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Review

Nighttime sleep and daytime functioning (sleepiness and fatigue) in well-defined chronic rheumatic diseases

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Abstract

Wake/sleep complaints are very common in the rheumatic diseases, and include: insomnia, non-restorative sleep, frequent awakenings, daytime fatigue and excessive daytime sleepiness. Imprecise use of terminology has confused 'sleep dissatisfaction' (i.e. 'non-restorative sleep') with specific sleep disorders (i.e. 'insomnia' or 'sleep fragmentation') and 'fatigue' with 'daytime sleepiness'. This review examines current concepts from the literature of disparate disciplines pertaining to the complaint of poor sleep and daytime fatigue in patients with rheumatic disorders. The ability to monitor multiple physiologic parameters during sleep (polysomnography) has led to a greater understanding of normal and abnormal phenomena which occur during sleep, and has resulted in the identification of a variety of sleep disorders which have specific therapeutic implications. Actigraphy allows the prolonged monitoring of wake/sleep patterns, and the multiple sleep latency test permits the determination of physiologic sleepiness during the daytime. These techniques enable identification of objective sleep disorders in those whose complaint is subjective sleep dissatisfaction, and permit differentiation between the easily confused complaints of excessive daytime sleepiness and fatigue. The abnormal sleep/wake symptoms in patients with rheumatic diseases may not simply be a 'non-specific' or systemic effect of the disease. Some patients may have a specific sleep disorder (either independent from, or due to, the underlying rheumatic condition) which should be diagnosed and treated specifically. Conversely, subjective 'sleep dissatisfaction' does not necessarily imply an underlying sleep disorder. The primary intent of this review is to encourage systematic, objective study of sleep and daytime function in these common, often disabling conditions.

1. Introduction: sleep and daytime alertness

Sleep is an active physiologic process, not the passive absence of wakefulness. Sleep consists of two completely different physiologic states: non-rapid eye movements (NREM) and rapid eye movement (REM) sleep. REM and NREM sleep oscillate throughout the night's 'sleep' with periods of wakefulness. NREM sleep is divided into four numbered stages. Stages 3 and 4 are commonly combined and termed 'delta' or 'slow-wave' sleep [1]. The daily (circadian) cycling of nocturnal sleep and daytime wakefulness is controlled by a pacemaker (the suprachiasmatic nucleus) in the hypothalamus [2]. The ultradian (<24 h) cycling of the wake/REM/NREM periods appears to be generated by the brainstem [2].

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Theories for the function of sleep include: restorative, protective, energy conservation, ethological, instinctive, and maintenance of neuronal integrity [3–5]. Although the true physiologic function of sleep is unknown, satisfactory daytime functioning depends upon adequate quality and quantity of sleep.

The 'restorative' nature of sleep depends primarily on the variables of the timing, duration, and continuity of sleep, but is influenced by aging and medication effects. The only organ of the body known to need and benefit from sleep is the brain, which raises interesting questions regarding the relationship between sleep and musculoskeletal symptoms [6].

2. Assessment of sleepiness vs. fatigue

The symptom of the complaint of 'fatigue' is difficult to study, because it has many definitions. The observation that 'fatigue' is the seventh most frequent initial complaint in U.S. medical offices and has a prevalence of 24% in primary care clinics should be incentive enough to address this problem [7]. Systemic fatigue occurs as a constitutional symptom in a variety of organic diseases including rheumatoid arthritis, systemic lupus erythematosus, infections, malignancies, asthma, emphysema, anemia, post-polio syndrome, multiple sclerosis, Parkinson's disease, polyneuropathies, biliary cirrhosis, and in post-viral syndromes [8–16]. Fatigue is also a symptom of psychological conditions such as depression, anxiety, and emotional stress [17]. The pathophysiologic mechanisms causing fatigue in these disorders remain unknown.

The clinical differentiation between 'fatigue' or 'lack of energy' on one hand, and 'sleepiness' or 'tiredness' on the other, is very important but may be difficult. The adage that the subjective and vague nature of the complaint of fatigue renders quantification 'an impossibility' is unnecessarily nihilistic [18,19]. Accurate clinical interpretation of fatigue as muscular tiredness or exhaustion, breathlessness with exertion, insufficient motivation, or true daytime sleepiness requires that these conceptual differences be thoroughly explained to the patient by the interviewer. As a first step, three distinct forms of fatigue should be defined.

True muscular (acute, peripheral, physiologic) fatigue is reduced physical performance induced by muscle activity that is relieved by resting the affected muscle(s): sleep is not necessary. The metabolic and physiological factors in muscle fatigue have been reviewed [20]. This form of fatigue usually poses no clinical diagnostic difficulty if the features are thoroughly defined to the patient during the interview.

'Central' fatigue has eluded definition and measurement [21]. It encompasses different phenomena including: boredom, impaired motivation, vigilance, attention, enthusiasm or energy, and depression. Regrettably, the terms 'fatigue' and 'sleepiness' are frequently confused on subjective fatigue ratings scales [22–25].

Excessive daytime sleepiness is the overwhelming urge to sleep during the day when one would rather be active. The identification of true daytime sleepiness (EDS), which can be measured by the multiple sleep latency test, is very important, because there are clear-cut management implications. Patients with daytime sleepiness in the absence of sleep-deprivation usually have a primary sleep disorder such as a obstructive sleep apnea, narcolepsy, idiopathic hypersomnia, or nocturnal sleep deprivation and/or severe sleep fragmentation caused by pain. True hypersomnolence is relieved only by sleep, and not by rest.

3. Measurements of daytime sleepiness

3.1. Subjective sleepiness scales

Because formal, all-night sleep studies and the multiple sleep latency tests are expensive, attempts have been made to use self-reports of subjective sleep quality/quantity. Subjects recall the time required to fall asleep and after 'lights out' (sleep latency); number of hours slept and; number of arousals or awakenings, and sleep 'quality'. A person's perception of 'having slept' is imprecise and is highly dependent upon sleep continuity such that time spent asleep between frequent arousals may not be perceived as having been a 'sleep period' [26–29]. Subjective introspective alertness/sleepiness scales such as the Stanford Sleepiness Scale and the Epworth Sleepiness Scale (ESS) have been developed [1,30]. The ESS is frequently used as a screening tool for identifying excessive daytime sleepiness, and gener-

ally correlates with other measures of sleep propensity [31,32] Such instruments are limited by their lack of sensitivity: there may be a striking discrepancy between the self-perceived sleepiness and the underlying true physiologic sleepiness in a given individual [33,34]. In one study, neither patient nor partner ESS ratings were strong predictors of the degree of sleep apnea severity [35]. The results of a recent study in patients with obstructive sleep apnea failing to reveal a correlation between the subjective ESS and either the apnea index or degree of hemoglobin oxygen desaturation and objective sleepiness as determined by the multiple sleep latency test (see below) should discourage the use of subjective sleepiness rating scales as valid surrogates for true sleepiness [36]. The ESS may be influenced by psychological factors not affecting the MSLT, and, therefore, should not be used to demonstrate sleepiness as measured by the MSLT [37].

Results from clinical trials relying upon subjective sleep reports must be interpreted with great caution, as the self-perception of these sleep parameters is often very inaccurate in normal individuals and much worse in patients with sleep complaints [38]. In one study of sleep in patients with active rheumatoid arthritis, objective sleep parameters were correlated with the self-report of depth, length, degree of interruption, and restlessness of the preceding night's sleep: all patients demonstrated a striking lack of perception of the objectively observed sleep fragmentation [39].

3.2. Sleep/wake diaries

Prolonged sleep/wake diaries completed by the patient or observer may give an at-a-glance overview of wake/sleep patterns not obviously apparent by clinical history.

3.3. Actigraphy

Analysis of sleep diaries may be insufficient to verify a tentative diagnosis in patients with reported insomnia or suspected wake/sleep cycle abnormalities. In such cases, definitive objective data may be obtained by actigraphy, a recently-developed technique to record activity during wake and sleep that supplements the subjective sleep log. An actigraph is a small wrist-mounted device which records the activity plotted against time – usually for a week or two [40]. When data collection has been completed, the results are transferred into a personal computer, where software displays activity versus time. There is direct correlation between the rest/activity recorded by the actigraph and the wake/sleep pattern as determined by polysomnography [41,42]. Indications for the use of actigraphy include: insomnia, wake/sleep schedule disorders, and monitoring treatment response [43,44]. It may be impossible to evaluate some bizarre sleep complaints (as in the case of a patient who claims to sleep only 1 or 2 h per night) without actigraphy. In such cases, actigraphy is mandatory to confirm or refute the perceived sleep pattern before a treatment plan can be developed [45].

3.4. Polysomnography and multiple sleep latency test

Polysomnography (PSG) is the gold standard for the physiologic evaluation of sleep and for the identification of sleep continuity and sleep pathologies such as sleep apnea. The multiple sleep latency test (MSLT) is a well-validated, objective measurement of daytime sleepiness. This test consists of four to five 20-min nap opportunities at 2-h intervals following all-night PSG. The mean interval between 'lights out' and the onset of polygraphically defined sleep is the mean sleep latency which quantitates the degree of physiologic sleepiness. In normals, the mean sleep latency is correlated with the duration and continuity of the preceding night's sleep, age, time of day, and medications. Following a normal night's sleep, a mean sleep latency of 5 min or less is considered evidence of severe hypersomnolence. REM sleep frequently occurs during daytime naps in patients with narcolepsy, and uncommonly in non-narcoleptics [45,46].

4. Sleep in well-defined rheumatologic conditions

4.1. Osteoarthritis

Nighttime pain and sleep complaints are common in patients with osteoarthritis (OA), and it had been speculated that insomnia reported by OA patients is related to discomfort [47]. Existing objective sleep studies in patients with OA are technically flawed due to lack of such critical data as: total sleep time and sleep efficiency, respiration or extremity move-

ment monitoring, arousals, and/or indicators of daytime sleepiness [48–50]. One study reports 'impaired sleep', but provides no data [51]. Moldofsky reported that OA patients who complain of morning pain are more likely to have periodic movements of sleep than those denying morning pain. Interestingly, the incidence of the 'alpha/delta' sleep EEG pattern (see accompanying review) was identical in the two groups, suggesting that this sleep EEG pattern was related to neither the morning pain complaint nor subjective daytime fatigue/sleepiness. Objective measures of daytime sleepiness were not performed [52].

4.2. Rheumatoid arthritis

Fatigue is a frequent constitutional symptom reported by patients with rheumatoid arthritis (RA), affecting nearly 80% of patients compared with 21% of controls, and is generally attributed to the systemic nature of active RA [53]. The time to onset of fatigue after arising is used clinically as an index of disease activity [53–55] or as an indicator of response to therapy [56]. Conversely, the absence of fatigue is one of the five criteria of clinical remission in RA [57].

The cause of fatigue in patients with RA is unknown, but in some cases, may be due to abnormalities of sleep. Although the complaint of 'sleep disturbance' is reported by 2/3 of RA patients [58], their sleep physiology and evidence of objective daytime sleepiness have not been systematically characterized. Sleep abnormalities in RA patients might include:

1. interference of sleep by joint pain resulting in sleep deprivation [59–61];
2. sleep disordered breathing related to anatomical lesions including craniovertebral junction abnormalities such as atlanto-axial dislocation [62,63] cervical spine instability [64–66], acquired micrognathia [67–70] or cricoarytenoid joint involvement [71,72] or;
3. periodic limb movements of sleep (nocturnal myoclonus)

[73].

On the other hand, the subjective complaint of daytime fatigue might be present in RA patients due to:

1. depression [74];
2. chronic insomnia;
3. 'non-restorative sleep' [75,76] as described in patients with fibromyalgia, or;
4. some yet-to-be identified factor.

Numerous studies have documented severe sleep fragmentation and underlying primary sleep disorders in patients with RA [39,77,78] and may be worse during a flare [79]. Sleep fragmentation has also been found in children with juvenile RA [80].

Most therapeutic studies of sleep and daytime alertness in RA patients employ only subjective reports [81–91]. One objective study, employing triazolam, documented improved sleep and morning stiffness, and reduced daytime sleepiness [92]. In another, zopiclone resulted in subjective, but not objective improvement in sleep, with no improvement in subjective daytime symptoms [93].

The high prevalence of restless legs syndrome in patients with RA (30%) bears further investigation [94].

Table 1 includes all available objective studies of sleep in RA.

4.3. Systemic lupus erythematosus

Fatigue is the most common symptom among patients with SLE and can be disabling. Rothfield noted fatigue at the time of diagnosis in 76% of 209 patients with SLE, with another 5% developing fatigue later in their course [95]. In another survey of SLE patients, fatigue was identified as the single most important problem by 27% of patients [96]. Some presence of fatigue is also been used clinically as an indicator of SLE disease activity and may occur prior to other symptoms or signify a flare of disease [97]. A recently developed 'fatigue severity scale' to investigate fatigue in SLE and multiple sclerosis [23] makes no distinction between sleepiness and fatigue. It is not clear whether the scale will be clinically useful to follow changes in fatigue in patients with SLE over time. In another SLE 'fatigue scale' [98], two of the four items use the term 'tired' to describe the patient's symptoms, promulgating confusion between sleepiness and fatigue. One subjective study of sleep in SLE reported a prolonged sleep latency and increase in total sleep time [99]. SLE patients could also develop obstructive sleep apnea due to laryngeal

Table 1
Sleep studies in rheumatoid arthritis (RA)

Reference	Study description	Outcome measures	TSO[a]	TST[a]	AASO[a]	Sleep efficiency	Arousals and awakes	Comments
Moldofsky et al., 1983 [155]	RA patients 'in flare' 15 in hospital	Mean of 4 nights study; 4 channel EEG; no limb leads; sleep questionnaire	75.7	487.5			Movement arousals 52.5; Said all patients had prominent alpha rhythm EEG in NREM (shows alpha EEG intrusion)	Alpha EEG NREM 'sleep disturbance' and 'similar EEG disturbance' artificially induced also had muscle stiffness or pain and tenderness and mood disturbance therefore a 'physiologic nonrestorative sleep syndrome'; 1 patient had clinical remission and %alpha decreased from 20 to 7.9%
Crosby, 1989 [79]	Exploratory study; RA 15 (11F); 12 controls; 5 'flare' controls gender matched	PSG; no limb leads; assessed evening pain	5 RA flare; 23 m; C 11m; RA non-flare19m; C 16m	RA flare 300m; C 363; RA non-flare 366m; C 371m	Flare 158; C 50	Flare 61%; C 85%; non-flare 75%; C 85%	Sleep state changes; RA flare 72; C 49; Non-flare 54; C 43; # awakes: RA flare 19; C 10; non-flare 12; C 9	1 patient and 2 controls said to have 'alpha-delta' but described as alpha bursts; No mention of correlation data for evening pain to sleep parameters; 'Flare' defined a numerous tender swollen jts i.e. active disease; RA diagnosis not by diagnostic criteria, Sleep architecture normal
Mahowald et al., 1989 [39]	16 active RA with fatigue <6 h	PSG lab; MSLT; 5 did not sleep; 7/11 <8.5m	22	355		79%	3.4 awakes/h; 43 arousal/h; 10/13 RLS; 12/16 PLMs	13/16 had AD rhythm in 50% NREM sleep stages striking lack of perception of sleep fragmentation with subjective error of SL 21m, TST 45m, # awakes reported as 4.4 but was actually 10 per night
Lavie et al., 1990 [156]	30 RA; 14d tenoxicam vs. diclofenac vs. placebo	Actigraph	No data given	No change			Decreased mean sleep activity level with both	Only effects on RA disease activity; lower AM motility after NSAID Rx

Table 1 (*continued*)

Reference	Study description	Outcome measures	TSO[a]	TST[a]	AASO[a]	Sleep efficiency	Arousals and awakes	Comments
Lavie et al., 1991 [157]	13 RA all F washout, 4d placebo then 14d and 90d tenoxicam	PSG lab Actigraph on wrist Accelerometer on foot	P21.8; 14dT 27.1; 90dT 19.8	P 338.7; 14d T 319.9; 90dT 274.8	P18.4; 14dT 118.3; 90dT 19.1	P 76.2%; 14dT 77.4%; 90dT 77.3%	I 'severe sleep fragmentation'	8/13 had a primary sleep disorder 5 PLMs (>40/night),4 OSA, 1 both AM stiffness and pain decreased with Tenoxicam; No change in sleep parameters with NSAID. Concludes subjective report on NSAID effects on sleep should be interpreted with great caution
Lavie et al., 1992 [78]	13 F RA vs 9 F CLBP vs 12 F controls	Actigraphy; PSG - no data given	nd	RA 405.1; CLBP 389.9; C 374.9		Actigraphy RA 79.33%; LBP 86.74%; C 93.79%	#PLMs neg correlated with sleep efficiency; CLBP patientts sleep same as controls except twice as many sleep stage transitions	5/12 >30 PLMs; 2/12 osa (1 both); evening, morning and pain during sleep not correlated with TST. evening pain but not pain during sleep correlated with activity in sleep, dec sleep efficiency, and shorter time with zero activity
Hirsch et al., 1994 [77]	Controlled comparison; 19RA; 19C; RA patients not selected for fatigue; Normal sleep construction not disturbed	PSG; MSLT; MSLT = normal in all but one RA was <6m	RA 22.6;[a] C 10	RA 418.8; C 457 not significant difference	RA 87.3[a]; C 30.6	RA 80.9[a]; C 93.5	#Awakes; RA 19.1[a]; C 7.4; In contrast to FM patients RA patients overestimate the quality of their sleep despite severe sleep frag and PLMs	RA had severe sleep fragmentation: awakes, AASO, dec sleep eff 15/19 RA pts had primary sleep disorders 14 plms, 13, rls, 2 hypopnea, no osa; Alpha-delta pattern in 6, none met criteria for dx of fibromyalgia; In subj sleep report correct on TST but not TSO or # awakenings; No correlation of sleep disturbance and RA disease activity

Table 1 (*continued*)

Reference	Study description	Outcome measures	TSO[a]	TST[a]	AASO[a]	Sleep efficiency	Arousals and awakes	Comments
Walsh et al., 1996 [92]	15 RA patients with daytime fatigue RCT crossover 1 wk Triazolam vs Placebo	PSG; MSLT; mean 8.1m; T MSLT 11[a]; P MSLT 7.9	45.5; T 24l P 29.9	364.5; T 408.2[a]; P389.1; Patient estimate 434m on T	ng; T 46.7; P 70.5	75.9%; T85%; P80%	PLM 18.6/h; Arousals 5.6/h	Only study of benzodiazepine in RA, Mild to moderate RA disease, 19m more sleep/night on T and less daytime sleepiness, No difference in alpha activity; On T perceived longer sleep, shorter SL and fewer awakenings than on placebo; On T 1 h less AM stiffness and said sleep less disturbed by arthritis
Drewes et al., 1988 [158]	41 RA; 19 Controls	Home PSG; HAQ; McGill		RA 402.2; Controls 395.1	RA 29.4; Control 24.9	RA 93.6%; Control 94%	PLMs index, RA 10.8*; C 4.1; Arousal index, RA 9.1; C 7.7	RA with active and inactive disease, not selected for fatigue; No correlation of pain to sleep parameters; Subset analysis active vs inactive, no differences in sleep parameters
Drewes et al., 1998 [93]	RCT in 41 RA Zopiclone Placebo 2 week study	PSG home; HAQ McGill	Baseline ave 22 2 weeks rx; Z 21.2; P 18.6	Baseline ave 430 2 weeks; Z 419.2; P 435.2	Ave 29 2 weeks; Z 23.7; P 22.5	Ave 94% 2 weeks rx Z 94.9 P 95.	Ave PLMs Index baseline = 12/h; 2 wks rx; Z 9.4/h; P 11.8/h; Arousal Index baseline 9.5; 2 wks rx; Z 7.5/h; P 9.7/h	Patients reported improvement in sleep quality but there was no change in measured parameters. Zopliclone Altered sleep perception not sleep parameters

[a] TSO, time to sleep onset'; TST, total sleep time; AASO, awake after sleep onset (all in min); C, controls; CLBP, chronic low back pain; LBP, low back pain.

obstruction, crycoarytenoid arthritis, and recurrent laryngeal palsy [100–105]. Respiratory and movement disorders (periodic limb movements) have also been described in association with SLE [106,107].

SLE has been reported to coexist with narcolepsy, which raises interesting genetic questions, as both conditions have been associated with HLA DR2 antigens [108].

4.4. Ankylosing spondylitis

Fatigue is a major symptom in the majority of patients with ankylosing spondylitis (AS), and is often ignored by physicians [109,110]. Poor sleep has been anecdotally reported [111]. In one self-report study, patients with AS reported a mean number awakenings per night of 2.8 ± 0.7 and 1.2 ± 0.3 h of wakefulness during the night [112]. Mass et al. obtained evidence of excessive daytime sleepiness and snoring from 8/11 AS patients [113]. PSG studies of five of these patients demonstrated significantly disrupted sleep in three and obstructive sleep apnea in four. Only one patient had in abnormal MSLT, and none complained that pain as disturbing their sleep. Jamieson et al. found that poor sleep in patients with AS was associated with decreased pain, suggesting that movements during sleep may reduce pain, and recommended a study of the effect upon pain of deliberate awakenings with exercise in AS [114]. A single study reported subjective improvement in sleep by amitriptyline in AS [115].

A single case of OSA has been reported in association with seronegative spondyloarthropathy [66] and crycoarytenoid arthritis which could lead to sleep-disordered breathing has been described in AS [116].

4.5. Sjogren's syndrome

Subjective sleep complaints have been reported in 75% of patients with Sjogren's syndrome (SS) [117]. The only identified objective study of sleep in SS revealed that all ten patients had reduced sleep efficiency, in part attributed to 'muscular tension' and restless legs syndrome. Regrettably, extremity movements, respiration, and objective daytime sleepiness were not measured [118].

4.6. Bechet's syndrome

Sleep apnea has been reported in a single male patient with neuro-Bechet syndrome [119]. This must be interpreted with caution, given the high prevalence of sleep apnea in adult males.

4.7. Lyme disease

Sleep complaints are common in Lyme disease [120]. The one available objective study of 11 patients with Lyme disease found subjective complaints of difficulty initiating sleep (27%), frequent nocturnal awakenings (27%), excessive daytime sleepiness (73%), and restless legs/nocturnal leg jerking (9%). Objectively, there was a prolonged sleep latency, decreased sleep efficiency, and a greater arousal index. The multiple sleep latency test was normal [121]. The striking discrepancy between the subjective and objective data on excessive daytime sleepiness should be noted.

4.8. Vasculitis

Fatigue and malaise are common complaints in patients with vasculitis, but no objective sleep study data are available. Malaise is a presenting complaint in 13% of patients with polyarteritis nodosa, 4% with Wegener's granulomatosis, and 35% with lymphomatoid granulomatosis [122]. In one clinical study of patients with giant cell arteritis, fatigue was the initial manifestation in 5% and present on initial work up in 40% [123]. Although not yet documented, airway obstruction might develop with upper respiratory tract involvement in Wegener's granulomatosis and/or giant cell arteritis [124].

5. Sleep in less-well defined musculoskeletal conditions

This topic is discussed in the accompanying review.

6. Sleep and pain

Dudley Hart suggested that 'persistent and repeated recurrence of discomfort produces physical and mental fatigue and depression' [59]. It appears that pain plays a lesser role in insomnia than might be

thought [125]. In one small series of patients complaining of low back pain and poor sleep, the objective sleep parameters displayed wide variability [126]. Another objective study indicated that the sleep of patients complaining of pain was less disturbed than that of patients suffering from psychiatric disease [60]. It is doubtful that clinician or patient would disagree, but objective data from sleep studies are lacking or insufficiently studied in the rheumatic diseases. The intuitively attractive assumption that pain causes insomnia remains to be demonstrated.

7. Insomnia and depression in rheumatic diseases

The complaint of significant insomnia is reported by approximately 30% of the general population, and is described as a 'serious' problem by 17% [127]. In the rheumatologic population, insomnia is often attributed to nocturnal pain – something to be tolerated by the patient but yet is another manifestation of the underlying condition. All too often, insomnia is attributed to a psychiatric condition, and not evaluated thoroughly. It must be remembered that insomnia, like pain, is merely a symptom, and may be due to a wide variety of underlying conditions. Treating insomnia without proper evaluation is analogous to treating pain without searching for a specific cause. A recent study underscores the pitfalls of such egregious assumptions: in 123 consecutive patients with the complaint of insomnia, formal all-night PSG evaluation 'added to, refuted, and/or failed to support the clinical impression' in 49% of cases [128]. Even in experienced hands the identification, by history, of a condition later revealed by PSG, is very poor [129].

One very common type of insomnia is 'psychophysiologic', or 'conditioned' insomnia, the manifestation of having conditioned oneself to associating the bed with the unpleasant sensation of not sleeping, rather than the anticipation of falling asleep. The inciting event may be legitimate (fear, excitement, pain, medication – effect), and transient – however the conditioned component persists. Typical symptoms of this form of insomnia are: anticipatory anxiety (worrying about having yet another poor night's sleep – often beginning in the afternoon or evening), lying in bed trying to 'will' oneself to sleep, ruminating about the perceived dire consequences of sleeping poorly, and being able to fall asleep in places other than one's own bed (such as while sitting in a chair reading, sleeping away from home while on vacation) [130]. Behavioral therapies are very effective in 'deconditioning' patients with psychophysiologic insomnia [131,132]. Combined pharmacologic and behavioral treatments may also be effective [133].

Depression is common in rheumatoid disease [134]. Depressed patients have difficulty in initiating or maintaining sleep and report early morning awakenings. The complaint of daytime 'fatigue' is common, however, depressed patients with insomnia tend not to have objective hypersomnolence by MSLT, and the fatigue improves as the day progresses. In contrast, patients with true daytime hypersomnolence report progressively severe sleepiness as the day progresses. Effective treatment of the depression should be associated with improved sleep perception and daytime vigor. Although it is commonly assumed that depression causes insomnia, there are compelling studies indicating that untreated insomnia, in the absence of depression, is a major risk factor for the development of depression [135–139]. Therefore, the coexistence of depression and insomnia in a given patient does not necessarily imply that the depression caused the insomnia. That untreated insomnia may precede depression is indication enough for the aggressive treatment of insomnia.

As mentioned above, the intuitively attractive association between pain and insomnia remains to be determined. Aggressive night-pain management is indicated in those patients who report definite pain-related sleep interruption.

Circadian factors may play a role in the complaint of 'insomnia' by prohibiting sleep onset at socially or personally desired times [140]. Insomnia associated with circadian factors is readily identifiable by 2–3-week sleep diaries, and may be treated by chronotherapy or phototherapy [141]. Actigraphic monitoring may be of invaluable assistance if information from sleep diaries is not diagnostic [45].

The extremity-movement-associated sleep fragmentation and 'nocturnal myoclonus' or 'periodic leg movements of sleep' (PLMs), is characterized by frequent, periodic movements of the lower extremities during sleep, often associated with EEG evidence of arousal. PLM has been associated with a variety of underlying medical conditions but often

no specific etiology is found [142]. Periodic limb movements are common in the general population, increasing with advancing age, and may be completely asymptomatic [142]. There is a growing body of evidence that PLMs, as a polysomnographic observation, may be of no clinical significance, and that the 'periodic limb movement disorder' (PLMD) may not be a distinct syndrome [143–146].

8. Diagnosis, evaluation, and treatment of wake/sleep complains in rheumatic disorders

The diagnosis and treatment of sleep disorders and daytime functioning complaints in patients with rheumatologic disorders is identical to that it any group of patients complaining of sleep/wake dysfunction. The initial step must be a detailed history and physical examination, with particular attention to the sleep pattern. Knowledge of all prescribed and over-the-counter medications is mandatory. Every effort must be made to differentiate between daytime fatigue and true excessive daytime sleepiness. Sleep diaries, actigraphy, and formal sleep studies (polysomnography and multiple sleep latency tests) should be completed as appropriate [45].

Aside from corticosteroids, which may cause severe insomnia [147,148], there are very few objective studies of the effects of medications commonly prescribed for rheumatic conditions upon sleep quality or quantity, or their effect upon daytime alertness. The effect of commonly prescribed benzodiazepine sedative-hypnotics upon sleep in rheumatic conditions remains to be determined. Careful review of the 'documented efficacy' of these agents often reveals more statistical significance than clinical effectiveness [149] and salutary effect upon nighttime sleep and may be canceled by residual daytime sedation. There are no data regarding interactions between these agents and those commonly prescribed for rheumatic conditions. Caution must be exercised in extrapolating medication effects in normal volunteers or insomniacs to those with chronic medical conditions. Medications administered for coincident medical problems may also affect sleep and daytime symptoms.

One very important and very unstudied aspect of therapy in the rheumatic conditions is that of chronobiology. Most diseases, including rheumatoid arthritis, display striking circadian variability in symptom severity [150]. Furthermore, virtually every medication studied to date exhibits variability in efficacy and toxicity – depending upon time of circadian cycle administration [151]. There are virtually no studies of the chronopharmacology of any medications prescribed for rheumatic disorders.

An unknown percentage of patients with rheumatic conditions who complain of daytime fatigue are actually reporting symptoms of excessive daytime sleepiness. These two complaints may be difficult, if not occasionally possible, to differentiate solely by history. If there is any evidence of true and inappropriate hypersomnolence (such as falling sleep at work, while driving, visiting with others, etc.), formal sleep studies are indicated. The presence of rheumatic disorder does not preclude the coexistence of an additional primary sleep disorder such a sleep apnea, narcolepsy, or periodic movements of sleep. Demographics indicate that 2–4% of patients with RA would be expected to have OSA independent of the RA, and 30% would have coincidental insomnia, chronic in 9–12% [152,153]. A PSG study followed by a MSLT will identify the presence or absence of a primary sleep disorder, and will objectively confirm or refute the clinical suspicion of true hypersomnolence.

9. Summary, implications, and imperatives

Although many patients with rheumatologic conditions complain of sleep/wake symptoms, little scientifically valid data are available which evaluate objective parameters, rendering the interpretation of such complaints and a response to specific therapies difficult. There is a compelling need for accurate use of terminology: i.e. the use of 'sleep dissatisfaction' in the absence of PSG data, rather than 'sleep disorder', which implies objective identification of any abnormality of sleep physiology by PSG. Unfortunately, even in recent studies, the 'fatigue' reported by patients with a variety of rheumatic conditions is subjective, with likely confusion of fatigue with true sleepiness, and sleep dissatisfaction with sleep disorders [154]. The MSLT is a powerful, well-validated tool to identify true daytime sleepiness in patients complaining of

'fatigue'. Clearly, more detailed studies are necessary to evaluate the prevalence and significance of the 'alpha/delta sleep EEG pattern' in various rheumatic conditions and in the general population. Studies evaluating EEG frequency distribution or power must include control groups (see accompanying review.) Objective parameters (PSG/MSLT) including both respiratory and extremity monitoring are mandatory when evaluating sleep/wake function, due to the unacceptable discrepancy between subjective and objective sleep/wake parameters. Such careful and thorough studies will be necessary when exploring such exciting issues as immune function, circulating humoral factors (interleukin-1), and circadian effects of symptom severity and response to medication in rheumatic disorders. Future studies should strive toward distinguishing among the various types of fatigue and/or sleepiness in patients with chronic rheumatic diseases. Results will serve to teach us much about chronic disease and sleep/wakefulness, and will undoubtedly result in important therapeutic implications for our patients.

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