

A REVIEW OF SLEEP IN SELECTED IMMUNE AND AUTOIMMUNE DISORDERS

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Evidence for the reciprocal role of the immune system in sleep is growing. Sleep disturbances are believed to be both a cause and a consequence of various immune and autoimmune conditions.

KEY WORDS: *autoimmune disorders, chronic fatigue syndrome, fibromyalgia. HIV, immune disorders, sleep, sleep disorders. Holist Nurs Pract 2003;17(2):65-80*

IN THE INTERNATIONAL CLASSIFICATION of Sleep Disorders, first disseminated in 1990, 1 of the 4 major categories is that of disorders of sleep associated with medical or psychiatric disorders. When examining disordered sleep in any disease, comorbid conditions such as anxiety and depression as well as primary sleep disorders and other conditions that contribute to a poor night's sleep such as pain or the need to arise frequently because of a full bladder must be sorted out from direct effects of the disease. Likewise a poor night's sleep can exacerbate certain disease symptoms. For example, pain may cause disturbed sleep or insomnia, and lack of sleep or unrefreshing sleep can lower the pain threshold resulting in more severe pain. Some medical conditions directly affect sleep through the basic disease mechanism; sometimes this relationship is also reciprocal.

INFECTION, IMMUNITY, AND SLEEP

The idea that sleep is necessary to combat infection was noticed by Hippocrates and others, and getting extra and/or restful sleep is considered part of the conventional wisdom on fighting colds, fever, and other illnesses. It is also recognized that nights of poor sleep can adversely affect health, physiological parameters, and a sense of well-being. Yet, it is relatively recently that sleep has been objectively observed over the course of infection. In addition, a beginning understanding of the relationship between immune function and sleep is emerging.⁴ Sleep pattern alterations were first objectively observed in humans with infections in the 1980s.⁵ Systemic infection usually results in both fever and sleep responses. The latter may be directly caused by microbial products and/or the induction of cytokine production.⁶ There seems to be a bidirectional relationship between the immune system, the neuroendocrine system, thermal regulation, and the sleep-wake system of the body that also affects circadian patterns. Thus, relationships and the effects of immune malfunction on sleep are complicated.⁷

Cytokines became recognized as key in the humoral immune system regulation. Several cytokines promote sleep in animals. For example, interleukin-1 (IL-1), tumor necrosis factor, and alpha interferons are cytokines that have been shown to promote slow-wave sleep in animals⁸⁻¹¹ and IL-6 increases in the plasma over periods of wakefulness.¹² Interactions between sleep and host defense mechanisms such as cytokines, neuropeptides, and neurotransmitters have been reported and are the subject of increasing research in human subjects.⁶ In low doses, bacterial endotoxins increase nonrapid eye movement (NREM) sleep and activate certain cytokines, while they disturb sleep at high doses. The sleep-wake cycle is believed, then, to play a role in

regulation of the immune system, affecting immunomodulation and neurobehavioral functioning.¹³

SELECTED DISORDERS OF IMMUNITY, AUTOIMMUNITY, AND SLEEP

Sleep disruption in some of the immune and autoimmune disorders is believed to be more involved than merely the result of uncomfortable disease symptoms or manifestations such as pain. In fact, the relationship among fatigue, pain, musculoskeletal aches and stiffness, and poor sleep are observed but are not well explicated.¹⁴ Whether or not disorders such as fibromyalgia may be considered as having an etiology stemming from disturbed sleep was an early question. Selected disorders that are mainly of unclear etiology and that are known to be associated with disturbed nighttime sleep and/or daytime manifestations of sleep disturbance such as fatigue will be discussed below. These are fibromyalgia, chronic fatigue syndrome, systemic lupus erythematosus (SLE), human immunodeficiency virus (HIV) infection, myasthenia gravis, multiple sclerosis (MS), rheumatoid arthritis (RA), and certain other arthritic syndromes.

Fibromyalgia

Fibromyalgia is a rheumatologic condition of unknown etiology and in earlier literature was also known by the term *fibrositis*.¹⁵ The overall prevalence in the United States is 2.0%, 3.4% in women in whom it is more prevalent, and 0.5% in men.¹⁵ While the cause is unknown, neuroendocrine dysfunction is believed to be central to etiology, especially the hypothalamic-pituitary-adrenal axis (HPA) as well as autonomic nervous system alterations.^{18,19} The immune and nervous systems communicate and adjust to each other by a variety of means including neuromodulators, hormones, growth factors, and neurotransmitters.^{20,21} Genetic predisposition is also suspected, and there may be an infectious or other type of environmental trigger that acts on persons with susceptible genotypes as is believed to occur in some cases of various chronic disorders.^{22,23} Organisms that have been suspected to play this type of role are parvovirus B19, Epstein-Barr virus, and the organism that causes Lyme disease, *Borrelia burgdorferi*.²⁴ Further, the influence of psychological distress such as depression and anxiety is difficult to determine because of bias and other methodological flaws in many of the studies and the relatively common independent occurrence of these disorders^{14,25} as well as that such distress could develop secondary to the disease because of the nature of the symptoms and their toll, particularly since misdiagnosis may be frequent and there is no quick cure available.

Fibromyalgia has been extensively described by the American College of Rheumatology (ACR) classification criteria of 1990,²⁶ with additional elaboration from a World Conference in 1992.²⁷ A key element in the description is chronic generalized pain, with evidence of pain in 11 of 18 specific local tender points at palpation with an approximate force of 4 kg.²⁶ The chronic pain in the joints, muscles, and spine is nonarticular and is considered to be a "soft tissue" type of rheumatism. Early morning stiffness but no inflammation is usually found. Other frequent symptoms are relatively nonspecific such as fatigue, sleep disturbances, paresthesias, headache, anxiety, and irritable bowel. These latter symptoms are considered useful, but not definitive, in the diagnosis.²⁸ Defects in cognitive functioning and reduced concentration may occur.²⁹ Particularly in many early reports, fibromyalgia was thought to have a significant psychogenic component: the condition was not readily identified by clinicians, and diagnosis was often by exclusion.^{30,31} Clinical and demographic similarities exist between fibromyalgia and chronic fatigue syndrome.^{32,33} including chronicity and response to therapy, and it has been suggested that they share a common pathophysiologic mechanism and perhaps a common etiology.^{15,34} In a broader look at fibromyalgia, chronic fatigue syndrome, temporomandibular

disorder, tension and migraine headaches, interstitial cystitis, and irritable bowel syndrome may be part of a related spectrum of disorders,³⁵ and many of these were considered to be "functional" or "psychogenic" disorders early in their description.

Various reports estimate that somewhere between 40% and 96% of patients with fibromyalgia complain of sleep disturbance^{28,30,31,35-40} and certain sleep disruptions were considered as part of early diagnostic criteria before the ACR criteria were developed.^{30,36,41} The sleep that patients do experience is described as nonrestorative and daytime fatigue is often present.¹⁹

Many of the studies of sleep disruption in fibromyalgia have been conducted by Moldofsky with various colleagues. Selected examples will be reviewed here. An early sentinel study examining sleep disturbance in 10 patients with fibromyalgia was reported by Moldofsky and colleagues⁴² in 1975. They used polysomnography to measure sleep in patients who reported a major stressful life event at the time of the onset of their symptoms and sleep disturbance.

Among the findings were an alpha (7.5-11 Hz) electroencephalographic NREM sleep anomaly occurring during stages 2, 3, and 4 NREM sleep and an overnight increase in self-reported pain and stiffness as well as localized areas of tenderness. They called this sleep anomaly *alpha-delta* sleep. In a second study described in the same publication, 6 healthy men were deprived of stage 4 sleep for 3 nights and then allowing recovery, musculoskeletal tenderness occurred during deprivation, and an alpha-delta pattern similar to that described in fibromyalgia was seen. In a following report detailing more extensively the second part of their 1975 report, Moldofsky and colleagues deprived 6 healthy, sedentary subjects of NREM stage 4 sleep and 7 subjects of REM sleep. They concluded that musculoskeletal symptoms and increased muscle tenderness as well as an overnight increase in pain as measured by dolorimeter scores resulted from deprivation of NREM stage 4 sleep. These were not reported in the subjects deprived of REM sleep. They suggested that this temporary induction of musculoskeletal pain, sleep disturbance, and fatigue could provide a model for what was then called *fibrositis syndrome*.^{29,42}

Moldofsky⁴² has suggested that both pain and sleep disturbances in fibromyalgia could be related to low serotonin in the central nervous system. Low serotonin might be related to disrupted pain perception via substance P since substance P is elevated in fibromyalgia.⁴⁴ Low serotonin levels are also found when stage 4 sleep is depressed. Decreased secretion of growth hormone may result from slow wave sleep disruption and some patients with fibromyalgia have lower levels of growth hormone-related peptide, and in a few cases growth hormone has been used to treat these sleep disturbances.⁴⁵ A biopsychosocial unifying hypothesis has been described by Ang and Wilke⁴⁶ that has led not only to better understanding and legitimization of the illness but also to new therapeutic approaches. The alpha EEG anomaly described by Moldofsky and coworkers^{42,43} has been described by other researchers.⁴⁷⁻⁴⁹ It was also found in 9 patients with fibromyalgia and 9 patients with postfebrile fibrositis in one study,⁵⁰ as well as others, indicating that it is not an independent diagnostic marker for fibromyalgia. Alpha arousal reflects a state of vigilance during sleep and is associated with unrefreshing sleep and fatigue.⁵⁰⁻⁵²

Various other sleep disturbances during the night have been described in fibromyalgia but not consistently, and they may be coexisting coincidentally. These have included sleep-related periodic K-alpha (a periodic arousal disturbance in the EEG sleep),⁵³ periodic involuntary limb movements, and sleep apnea.^{48,54,55} When Hyypya and Kronholm examined sleep disturbances

in 24 patients with fibromyalgia, 60 patients with other musculoskeletal disorders, and 91 healthy controls, they found that the 2 patient groups reported insomnia and poor sleep that were not reported by the control group. However May and colleagues⁴⁵ screened patients with fibromyalgia for sleep apnea and concluded that fibromyalgia might be a marker for sleep apnea in men but in another study, Alvarez Lario and coworkers⁵⁷ and Donald and coworkers⁵⁸ did not find such an association. In a further study, Alvarez Lario and colleagues⁵⁹ studied 30 patients with sleep apnea, frequent arousals, and decreased stages 3 and 4 NREM sleep but found no musculoskeletal manifestations. Molony and coworkers⁶⁰ found comparable occurrences of sleep apnea in both patients with fibromyalgia as well as controls.

Older and colleagues⁵¹ replicated the prior study of Moldofsky and coworkers in 13 healthy volunteers but did not find reductions in pain thresholds or self-reported discomfort that were statistically significant nor did they report the alpha-delta pattern previously described. They also did not find alterations in insulin-like growth factor 1 and postulated that low levels seen in patients with fibromyalgia might result from chronic, not acute, delta wave sleep disturbances.⁶² Lentz and colleagues⁶² studied the effects of sleep deprivation in 12 healthy, sedentary middle-aged women. They used an automated slow wave sleep deprivation protocol of NREM sleep stages 3 and 4 for 3 nights. The tender point scores decreased (tolerated less pressure) across the deprivation nights in 6 of 7 subjects studied. Subjects also reported increased musculoskeletal discomfort, fatigue, tiredness, and reduced vitality but did not find changes in other indicators of altered mood state. They did not find the described alpha NREM sleep anomaly described in some other studies although the investigators did not have measures that would detect a low-frequency band of 7.5 Hz.⁶²

Jennum and colleagues⁶³ and Molony and colleagues⁶⁰ did not find a significantly reduced percentage of NREM stages 3 and 4 across the entire night of sleep. They did find more arousals but no significant sleep efficiency differences as compared to controls. Shaver and coworkers¹⁴ studied a subsample of 11 midlife women with fibromyalgia and healthy controls who completed the Specific Health Symptom Questionnaire and participated in polysomnography. Self-reported abnormal sleep was reported by 73% of the women with fibromyalgia and none of the control women. They also reported significantly more difficulty on the SCL-90 sleep quality subscale. On polysomnography, sleep was lighter in women with fibromyalgia but no excessive alpha wave intrusions in NREM sleep were found.¹⁴

Using the Pittsburgh Sleep Quality Index (PSQI), sleep in 16 Turkish outpatients with fibromyalgia was measured. When compared to mechanical pain threshold as measured with an algometer, pain threshold was negatively correlated with scores for subjective sleep quality, habitual sleep efficiency, and sleep disturbance as well as the PSQI global severity score. The researchers postulated that alterations in substances such as serotonin, endorphins, or substance P may play an important role in sleep disturbances in fibromyalgia.⁶⁴

Gamma-hydroxybutyrate (GHB) therapy in 11 patients with fibromyalgia resulted in increased slow wave sleep and decreases in alpha wave intrusion in non-REM sleep as measured by polysomnography with improvement in fatigue and pain.⁶⁵

Affleck and colleagues⁶⁶ used palm-top computers programmed as electronic interviewers to explore sleep, pain, and attention to pain in 50 women with fibromyalgia. Among the findings were that a poorer night's sleep followed a day with more attention to pain and likewise, a

disturbed night of sleep leads to a day with more attention paid to pain. They postulated that poor sleep may impair effective use of cognitive coping mechanisms.⁶⁶

Roizenblatt and colleagues⁴⁸ enrolled 40 women with fibromyalgia and 43 control women in Brazil and analyzed using polysomnography, self-rated sleep, self-rated pain, and tender point counts. Poor sleep was significantly more common in those with fibromyalgia, and these patients had significantly less total sleep time, lower sleep efficiency, a lower percentage of slow wave sleep, more alpha EEG activity in slow wave sleep (alpha/delta intrusion), more self-rated pain, and more tender points. Three patterns of alpha sleep activity were seen in those with fibromyalgia: phasic alpha, tonic alpha, and low alpha activity. Those patients with fibromyalgia who had phasic alpha sleep intrusion had significantly more pain after sleep and poorer sleep efficiency than was seen in the other 2 patterns. Pain was worse in those patients with fibromyalgia after a poor nights sleep and the phasic alpha sleep pattern was associated with both superficial sleep and longer pain duration.⁴⁸

In a study primarily aimed at studying prolactin and growth hormone levels during sleep in 25 women with fibromyalgia and 21 healthy controls, Landis and colleagues⁶⁷ used polysomnography. They found no significant differences in sleep efficiency or indicators of sleep quality between those with fibromyalgia and controls. They did find reduced levels of growth hormone and prolactin in women with fibromyalgia as compared to the control women, leading them to speculate that neuroendocrine dysfunction in sleep may play a pathophysiologic role in fibromyalgia.⁶⁷

Studying 8 persons with fibromyalgia and 8 healthy controls, Wikner and colleagues⁶⁸ found melatonin secretion during darkness was significantly less in those with fibromyalgia than in controls. Since melatonin has sleep promoting qualities, low secretion might contribute to impaired sleep. However, Press and coworkers⁶⁹ in their study of 39 persons with fibromyalgia and 39 controls did not find significant differences in melatonin secretion between the groups.

As part of the development of a rheumatic disease distress index, a relatively nonspecific visual analogue scale was used to determine if sleep was problematic for persons with rheumatoid arthritis, osteoarthritis, and fibromyalgia. All 3 groups reported problematic sleep but the most severe disturbances were reported for those with fibromyalgia.⁷⁰

By both objective and subjective reports, sleep in fibromyalgia has been found to be disrupted and is often described as unrefreshing and nonrestorative. Typical subjective sleep complaints in fibromyalgia are consistent in studies and show light, nonrefreshing sleep with fatigue in the morning and pain exacerbation associated with a poor night sleep. Sleep studies show increased NREM stage 1 sleep, decreased delta sleep, an increased number of arousals, an alpha delta sleep anomaly with an increased number of arousals or stage 3 sleep across most studies; they also show an association with deep pain.³⁶ The rather constant finding of alpha EEG intrusion is not specific for fibromyalgia but may be seen in other persons with nonrestorative sleep and daytime symptoms.

Chronic fatigue syndrome

Chronic fatigue syndrome is a disorder of unknown cause. It affects multiple body systems. The Centers for Disease Control and Prevention (CDC) developed criteria for diagnosis of chronic

fatigue syndrome.⁷¹ These are shown in Table 1. Among the proposed etiologies have been infectious agents, especially Epstein-Barr virus, cytomegalovirus, Coxsackie virus, human herpesvirus 6, parvovirus B-12, *B. burgdorferi* (the agent of Lyme disease), and human T-cell lymphotropic virus (HTLV-11); immune dysregulation; neurologic abnormalities; psychiatric illness such as depression; musculoskeletal disorders; and allergic disorders.³⁴ However, to date there have not been any definitive findings and so an infectious etiology remains unproven. Persons with chronic fatigue syndrome were often labelled as having symptoms that were "all in the mind." Several new reviews urging understanding, more consistent therapies, and action have recently been published.⁷²⁻⁷⁵

Table 1: CDC Definition of Chronic Fatigue Syndrome

- Clinically evaluated, unexplained persistent or relapsing chronic fatigue that is of new or definite onset (ie, not lifelong), is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities.
- The concurrent occurrence of 4 or more of the following symptoms: substantial impairment in short-term memory or concentration; sore throat; tender lymph nodes; muscle pain; multi-joint pain without swelling or redness; headaches of a new type, pattern, or severity; unrefreshing sleep; and postexertional malaise lasting more than 24 hours. These symptoms must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue.

Source: Reference 72.

Current theories favor a role for disturbances in the neuroendocrine-immunologic network in which an allergen might serve as a triggering event,³⁴ and genetic predisposition may also play a role in etiology and in manifestations as well as response to therapy as occurs in a number of other complex illnesses.²² Symptoms may result from disturbance of central neurotransmitters and low cortisol from disruption of the hypothalamic-pituitary-adrenal axis.⁷⁶ Immunological disturbances are noted.²⁰ While it may seem somewhat paradoxical, persons with chronic fatigue syndrome may suffer from disturbed sleep. In fact, while fatigue is listed as a symptom 100% of the time, difficulty in sleeping is estimated to occur in about 70% or even more.^{77,78} This has been variously described but includes sleep that is unrefreshing.

Krupp and coworkers⁷⁹ evaluated 72 outpatients with chronic fatigue syndrome using healthy controls and a control group with multiple sclerosis (MS). They completed a modified version of the St. Mary's Sleep Questionnaire and a self-report of fatigue severity. Sleep in a subsample of 16 (22%) with chronic fatigue syndrome was measured by polysomnography and the daytime Multiple Sleep Latency Test (MSLT).

Statistically significant differences were found between those with chronic fatigue syndrome and healthy controls in regard to self-report of the following parameters: "slept lightly," "slept badly," "bothered by early morning waking," and "felt drowsy on awakening." Sleep disturbances were significantly greater in those with elevated fatigue severity and in those with a high measure of depressive symptomatology using the Center for Epidemiologic Studies Depression (CES-D) Scale; however, the correlation was only 0.26, representing about 7% of the variance. Overall, sleep disturbance scores were significantly higher for those with chronic fatigue

syndrome in comparison to both control groups. In regard to polysomnography, some pathophysiological abnormality of sleep occurred in 16 (62.5%). However, there was not any common finding for those with chronic fatigue syndrome and polysomnography was not performed on the control group. The findings were periodic leg movement disorder (n = 4), alpha wave intrusion (n = 2), excessive daytime sleepiness (n = 2), obstructive sleep apnea (n = 2), and narcolepsy (n = 1). The authors concluded that, in some patients diagnosed with chronic fatigue syndrome, a treatable sleep disorder is present that may represent the true diagnosis such as the patient in their study who actually had narcolepsy.⁷⁹ In another study involving 38 persons with chronic fatigue syndrome and other chronic fatigue, a high frequency of sleep disturbance was found but there were no statistically significant differences. Sleep apnea was present in 41% of those with chronic fatigue syndrome but they did not find any NREM sleep disturbances.⁸⁰

Sharpe et al⁸¹ in studying the sleep of patients with chronic fatigue syndrome after excluding those with major depression found that patients with chronic fatigue syndrome felt less refreshed after sleep and slept less efficiently than healthy controls but a follow-up of this study found that major sleep abnormalities occurred in a minority of patients with chronic fatigue syndrome. Schaefer⁸² examined sleep in 13 women with chronic fatigue syndrome and 50 with fibromyalgia. She found that women with chronic fatigue syndrome by self-report had significantly more trouble staying asleep than women with fibromyalgia but both groups reported trouble staying asleep as the highest rated sleep disturbance. She also found a significant positive correlation of 0.63 between fatigue and sleepiness in the total population studied.⁸²

Fischler and coworkers⁸³ used polysomnography to compare sleep between new patients with chronic fatigue syndrome (n = 49) attending a fatigue clinic, and a matched healthy control group (n = 20). The former was measured on the third night of sleep and the latter on the second night. Their major findings were sleep initiation problems including a longer sleep onset latency (SOL), and sleep maintenance disturbances. They observed a significantly lower percentage of stage 4 sleep and a higher percentage of movement time, number of awakenings, and the number of stage shifts per hour. They also found a significantly higher percentage of stage 1 sleep and a lower percentage of stage 2 sleep with a "marginally lower percentage of REM sleep."^{83(p120)} A significantly lower sleep efficiency index was found. They did not find that anxiety or depression (as measured by the SCL-90-R anxiety subscale and the Hamilton Rating Scale for Depression) were associated with sleep abnormalities nor did they find an association between sleep disturbances and the degree of functional status impairment as measured by the Sickness Impact Profile.⁸³

Longer SOLs were also found by Whelton et al⁸⁴ who also found reduced sleep efficiency and reduction in REM sleep but not sleep fragmentation. Morriss et al,⁸⁵ however, found sleep fragmentation but not a significantly longer SOL in their sample of subjects with chronic fatigue syndrome. Morriss and coworkers examined sleep in 12 persons with chronic fatigue syndrome and 12 healthy controls by self-reports and polysomnography. Significant differences between controls and patients were found in that those with chronic fatigue syndrome spent more time in bed, had lower sleep efficiency, awakened more often during the night and had more periods of awakening, spent more time awake after the start of sleep, felt less refreshed on awakening, felt sleepier, and felt lower in mood and weaker. A sleep disorder was present in 7 of the patients and none of the controls--5 of the patients had an inability to maintain sleep, 2 had difficulty in getting to sleep, and 1 had difficulty in both. One patient had hypersomnia.⁸⁵

In what they called a pilot study, largely because of design issues discussed in the article, Buchwald and colleagues⁸⁶ also used polysomnography at a sleep disorders clinic to examine sleep disturbances in 59 patients with chronic fatigue. Of these, 38 (64%) met the CDC criteria for chronic fatigue syndrome. While 82% of the patients with chronic fatigue syndrome were found to have a sleep disorder, this was found in 81% of the other patients with chronic fatigue. In both groups, the type most frequently found was sleep apnea, and in those with chronic fatigue syndrome, 11% evidenced restless legs, excessive daytime/pathological sleepiness, or periodic limb movements/nocturnal myoclonus. On a 10-item questionnaire measuring the frequency of sleep symptoms, the mean number reported was 5.3 for those with chronic fatigue syndrome and 4.9 for those with chronic fatigue, and this was statistically significant at $P < .05$. For both groups, the most prevalent ones follow with the percentage for subjects with chronic fatigue syndrome given in parentheses: "almost daily daytime sleepiness" (92%) followed by "resistible persistent daily drowsiness that can be followed by napping" (87%), "daytime sleepiness at inappropriate times" (74%), and "consistently broken restless unrefreshing sleep" (71%). They did not find significant differences in individual sleep symptoms or sleep disorders between those with chronic fatigue syndrome and those chronic with fatigue. They concluded that potentially treatable comorbid sleep disorders were present in their sample.⁸⁶

In a study of teenagers with chronic fatigue syndrome who were studied by home polysomnography, 18 were compared with matched controls. The adolescents with chronic fatigue syndrome were significantly different than the controls in lower sleep efficiency, a greater number of awakenings, less time in stage 2 NREM sleep, and a smaller percentage of time spent in REM sleep. The latter difference was attributed to medication.⁸⁷

In summarizing the results of polysomnography in chronic fatigue syndrome, one summary concluded that chronic fatigue syndrome "does not at present seem to have an objective "sleep fingerprint".^{78(p1043)} However, sleep is disturbed, and unrefreshing sleep is part of the CDC criteria for the diagnosis of chronic fatigue syndrome. Whatever the disturbance experienced by the patient is, the result often is that they do not feel rested or alert in the morning.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) results from damage to tissues from autoantibodies and immune complexes that includes abnormal immune responses such as polyclonal and antigen-specific T and B lymphocyte hyperactivity and defects in regulation of the hyperactivity. The etiology is unknown but evidence exists for a genetic predisposition or susceptibility, and certain HLA haplotypes and defects in complement components have been implicated along with environmental factors that are still mostly unknown, except for ultraviolet light. Females are more frequently affected, especially in childbearing years. The prevalence in the United States varies from 15 to 50 per 100,000 population.⁸⁸ Exacerbations and remissions occur. One or more organ systems may be involved. Depending on the organs affected, signs and symptoms may include fatigue, arthralgias, polyarthritis, myopathy, photosensitivity, anemia, leukopenia, cognitive dysfunction, proteinuria, cardiopulmonary features, nephrotic syndrome, abnormal liver enzymes, and mood disorders.

Sleep disruption has been reported in SLE, and may be associated with fatigue and depression.^{89,90} Of women with SLE who were participating in an aerobic conditioning program, 61%, reported sleep disturbance.⁹¹ In another study, sleep was examined by the Sleep Symptom Questionnaire given to 48 women with SLE and 27 controls. The SLE group reported

significantly more sleep problems primarily due to longer sleep latency. Sleep disruption and depression had a reciprocal relationship in this study.⁸⁹

Valencia-Flores and colleagues⁹² used polysomnography, the MSLT, the Sleep Disorders Questionnaire, and the Beck Depression Inventory to study 14 women with SLE and 11 controls in a Mexican population. Patients with SLE reported significantly more complaints in relation to poor night's sleep, awakening often during the night, restless and disturbed night sleep, "restless legs" at night, "trouble doing their job because of sleepiness or fatigue, and in addition reported getting up to urinate at night more frequently than the control group. On polysomnography, the main sleep disturbances were more light sleep, a greater number of arousals, and more daytime sleepiness than for controls. Three of the SLE patients had sleep apnea syndrome and 28.6% of SLE patients had a slight abnormality in respiration during sleep. The authors concluded that abnormalities in respiration and movement during sleep are common in patients with SLE. The small sample size should be noted.⁹²

A sample of 120 women with SLE was assessed for sleep difficulties using the PSQI and for other parameters such as disease activity, depression, anxiety, and fatigue. About two thirds of the patients reported poor sleep quality, and found a moderate correlation between the PSQI and the SF-36 bodily pain score and a weak correlation with disease activity score, depression, and anxiety. The researchers suggest that joint and muscle pain as well as anxiety and depression may contribute to poor sleep. They did not show a significant difference in sleep quality' between those on no, low dose, and >7.5 mg of prednisolone per day.⁹³

In Sweden, the Uppsala Sleep Inventory was used to assess sleeping in 30 female outpatients with SLE and 30 age-matched controls. Statistically significant differences included a higher frequency of pain when trying to fall asleep and during the night, being awake more than 30 minutes during the night if awakened, waking up with a headache, fatigue during the day, and were more likely to nap during the day. While 34.5% of those with SLE stated they were not rested after sleep, 16.7% of controls also reported this and the difference was not statistically significant. The researchers concluded that the central nervous system might play a role in sleep disturbances reported in SLE.⁹⁴

Myasthenia gravis

Myasthenia gravis is an autoimmune disorder of the neuromuscular junction, resulting from binding of autoantibodies to muscle acetylcholine receptors resulting in disruption of neuromuscular transmission.⁹⁵⁻⁹⁷ This may result in muscle fatigue and weakness particularly involving the diaphragm and accessory respiratory muscles especially in untreated patients. Other signs and symptoms may include diplopia, ptosis, and a characteristic pattern of muscle weakness. Other symptoms such as difficulty in swallowing or speech effects occur secondary to affected muscles. Respiratory dysfunction may result in the need for ventilatory assistance. Polysomnography has shown decreased slow wave sleep (stages 3 and 4) and REM sleep with increased stage 1 sleep. Central apnea as well as some mixed and obstructive apneas may be seen.^{96,95} Myasthenia gravis may occur in about 1 in 7500 persons.⁹⁹

In a prospective study of 20 patients with myasthenia gravis, polysomnography, pulmonary function measurements, and self-evaluation of sleep complaints were done. Disrupted nocturnal sleep was reported by 12 patients, and 4 had daytime somnolence and morning headaches. Patients were most vulnerable for abnormal breathing during REM sleep and both mixed and obstructive apneas were described.⁹⁵ Manni and colleagues¹⁰⁰ assessed 14 patients with

myasthenia gravis by polysomnography. They found mild breathing irregularities during sleep without significant sleep complaints. These mainly consisted of central apneas with decreased hemoglobin oxygen saturation often occurring during REM sleep as also found by other researchers.^{95,100-102} Polysomnographic studies of 16 patients revealed that 12 had obstructive and/or central sleep apnea. In 9 of the 12, studies were repeated after thymectomy; 6 experienced resolution.¹⁰² Other findings include increased stage 1 sleep and decreased proportion of stages 3, 4, and REM sleep.⁹⁶

Patients with myasthenia gravis who exhibit daytime somnolence or nighttime awakenings or breathlessness should be evaluated for breathing abnormalities while sleeping, with appropriate therapeutic options being made available. Sleep apneas are relatively frequent in myasthenia gravis.¹⁰¹⁻¹⁰³

Multiple sclerosis

Multiple sclerosis (MS) is a relatively common inflammatory demyelinating disease of the central nervous system. It affects about 350,000 persons in the United States. While the etiology is still unknown, it is now believed that MS is an autoimmune disease in which injury occurs to the central nervous system and plaques usually are visible.¹⁰⁴ There is evidence that suggests that both susceptibility to MS and the course, severity, and pathology may be at least partly, genetically determined.^{105,106} In models of genetic contribution to common or complex diseases, an environmental trigger or contributing agent(s) also plays a role in disease development.²² In MS it seems likely that this environmental factor may be an infectious agent such as a virus.¹⁰⁷ Candidate infectious agents currently under investigation include human herpesvirus 6, Epstein-Barr virus, and *Chlamydia pneumoniae*. A number of candidate genes have also been identified including alleles of the HLA system, apolipoprotein E, tumor necrosis factor alpha, and interleukin.¹⁰⁶ Manifestations vary widely and illness may be benign or rapidly progressive or somewhere in between with exacerbations and relapses. Frequent symptoms include fatigue, weakness of the limbs, sensory impairment and paresthesias, ataxia, optic neuritis, bladder dysfunction, diplopia. (More details on diagnostic criteria may be found in Hauser and Goodkin.¹⁰⁴)

Significant investigations of sleep in MS have not been extensive in the past and have occurred mainly in the last 15 years. Fatigue is a common problem in MS, and disturbed sleep could reasonably contribute to the fatigue. In one study, when comparing self-reported fatigue in a sample of 65 patients with MS with 69 patients with chronic fatigue syndrome, no significant differences were found.¹⁰⁸ Sleep disturbance in MS has been described as daytime fatigue, hypersomnolence, insomnia, and as associated with depression.¹⁰⁹ In addition, sleep disturbance may result from immobility, spasticity, and sphincter disturbances.^{108,109} Bulbar or respiratory muscle weakness as a manifestation of disease may contribute to the development of central or obstructive sleep apnea.^{108,109} Tachibana and colleagues studied 28 patients with MS admitted to a hospital. Fifteen (54%) reported sleep-related problems. These were as follows: difficulty initiating sleep/and or frequent awakenings due to spasms or discomfort in the legs (n = 8); difficulty initiating/maintaining sleep with early morning waking (n = 3, of these 2 appeared medication related and 1 appeared related to nocturia); and snoring (n = 4 habitual, 1 occasional). In laboratory studies, 10.7% suffered from sleep-related oxygen desaturation, and 4 were habitual snorers of which 3 showed sleep disordered breathing, findings that were only slightly higher than would be expected in a comparable population without MS. The authors¹⁰⁹ concluded that sleep disturbances were common in MS usually because of leg spasms, pain, immobility, nocturia, or medication but that in their sample, nocturnal hypoventilation was

relatively infrequent. Sleep latency was altered in MS patients but no circadian rhythm disturbances were seen.¹¹⁰ Funakawa et al¹¹¹ reported sleep apnea syndrome in 2 patients with MS who had medullary plaques.

Clark and colleagues¹¹² recruited 143 patients with MS and 70 matched control subjects. Ten sleep-related items on the Minnesota Multiphasic Personality Inventory were compared. Those items that were significantly more problematic for MS patients were sleep initiation, sleep maintenance, and sleep outcome (how restful sleep was or not). A sleep score was created that could range from 0 (no sleep complaints) to 4; 25.2% of the MS patients scored 3 or 4 compared with 8.2% of the control subjects. Higher levels of depression as measured by the Beck Depression Inventory were noted for those with MS. A subsample of 117 patients with MS underwent magnetic resonance imaging scans and these results suggested that lesions in 3 specific regions were related to the presence of sleep complaints.¹¹² Sandyk described a case report of a woman with MS who experienced sleep paralysis and suggested that MS "may be associated with deficient rapid eye movement (REM) sleep inhibitory neural mechanisms leading to sleep paralysis secondary to the intrusion of REM sleep atonia and dream imagery into the waking state."^{113(p145)} He compared similar elements of narcolepsy and MS especially in regard to a common immunologic etiology.¹¹³ Similarly, others have reported an association of narcoleptic symptoms such as sleep attacks, cataplexy, and hypersomnia in MS.¹¹⁴⁻¹¹⁶

Other studies also report that sleep disturbances are more frequent in persons with MS than healthy controls. Self-reports of 47 persons with MS and 63 healthy controls revealed that both had about the same number of hours of nighttime sleep but that persons with MS were significantly more likely to nap during the day (53% vs 21%), had more frequent nocturnal awakenings, had poorer dream recall, and had longer SOLS. The nocturnal awakenings were often due to the need to urinate and spasticity. The nocturnal awakening was related to daytime fatigue.¹¹⁷ Similar conclusions were found in the Saunders et al¹¹⁸ study of 100 patients with MS and matched controls in which there were significant differences between the 2 groups in difficulty falling asleep, restless sleep, nonrestorative sleep, SOL, number of daytime naps, nocturnal awakening, and early morning awakenings. As in other studies, causes of awakening were bladder difficulties, muscle spasms or stiffness, and in this study, anxiety. Sleep difficulties were also associated with depression.¹¹⁸ In a study of 11 patients with MS, using polysomnography and sleep history questionnaires, Potolicchio and colleagues¹¹⁹ found that 64% had periodic limb movements of sleep. Using polysomnography in 25 patients with MS and 25 healthy controls, Ferini-Strombi and colleagues¹²⁰ found that those with MS had significantly decreased sleep efficiency, more awakenings during sleep, and more periodic leg movements. No differences were found in either sleep architecture or latency.¹²⁰ In a sample of 53 elderly patients with MS, they complained more frequently of not getting enough sleep (18.9%), poor nighttime sleep (34%), problems falling asleep (37.7%), waking up too early (35.8%), and awakening several times during the night (71.7%).¹²¹ In a study comparing patients with end-stage renal disease, MS, and RA and healthy controls, using a sleep-related item on the Center for Epidemiologic Studies Depression (CES-D) Scale, those with MS reported restless sleep approximating that of the control group while those with RA were most frequently affected and this correlated with a higher degree of physical disability due to RA.¹²²

Generally, it can be said that sleep disruption is underrecognized in MS. Physical manifestations such as spasticity, periodic limb movements, and the need to urinate at night and anxiety and depression contributed to this disruption. Addressing sleep problems is essential especially because nonrestorative sleep contributes to impaired daytime functioning and fatigue.

Human immunodeficiency virus infection

Human immunodeficiency virus (HIV) is known to be the cause of acquired immunodeficiency syndrome and a spectrum of conditions known collectively as *HIV disease*.¹²³ Because sleep in relation to HIV infection is covered in depth elsewhere in this issue, the topic is reviewed only briefly here. A number of studies have looked at sleep disruption in HIV. Norman and colleagues^{124,125} conducted an early study of HIV infection and sleep, finding that the amount of slow wave sleep in the 8 asymptomatic subjects with HIV infection was greater than that in the 4 control men, a finding that was reaffirmed in a subsequent study of 10 HIV-infected men and 10 controls. Using polysomnography. Wiegand and colleagues¹²⁶ studied 14 patients with HIV and found longer SOL, shorter total sleep time, reduced sleep efficiency, and more time spent awake and in stages 1 and 2 sleep in these patients than in healthy controls. On computed tomography scan, certain findings such as ventricular size were related to reduced sleep quality as were decreased tryptophan plasma levels.¹²⁶ Another early study was by Darko and colleagues¹²⁷ in which they looked at 62 HIV-positive subjects and 50 HIV-negative controls and found that those with HIV infection reported significantly greater fatigue, more sleep, and more naps, and felt more daytime fatigue and less alertness.¹²⁷ In a subsequent publication, they noted an increase in slow wave sleep early in HIV infection. They postulated a role for the immune peptides such as tumor necrosis factor alpha and interleukins in sleep changes.¹²⁸

Cohen and colleagues¹²⁹ studied sleep in 50 subjects by self-report. They found that 60% of HIV-infected subjects reported moderate or severe restlessness during sleep, 44% reported being moderately or very tired in the morning and 56% reported some degree of tiredness, 26% reported sleep quality was poor or very poor, and 70% of respondents reported awakening more than once per night. Many of the reasons for awakening were related to symptoms especially those related to using the bathroom.¹²⁹ Nokes and Kendrew¹³⁰ described impaired sleep quality in persons with HIV infection. In a later paper, the same researchers studied sleep quality using the PSQI in a convenience sample of 70 persons with HIV infection. They found that the health status variables with a significant positive correlation with impaired sleep quality were symptom severity, depressive symptomatology, daytime sleepiness, and state anxiety while functional status was negatively correlated. Illness variables such as CD4 cell counts and viral loads were not. However, use of antiretroviral drugs in treatment was significantly associated with impaired sleep quality.¹³¹

In a study examining fatigue in women with HIV, sleep was assessed by wrist actigraphy in 100 women. It was found that these women averaged 6.5 hours of sleep per night and 45% of the sample took daytime naps. Women with higher as opposed to lower fatigue had significantly more difficulty falling asleep, more awakenings at night, poorer daytime functioning, and more depressive symptoms.¹³² Rubinstein and Selwyn¹³³ studied sleep in 115 persons with HIV infection by means of the PSQI. They found that 73% had a sleep disturbance and this was higher in those with cognitive impairment.¹³³ Phillips and Skelton¹³⁴ explored sleep quality and the effects of acupuncture in a sample of persons with HIV diseases using the Current Sleep Quality Index and the PSQI. This identified the following percentage reporting frequent or very frequent problems getting to sleep (51.0%), staying asleep (71.4%), and getting enough sleep (71.4%).¹³⁴

Other findings in regard to sleep are that obstructive sleep apnea may occur secondary to enlarged tonsils, a finding that may occur early in HIV infection. Epstein and colleagues¹³⁵ found

that 12 patients out of 134 studied had both as well as daytime sleepiness as measured by the Epworth Sleepiness Scale.

Darko and colleagues examined the relationship between growth hormone secretion and sleep in 6 HIV-positive and 8 HIV-negative subjects. They believe that growth hormone may contribute to the deterioration of sleep early in HIV infection.¹³⁶ The use of HIV medications such as zidovudine was implicated earlier in the HIV epidemic as interfering with sleep. More recently it has been noted that higher efavirenz plasma levels are related to the development of insomnia.¹³⁷

Rheumatoid arthritis

The etiology of rheumatoid arthritis (RA) is also unknown. Genetic susceptibility involving the HLA system along with environmental factors play a role. It is possible that the environmental factors are infectious agents such as Epstein Barr virus, cytomegalovirus, mycoplasmas, and parvovirus, or a response to microbial products. RA is a chronic multisystem disease with inflammatory synovitis of the joints serving as a major feature. Besides the pain and swelling in joints, morning stiffness, fatigue, and generalized weakness may occur and the clinical course may be variable. Therapy may consist of nonsteroidal anti-inflammatory drugs, cox-2 specific inhibitors, glucocorticoids, disease-modifying antirheumatic agents, the TNF-neutralizing agents, and immunosuppressive and cytotoxic drugs.¹³⁸ In most studies of RA, sleep disturbances are often associated with pain. However, disease activity may lead to the release of cytokines affecting multiple neurobiological mechanisms.^{139,140} As discussed earlier in this article, a pain-poor sleep cycle may become established wherein medications may also add to the complexity. Some studies involving patients with RA have been discussed under the other disorders discussed above.

Drewes and colleagues studied 41 patients with RA and 19 age- and sex-matched controls using polysomnography, the Basic Nordic Sleep Questionnaire (BNSQ), and a visual analogue scale on sleep, as well as looking at other parameters. On the BNSQ, persons with RA had significantly more difficulty falling asleep, nonrestorative sleep, higher sleep latency, more daytime sleepiness, and poorer quality of sleep than the controls. Polysomnography revealed significantly more periodic leg movements, more time in stage NREM3, and a tendency toward more sleep shifts than in controls. When sleep microstructure was examined, patients with RA had more alpha-EEG sleep. These were the only major findings.¹³⁹ Drewes et al¹⁴⁰ conducted a longitudinal study of 35 outpatients with RA using polysomnography and the Spiegel Sleep Questionnaire. After baseline data were collected, a second period of collection was performed after a mean of 175.8 days. A deterioration in disease activity was followed by an increase in slow wave sleep, which the authors speculated might represent "a bodily counter-reaction to the joint inflammation that is reflected in pain and stiffness."^{140(p1288)} Increased pain and morning stiffness resulted in increased slow wave sleep and stage "wake" and decreased NREM2 sleep. There was a positive relationship between pain and time spent awake during the night. They concluded that improving sleep may be helpful in treating the disease.¹⁴⁰ Stone¹⁴¹ examined pain in relation to fatigue and sleep in 35 patients with RA and no control group. He found that poorer sleep was related to more pain and fatigue and vice versa. He concluded that probably this was reciprocal.¹⁴¹

Crosby¹⁴² measured sleep in a larger study that included a self-report of 100 people identifying factors related to fatigue in RA. Disturbed sleep was among the top 3. In a substudy of 15

patients with RA and 12 controls, the number of intermittent awakenings as measured by EEG was used to define sleep fragmentation. Subjects in RA flare had more fragmented sleep than did the nonflare RA patients and the control group and also more fatigue. Fatigue was correlated with fragmented sleep ($r = 0.42$).¹⁴² Using a visual analogue scale to measure sleep and pain, positive significant correlations were found in fibromyalgia, RA, and ankylosing spondylitis in regard to pain intensity and sleep problems. Fatigue intensity in this sample was significantly positively correlated with sleep problems in regard to RA and ankylosing spondylitis but not fibromyalgia.¹⁴³ Hirsch et al¹⁴⁴ studied 19 persons with RA and 19 controls, finding severe sleep fragmentation but no relationship between disease activity and sleep disorders.

Juvenile rheumatoid arthritis (JRA) is similar in many ways to RA.¹⁴⁴ Polysomnography and questionnaire data were collected from 16 patients with JRA and 9 controls in Israel. Significant differences were found in daytime naps, which were longer for those with JRA than for controls, but other parameters were not significantly different. On polysomnography, there were no significant differences in sleep latency, total sleep time, sleep efficiency, or time spent in any sleep stage. Significant differences were found in sleep fragmentation and the JRA group had more arousals and awakening per hour as well as frequent stage shifts than did the controls. In the JRA group, arousals were more likely to be associated with leg movements. In a smaller sample of patients with JRA and without a control group, the researchers found excessive daytime sleepiness and shortened sleep latency scores.¹⁴⁵ Bloom and colleagues¹⁴⁶ studied 25 children with JRA and their parents as well as 45 healthy age- and sex-matched controls using self-report and the Children's Sleep Habits Questionnaire (CSHQ). Children with JRA had significantly higher total scores on the CSHQ as well as on subscales examining nighttime awakenings, parasomnias, sleep anxiety, sleep-disordered breathing, and daytime sleepiness but there were no correlations between these scores and disease activity or pain variables. The total score on the sleep self-report did correlate positively with pain.¹⁴⁶

Other researchers report the occurrence of sleep apnea in patients with RA, in some instances secondary to rheumatoid cervical spine disease. The number of patients studied has been small but this is a serious complication that should be watched for.¹⁴⁷⁻¹⁵⁰ Obstructive sleep apnea in adults with RA has been reported¹⁵¹ Sugahara and colleagues¹⁵² described this in patients with temporomandibular joint destruction.

To date, however, while fragmented sleep and a high prevalence of periodic limb movement may be found, no definitive abnormality of sleep architecture has been reported in RA. Pain and fatigue are highly related to sleep disruption, often in a reciprocal way.

Other conditions

Sjögren's syndrome is an autoimmune exocrinopathy that may occur alone or in conjunction with fibromyalgia, SLE or RA. Severe fatigue is a component and sleep disturbance reports have been relatively recent.^{153,154} Tishler and colleagues¹⁵⁴ administered a Mini Sleep Questionnaire to 65 patients with Sjögren's syndrome and 3 control groups with RA, RA and sicca symptoms, and osteoarthritis. Sleep disturbances were identified by 75% of the group as compared to 33% in the group with RA only.¹⁵⁴ These findings were similar to those of Gudbjörnsson and colleagues¹⁵³ who found that 72% of the patients with Sjögren's syndrome complained of too little sleep as compared to 33% in their RA control group.

Various rheumatic manifestations may be related to infections. These include inflammatory arthritis, Lyme disease, ehrlichiosis, reactive arthritis, and inflammatory myositis.¹⁵⁵ Major complaints accompanying Lyme disease are chronic fatigue and sleep disturbance. If the disorder reaches a chronic form, among the manifestations are arthritis and chronic fatigue.¹⁵⁶ It has been suggested that Lyme disease may trigger fibromyalgia.¹⁵⁷ In a study of 11 patients with Lyme disease and 10 age-matched controls, all of the patients with Lyme disease had some sleep-related complaints. Most common were excessive daytime sleepiness (73%), difficulty in initiating sleep (27%), frequent nighttime awakenings (27%), and restless legs/nocturnal leg jerking (9%). They also had longer sleep latency, decreased sleep efficiency, and a greater arousal index while 3 patients had alpha wave intrusion into NREM sleep.¹⁵⁸ In another study, it was noted that patients with facial palsy not treated for that manifestation with antibiotics had significantly more joint pain and sleep difficulty than did the treated patients.¹⁵⁹ In a subset of cases of Lyme disease, there is overlap of features with chronic fatigue syndrome.¹⁶⁰

CONCLUSIONS

Evidence exists for complex interactions between the immune system and the sleep-wake cycle, which is involved in regulating normal immune functioning. Several medical disorders that involve immunity and/or autoimmunity are associated with sleep disruption either in regard to etiology or to exacerbation of symptoms. In fibromyalgia, research rather consistently demonstrates that sleep is nonrestorative and often restless. Many of the studies also show alpha wave intrusion during slow wave and specifically stage 4 NREM sleep that do not appear to be specific to fibromyalgia. Whether sleep disturbances have a causal relationship with symptoms of fibromyalgia or are secondary to pain and pain perception is not clear.

In the other disorders discussed in this review, findings are less specific. In chronic fatigue syndrome, the prevalence of sleep difficulty is high and a constant but nonspecific finding is that of nonrestful or restorative sleep with the consequent effects of not feeling rested or alert during the day. In SLE, no specific pattern of sleep disruption has emerged but the reported disturbances of sleep appear related to depression, fatigue, and joint and muscle pain. The sleep compromises in myasthenia gravis are primarily related to the effect of the disease on muscles especially respiratory muscles. Sleep apneas appear relatively frequently with the morning effect of daytime somnolence. In MS, restless sleep and insomnia may appear related to physical symptoms such as periodic limb movements, spasticity, and the need to urinate as well as depression. However, no clear pattern has emerged.

Persons with HIV disease also experience sleep disruption, Studies vary as to the nature of the disruption and some may be related to symptoms such as pain, fatigue, and the need to urinate at night as well as to the effects of medications used in treatment. Sleep disruption occurs in RA and related arthritic conditions. No definitive consistent sleep abnormalities can be established but pain and fatigue are related to disturbed sleep, often establishing a vicious cycle. Sleep apnea occurs in some cases and is a serious complication and so impending signs should be watched for. Increased disease activity may also increase sleep disruption through alteration of immune parameters as appears to occur in both RA and Lyme disease. In all of the diseases, medications used in treatment of the symptoms and of the disease may also affect sleep. In diseases with inflammatory aspects, the immune system disruption may have causal effects on sleep but firm data in this regard are lacking.

One is handicapped in drawing firm conclusions by methodological flaws and variation across many of the studies since they may or may not have used control groups, may have classified groups of patients with the given disease differently, may not have had "blinded" evaluation, had small sample sizes. used nonrandom samples, and may have used varying assessments of sleep and various parameters of measurement of the disease. Nonetheless, sleep and sleep loss play a role in immune and autoimmune disorders. Therefore, it is important that clinicians, including nurses, include sleep assessment as part of their appraisal of the patient, evaluating also for comorbid primary sleep disorders. If it is found that sleep disruptions are present, then the treatment plan should include appropriate measures to aid in attaining more restful sleep. These measures should be closely evaluated for efficacy, and adjustments made as needed. The exact nature of the sleep disruptions present in immune and autoimmune disorders, their relationship to causality and pathophysiology, and eventually their role in treatment remain to be elucidated.

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