2 EEG sleep spindles [27]. The presence of EEG sleep spindles, a characteristic of this stage of NREM sleep, is hypothesized to be a physiological feature of sleep stability. This hypothesis is supported by the shorter duration of stage 2 sleep periods, which is normally dominated by CAP A1. In addition, there is increased frequency of EEG sleep stage shifts [28], increased sleep awakenings, and decreased sleep efficiency (ratio of time asleep/time in bed) [23, 29].

Moreover, there is a reduction of SWS in FM patients [11, 19–21, 29]. One such study showed that decreased SWS is correlated with high-phasic EEG alpha rhythm [21]. The finding of reduced SWS in FMS patients also coincides with nocturnal neuroendocrine abnormalities of increased nocturnal cortisol levels and decreased release of growth hormone (GH) [30]. Quantitative studies suggest that the duration of SWS serves to regulate homeostasis and is correlated with the amount of prior waking. That is, SWS increases following extended wakefulness and is decreased during nocturnal sleep following a daytime nap containing SWS [31]. This decreased amount of SWS in FM might indicate an impairment of the SWS homeostatic drive.

Some sleep abnormalities in FM patients have not been consistently reported. In some studies, for example, FM patients are reported to be not significantly different from controls with respect to alpha sleep EEG activity or the duration of SWS [28, 32]. It is unclear whether these discrepancies result from heterogeneity of sleep pathology in FM patients, technical considerations such as differences in scoring of sleep EEG alpha anomalies, or the night-to-night variability in many sleep measures, including SWS [33].

Relationship Between Sleep and Pain Processing

Epidemiological Studies

Among patients with FMS, poor sleep quality is shown to be a key in the vicious cycle of feeling unrefreshed after sleep, morning aching/stiffness, fatigue, and dyscognition. Several prospective clinical studies report a correlation between poor sleep quality and FM symptoms. A statistical path analysis of a large population of FM patients found that a night of increased sleep disturbance correlates with increased pain, which predicted poorer physical functioning and subsequently greater depression [9]. In another study, poor sleep quality mediates the impact of increased pain upon fatigue [34]. These studies extend previous findings that a night of poor sleep is followed by a day of increased pain [35]. Moreover, after accounting for the effects of positive and negative events and pain on daily mood ratings, sleep duration and quality are prospectively related to affect and fatigue. Inadequate sleep has a cumulative effect on negative affect and prevents mood recovery from days with a high number of negative events [36].

Clinical Experimental Studies

As described above, Moldofsky and colleagues were the first to attribute functional disturbances in the sleeping–waking brain to the etiological core of promoting FM symptoms. In 1975 and 1976 publications, they showed that by interrupting SWS with auditory stimuli, an FM-like state including variable aching, fatigue, and increased sensitivity to pain pressure could be induced in healthy normal nonathletic subjects [11, 37]. They also showed in a small pilot study that under similar experimental prospective sleep and symptom test circumstances, several members of the University of Toronto track team did not experience such pain and fatigue symptoms. This preliminary finding suggests that aerobic physical fitness is involved in preventing or reducing the emergence of these symptoms. Since then, other researchers have confirmed that selective deprivation or disruption of sleep induces increased bodily sensitivity, decreased pain threshold, and reports of nonrestorative sleep [8, 38–42]. One study involving presumably fit US military men found a reduction of pain threshold, albeit not significantly different from controls [42]. Another experimental clinical study of sleep deprivation does not alter somatosensory (nonnociceptive) functions [39]. Furthermore, the effects of interruptions of SWS increases sensitivity to both painful and nonpainful stimuli, such as bright light, loud sounds, and strong odors [40]. In this study, selective sleep deprivation of middle-aged, sedentary women (similar to the major demographic

population of FM patients) also produced impairment in diffuse noxious inhibitory controls (DNIC), similar to that observed in FM patients [40]. Recovery after sleep deprivation results in increased amounts of SWS and normalization of pain threshold [8]. The importance of SWS in maintaining homeostatic properties of the CNS is purported to involve downregulation of synapses [43, 44].

Synaptic upregulation, a feature of a state of central sensitization and pain augmentation, may be caused by disturbances in the physiology of sleep that leads to impaired sleep quality and nonrestorative sleep symptoms. Consequently, total sleep deprivation and REM sleep deprivation adversely affects pain threshold and pain behavior [40], which also occurs as the result of the experimental induced loss of the terminal four hours of sleep with its REM and non-REM sleep [45].

Disordered Metabolic Functions

Despite the absence of specific structural pathology, there is evidence for disordered metabolic functions that involve the sleeping/waking brain. These include a decrease in sleep-related prolactin, decrease in GH and its metabolites, disturbances in the hypothalamic-cortical adrenal axis, and elevation of cerebral spinal fluid substance P (SP) [46–53]. Furthermore, specific dysfunctions in neurotransmitter functions are shown to contribute to bodily sensitivity and disordered sleep. For example, inhibition of serotonin (5HT) synthesis by p-chlorophenylalanine induces insomnia and a hyperalgesic state in animals and humans [54]. The increased levels of SP that are found in the CSF of FMS patients led to experimental studies that demonstrated that SP operates through a neurokinin (NK) pathway to influence nociception and sleep. Intracerebral ventricular administration of SP in sufficient quantities that did not induce nociceptive response in mice delayed onset of sleep and provoked awakenings from sleep. An NK-1 receptor antagonist reversed the interfering effect upon sleep by SP [55]. This research demonstrates that the blocking of the SP-induced insomnia by prior treatment of the mice with NK1 receptor antagonist provides support to the notion of the arousing effect of increased SP on the sleeping/waking brain. Moreover, this research provides an experimental animal model for studying sleep disturbances and musculoskeletal pain.

Functional neuroimaging of FMS patients support the hypothesis of deficits in CNS inhibition and central pain augmentation. FMS patients are reported to have a premature decrease in gray matter volume in the cingulate, insular, medial frontal cortices, and parahippocampal gyri, which may be associated with affective disturbances and chronic widespread pain [56]. Whereas the duration of pain or functional pain disability was not related with gray matter vol-

umes, there is the suggestion that there is a trend of reduction in the anterior cingulate cortex (ACC) gray matter volume. In another brain imaging study, FM patients showed lower ACC connectivity to the bilateral hippocampi, amygdala, brainstem, and rostral ventromedial medulla, which are brain areas involved in the descending inhibitory modulation of pain and increased central nervous system sensitization [57]. Furthermore, sleep deprivation that has an adverse effect on pain perception and cognitive functioning alters dopamine metabolism (D2 receptor) in the striatum, which merits further study because of this neurotransmitter involvement in sleep/wake mechanisms [58].

Increased overnight sympathetic activity using electrocardiographic methodology is consistent with the notion of circadian autonomic metabolic dysfunction associated with an arousal disturbance during the sleep of patients with FM [59].

In conclusion, the continuing search for biological and behavioral etiological factors has resulted in the absence of a specific triggering event to the onset of symptoms. This absence of a medically explanatory specific triggering etiological agent has led to the belief in a combined genetic and environmental predisposition to these pain and fatigue syndromes. Accordingly, a pattern of specific genes may become activated by a variety of noxious triggering influences. Examples include industrial or motor vehicle accidents, psychologically traumatic events (e.g., posttraumatic stress injury), and viral infection with a consequent chronic M.E. or post viral CFS, e.g., post-viral SARS [6]. These potential triggering events may adversely affect the operations of the sleeping/waking brain with associated abnormal metabolic and neurophysiologic functions. The resulting neurophysiological dysfunctions affect inhibitory and reciprocal excitability sensory operations, which clinically manifest as hypersensitivities to various external noxious stimuli, e.g., application of pressure, loud noise, bright light, or unpleasant odors. Organ sensory dysfunctions may be affected with reactive hypermotility (e.g., irritable bowel or bladder syndromes). Such clinical experiences may evolve into a psychological distressing pattern of self-perpetuating chronic unrefreshing sleep, widespread pain, fatigue, and psychosocial behavioral problems. In their search for help, those affected (often females) are labeled with diagnoses that reflect the education, special focus of interest, and belief system in particular methods of treatments employed by health professionals in their practices (see Table 48.1).

Management

Currently, although no cure is on the horizon, the awareness, research, and improved knowledge of FMS are benefitting the development of methods of management of the illness.

Nonspecific sleep and behavioral measures such as sleep hygiene, gentle aerobic fitness, and cognitive behavioral techniques, together with a variety of sleep-promoting sedative, analgesic, and antidepressant remedies are being employed to treat pain symptoms. These include reports of experimental trials of medications, various remedies, and behavioral procedures based upon various ideas about mechanisms involved in the promotion of pain and fatigue symptoms. Some have resulted in the government approval of pharmaceutical agents. Some have been rejected for a variety of reasons and some are in various phases of experimental trials. These are briefly reviewed below.

Approved Neuroregulatory Drugs

Over the past several years, three CNS drugs, pregabalin (a drug with anticonvulsant properties), duloxetine, and milnacipran (drugs initially marketed as antidepressants), have been approved for the treatment of FM by the US Food and Drug Administration (FDA). Pregabalin and duloxetine are approved by Health Canada, but none of these drugs are approved by the European Medicines Agency. The neurotransmitter modulatory agent pregabalin, which is an α_2 -delta ligand that causes increased cellular expression of calcium channels, reduces the expression of SP and noradrenaline. Studies show that this drug improves the pain, quality of sleep, and fatigue in FMS. Duloxetine and milnacipran are noradrenaline-serotonin reuptake inhibitors, which are known to be helpful in improving mood and also benefit pain and sleep in animal studies and neuropathic pain in humans.

Unapproved Randomized Control Trials of Neuroregulatory Medicinal Agents

A US multicenter randomized placebo-controlled 8-week trial (RCT) with sodium oxybate given in a 4.5- or 6-g qhs dose improved sleep physiology with reduced percent CAP A2/A3 rate and increased SWS in addition to improvement of the self ratings of quality of sleep and reduction of pain and fatigue in FMS patients [24].

A meta-analysis of five RCT trials with 10–40 mg cyclobenzaprine, given at variable times during the day, showed an overall global improvement in FM, a short-term modest improvement in pain, moderate improvement in sleep, and no improvement in fatigue or tender points. However, 85% of patients experienced untoward effects, commonly drowsiness, dizziness, and dry mouth [60]. A recent two-site RCT of 1–4 mg cyclobenzaprine at bedtime (mean dose of about 3 mg) showed improved pain, tenderness, depression, and sleep quality or sleep stability as measured with sleep EEG CAP. More subjects taking the low dose of cyclobenzaprine

versus the placebo group had more nights of restorative sleep which was accompanied by improved fatigue and depression [25]. This drug is under further FDA development.

Some effort has been directed to remedying aspects of abnormal neuroendocrine function, e.g., about one third of patients with low levels of insulin-like growth factor 1 (IGF-1), a surrogate marker for low GH secretion, have been treated with daily injections of GH. In a 9-month randomized, placebo-controlled, double-blind study, there was an increase in IGF-1, and a reduction in pain and tenderness. On the other hand, GH, which is reduced in patients with FMS, improved symptoms, but its high cost and the need for daily injections make its use impractical [61].

A single non-RCT of pramipexole, a dopamine agonist, is reported to be helpful for pain, fatigue, and overall function in a subset of FMS patients, half of whom were also taking narcotics [62].

No consistent abnormalities have been reported in the secretion of melatonin in patients with either CFS or FMS, nor has its administration been found to be useful in controlled studies [63]. Furthermore, the use of morning bright light treatment, which tends to modify the timing of the nocturnal secretion of melatonin and is helpful in seasonal affective disorder, does not benefit sleep, pain, or mood symptoms in patients with FMS [64].

Finally, patients with primary sleep disorders such as restless legs/PLM disorder and sleep apnea have not as yet been subject to RCT for pain and fatigue with the well-established remedies for such conditions. In particular, a further study of pramipexole (and similar dopamine agonist) is required to determine whether the improvement noted in some patients [62] may be related to the reduction in restless legs/PLM sleep disorder that occur in some patients.

In conclusion, advances in our scientific understanding of how the sleeping-waking brain is intimately connected to the widespread musculoskeletal pain, fatigue, and psychologically distressing symptoms of previously presumed to be unexplained medical illnesses, and current advances in medical knowledge is leading to the improved management of the FMS and similar pervasive syndromes with chronic unrefreshing sleep, diffuse myalgia, fatigue, and psychological distress.

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