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SLEEP AND PAIN (L FERINI-STRAMBI, SECTION EDITOR)

Sleep and Pain: the Role of Depression

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Abstract

Purpose of Review Good nighttime sleep is essential for maintenance of optimal daytime functioning. When nighttime sleep is disrupted, there are countless associated daytime consequences. One of the more prominent daytime consequences of disrupted sleep is pain. While the association between sleep and pain has received great empirical attention, there is still much unknown. This paper aims to summarize and evaluate the state-of-the-science of the interrelations among sleep, pain, and mood.

Recent Findings Cumulative scientific evidence suggests that nighttime sleep is associated with both daytime pain and daytime mood disturbances. A growing body of research indicates that disruptions in mood may be one mechanism through which sleep disruptions are related to daytime pain. The study of common biological substrates may shed additional light on the interrelations among sleep, pain, and mood.

Summary Mood represents an important link between sleep and pain. Future investigations would be well suited to appropriately sample a variety of indicators from the domains of sleep, pain, and mood. Studies that test triadic treatments that simultaneously address sleep, pain, and mood are needed.

Keywords Sleep · Insomnia · Sleep apnea · Sleep problems · Pain · Depression · Mood · Affect

Introduction

Sleep was once described by Thomas Dekker as the "golden chain that ties health and our bodies together." The fundamental nature of sleep can be clearly seen when examining some of the correlates of disrupted sleep. For example, poor sleep has been shown to relate to disruptions in cognitive functioning, social functioning, and physical functioning [1–3]. Making the matter more dire, sleep disruption is a very common phenomenon. The focus of the present article is on the associations among sleep, pain, and depression. Specifically, we aim to review the literature examining: (1) sleep and pain, (2) sleep and depression, and (3) depression and pain. We then provide a synthesis of the sleep, pain, and depression literature and present a conceptual model tying these three important, interrelated concepts together.

This article is part of the Topical Collection on *Sleep and Pain*

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Sleep and Pain

Sleep disorders are common and costly. Prevalence estimates for insomnia vary across the literature, with approximately 30% of the general population reporting symptoms of insomnia [4] and approximately 11% meeting DSM-5 criteria [5]. Prevalence estimates for obstructive sleep apnea (OSA) in the general population ranges from 9 to 38%, with rates spiking to 90% in men and 78% in women for some elderly samples [6]. These disorders exact an economic cost, with estimates in the multiple billions annually in the USA [7–9].

An estimated 25.5 to 39 million Americans experience constant or frequent pain lasting a minimum of 3 months [10, 11]. Rates of chronic pain are disproportionally higher among females, older adults, and individuals in poor health [10]. Chronic pain has a wide ranging impact, including well-known physical and emotional consequences on the individual, but also a significant detrimental effect on one's social and family environment, such as limiting social interactions and increasing caregiver burden [12]. Chronic pain also has a large economic impact, with financial costs estimated in the hundreds of billions annually in the USA [13].

A growing body of literature documents the connection between sleep disruption and pain. The first line of evidence comes from experimental research examining the effect of

sleep disruption on pain perception in healthy individuals. In this vein, it has been shown that sleep fragmentation increases pain sensitivity, suggesting that frequent awakenings—in addition to limited sleep duration—alters pain perception [14]. Similarly, Simpson, Scott-Sutherland, Gautam, Sethna, and Haack examined the mechanisms underlying the relationship between sleep and pain via a sleep restriction paradigm. Sleep restriction was associated with decreased habituation and increased sensitization to cold pain, lending support to the theory that long-term sleep insufficiency increases risk of chronic pain through degrading pain-modulatory circuits [15]. Finally, a meta-analysis synthesizing experimental studies on sleep deprivation's impact on pain reported a medium to large effect [16].

The second line of evidence comes from cross-sectional research documenting comorbidity of sleep disturbance and chronic pain. The association between insomnia and chronic pain is well-documented [17], whereas the link between OSA and chronic pain is less clear [18, 19]. A recent meta-analysis by Mathias, Cant, and Burke synthesized two areas of this literature (1) studies using objective measurement of sleep and (2) studies examining prevalence of sleep disorder in chronic pain patients. Chronic pain patients showed significant differences in polysomnography-measured sleep onset latency, time awake after sleep onset, number of awakenings, total sleep time, sleep efficiency, light sleep duration, number of stage-shifts, respiratory-related events, and periodic limb-movements compared with healthy individuals. Moreover, rates of insomnia (72%) and OSA (32%) were elevated, indicating that these conditions are more common in chronic pain patients than the general population [20].

Longitudinal investigations also shed light on the sleep–pain connection. A review of 16 longitudinal studies examining the effect of changes in sleep on pain-related outcomes found that decreases in sleep quality and duration are associated with a two- to threefold increase in developing a pain condition [21•]. The influence of sleep on pain outcomes is also found among individuals with existing pain conditions. For example, a longitudinal study examining emerging adults (ages 18–25) found that sleep problems predicted the onset of chronic pain, as well as increases in musculoskeletal pain severity 3 years later [22]. Additional research suggests that the aforementioned sleep–pain relationship is consistent across age groups. Among a sample of community-dwelling older adults in Japan and Singapore, initial short sleep duration was associated with the presence of any pain, multiple pain locations, and pain-related disability at 2 to 3 years later [23].

Interventional research treating comorbid chronic pain and sleep conditions show mixed results. A prior review of six RCTs of cognitive-behavioral therapy for insomnia (CBTI) for individuals with comorbid insomnia and chronic pain concluded that the treatment produces significant improvement in sleep outcomes but inconsistent changes in pain severity, with some evidence that it may improve pain-related functioning [24]. More recent research corroborates these findings. A meta-analysis of 24 studies examining the effect of either cognitive-behavioral therapy or pharmacological treatment for insomnia showed significant reductions in insomnia symptoms for participants with either osteoarthritis or low back pain, while pain was only decreased among individuals with osteoarthritis [25]. Recent research has examined the potential benefits of combining psychosocial treatments for insomnia and pain. Participants with insomnia and fibromyalgia who received CBT for insomnia and chronic pain (CBT-IP) reported greater improvements in sleep (e.g., subjective sleep quality, sleep latency, sleep efficiency, and sleep medication use) compared with participants assigned to treatment as usual or CBT for chronic pain (CBT-P), as well as similar decreases in pain intensity as participants who received CBT-P [26].

In conclusion, sleep and pain are intertwined. Sleep deprivation heightens pain sensitivity [14–16], insomnia and chronic pain are frequently comorbid [17, 20], and sleep disturbance is a risk factor for chronic pain. Further research is necessary to examine the indirect benefits of insomnia treatment on chronic pain and vice versa, as well as to assess the benefits of treating insomnia and chronic pain jointly.

Sleep and Depression

In addition to pain, sleep is related to mood, in particular depression. Evidence for this connection comes from observational investigations [27, 28], sleep deprivation studies, longitudinal work, and interventional studies. Sleep deprivation impairs multiple domains of emotional functioning. Experiments indicate that sleep deprivation increases negative reactivity to stressors and stimuli [29] and negative mood [30, 31], as well as impairs coping, frustration tolerance, and emotional intelligence [32, 33].

Sleep disturbance is a core symptom of depression, with disrupted sleep presenting in over 90% of patients diagnosed with depression [34, 35]. Less work has examined the link between OSA and depression, but a recent review revealed elevated rates of depression in patients with OSA [36]. Moreover, longitudinal research has identified insomnia a risk factor for depression. Li, Wu, Gan, Qu, and Lu conducted a meta-analysis indicating that insomnia increases the risk of depression by more than twofold [37••]. Less longitudinal work has examined the link between OSA and depression; however, Peppard, Szklo-Coxe, Hla, and Young followed 1408 persons over 4 years and found that an increase in OSA severity corresponded with increased risk of depression [38].

Final evidence for the connection between sleep disturbance and depression comes from intervention studies. A meta-analysis of 23 studies examining the impact of insomnia

treatment on comorbid depression found a moderate to large effect of insomnia treatment on depressive symptoms, suggesting that treating insomnia improves mood [39•]. There is less work on the indirect effects of OSA treatment on depression, but the existing research reveals a similar trend. Edwards et al. followed patients being treated for OSA at a sleep clinic ($n = 426$) for 3 months and found that CPAP treatment reduced symptoms of depression [40].

To conclude, there is a large body of research showing that insomnia is related to depression: sleep deprivation disrupts mood [29–31], insomnia is a risk factor for depression [37••], and effective treatment of insomnia relieves depressive symptoms [39•]. Further research is necessary to elucidate the relationship between depression and OSA.

Depression and Pain

Considerable experimental work has examined whether individuals with depressed mood have altered perceptions of pain compared with non-depressed individuals. A meta-analysis found mixed results, with some evidence for similar pain tolerance among depressed and non-depressed individuals, though this relationship may vary based on the intensity of the pain stimuli [41]. Importantly, the meta-analysis was limited to individuals without chronic pain conditions. In a cross-sectional sample of individuals with chronic low back pain, depression was the strongest predictor of pain-related disability, higher than pain intensity, anxiety, or somatic symptoms [42]. Depression can also influence pain-related treatment decisions. A study examining over 2000 patients at a chronic pain clinic found that, among non-depressed participants, pain severity predicted opioid use; however, among participants with depression, the probability of taking opioids did not change based on pain severity [43].

Longitudinal studies suggest a high synchronicity between depressive symptoms and chronic pain. For example, a 4-year longitudinal study found that changes in depressive symptoms positively predicted changes in pain symptoms [44••]. Additionally, compared with participants without a mental health disorder, the presence of depression was associated with both greater pain severity and a higher reported number of pain locations over time. Of note, the study found evidence indicating that depression continues to negatively influence pain ratings, even after the remission of mental health symptoms [44••]. Another longitudinal study examining patients with a variety of pain conditions found that the presence of depression symptoms predicted both pain and pain-related disability over several months [45]. In contrast, pain and pain-related disability both failed to predict depression symptoms. Evidence also supports the presence of a bidirectional relationship between depression and pain. An 8-year longitudinal study found that participants with fibromyalgia had an increased risk of developing subsequent depression and that participants with depression had a significantly elevated risk of developing future fibromyalgia syndrome [46].

A variety of interventions have shown promise in treating comorbid depression and chronic pain. Traditional psychosocial interventions, such as CBT, are associated with known improvements in both pain and depression [47]. As a result, recent research has examined the effect of these treatments using novel delivery methods. For example, compared with those randomly assigned to a control group, participants with comorbid depression and pain who received internet-delivered CBT showed significant decreases in depressive symptoms and pain [48]. Newer "third-wave" psychosocial interventions have also shown promise. A meta-analysis of 25 RCTs examining the effect of acceptance and mindfulness-based interventions for chronic pain showed small effects for both pain and depression [49].

The overlap between depression and chronic pain is well-established, with recent evidence highlighting the bidirectional relationship between both conditions [44••, 45, 46]. Perhaps in part because emotions are known to contribute strongly to the perception and management of chronic pain, behavioral interventions have shown success in treating individuals with comorbid pain and depression [47, 48]. Further research is needed to examine how such interventions can be the most widely and efficiently implemented.

Putting It All Together: Sleep, Depression, and Pain

Experimental work examining sleep, pain, and depression is currently limited. One study examined the interaction between experimentally induced sleep fragmentation and negative mood on pain perception among young healthy adults [50]. Compared with a night of undisturbed sleep, a night of induced sleep fragmentation was associated with increased pain sensitivity. In contrast, no interaction effect between sleep and mood on pain was observed. These findings are incongruent with a prior study that examined the effect of one night of sleep disruption via forced awakening compared with a night of uninterrupted sleep among healthy adults [51]. Neither negative affective state, negative affective pain facilitation, nor negative attention bias were altered by sleep continuity disruption. In contrast, sleep disruption attenuated the inhibition of pain by positive affect as well as attention bias to positive affective stimuli. Future research would benefit from examining the effect of experimentally manipulated sleep among clinical pain populations or individuals with clinical depression.

Growing evidence from observational studies suggests that depression may mediate the relationship between sleep and pain, though some heterogeneity in the results exists. A cross-sectional study examining individuals with osteoarthritis found that sleep was independently associated with both pain and depression and that the sleep–pain relationship was

fully explained by depressive symptoms [52]. Support for the role of depression as a mediator is also found among younger chronic pain populations. In a study examining a pediatric chronic pain sample, depressive symptoms mediated the relationship between sleep quality and pain intensity, as well as the association between sleep quality and pain interference [53]. Preliminary evidence suggests that the influence of depressive symptoms may be counteracted by protective factors. In a nationally representative sample of older adults, negative affect mediated the relationship between sleep and pain interference; however, the relationship between sleep and pain was also found to be buffered by positive affect [54•]. Different combinations and ordering of sleep–depression–pain may exist. For example, in a cross-sectional sample of individuals with multiple sclerosis, chronic pain–predicted depression and 80% of the variance in depression were accounted for when sleep disturbance, fatigue, and anxiety were included in the models [55].

The longitudinal research on sleep, depression, and pain is variable in terms of measurement frequency (e.g., ecological momentary assessment design versus yearly assessment), sample size, sample (headache, osteoarthritis, and those experiencing a depressive episode), and other factors examined (e.g., stress, anxiety, catastrophizing, and physical function). As such, it is unsurprising that findings differ across studies, whereby a risk factor is identified in one study but not another. Across the literature, there is evidence that sleep predicts subsequent pain [56–61] and depression [52] and pain predicts subsequent depression and sleep disturbance [62]. For example, Nicassio and Wallston (1992) examined 242 rheumatoid arthritis patients over a 2-year period and found that patients with high levels of pain and sleep problems were at greater risk of developing depression than patients with high levels of pain but normal sleep [62]. In a similar vein, Hamilton, Catley, and Karlson (2007) used ecological momentary assessment over 2 days in patients with fibromyalgia or rheumatoid arthritis ($n = 49$), revealing that sleep buffered the relationship between pain and affect [63].

Emerging Science in Sleep, Depression, Pain: a Conceptual Model

Recent literature has increasingly turned towards biological factors to explain the co-occurrence and interactions among sleep disturbance, pain, and depression. The vulnerability model of tonic/phasic dopamine dysregulation proposes that abnormalities in the mesolimbic dopamine system promotes insomnia, chronic pain, and depression symptoms and that persistent exacerbations of these symptoms create a feedback loop, which further contribute to dopamine dysregulation [64]. Since this original model was proposed, more recent work has attempted to identify additional biological correlates implicated in all three conditions. A recent critical review concluded that shared biological mechanisms include HPA axis dysregulation, decreased levels of brain-derived neurotropic factor, decreased levels of serotonin (5-hydroxytryptamine, 5-HT), and increased levels of proinflammatory cytokines [65••]. These findings point to the need for a collaborative effort between basic science researchers and clinicians in the design, formulation, and implementation of studies to further tease out the shared complex neurobiological and behavioral pathways between these three conditions. Further insight on the mechanisms underlying the relationship between sleep, pain, and depression comes from a recent twin study of 400 individuals [66]. The study estimated heritability for sleep quality at 37%, pain at 25%, and depression at 39%, with a genetic correlation between sleep quality and pain ($r_g = .69$), pain and depression ($r_g = .56$), and depression and sleep quality ($r_g = .61$). These findings provide initial evidence for a genetic link between sleep quality and both pain and depression. Please see Fig. 1 for a proposed model of insomnia, depression, and pain.

Clinical Recommendations Given the prevalence of the sleep–depression–pain triad and the efficacy of behavioral treatments for all three individual disorders, the time has arrived for developing and testing interventions that address all components simultaneously to harness a synergistic effect. In other words, the pernicious downward spiral where insomnia, pain, and negative mood amplify and exacerbate each other presumably operates in a reverse, positive upward spiral where enhancements in one domain lead to improvements in the others. Although research on treatments for the full triad are lacking, there is a large body of research on hybrid treatments for pain and depression (see discussion above) and a considerably smaller group of studies testing hybrid CBT for pain and insomnia [26, 67–70]. Several of these studies in the latter group provide initial support for treating pain and insomnia in tandem.

There are two potential approaches to creating a triadic intervention that is both efficient and efficacious. One would be an omnibus approach that combines the briefest elements of proven treatments for each separate condition. Abbreviated behavioral therapy for insomnia [71] lends itself well to this hybrid method because it has been shown to be effective using a total of 130 min of treatment time. That means that CBTI can be fully delivered using approximately 25% of the content of an 8-session combined treatment protocol, leaving the remaining 75% for the most efficient modules derived from evidence-based approaches for depression and pain, respectively. Examples of brief modules for those disorders include behavioral activation for depression, pacing for chronic pain, and problem solving for both depression and pain.

Another approach with promise would be to create a hybrid treatment that addresses common factors that underlying all three conditions. For example, mindfulness training has

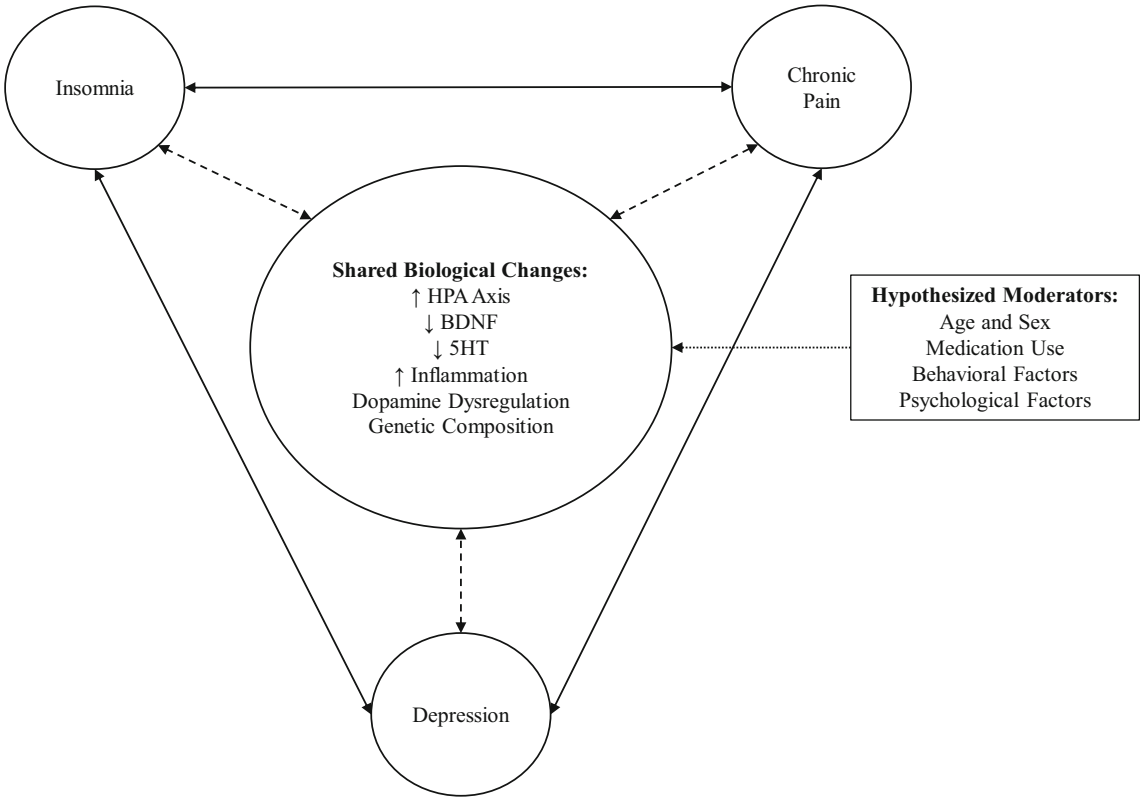

Fig. 1 Integrated model of insomnia, chronic pain, and depression. Solid arrows represent bidirectional pathways connecting insomnia, chronic pain, and depression. Dashed arrows represent hypothesized pathways through which each condition influences the other conditions. HPA Axis hypothalamic–pituitary–adrenal axis, BDNF brain-derived neurotrophic factor, 5HT 5-hydroxytryptamine (serotonin receptors). Model is an integrated model based on previous conceptualizations of the sleep-depression-pain triad [64, 65••]

demonstrated efficacy for the treatment of all three conditions and might serve as a foundational aspect of such a triadic treatment approach. Similarly, a common factor in all three conditions is a tendency to become reactive rather than acting in ways that are consistent with life values and goals. Acceptance and commitment therapy has the goal of teaching patients to be less reactive to their symptoms and more value oriented. Such an approach could be applied to individuals with comorbid sleep, pain, and mood difficulties by reducing reactivity to and preoccupation with sleeplessness and chronic pain and promoting value-based activities to improve mood. Cognitive approaches that teach patients to identify and counteract dysfunctional thinking and erroneous beliefs are another prime candidate for a common factor approach. For example, there is good evidence that catastrophizing is a frequent cognitive error in all three conditions.

Future Research Directions Sleep, mood symptoms, and pain all display significant day-to-day fluctuations. Exploration and examination of these fluctuations are of critical importance. One method used to assess variability is by calculating average fluctuations in symptoms [72]. For example, a study examining community-dwelling older adults found a relationship between the average day-to-day inconsistencies in pain reported over a week and self-reported sleep disturbance [73]. Additionally, this relationship was found to be partially mediated by depressive symptoms. Another method for assessing daily fluctuations is via the use of daily self-report diaries. In a microlongitudinal study examining the bi-directional relationship between sleep and pain, better sleep predicted lower pain the following day; however, daily pain ratings did not predict subsequent night's sleep [59, 74]. Finally, novel self-report measures, such as the Pain-Related Beliefs and Attitudes about Sleep (PBAS) may shed light onto the prevalence and role of dysfunctional sleep beliefs within the context of chronic pain [75]. Examinations into patients' beliefs may be useful given research indicating that patients hold stronger beliefs about the effect of pain on sleep and mood, than the effect of sleep and mood on pain [76].

Conclusion

Sleep is fundamental to optimal human functioning. Unfortunately, large segments of the population suffer from any number of sleep disturbances. Growing empirical and

clinical evidence suggests that disruptions in sleep are associated with increased frequency and intensity of pain. A smaller, yet growing, body of evidence has identified depressive symptoms as a potential important third variable linking sleep and pain. This negative triad of sleep, depression, and pain presents numerous conceptual and clinical challenges. We summarized the evidence for the relationships between: (1) sleep and pain, (2) sleep and depression, and (3) depression and pain. We then presented a conceptual model of the sleep-depression-pain triad, along with clinical recommendation and future scientific directions. Increased recognition of the complex interrelations among sleep, depression, and pain is needed to promote professional discourse and scientific discovery.

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Compliance with Ethical Standards

Conflict of Interest Scott Ravyts, Sarah C Griffin, and Bruce Rybarczyk each declare no potential conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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