Research Review™ STUDY REVIEW

Sleep loss exacerbates fatigue, depression, and pain in rheumatoid arthritis

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Independent commentary by Dr Mona Marabani

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Publication overview

This study review summarises data from a comparative investigation that evaluated the effect of sleep loss during part of the night on daytime mood symptoms and pain perception in patients with rheumatoid arthritis (RA) compared with control subjects.[1] The study provided evidence of an exaggerated increase in symptoms of pain in patients with RA compared with control subjects after sleep loss.[1] The study outcomes suggest that the clinical management of pain in patients with RA should include an increased focus on sleep, and the prevention and treatment of sleep disturbance.

Study background

Rheumatoid arthritis (RA), an inflammatory autoimmune disorder, is characterised by joint pain and swelling.[2] In patients with RA, the prevalence of sleep disturbance (e.g., sleep fragmentation) has been reported to be two to three times greater than that found in the general population.[3-5] In addition, cross-sectional studies have found that sleep disturbance correlates with greater pain and disease activity.[5-7]

The researchers of this study hypothesised that sleep disturbance and pain were bidirectionally related, with sleep disturbance driving RA-related pain and *visa versa*.[1] Studies in healthy volunteers suggest that sleep loss influenced pain reporting, although these studies are limited by lack of controls or small patient numbers.[8-13] Additionally, most of these studies involved selective sleep stage deprivation or total sleep deprivation, which does not mimic the kind of sleep disturbance found in patients with RA who typically experience loss of sleep during part of the night or sleep fragmentation.[4] However, one study in healthy female volunteers reported that disturbances of sleep continuity, as opposed to total sleep restriction, increased spontaneous pain.[14]

In the study reviewed herein, an experimental model of partial night sleep deprivation (PSD) was used to activate self-reported symptoms of pain and to determine whether sleep loss induced a differential increase in symptoms of self-reported pain, as well as daytime mood symptoms, in patients with RA compared with control subjects.[1] Self-reported arthritis-specific and clinician-rated measures of joint pain in patients with RA were also assessed.[1]

Study methods

Design

This comparative study was conducted at the UCLA General Clinical Research Center (GCRC), with participants blinded to the study objectives and outcomes for self-rated measures of mood symptoms and pain perception.[1]

Prospective patients with RA were referred to the UCLA Division of Rheumatology where a diagnosis of RA was confirmed by conducting diagnostic evaluations that included a review of medical records, completion of a medical history, and an assessment of tender and swollen joints, and an assessment of disease activity.[15] A structured comprehensive joint count assessment was completed, with scoring of the number of joints that were tender and/or swollen.[1] Sixty joints were evaluated on a scale from 0 (none) to 3 (severe) to indicate the extent of pain and swelling.[1]

Patients

Eligible patients with RA were:[1]

- aged ≥18 years;
- met the 1987 American College of Rheumatology revised criteria for RA;
- were stable on a disease-modifying drug regimen for 3 months;
- did not have serious co-morbid medical conditions such as diabetes, congestive heart failure, renal failure, or cancer.

Comparison control subjects were:[1]

- aged ≥18 years;
- did not have any history of an inflammatory disorder, cancer, or chronic or active infections.

All participants had reference range results from screening laboratory tests (complete white blood cell count, metabolic panel) and, for women, a negative pregnancy test.[1]

Two-week sleep diaries confirmed that participants regularly slept between 22:30 and 07:30 hours prior to study entry.[1]

Procedures

Eligible participants spent four nights in the GCRC, including:

- An *adaptation* night to acclimate participants to the recording environment and to screen for sleep apnoea (>15 desaturation events per hour) and/or nocturnal myoclonus (>10 movement-related, 3 second arousals per hour);
- A *baseline* night involving uninterrupted sleep between 23:00 and 07:00 hours;
- A *PSD* night in which participants were awake between 23:00 and 03:00 hours, with sleep occurring between 03:00 and 07:00 hours. Objective measures of sleep continuity at baseline and during the sleep interval (i.e., after PSD and prior to the morning assessment) were obtained by polysomnography;
- A *recovery* night involving uninterrupted sleep between 23:00 and 07:00 hours.

During the days after baseline and PSD nights, measures of mood symptoms and pain perception were repeatedly obtained. In patients with RA, clinician-rated joint counts were measured at 08:00 hours after baseline, PSD, and recovery nights.[1]

Patients were monitored by GCRC nursing staff with routine checks every 15 min to prevent napping behaviour.[1]

Participants with sleep apnoea and/or nocturnal myoclonus (during the adaption night) were excluded.[1]

Study endpoints

Severity of sleep disturbance was evaluated by the self-reported Pittsburgh Sleep Quality Index (PSQI).[16, 17]

All-night polysomnography was used to obtain objective measures of sleep continuity (i.e., total sleep time, sleep latency, wake after sleep onset, sleep efficiency)[18] during the PSD night (at baseline and during the sleep interval i.e., after PSD and prior to the morning assessment). Polysomnography was performed with ambient light less than 50 lux.[1]

The Profile of Mood States[19] evaluated changes in fatigue, depression, and anxiety and the McGill Pain Questionnaire (MPQ)[20] evaluated changes in subjective pain perception.[1]

A 5-point visual analogue scale was also used to estimate RA-specific disease activity (i.e., number of painful joints, overall pain severity).[1]

A structured 60-joint count was completed before and after the PSD night, with scoring of the number of joints that were tender and/or swollen.[1] Sixty joints were evaluated on a scale from 0 (none) to 3 (severe) to indicate the extent of pain and swelling.[1]

Study results

Patient characteristics

The study enrolled 27 patients with RA and 27 comparison control subjects (see **Table 1** for the key demographic and clinical characteristics).[1]

Table 1. Key demographic and clinical characteristics at baseline[1]

	Patients with rheumatoid arthritis (n=27)	Control subjects (n=27)
Mean age, years (SD)	59.9 (11.1)	60.4 (10.2)
Female, % pts	89	79
Non-Euro American ethnicity, % pts	59	33
Employed, % pts	30	48
Married/partner, % pts	44	48
Mean BMI, kg/m^2 (SD)	27.2 (4.6)	25.4 (5.0)
Mean PSQI (SD)	7.6 (3.8)*	2.4 (2.0)
Mean income, $k/year (SD)	64.5 (48.9)	66.1 (51.6)
Medication, % pts (RA only)		
DMARDs	55.6%	
Biologics	48.1%	
Steroids	14.8%	
NSAIDs	3.7%	

BMI = body mass index; **DMARDs** = disease-modifying anti-rheumatic drugs; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **pts** = patients; **PSQI** = Pittsburgh Sleep Quality Index; **SD** = standard deviation.

*p<0.001 vs control subjects.

At baseline, patients with RA reported significantly greater sleep disturbance (as assessed by mean PSQI scores) in comparison with control subjects (p<0.001).[1] At baseline, patients with RA had greater amounts of wake after sleep onset (p=0.03) and poorer sleep efficiency (p=0.04) compared with control subjects.[1] Among the patients with RA, covarying for the use of the various medications as a block on all disease-specific outcomes did not alter the outcomes.[1]

Outcomes

Self-reported mood responses to PSD

PSD induced differential increases in self-reported fatigue (p<0.009; **Figure 1A**) and anxiety (p<0.04; **Figure 1B**) in patients with RA compared with control subjects.[1]

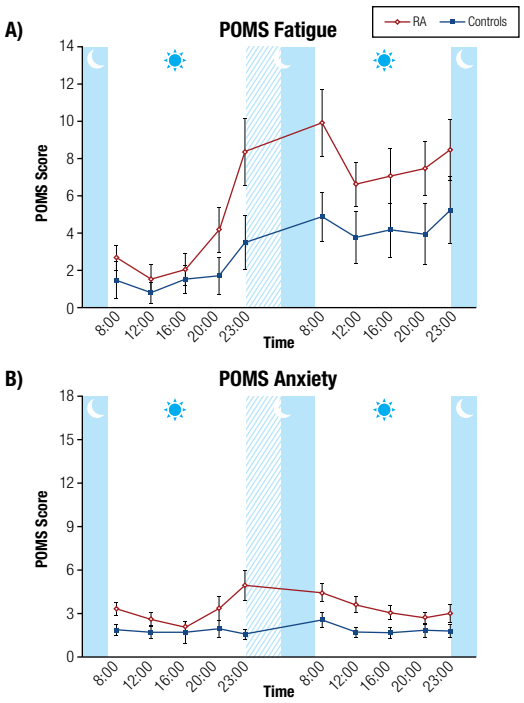

Figure 1. Effects of partial night sleep deprivation on **A**) self-reported fatigue, and **B**) anxiety as indexed by the Profile of Mood States (POMS) in patients with rheumatoid arthritis (RA) and control subjects.[1] The shaded area represents the sleep interval during the night, whereas the hatched area represents the sleep deprivation interval. Mean ± SEM (error bars).
Adapted from Irwin MR, et al. Sleep. 2012;35(4):537-43.

Self-reported pain responses to PSD

PSD also induced an exaggerated response in self-reported pain (as scored by the MPQ) in patients with RA compared with control subjects (p<0.02; **Figure 2**).[1] Differential increases in self-reported pain were independent of changes in mood, baseline PSQI scores, or sleep fragmentation.[1]

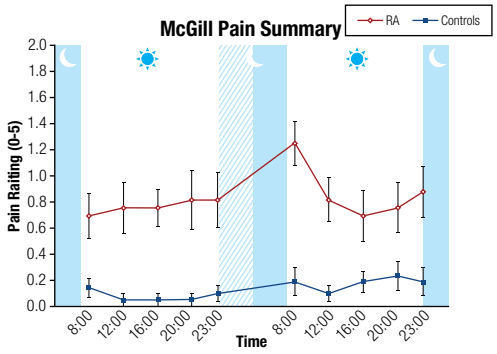

Figure 2. Effects of partial night sleep deprivation on self-reported pain (assessed by the McGill Pain Summary) in patients with rheumatoid arthritis (RA) and control subjects. The shaded area represents the sleep interval during the night, whereas the hatched area represents the sleep deprivation interval. Mean ± SEM (error bars).
Adapted from Irwin MR, et al. Sleep. 2012;35(4):537-43.

Although patients with RA had greater amounts of wake after sleep onset and poorer sleep efficiency at baseline compared with control patients (p<0.05; **Table 2**), in the immediate sleep interval after PSD, these objective markers of sleep fragmentation were similar in both groups (**Table 2**).[1] Measures of total sleep time and sleep latency were similar in patients with RA and the control subjects before and after PSD.[1]

Table 2. Polysomnographic measures of sleep continuity at baseline and during the sleep interval after early night partial sleep deprivation (PSD) in patients with rheumatoid arthritis and control patients

	Patients with rheumatoid arthritis (n=27)		Control subjects (n=27)	
	Baseline night	PSD sleep interval	Baseline	PSD sleep interval
Total sleep time, min (SD)	378 (34)	199 (28)	392 (33)	202 (35)
Sleep latency, min (SD)	25.1 (18)	16.8 (24.3)	25.2	8.6 (8.4)
Wake after sleep onset, min (SD)	73.3 (32.3)*	24.4 (18.7)	53.7 (30.1)	26.4 (33.3)
Sleep efficiency, % (SD)	83.8 (7.0)*	89.1 (7.9)	88.0 (6.6)	88.4 (14.1)

SD = standard deviation. *p<0.05 vs control subjects.

RA-specific self-reported and objective pain responses to PSD

PSD induced increases in self-reported pain severity (p<0.01) and the number of painful joints, with pain severity (p<0.03) and joint pain (p<0.05) at 08:00 hours immediately after PSD being significantly greater than all other time points (**Figure 3A and 3B**).[1]

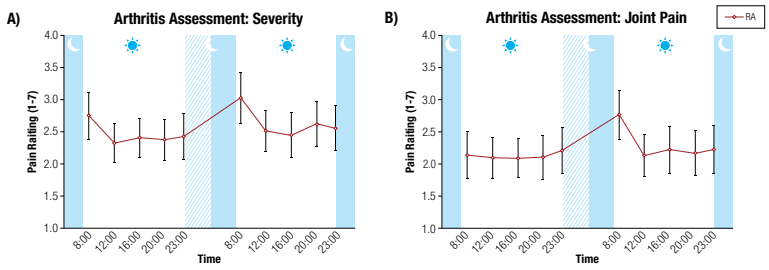

Figure 3. Effects of partial night sleep deprivation on **A**) self-reported joint pain severity and **B**) self-reported number of painful joints in patients with rheumatoid arthritis. The shaded area represents the sleep interval during the night, whereas the hatched area represents the sleep deprivation interval.[1] Mean ± SEM (error bars).

Clinician-rated joint counts were increased in the morning after PSD compared with baseline (p<0.03) and in the recovery morning (p<0.04).

Expert comment

We have long been aware of relationships between sleep disturbance, depression, fibromyalgia, and pain amplification. In recent years, intriguing associations have been found between poor sleep and breakdown of immune regulation with increases in pro-inflammatory cytokines. Sleep deprivation has been associated with a chronic inflammatory state that increases the risk of infections, autoimmune disease, cardiometabolic disease states, and neurodegenerative problems.

This study aims to explore the relationship between sleep deprivation, mood, and pain perception in people with RA.

The study indicates that the RA patients had impaired sleep at baseline compared with controls. However, RA patients deprived of sleep showed much worse fatigue and anxiety than controls. In the RA group, there was not just an increase in diffuse pain or fibromyalgia, but an increase in the number of tender joints, both self-reported and in clinician performed joint counts, independent of effects on mood. It has always been assumed that people with RA have poorer sleep because of pain, but it appears that this relationship goes both ways.

Study interpretation

This study provided evidence that sleep loss resulted in an exaggerated increase in symptoms of pain in patients with RA compared with in control subjects.[1] In the morning after PSD, self-reported pain symptoms were elevated in RA patients compared with in control subjects. In addition, sleep loss induced RA-related joint pain as indicated by the increases in the number of painful joints and the severity of associated joint pain. Clinician-rated painful and tender joints were also increased after this modest sleep loss in patients with RA. The objective measures of sleep fragmentation were similar in patients with RA and the control subjects during the sleep interval immediately after PSD, suggesting that sleep loss, as opposed to sleep fragmentation, has a unique role in the differential induction of pain symptoms in patients with RA versus in control subjects.

Mood symptoms including fatigue, depression, and anxiety have been reported in patients with RA.[21] This study demonstrated that, in patients with RA compared with in control subjects, sleep loss was associated with exaggerated increases of these mood symptoms, which is due either to the direct effects of sleep loss (e.g., fatigue) or indirectly due to the anticipation of sleep loss (e.g., anxiety). Importantly, this study suggests that the effect of sleep loss on pain symptoms is independent of changes in mood symptoms, with increases in mood symptoms in response to sleep loss not appearing to mediate increases in self-reported pain responses.

Although increases of self-reported pain were short-lasting, transient increases in symptoms of pain after sleep loss may result in increased RA disease activity as demonstrated in other studies.[3,22-26] As a consequence of recurrent nights of sleep loss, it is possible that repeated, transient elevations of RA-specific joint pain might lead to an exacerbation of RA symptomatology. Importantly, efforts need to be made to prevent and treat sleep disturbance (e.g., improving sleep duration) in patients with RA as a means of potentially reducing pain.[1]

The study had a number of limitations including:[1]

- the single-blinded nature (patients and control subjects) of the experimental sleep deprivation study which may introduce bias into the study.[1] However, the researchers noted that it is unlikely that expectancy effects contributed to differences in response between the two treatment groups, as both groups were given similar information about the study. Moreover, any introduced bias would not likely have contributed to the changes in objective, clinician-rated joint counts, as the clinician(s) were blinded to the experimental condition;
- the study relied on reports of spontaneous pain and/or RA-related joint pain by self-report and clinician ratings, and laboratory assessments of pain were not used.[1] However, the assessments used followed clinical guidelines for the evaluation of joint pain in patients with RA;
- the sample population was composed mainly of female participants, and so the outcomes of the findings may not necessarily be generalisable to males;
- although an attempt was made to control for baseline differences in PSQI scores, the combination of modest sample size, and limited power for testing interactions with continuous variables, may mean that the PSQI scores may be more important than the current results suggest.

In conclusion, the researchers noted that although it is widely thought that sleep disturbance is a consequence of joint pain in patients with RA, outcomes from this study support an alternative hypothesis that sleep loss leads to increases in joint pain in patients with RA. Sleep loss during part of the night, in patients with RA, may result in a vicious cycle in which sleep disturbance activates clinical symptoms of pain, which then contribute to further sleep loss. The researchers emphasised that the outcomes of this study indicate that the clinical management of pain in patients with RA should include an increased focus on sleep, and the prevention and treatment of sleep disturbance.

Take home messages

- Sleep loss resulted in an exaggerated increase in symptoms of mood and pain, and RA-related joint pain in patients with RA.
- In the light of the reciprocal relationship between sleep disturbances and pain, clinical management of pain in patients with RA should include an increased focus on the prevention and treatment of sleep disturbance in this clinical population.

Expert concluding remarks

This study reminds us of the importance of taking a sleep history in our patients, and raises the possibility that interventions that produce a more normal sleep pattern have the potential to reduce disease activity and pain.

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