Sleep in Women with Chronic Pain and Autoimmune Conditions
A Narrative Review

Joan L. Shaver, PhD, RN[a,*], Stella Iacovides, PhD[b]

KEYWORDS

• Chronic pain • Autoimmune • Stress-immune • Pain sensitivity • Sleep quality • PSG sleep • Women

KEY POINTS

- Across clinical conditions that manifest with chronic pain and predominantly in women, lighter and more fragmented sleep and vulnerability to sleep-related disorders are evident.
- Persistent pain is one of the most common reasons patients seek medical care, patients with chronic pain often report sleep difficulties, and patients with persistent insomnia commonly report suffering with pain.
- Chronic pain and poor sleep each involve persistent stress-immune activation with physiologic and behavior changes that signify life-quality threatening morbidity.
- The combined synergistic impact of chronic pain and sleep warrants comprehensive clinical assessment and treatment.
- More research is needed to determine the mechanisms that underlie concurrent poor sleep and chronic pain in women, including the context of menstrual cycles or stages of reproduction.

INTRODUCTION

In this narrative review, we comment on chronic pain and sleep with exemplar papers, published mostly within the last 10 years, for chronically painful conditions manifested predominantly in women. The selected conditions are functional somatic syndromes of chronic pelvic pain (CPP), endometriosis, dysmenorrhea, and fibromyalgia (FM); and the autoimmune (AI) conditions of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and multiple sclerosis (MS). We did a PubMed, Medline (Ovid) search from 2007 to 2017, using headings of sleep with pain and immune and pain sensitivity and each of the selected conditions. We did not select papers by systematic determination of design or measurement quality but rather if the abstract indicated sleep data and predominantly women in the sample. **Box 1** contains the definition of terms used in the text.

Generally, compared with men, women show an excess vulnerability to conditions that are chronically painful and fatiguing. Many conditions exhibit a plethora of symptoms, such as skeletal, gut, or bladder muscle pain; profound fatigue; mental clouding; depressed mood; and almost ubiquitously, sleep disturbance.[1] Generally believed to be at the root of many conditions is stress-immune activation, commonly seen in elevated

Disclosure Statement: The authors have nothing to disclose.
[a] Biobehavioral Health Science Division, University of Arizona College of Nursing, 1305 North Martin Avenue, Tucson, AZ 85721, USA; [b] Faculty of Health Sciences, Brain Function Research Group, School of Physiology, University of the Witwatersrand, 7 York Road, Parktown 2193, Johannesburg, South Africa
* Corresponding author.
E-mail address: jshaver@email.arizona.edu

Sleep Med Clin 13 (2018) 375–394
https://doi.org/10.1016/j.jsmc.2018.04.008

Box 1
Definition of terms

- Sleep disturbances or poor sleep: general reference to nonnormative sleep.
- Sleep quality: self-reported sleep indicators from subjective sleep measures obtained using sleep diaries or logs and questionnaires, including Pittsburgh Sleep Quality Index, Athens Insomnia Scale, Insomnia Severity Index, Epworth Sleepiness Scale, General Sleep Disturbance Scale, and Medical Outcomes Study sleep scale.
- Sleep patterns: recorded sleep indicators from polysomnography and activity monitoring (actigraphy). Indicators include stages of rapid eye movement sleep and non–rapid eye movement stages 1 and 2 (N1, N2) or deep sleep (N3) and calculations of total sleep time, minutes to fall asleep or sleep latency, wakefulness after sleep onset, sleep fragmentation (arousals, wake times), and sleep efficiency (sleep efficiency = total sleep time/time in bed trying to sleep).
- Sleep-related disorders: conditions manifested around or during sleep, such as sleep-related breathing disorders, obstructive sleep apnea, restless leg syndrome, periodic leg movement disorder, and narcolepsy.

proinflammatory cytokines (PICs), such as interleukins (IL)-1 or -6, and pain dysregulation and hypersensitization. Still to be clarified is whether poor sleep predisposes, precipitates, is a consequence of chronic pain conditions, or some combination thereof, and precisely how sleep regulation and disturbance is intertwined with contributors to prolonged stress-immune activation and pain hypersensitivity.

STRESS-IMMUNE ACTIVATION AND SLEEP

Sleep is altered in the face of stress-immune activation and reciprocally, sleep disturbances can activate the stress-immune system. For example, elevated PIC levels of IL-1 and tumor necrosis factor-α have been associated with more non–rapid eye movement (NREM) sleep. Depleted serotonin (a key sleep regulator and mood factor) or inhibitors of serotonin receptors block IL-1-induced augmented NREM sleep. Manipulations to elevate IL-6 inhibits rapid eye movement (REM) sleep and induces fatigue.[2] When sleep is manipulated, sufficient sleep disturbance coincides with immune cell activation (eg, changes to monocyte, lymphocyte, and neutrophil function and accentuated PIC levels).[3]

Determining the contributors to stress-immune activation is complex as illustrated by a meta-analysis of 72 studies to evaluate sleep quality or sleep patterns as related C-reactive protein (CRP), IL-6, or tumor necrosis factor-α changes.[4] Across sleep deprivation or restriction studies done in healthy individuals, evidence of inflammatory accentuation was sparse. With habitual poor sleep, short sleep duration (<7 hours/night), or extreme long sleep compared with reference groups with normal sleep duration of 7 to 8 hours/night, elevated CRP levels and IL-6 levels (except in short sleep) pertained. None of the sleep variables were related to tumor necrosis factor-α, age was not an influential factor, and results were comparable between men and women. However, a few high-quality studies showed that women were more vulnerable than men to inflammatory activation with sleep difficulties as seen, among other factors, in accentuated CRP, IL-6, and stimulated monocyte production of PICs.[4]

CHRONIC PAIN AND SLEEP DISTURBANCE

People with chronic pain report poor sleep (50%–90%),[5,6] people with insomnia express significant pain, and experimental sleep disruption is associated with augmented pain perceptions.[7] Although a bidirectional relationship between pain and sleep is espoused, data suggest a stronger valence for sleep disturbances driving the development of chronic pain.[5,8] Sleep disturbance can (1) increase vulnerability for new-onset pain when initially pain-free, (2) worsen chance of long-term chronic pain remittance, and (3) impact next day pain expression.[6] Nevertheless, stronger evidence is needed, provoking a call for more longitudinal studies.[9]

In general, patients with significant pain report less total sleep time, long sleep latency, more awakenings, nonrestorative sleep, and daytime sleepiness and fatigue.[10,11] In addition, patients may have sleep-related disorders, such as sleep apnea or restless leg syndrome (RLS).[12] Sleep loss, especially loss of deep sleep, has a significant negative effect on perception of recuperation following a sleep period. Sleep fragmentation, common in chronic pain, may also impact ratings of restoration after sleep, although whether it has a comparable impact to sleep loss is still debated.[13,14] In a review of 29 controlled polysomnography (PSG) studies across various chronic pain populations, the most common disturbance of sleep architecture was sleep continuity disruption.[15] Because perceived arousals or awakenings often fail to coincide in number or duration with