

Assessment of sleep health in patients with rheumatic disease

Rheumatology clinic patients frequently experience sleep disturbances and poor sleep. Increased frequencies of primary sleep disorders, including obstructive sleep apnea and restless legs syndrome, have been reported in rheumatic disease patient populations. Disturbed sleep with fragmentation is commonly observed and has been associated with pain, depression and increased inflammatory disease activity. In recent years, there has been increased investigation into relationships between sleep regulation and inflammatory mediators. The role of TNF- α in sleep physiology and pathology has been intensively studied. The generally positive effect of biologic agents such as anti-TNF- α therapy on sleep in rheumatology patients has been observed in polysomnographic studies and in larger clinical trials. In this article we review the primary sleep disorders with reference to the rheumatology patient, provide an overview of sleep regulation with specific attention to inflammatory cytokine influences and discuss the approach to sleep problems for the rheumatology clinic patient.

KEYWORDS: ankylosing spondylitis ■ cytokines ■ obstructive sleep apnea ■ polysomnography ■ restless legs syndrome ■ rheumatic disease ■ rheumatoid arthritis ■ sleep disorders ■ systemic lupus erythematosus ■ tumor necrosis factor

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Poor sleep is a common complaint of patients attending rheumatology clinics and has been observed to frequently accompany symptoms of depression, fatigue, pain and increased rheumatic disease activity [1–3]. In the past, sleep difficulties had been understood and/or perhaps dismissed as expected sequelae of the articular pain and discomfort in this patient population. More recently, there has been recognition of a more complex and intertwined relationship between rheumatic diseases and sleep disorders.

Abnormal sleep has been reported in a number of rheumatologic disorders with the majority of observations based upon the rheumatoid arthritis (RA) patient and fibromyalgia populations [4,5]. However, sleep abnormalities or dysfunction have also been identified in juvenile rheumatoid arthritis [6], Sjögren's syndrome [7], systemic lupus erythematosus (SLE) [8], scleroderma [9], spondyloarthropathy [10,11], osteoarthritis [12], gout [13] and sarcoidosis patients [14].

The nature of sleep disturbances or abnormalities in rheumatic disease patients varies from clinically recognized distinct sleep disorders to a spectrum of difficulty with sleep initiation and fragmentation, or 'insomnia' symptomatology [4]. An increase in primary sleep disorders, specifically obstructive sleep apnea (OSA) and restless legs syndrome (RLS), has been reported in RA patients [15–18]. In addition, subjective symptoms of poor sleep quality,

self-reported sleep fragmentation and prolonged sleep initiation are common in patients with RA, SLE, spondyloarthropathies and fibromyalgia [2,4,11,19,20].

Distinguishing a primary sleep disorder from a more nonspecific poor sleep quality symptomatology is clinically important. An accurate understanding of the nature of the sleep disorders permits appropriate choice of a therapeutic program.

Sleep disorders & dysfunction

■ Obstructive sleep apnea

Obstructive sleep apnea is a well-recognized syndrome characterized by recurring apneas (cessation of airflow for 10 s or longer) or hypopneas during sleep, despite respiratory muscle effort. A hypopnea is defined as a 30% reduction in thoracoabdominal movement or airflow for at least 10 s and accompanied by a 4% oxygen desaturation. An alternative definition is a reduction in airflow of at least 50% for 10 s or longer and accompanied by a 3% oxygen desaturation or an arousal [21]. The American Academy of Sleep Medicine defines OSA as repetitive episodes of upper airway obstruction that occur during sleep, usually associated with a reduction in blood oxygen saturation [21]. OSA syndrome is OSA accompanied by excessive daytime somnolence or fatigue. In OSA, a history of frequent and loud snoring is a common and well-recognized feature.

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Often, accessory history from the patient's bed partner yields information on apneic pauses while sleeping. This syndrome has been associated with general obesity (BMI >30 kg/m²), as well as neck circumference of greater than 43 cm [22]. Overall, the underlying pathophysiology of OSA involves partial or complete collapse of the posterior oropharyngeal area. Due in part to loss of upper airway muscle tone during rapid eye movement (REM) sleep, patients at risk for OSA are particularly susceptible to apneas/hypopneas during REM stage sleep. A recent study by Oksenberg *et al.* suggests that body position during sleep has a contributing effect [23].

Substantial morbidity and mortality has been associated with OSA [24]. In part this increase in adverse outcomes relates to associated hypersomnolence and an increase in motor vehicle accidents, work-related accidents and other traumatic events [25,26]. In part these outcomes also relate to the pathophysiological changes induced by prolonged hypoxia, including development of pulmonary and systemic hypertension, myocardial infarction, cardiac arrhythmias and stroke [27,28]. Finally, an increase in vascular inflammatory markers has been observed in OSA patients independent of obesity and has been postulated to be associated with cardiovascular morbidity [29,30].

The diagnosis of OSA is ideally based primarily on polysomnographic findings. When scoring a polysomnography (PSG) sleep study, the total number of apneas and hypopneas are added and divided by the total sleep time, which is expressed as the apnea-hypopnea index (AHI). An AHI of more than five (events/hour of sleep) is considered abnormal and consistent with OSA. An AHI of more than 30 is considered consistent with severe OSA. It should be noted that there is some controversy about the exact definition of a hypopnea and alternative definitions may affect the overall AHI score [31].

Unfortunately, problems with cost and accessibility may limit utilization of overnight PSG, despite it being the diagnostic gold standard. Alternate diagnostic tools include type III portable monitoring, which is a less expensive and home-based monitoring method validated for use in diagnosis of OSA [32,33]. A screening questionnaire commonly used to assess risk for OSA is the Berlin Questionnaire [34]. The Berlin questionnaire is a three-part instrument that categorizes respondents into low or high risk for OSA based on their score. This instrument has been validated by comparison with PSG [35]. Interestingly, a recent study reported that the Berlin Questionnaire, when completed by sleeping partners, had better predictive value

for OSA than when self-completed [36]. Another commonly used tool is the Epworth Sleepiness Scale (ESS) for evaluation of hypersomnolence, which is often associated with OSA. The ESS is an eight-item instrument evaluating daytime somnolence; a value of more than 10 is considered abnormal [37]. In patients with excessive daytime sleepiness felt not related to OSA, it may also be useful to do a multiple sleep latency test following the overnight PSG. This may help to differentiate from other causes of daytime hypersomnia [38].

There have been several population-based OSA or OSA risk prevalence studies. The National Sleep Foundation Sleep in America 2005 Poll of 1506 adults utilized the Berlin questionnaire criteria and classified 31% of men and 21% of women as high risk for OSA [39]. Kapsimalis and Kryger reported in a 2007 Berlin questionnaire survey of 1254 women that 25% of participants were at high risk for OSA [40]. Baldwin *et al.* reported a prevalence of 17% in the 5237 participants from the Sleep Heart Health Study [41]. A Norwegian general population study with over 16,000 participants found 24.3% were at high risk for OSA according to the Berlin Questionnaire. A random sample of participants subsequently underwent PSG testing from which 16% met PSG criteria for OSA [42].

Recently, there has been increasing awareness of variation in symptomatology and even polysomnographic features in OSA between genders [43,44]. These differences may potentially result in underestimation of OSA in women. As a majority of patients with inflammatory rheumatological disease are women this may be cause for concern in clinical rheumatology practice.

In the rheumatic disease population OSA has also been observed. Several investigators have reported the detection of OSA by PSG criteria in RA patient groups [15,16,45]. In a larger RA population, Reading *et al.* utilized the Berlin questionnaire to screen for risk of OSA in 164 RA patients and 328 non-RA controls. They observed that 50% of RA patients compared with 31% of controls were at high risk of OSA by the Berlin classification [46]. In other rheumatic disease groups, Solak *et al.* reported a prevalence of 22.6% for OSA in 31 ankylosing spondylitis patients based on PSG results [47]. In a sample of 35 SLE patients complaining of excessive fatigue, Iaboni *et al.* determined that 26% had OSA by PSG findings [48]. In a mixed general rheumatology clinic population screened by the Berlin Questionnaire, 35.2% were classified as being high risk for OSA [3]. May *et al.* found 44% of male fibromyalgia patients had OSA by PSG [49].

Rheumatology patient subsets identified to be at increased risk of OSA include those with increased BMI as well as those with characteristics specifically related to rheumatologic disease sequelae. This would include those patients with micrognathia, retrognathia or temporomandibular joint pathology [50–52]. Crico-arytenoid joint involvement has also been suggested to increase susceptibility [4]. In these cases the OSA is probably directly attributable to airway closure mechanisms. In children with juvenile idiopathic arthritis, increased sleep-disordered breathing has been observed [53,54]. There are distinct pediatric and adult PSG criteria for OSA; these have both been recently applied to an adolescent population with comparable results [55]. Cases of sleep apnea have also been reported in patients with cervical spine instability related to RA [56]. Shoda *et al.* recently observed an OSA prevalence of 79% in 29 RA patients with progressive myelopathy due to occipitocervical pathology [57]. Ataka, in a recent case series, has suggested that occipitocervical fusion has the potential to improve sleep apnea in RA patients with upper cervical lesions [58]. Cases of sleep apnea have also been reported to be associated with neuro-Behçet's disease or neurologic involvement from sarcoidosis [59,60].

The main therapy for OSA at present is the use of continuous positive airway pressure (CPAP) during sleep. There is good evidence that CPAP therapy improves the AHI, decreases daytime sleepiness and may improve cardiovascular complications of OSA [61]. However, it should be noted that some individuals find it difficult to tolerate CPAP therapy and long-term compliance may be suboptimal [62].

Other OSA therapies include addressing patient-related issues that increase susceptibility to sleep apnea, such as obesity, positional therapy (sleeping in a nonsupine body position) and mandibular advancement devices or similar oral appliances that help to thrust the lower jaw or tongue forward [63]. Surgical approaches to OSA are less commonly used. The uvulopalatopharyngealplasty (UPPP) surgical approach is the most frequent approach but has suboptimal OSA control [64]. Indeed, using stringent criteria for OSA control, Olson and colleagues at the Mayo Clinic found that only 24% of OSA patients at 6 months post-UPPP had an AHI of less than 5 [65]. More aggressive surgical procedures may provide improved OSA control; however, there are limited published, peer-reviewed efficacy data and long-term follow-up studies.

■ Restless legs syndrome

Restless legs syndrome is a common yet frequently underdiagnosed sensorimotor disorder. It is characterized by an urge to move the legs generally during the evening while at rest and accompanied by unpleasant sensations in the legs. Movement may partially or totally relieve these symptoms at least as long as the movement continues. As the term sensorimotor describes, there are two components experienced by patients, the abnormal and generally unpleasant sensations in the legs, often described as crawling or painful, although a wide spectrum of descriptive terms have been applied, and second the increased movements of the legs while awake or asleep. Both components must be present to confidently diagnose RLS [66].

The etiology of RLS is still ill defined. Associations with various comorbidities/conditions including peripheral neuropathy, cryoglobulinemia-associated neuropathy, spinal disease, multiple sclerosis, pregnancy and end-stage renal disease have been made [67–72]. Recently, an association with obesity has been reported [73]. There is evidence of a strong linkage with iron deficiency, with abnormalities reported in studies of CNS and peripheral iron stores and a relationship noted between severity of RLS and serum ferritin levels [74–76]. A recent case–control study observed a significant association between blood donation and occurrence of RLS in men [77]. Iron supplementation has been associated with improvement in RLS symptoms in iron-deficient patients [78]. A central dopaminergic abnormality has also been postulated and supported by clinical response to therapy with dopamine agonists [79,80]. A heritable form of RLS has been described with an autosomal mode of transmission [81]. There have been major genetic susceptibility loci for RLS identified on chromosomes 12q22–23, 14q13–21 and 9p24–22 [82]. It is likely that the etiology of RLS is multifactorial.

The prevalence of RLS in the general population has been said to be between 3 and 10%. The prevalence has been reported to increase with age [83]. It has also been remarked that RLS patients may be divided by age of onset, into those with early onset, which may be gradual, and those with onset later in life, in which the onset may be abrupt [84]. There is variation by gender with a higher prevalence of RLS in women. It was observed in both the INSTANT study [83] and the REST General Population Study that women are twice as likely to meet RLS criteria than men [85]. The impact or burden of RLS is not inconsequential. This disorder

may contribute to poor sleep quality with sleep fragmentation. Furthermore, a decrease in quality-of-life measures has been reported in RLS patients [86].

Diagnostic criteria for RLS were revised in 2003 by the International Restless Legs Syndrome Study Group (IRLSSG) [87]. The essential criteria consist of four questions, all of which must be answered positively to support a diagnosis of RLS. These four questions are [87]:

- Do you have an urge to move the legs, usually accompanied by or caused by uncomfortable and unpleasant sensations in the legs?
- Does the urge to move or the unpleasant sensation begin or worsen during periods of rest or inactivity such as lying or sitting?
- Is the urge to move or the unpleasant sensation partially or totally relieved by movements, such as walking or stretching, at least as long as the activity continues?
- Is the urge to move or the unpleasant sensation worse in the evening or night than during the day or does it only occur in the evening or night?

Polysomnographic or actigraphic evaluation reveals an increase in periodic limb movements (PLMs) in 80% of RLS patients [88]. PLMs are commonly seen on polysomnographic records. Actigraphy is another monitoring tool for PLMs, which has the advantage of greater accessibility and lower cost than PSG as it can be performed in the patient's home [89]. In the majority of RLS patients, the frequency of the PLMs increases substantially over what is generally considered to be within the normal or acceptable range. However, an increase in PLMs is not specific to RLS and may be observed in a number of medical disorders, including the primary sleep disorder PLM disorder (PLMD), which is viewed as distinct from RLS [90].

In the rheumatic disease population, increased frequency of RLS has been reported in RA (27.7–31%) [18,70], osteoarthritis (24.4%) [18], Sjögren's syndrome (24%) patients [91] and scleroderma [9]. Increased frequency has also been reported in the fibromyalgia population [92]. It has been observed that patients who meet diagnostic criteria for RLS infrequently have any awareness of ever having been given such a diagnosis, despite having sought medical attention for their symptoms [18]. There is a strong sense that RLS is underdiagnosed and therefore undertreated [80]. In the rheumatic disease patient population, it is possible extremity symptoms are attributed to the

rheumatologic diagnosis. This is unfortunate as specific therapeutic interventions are possible for a diagnosis of RLS.

In the treatment of RLS, the primary goal should be to identify and, if feasible, treat any underlying disorder, such as iron deficiency, that may be associated with RLS [93]. Evaluating the current medications is also important as there are a number of agents that have been found to aggravate RLS, including antidepressants [94]. Nonpharmacologic therapies for RLS include improving sleep hygiene, moderate exercise and good nutrition. In terms of pharmacotherapy, the intensity of the symptomatology and the frequency with which it occurs must be considered. For those with daily and troublesome symptoms the dopamine agonists are one of the major classes of therapeutic agents available. A recent study of ropinirole in RLS patients has demonstrated improvement in both depressive symptoms and RLS symptom severity [95]. Other classes of drugs used in the treatment of RLS include anticonvulsants, opioids and benzodiazepines [93,96].

■ Other primary sleep disorders

Primary sleep disorders aside from the above-mentioned OSA and RLS include the parasomnias (sleepwalking, sleep terrors and nightmare disorder) and dyssomnias (primary insomnia, narcolepsy and circadian rhythm disorders) [97]. Narcolepsy is a relatively rare sleep disorder characterized by a classic symptom tetrad of excessive daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations [97]. Apart from insomnia, which may be seen in patients with rheumatic diseases [4], there is limited evidence of clinical associations with these sleep disorders. There is one reported case of a patient with SLE diagnosed with narcolepsy [48]. Iaboni *et al.* have also reported a possible increase in PLMD in SLE patients [48].

■ Nonspecific sleep dysfunction

The relationship between fatigue, pain and sleep has been evaluated by many investigators. Positive correlations between sleep complaints and rheumatic disease activity have been reported [1–3]. The contribution of depression and increased psychosocial stress towards sleep dysfunction has been recognized [1,98]. The coexistence of depression for many rheumatic disease patients adds greater difficulty in isolating and delineating other sleep problems. It is apparent that daytime somnolence is a frequent problem in patients with rheumatic

diseases [3]. This may be attributed in part to poor quality sleep and impaired sleep efficiency. Difficulties in initiating or maintaining sleep, as well as fragmentation of sleep with increased arousals, are commonly observed features of sleep quality assessments in rheumatic disease patient groups [44]. Strategies for assessment and management of comorbid insomnia have been described by several investigators [99,100].

Physiology & pathophysiology of sleep

Humans spend approximately a third of their lives asleep. Sleep is a nonuniform activity and may be broadly divided into REM sleep and non-REM (NREM) sleep. Approximately 80% of adult sleeping time is spent in NREM. NREM may itself be understood to consist of three additional stages of sleep known as NREM stages 1, 2 and 3 (also known as delta or slow wave sleep). Sleep typically cycles through the night, alternating between various stages of NREM and REM sleep. This cycle repeats overnight with generally more REM sleep in the later part of the night [101].

There are multiple endogenous and exogenous influences on sleep. It is well recognized that mood disorders, some medication effects and pain may all have an adverse effect on sleep health [1,100,102,103]. Evidence of a relationship between sleep restriction and pain sensitivity has been reported [104]. Moldofsky has recently described how disturbances of sleep and sleep restriction may result in increased sensitivity and musculoskeletal pain [105].

The sleep phase comprises part of the physiologic diurnal cycle, which has been linked to predictable fluctuations in hormone and cytokine levels. The hypothalamic–pituitary axis has been especially recognized as contributing to sleep regulation. In general terms, it has been observed in experimental studies that pituitary peptides such as adrenocorticotrophic hormone and melanocyte-stimulating hormone increase wakefulness, whereas the somatotrophic system hypothalamic growth hormone-releasing hormone enhances sleep [106,107]. There have been numerous peptides and hormones that have been observed to have some effect either directly or indirectly on sleep physiology [108]. An increasing awareness of an interactive relationship between neural regulatory mechanisms and immune function is developing [109].

The importance of cytokines in mediating sleep regulation is increasingly recognized. As cytokines are intercellular signaling proteins,

it is not surprising that different effects are achieved through different signals. In a partial listing, it has been observed that IL-1, IL-2, IL-6, IL-8, IL-18 and TNF- α all promote NREM sleep. Conversely, IL-4, IL-10, IL-13 and TGF- β have all been reported to inhibit NREM sleep [110]. Of particular interest has been the observation that IL-1 β and TNF- α exhibit diurnal rhythm with peaks during sleep periods and lower levels during usual wake times [111–114].

TNF- α has been closely studied in sleep disorders. In those with insomnia who have difficulty sleeping at night despite increasing daytime fatigue, a shift to higher daytime levels of TNF- α has been observed [115]. Evidence of a functional alteration in the TNF- α system has been reported in patients with the primary sleep disorder narcolepsy [116]. An increase in TNF- α levels has also been observed by multiple investigators in patients with OSA, prompting extensive investigation in this population. Riha *et al.* reported TNF- α (-308A) gene polymorphism in OSA patients in a UK study employing population controls [117]. Ryan *et al.* assessed TNF- α levels in 30 patients with OSA and found intermittent hypoxia to be the strongest predictor of elevated TNF- α levels [118]. Treatment of OSA with CPAP therapy was observed to be associated with a decrease in TNF- α levels [118]. Less is understood about the role of TNF receptors in sleep regulation, although Yue *et al.* observed an association between higher levels of soluble TNF-receptor 1 and increased arousals on PSG [119]. Taking an interventional approach with biological therapy, Vgontzas tested eight OSA patients with the anti-TNF agent etanercept and found a marked decrease in sleepiness and a reduction in AHI [120]. As RA is also a disease state associated with an elevation in TNF- α [121] and also frequently with sleep disturbances, it is natural to question the effect of biologic therapy on sleep parameters in this patient population. In a group of six RA patients, Zamarrón reported the effect of the first infliximab infusion on sleep and alertness. He found improvement in multiple parameters, including sleep latency and sleep efficiency [122]. Conversely, Zamarrón has also reported a case of worsening OSA in a RA patient treated with infliximab [123]. Wolfe *et al.*, in a large rheumatic disease population study, did not observe any significant difference in subjective sleep scores in RA patients treated with anti-TNF therapy [124]. There has been more recent evidence of benefit in subjective sleep assessment outcomes

from clinical trials using methotrexate, adalimumab and the T-cell costimulation modulating biologic agent abatacept in RA patients [125–127].

IL-6 has also been reported to vary over 24 h in accordance with sleep, exhibiting elevation at night and lower levels by day. Elevation in IL-6 levels has been reported in volunteers undergoing prolonged sleep restriction. Interestingly, increased pain levels have been associated with increased IL-6 levels in this population [128]. Elevated IL-6 levels have also been observed in children with sleep-disordered breathing, adults with OSA syndrome and in sleep-deprived adults [115,129–132].

Additionally, altered acute immune responsiveness in people who are chronically sleep deprived has been noted. Diminished immune function both in antibody response to influenza vaccination and for magnitude of febrile response to endotoxin challenge has been observed [133,134]. Interestingly, Bollinger *et al.* recently reported evidence for a diurnal rhythm of T-helper cell activity influenced in part by humoral factors [135]. Advances in understanding of the interface between the immune system and neurobiology continue to reveal the complexity and dynamic nature of the relationship.

Sleep assessment tools

■ Questionnaire instruments

Tools employed to evaluate sleep pathology include questionnaire instruments to gather information on subjective sleep symptomatology and self-assessments of sleep measures. There are many different validated questionnaire instruments that have been employed in various clinical settings to evaluate sleep health. Among these are the ESS [37], the Berlin Instrument for Risk of OSA [34], the Pittsburgh Sleep Quality Index score [136], the Medical Outcomes Study Sleep score [137] and the Child Sleep Habits Questionnaire score [138], which is a partial list of questionnaires that have been previously employed in rheumatology patient populations. Each of these instruments has particular advantages. In choosing questionnaire instruments for use in a rheumatology clinic, consideration must be given to ease of application and scoring. Including the RLS essential diagnostic criteria [87] and a measure to screen for potential OSA [34,37] would be valuable in terms of identifying primary sleep disorders in the rheumatology clinic patient population. In terms of monitoring subjective sleep health or sleep quality as an outcome measure for therapeutic interventions or clinical trials,

Wells *et al.* recently suggested the Athen's Insomnia Scale, the Medical Outcomes Study Sleep instrument, the Insomnia Severity Index and the Women's Health Insomnia Rating Scale had the greatest degree of feasibility for use [139].

■ Diagnostic sleep tests

Diagnostic sleep testing provides objective evidence of sleep, including both normal sleep architecture and abnormal findings, such as apneas or hypopneas, leg movements, arousals and other events. Diagnostic sleep studies are generally divided into four categories [140]:

- Type I: full attended PSG ($\geq$ seven channels) in a laboratory setting
- Type II: full unattended PSG ($\geq$ seven channels)
- Type III: limited channel devices (usually using four to seven channels)
- Type IV: one or two channels usually using oximetry as one of the parameters

The most common sleep testing includes either type I full PSG or type III home-based portable monitoring.

A typical overnight PSG study includes channels measuring the electroencephalogram, electrooculogram, electromyogram, electrocardiogram, pulse oximetry with heart rate and oxygen saturation, body position, nasal airflow (thermal or pressure flow), respiratory muscle effort, snoring, chest wall motion and abdominal wall motion. Aspects of sleep health or architecture that are commonly measured by the polysomnogram include: total sleep time, sleep latency (a measure of sleep initiation or 'how long it takes to get to sleep'), sleep efficiency (a ratio of actual time asleep/time spent in bed), arousals, sleep fragmentation (wake after sleep onset time), PLM frequency, sleep stage transitions, percentage of NREM and REM sleep, AHI, oxygen desaturations and respiratory disturbance index (RDI). The RDI consists of apneas plus hypopneas plus respiratory effort-related arousals per hour of sleep.

In general, a type III portable monitor is much more limited and usually tests oximetry, nasal airflow, chest wall effort and body position. However, type III portable monitoring is known to underestimate the severity of apnea/hypopnea events in OSA [141]. The RDI in type III sleep testing is the apneas plus hypopneas divided by total recording time instead of the total sleep time used for PSG. This explains why the

type III tests may underestimate OSA severity and for indeterminate tests in a high-risk patient a formal PSG is recommended [142].

Another diagnostic sleep test is actigraphy. Actigraphs are devices usually placed on the wrist to detect movement. The resulting data are analyzed and used to estimate sleep/wake parameters. Actigraphy is useful in the assessment of PLMs, circadian rhythm disorders, excessive sleepiness and insomnia [143]. Finally, an additional sleep test useful in assessment of excessive daytime sleepiness is the multiple sleep latency test. This test consists of a series of four or five daytime 20-min naps following an overnight diagnostic PSG and helps to assess for narcolepsy as well as other causes of excessive daytime fatigue [38].

Conclusion & approach to evaluation

It is increasingly clear that sleep health contributes to a patient's overall wellbeing. Poor sleep has been recognized as being associated with and contributing to a poorer quality of life, an increase in morbidity and also mortality [144]. A variety of both personal and environmental factors influence the quality and quantity of sleep for any given individual, some of which are more amenable to modification than others. As the primary sleep disorders mandate specific therapeutic interventions, the necessity for identifying the presence of such a disorder is clear. Application in the clinic setting of appropriate screening tools for identification of primary sleep disorders will facilitate diagnosis. At present the IRLSSG essential diagnostic criteria for RLS and the Berlin questionnaire for OSA risk are both validated for specific primary sleep disorders and would be suitable for such a purpose [34,87]. Application of the ESS would aid in identification of hypersomnolence, which may be associated with sleep disorders, daytime dysfunction and increased risk of accidents [37].

Many rheumatic disease patients will have sleep abnormalities without clear evidence of a primary sleep disorder. In these patients other measures may be considered, such as a review of medications for sleep side effects, including use of herbal or over the counter preparations, caffeine ingestion and alcohol use. Frequently, patients report sleep disturbances related to needing to void multiple times at night. Consideration of modification of medication scheduling for those on diuretics, or urologic/urodynamic assessment may assist in identifying reversible causes for this issue. In women menopausal status may influence sleep health [145]. Treatment of such associated symptoms may be appropriate. The presence of an underlying or associated depression

or anxiety state would also contribute to poor sleep health and it would be important to identify and facilitate treatment of this. An overall review of sleep hygiene may prove helpful for many patients. It is recommended to establish a set bedtime and awakening time, avoid alcohol and caffeine 4–6 h before sleep, avoid napping during the day and similar sleep hygiene/habit issues [4]. Treatment of pain related to the rheumatic disease and/or optimization of therapy to reduce active inflammatory disease would likely prove beneficial to quality of sleep [125–127,146].

Although some rheumatologists may feel comfortable screening patients for sleep disorders, many would choose to refer their patients to a sleep physician for further diagnostic testing or treatment. When should one refer to the sleep medicine clinic? It would be appropriate to consider referral to a sleep medicine clinic when a primary sleep disorder is suspected, if general measures do not lead to improvement in a patient's sleep health, or if there is persistent hypersomnolence resulting in daytime dysfunction. A collaborative multidisciplinary approach to treatment of abnormal sleep in rheumatic disease patients should optimize patient care.

Future perspective

With the rapid advances being made in understanding the interplay between genetics, immunology and the neural regulatory sleep mechanisms, we anticipate an increased understanding of the pathophysiology underlying many of the sleep abnormalities and primary sleep disorders in the next decade. With this projected improved knowledge, more specific targeting of therapy for sleep outcomes would have greater feasibility. With increasing recognition of the pathophysiology underlying sleep symptoms and of the role of sleep health in overall medical care and wellness, we anticipate a more widespread inclusion of sleep parameters in general medical assessments and outcomes. This would be especially valuable in the chronic disease patient populations, including those suffering from rheumatic diseases.

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Executive summary

- Many patients with rheumatic diseases report sleep disturbance/dysfunction, which have been associated with pain, depression and inflammatory disease activity.
- An increased prevalence of primary sleep disorder, obstructive sleep apnea and restless legs syndrome have been observed in rheumatic disease patient populations.
- Screening rheumatology clinic patients for sleep pathology may benefit overall patient care as specific therapeutic interventions are available for the primary sleep disorders.
- There is increased understanding of the role of proinflammatory cytokines, particularly TNF- α , in the regulation of sleep.
- Sleep health is recognized to be an important outcome measure in clinical therapeutic trials in rheumatic disease populations.

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▪ of interest

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