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ALTERNATIVE TREATMENTS FOR PAIN MEDICINE (M JONES, SECTION EDITOR)

Sleep as a Therapeutic Target for Pain Management

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Abstract

Purpose of Review The purpose of this review is to provide a summary of the utilization of sleep as a therapeutic target for chronic pain and to evaluate the recent literature on current and proposed pharmacologic and non-pharmacologic sleep interventions used in the management of pain disorders.

Recent Findings Sleep is a promising therapeutic target in the treatment of pain disorders with both non-pharmacologic and pharmacologic therapies. Non-pharmacologic therapies include cognitive behavioral therapy and sensory-based therapies such as pink noise, audio-visual stimulation, and morning bright light therapy. Pharmacologic therapies include melatonin, z-drugs, gabapentinoids, and the novel orexin antagonists. However, more research is needed to clarify if these therapies can improve pain specifically by improving sleep.

Summary There is a vast array of investigational opportunities in sleep-targeted therapies for pathologic pain, and larger controlled, prospective trials are needed to fully elucidate their efficacy.

Keywords Chronic pain · Insomnia · Sleep disorders · Sleep hygiene

Introduction

Chronic pain is one of the most common conditions in the United States, impacting over 50 million adults nationwide [1]. In fact, the economic impact of pain disorders has been shown to surpass that of other prevalent conditions such as heart disease, cancer, and diabetes [2]. Accordingly, there is a great need for finding efficacious treatments for chronic pain. One potential therapeutic target in the management of chronic pain is sleep. Pain and sleep have a complex reciprocal relationship. Disordered sleep impacts 40–80% of patients with chronic pain conditions [3–7], and 25–50% of patients with sleep disorders have chronic pain [8–10]. Sleep disturbance is common regardless of the potential underlying pain mechanism (e.g., nociceptive [11], neuropathic [12], or nociplastic [13]), and is present in conditions ranging from cancer pain [14] and low back pain [15] to fibromyalgia [16]. Patients with concomitant sleep and chronic pain disorders are likely to experience significant lifestyle and social limitations and decreased work productivity, leading to significant quality of life and economic impacts [17, 18]. On the other hand, given the intertwined relationship between sleep disorders and chronic pain, effective interventions optimizing sleep thereby have great potential for improving chronic pain management. While many reviews evaluate the relationship between pain and sleep, none focuses on how sleep-targeted interventions specifically can be used as modalities to treat chronic pain. This narrative review focuses on the utilization of sleep as a therapeutic target for chronic pain and aims to evaluate the literature on current and proposed pharmacologic and non-pharmacologic sleep interventions.

The Effect of Sleep Disruption on Pain

It has long been observed that sleep, particularly disturbed sleep, worsens pain. In the 1930s, Copperman et al. found an inverse relationship between sleep deprivation and sensory thresholds to von Frey filaments [19]. Years later in 1976, Moldofky and Scarisbrick showed that non-REM

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sleep deprivation-induced diffuse musculoskeletal pain in healthy volunteers [20]. Since then, numerous studies have supported the concept that poor sleep increases pain sensitivity and severity. Notably, Haack et al. demonstrated that quantitative accumulation of sleep deprivation over a 12-day period can lead to the spontaneous development of body aches, stomach pain, and back pain [21]. Schuh-Hofer et al. showed that even just one night of sleep deprivation increased hyperalgesia to cold, pinprick, blunt pressure, and heat stimuli in healthy volunteers [22]. More recently, Iacovides et al. showed that healthy female volunteers experienced increased pain sensitivity to both superficial (pinprick) and deep (ischemic) pain after 2 days of fragmented sleep [23]. There has been special attention paid to slow wave sleep disruption with overall findings suggesting it may increase pain sensitivity [24–27]. Previous reviews by Smith and Haythornthwaite [28] and Finan et al. [29] list a plethora of articles demonstrating that sleep is both a predictor and aggravator of numerous pain disorders, including headache [30–32], fibromyalgia [33–35], burn injury pain [36], musculoskeletal pain [37], and rheumatoid pain [38, 39]. The effects of sleep deprivation may even apply to the so-called "chronification" of acute pain. In one observational study of 110 patients undergoing total knee replacement surgery, patients who experienced disordered sleep during their post-operative course had a greater risk of developing subsequent chronic pain [40]. Also of clinical interest is the potential for sleep deficiency to reduce the efficacy of opioids, leading to higher opioid requirements and a potentially greater risk of opioid use disorder [41]. Two secondary analyses of randomized controlled trial (RCT) data by Vitiello and colleagues found that improved sleep is associated with improved chronic pain symptoms [42, 43]. Overall, there is a significant volume of literature that associates sleep deprivation with diverse forms of pain and suggests that treating disordered sleep could have a secondary benefit of treating chronic pain conditions as well.

Non-pharmacologic Therapies

The non-pharmacologic sleep-targeted therapies for chronic pain have a favorable safety profile and avoid the side effects associated with pharmacologic sleep therapies (Table 1).

Cognitive Behavioral Therapy

Cognitive behavioral therapy for insomnia (CBT-I) involves multiple components including cognitive interventions, behavioral interventions, and psychoeducational interventions to improve sleep. Several systematic reviews and meta-analyses [44–46] and RCTs [47–50] have demonstrated that CBT-I improves both sleep quality and pain symptoms. Two of these RCTs specifically showed that reductions in sleep disturbance could predict subsequent pain reduction [49, 50]. CBT-I, which specifically addresses insomnia, may yield a longer duration of pain reduction compared to cognitive behavioral therapy for pain alone (CBT-P) [51, 52], and a combination of CBT-I and CBT-P techniques may be even more advantageous [53, 54]. An open-label study assessing changes on functional magnetic resonance imaging found that CBT-I was superior to CBT-P in decreasing neural activation in response to painful stimuli, suggesting improved sleep could be the underlying mechanism [55]. CBT-I has been shown to have superior outcomes for sleep quality, pain intensity, and emotional distress compared to sleep hygiene alone in fibromyalgia [56]. CBT-I has the additional advantage of being available via remote methods (e.g., internet or telephone), potentially facilitating improved patient access [57, 58]. There is some limited and conflicting evidence that suggests CBT-I only improves sleep quality and not pain symptoms, namely one RCT of 54 patients [59], one systematic review [60] in which only two RCTs were ultimately assessable, and one meta-analysis that was underpowered [61]. However, CBT-I overall appears to be a compelling sleep-targeted therapy for pain management given the breadth of evidence supporting its efficacy and its lack of reported adverse effects.

Sensory-Based Interventions

Other sleep-targeted pain therapies focus on the senses. One murine study found that exposure to pink noise could increase sleep spindle density with a correlated reduction in chronic pain [62]. Like pink noise, audio-visual stimulation (AVS) is another sensory-based intervention targeting sleep. Using pre-programmed light and sound patterns, AVS can promote sleep quality, as it has been shown to potentiate delta brain waves on electroencephalography [63]. A pilot study by Tang et al. showed that AVS may be efficacious in improving both insomnia and pain [64]. However, a third, albeit small scale, follow-up study failed to find significant differences between AVS and placebo, as patients in both groups reported an improvement in pain and sleep [65]. Bright light therapy, which targets sleep via the Circadian rhythm, has also been used. Bright light therapy has been shown to be effective in treating sleep problems such as circadian rhythm disorders and insomnia [66]. Two pilot studies [67, 68] and two prospective trials [69, 70] suggest it can also improve pain sensitivity across multiple chronic pain disorders. Considering their ease, accessibility, and lack of reported side effects, sensory-based interventions are an enticing target for future research into the utilization of sleep therapy in the treatment of pathologic pain, but larger-scale, placebo-controlled trials are needed.

Table 1 Recent clinical studies on the effect of non-pharmacologic therapy for insomnia on pain symptoms

Disease classification	Intervention	Study design (# subjects)	CBT-I benefit to pain	References
Fibromyalgia	CBT-I	Systematic review with meta-analysis (5 studies for meta-analysis with $N=294$)	CBT-I improves pain ($p=0.002$)	Climent-Sanz et al. [44]
Varied chronic pain disorders	CBT-I	Systematic review with meta-analysis (9 studies for meta-analysis with $N=385$)	CBT-I reduces pain ($p=0.02$)	Whale et al. [45]
Chronic non-cancer pain	CBT-I	Systematic review with meta-analysis (12 studies for meta-analysis with $N=762$)	CBT-I decreases pain symptoms ($p=0.006$)	Selvanathan et al. [46]
Chronic migraine	CBT-I	Bayesian analysis of 2 RCTs ($N=74$)	CBT-I decreases headache frequency by 6.2 days (95% CrI: −9.7 to −2.7)	Smitherman et al. [47]
Chronic non-cancer pain	CBT-I	Randomized controlled trial ($N=20$)	CBT-I reduces pain interference ($p<0.05$)	Tang et al. [48]
Knee osteoarthritis	CBT-I	Randomized controlled trial ($N=74$)	CBT-I shows longer sleep time in patients with pain reduction ($p=0.01$)	Salwen et al. [49]
Varied chronic pain disorders	CBT-I	Randomized controlled trial ($N=54$)	CBT-I improved sleep but not pain parameters	Wiklund et al. [59]
Chronic osteoarthritis	CBT-I	Systematic review (2 RCTs)	CBT-I/P may improve short-term sleep but not pain	Papaconstantinou et al. [60]
Traumatic brain injury pain	CBT-I	Systematic review with meta-analysis (12 trials with $N=476$)	CBT improves sleep quality but not pain	Li et al. [61]
Varied chronic pain disorders	AVS	Pilot study ($N=9$)	AVS resulted in improvement insomnia ($p=0.003$), pain severity ($p=0.005$), and pain interference ($p=0.001$)	Tang et al. [64]
Chronic osteoarthritis	AVS	Randomized controlled trial ($N=30$)	AVS did not significantly improve sleep or pain	Tang et al. [65]
Fibromyalgia	Bright light therapy	Pilot study ($N=10$)	Phase advancement in circadian rhythm was associated with improved pain tolerance ($p<0.05$)	Burgess et al. [67]
Chronic low back pain	Bright light therapy	Pilot study ($N=37$)	Bright light led to reduced pain intensity and improved sleep quality ($p<0.05$)	Burgess et al. [68]
Traumatic brain injury pain	Bright light therapy	Prospective trial ($N=33$)	Light therapy improved sleep ($p=0.0001$) and pain interference scores ($p=0.031$)	Elliott et al. [69]
Chronic low back pain	Bright light therapy	Prospective trial ($N=22$)	Bright light reduced pain intensity ($p=0.001$) and increased sleep quality ($p<0.001$)	Burns et al. [70]

CBT-I cognitive behavioral therapy for insomnia, *AVS* audio-visual stimulation

Pharmacologic Therapies

Many pharmacologic modalities for sleep may benefit pain (Table 2). However, it is important to remember that these agents may come with several adverse effects. Sleep medications have been linked to decreased physical quality of life [71] and increased mortality [72]. Drugs such as diphenhydramine may result in daytime sleepiness [73]. Notably, benzodiazepines are associated with a high risk for addiction [74]. However, according to the American Academy of Sleep Medicine, pharmacologic sleep aids may be indicated for people with short-term sleep disruptions caused by emotional upset, jet lag, and shift workers, and for those in whom behavioral therapies fail [75].

Table 2 Recent clinical studies on the effect of pharmacologic therapy for insomnia on pain symptoms

Disease classification	Drug	Study design (# subjects)	Notable outcomes	References
Breast cancer pain	Melatonin	Randomized controlled trial ($N=36$)	Melatonin improves pain scores (η^2 partial) but effect on pain was not dependent on sleep quality	Palmer et al. [77]
Myofascial temporomandibular disorder	Melatonin	Randomized controlled trial ($N=32$)	Melatonin lowered pain scores ($p<0.001$) and improved sleep quality ($p<0.001$) but effect on pain was independent of effect on sleep quality	Vidor et al. [78]
Fibromyalgia	Melatonin	Randomized controlled trial ($N=63$)	Melatonin reduced pain scores more than amitriptyline alone ($p<0.01$) but did not improve sleep	De Zanette et al. [79]
Endometriosis-related chronic pelvic pain	Melatonin	Randomized controlled trial ($N=40$)	Melatonin improved pain and sleep ($p<0.01$)	Schwertner et al. [80]
Primary headaches	Melatonin	Pilot Study (N=49)	Melatonin reduced headache frequency ($p<0.033$)	Bougea et al. [81]
Fibromyalgia	Melatonin	Systematic review (4 trials with $N=98$)	All studies show positive effect of melatonin on fibromyalgia symptoms	Hemati et al. [83]
Varied chronic pain disorders	Melatonin	Systematic review with meta-analysis (30 studies with $N=1967$)	Melatonin reduced chronic pain (95% CI −0.96 to −0.34)	Oh et al. [84]
Any type of pain	Melatonin	Systematic review with meta-analysis (19 studies with $N=1093$)	Melatonin had a strong anti-nociceptive effect ($p<0.00001$)	Zhu et al. [85]
Post-operative pain (colorectal surgery)	Zolpidem	Randomized controlled trial ($N=88$)	Pre-operative zolpidem for sleep improves post-operative pain ($p<0.01$)	Xiao et al. [88]
Post-operative pain (arthroscopic rotator cuff repair)	Zolpidem	Randomized controlled trial ($N=78$)	Zolpidem reduced the need for rescue analgesia ($p=0.033$)	Cho et al. [89]
Post-operative pain (total hip arthroplasty)	Zolpidem	Randomized controlled trial ($N=160$)	Zolpidem decreased sleepiness ($p<0.05$) and reduced hip disability and osteoarthritis outcome score ($p<0.05$)	Shakya et al. [90]
Post-operative pain (total knee arthroplasty)	Zolpidem	Randomized controlled trial ($N=148$)	Zolpidem resulted in lower pain scores and there was a correlation between sleep quality and range of motion ($p=0.015$)	Gong et al. [91]
Post-operative pain (anterior cruciate ligament reconstruction)	Zolpidem	Systematic review (77 RCTs)	Zolpidem decreased post-operative opioid consumption	Secrist et al. [92]
Varied post-operative pain	Zolpidem	Systematic review with meta-analysis (15 trials with $N=1252$. 8 trials for meta-analysis)	Zolpidem decreased pain intensity in short-term ($p\leq0.01$)	O'Hagan et al. [93]
Post-operative pain (fast-track knee and hip replacement)	Zolpidem	Randomized controlled trial ($N=20$)	Zolpidem had no pain benefit despite improvement in sleep quality	Krenk et al. [94]
Fibromyalgia	Suvorexant	Randomized controlled trial ($N=10$)	Suvorexant increased sleep time ($p<0.05$) and reduced next-day pain sensitivity measured by figner withdrawal ($p<0.03$)	Roehrs et al. [98]
Diabetic neuropathy	Filorexant	Randomized controlled trial ($N=170$)	Filorexant had no analgesic benefit	Herring et al. [99]

Table 2 (continued)

Disease classification	Drug	Study design (# subjects)	Notable outcomes	References
Diabetic neuropathy	Pregabalin	Randomized controlled trial ($N=83$)	Pregabalin provided equal analgesia compared to amitriptyline and duloxetine but superior sleep efficacy ($p<0.01$)	Boyle et al. [102]
Postherpetic neuralgia	Gabapentin	Pooled analysis (3 studies with $N=556$)	Gabapentin improved sleep interference and pain scores ($p<0.0001$)	Mehta et al. [103]
Postherpetic neuralgia	Gabapentin	Pooled analysis (3 studies with $N=546$)	Gabapentin reduced pain intensity ($p<0.0001$) with sleep interference being strongest predictor ($p=0.0117$)	Kantor et al. [104]
Restless leg syndrome	Gabapentin enacarbil	Pooled analysis (3 trials with $N=671$)	Gabapentin enacarbil decreased pain scores ($p<0.05$) and reduced sleep disturbance ($p<0.05$)	Bogan et al. [105]
Postherpetic neuralgia	Gabapentin	Pooled analysis (2 trials with $N=719$)	Gabapentin decreased pain scores ($p<0.05$) and sleep interference ($p=0.0008$)	Freeman et al. [106]
Neuropathic pain in spinal cord injury	Gabapentin and pregabalin	Systematic review with meta-analysis (8 studies)	Gabapentin and pregabalin decreased pain intensity ($p<0.001$)	Mehta et al. [107]
Postherpetic neuralgia	Gabapentin	Systematic review with meta-analysis (11 RCTs with $N=2376$)	Gabapentin decreased pain intensity ($p<0.00001$) and improved sleep quality (($p<0.0001$)	Meng et al. [108]
Neuropathic pain in spinal cord injury	Gabapentin and pregabalin	Systematic review with meta-analysis (8 studies with $N=491$)	Pregabalin reduced pain (95% CI − 0.78 to − 0.01) and sleep interference) 95% CI − 1.13 to − 1.02). There was no significant difference in the reduction of pain between pregabalin and gabapentin	Davari et al. [109]
Peripheral neuropathy in dialysis patients	Gabapentin vs. pregabalin	Randomized controlled trial ($N=50$)	Both gabapentin and pregabalin improved pain and sleep scores ($p<0.001$) with no significant difference between drugs	Bivik et al. [110]
Knee osteoarthritis	Pregabalin	Randomized controlled trial ($N=66$)	Pregabalin improved pain ($p<0.0001$) and sleep ($p<0.0001$) metrics	Illeez et al. [111]

Melatonin

Melatonin is an endogenous hormone which is thought to be involved in sleep and pain pathways. Melatonin is long known to play an essential role in the regulation of circadian rhythms [76]. Many studies suggest that melatonin can also reduce chronic pain symptoms, including four RCTs [77–80], a pilot study [81], two systematic reviews [82, 83], and two meta-analyses [84, 85]. However, it is not clear whether melatonin directly provides analgesia, or whether it simply promotes sleep with analgesia as an indirect consequence of improved rest. Four RCTs found that melatonin's analgesic properties were independent of its improvements on sleep quality [77–79, 81]. Perhaps, as one animal study suggests, sleep deprivation induces hyperalgesia by decreasing serum melatonin levels, and melatonin supplements can attenuate this effect [86]. Overall, whether and how melatonin directly provides analgesia remains unclear, with GABA receptors, opioid receptors, endorphins, and other neurotransmitters potentially involved [87].

Z-drugs

Non-benzodiazepine sedative hypnotics, commonly referred to as "Z-drugs" (e.g., zolpidem and zopiclone), act as $GABA_A$ receptor agonists. We did not identify any studies evaluating the utility of Z-drugs for chronic pain. However, there is evidence that zolpidem may have benefits for acute perioperative pain which includes four RCTs [88–91], a systematic review [92], and a meta-analysis [93]. Only one RCT, which involved 20 patients who underwent fast-track total hip or knee arthroplasty, found no benefit for perioperative pain despite an improvement in sleep quality [94]. Conversely, an RCT by Gong et al. assessing 148 patients undergoing total knee arthroplasty found that improved sleep quality from zolpidem was correlated with increased post-operative activity and lower reported pain scores [91]. Although these findings may suggest that Z-drugs could be a promising sleep-targeted therapy in the treatment of pain disorders, their use must be carefully weighed against their potentially serious side-effect profile, which can include sedation, driving impairment, mechanical falls and fractures, and misuse [95, 96].

Orexin Antagonists

Orexin antagonists (e.g., suvorexant, filorexant, daridorexant, and lemborexant) are a class of sleep-aiding medications that inhibits orexins. Orexins are neuropeptides produced by the hypothalamus and are thought to maintain the awake state [97]. Since orexin antagonists are relatively new to the market, studies assessing these drugs and their impact on chronic pain conditions are scarce. One double-blind crossover study in 2020 found that suvorexant improved sleep time and reduced next-day pain sensitivity for patients with fibromyalgia [98]. However, an RCT of 182 patients evaluating filorexant for painful diabetic neuropathy (PDN) found no analgesic benefit [99]. Orexin antagonists represent a new direction and opportunity for research into the pain-sleep interface, but more information will be needed to determine whether they are a promising treatment modality for patients with chronic pain and comorbid sleep disturbance.

Gabapentinoids

Gabapentinoids (e.g., gabapentin and pregabalin) are anticonvulsants commonly used to treat neuropathic pain. Gabapentinoids have well-established analgesic effects [100] and they have been shown to significantly improve sleep quality with treatment durations of 6 weeks or longer [101]. In one RCT assessing patients with PDN, pregabalin provided analgesia equal to that of duloxetine and amitriptyline, but superior improvement in sleep continuity [102]. A pooled analysis of 500 patients with postherpetic neuralgia from two phase 3 RCTs and one open-label phase 4 study found that gabapentin decreased pain and sleep interference, and improvements in sleep and pain control were correlated to each other [103]. Kantor et al. showed that sleep interference scores during the treatment of postherpetic neuralgia with gabapentin were the strongest predictor for pain quality and pain scores [104]. In addition to these, two pooled analyses [105, 106], two meta-analyses [107–109], and two RCTs [110, 111] demonstrate the simultaneous analgesic and sleep-promoting effects of gabapentinoids. Of note, gabapentinoids are often prescribed "off-label" for insomnia even in the absence of concomitant chronic pain [112]. However, gabapentinoids are associated with potentially serious adverse effects, such as sedation, mechanical falls, respiratory depression, and abuse [113]. Additionally, dosages must account for potentially vulnerable patient populations (e.g., older adults) and comorbid conditions (e.g., chronic kidney disease) [114].

Multimodal Therapy

Just as a multimodal approach has gained popularity in the management of acute [115] and chronic pain [116], a multimodal approach to sleep may also be effective. In one RCT, Cheah et al. showed improved analgesia, reduced opioid use, and increased sleep duration and quality in a population of post-operative shoulder arthroplasty patients treated with a multimodal approach of sleep hygiene combined with low dose zolpidem and melatonin [117]. A pilot RCT by Saxena et al. showed that cognitive behavioral therapy as an adjunct

to pregabalin had significant benefits for pain intensity in patients with postherpetic neuralgia [118]. There is a paucity of literature describing the combination of non-pharmacologic with pharmacologic sleep-focused interventions for the purpose of treating pain. However, it appears feasible that this could be a powerful new strategy in the simultaneous treatment of chronic pain and comorbid sleep disorders.

Conclusions

Given the widespread impact of chronic pain disorders and their frequent comorbidity with sleep disorders, therapies which benefit both pain and sleep are doubly beneficial. Disrupted sleep has negative implications for the management and prognosis of pain, supporting the idea that addressing sleep quality could be essential for optimizing pain care. From among the non-pharmacologic therapies, cognitive behavioral therapy has the strongest evidence for improving sleep disorders and pain symptoms. From among the pharmacologic therapies, melatonin has the most literature demonstrating benefits for both sleep and analgesia. However, it is unclear whether melatonin improves pain as a secondary effect of improving sleep, or whether it has independent analgesic mechanisms. Other potential therapies which require additional investigation include pink noise therapy to improve sleep spindle density, AVS, morning bright light therapy, and the novel orexin antagonists. "Z-drugs" and gabapentinoids may have a role in improving sleep quality and pain in selected patients, but these medications are susceptible to potential misuse and abuse, and their potentially serious adverse effects (e.g., sedation and mechanical falls in older patient populations) must be considered. The sleep-pain interface plays a significant role in chronic pain conditions, and additional studies assessing sleep as a therapeutic target are necessary.

Data Availability All data analysed during this study are included in this published article.

Compliance with Ethical Standards

Conflict of Interest None.

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

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