Sleep Deprivation and Pain

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Introduction

Sleep is an activity that is critical for maintaining our health and well-being. Unfortunately, however, sleep-related problems are one of the most common health problems in our society. Up to 40 % of adults report at least one symptom of insomnia annually [1]. Approximately 75 % of Americans report disturbed sleep in any given week [2]. Disturbance in sleep typically results in a range of physical and mental impairments, including alteration in the nervous, metabolic, endocrine, and immune systems, dermal changes, impaired sensory responses, and deterioration in mood and cognition [3].

It has been well established that disturbed sleep is very prevalent in the chronic pain populations. Clinically significant insomnia has been reported by 53 % of chronic pain patients attending pain clinics compared to 3 % of gender- and age-matched healthy people [4]. Approximately 89 % of chronic pain patients seeking treatments present at least one sleep-related complaint [5]. In people with temporomandibular disorder (TMD), the polysomnographic analyses showed that both insomnia and sleep apnea are common [6]. In fibromyalgia, sleep disturbance is ubiquitous, with the reported prevalence of up to 99 % [7].

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The close relationship between pain and sleep can also be seen in people with a primary presentation of insomnia. A large epidemiological study with 47,000 people [8] found that the presence of insomnia is associated with increased prevalence of pain conditions. Over 40 % of people with insomnia complain of at least one chronic pain problem [9].

In general, the relationship between pain and poor sleep is considered to be bidirectional [10]. That is, having pain disrupts the initiation and maintenance of sleep, whereas sleep disruption also worsens pain. In this chapter, we will review the experimental, clinical, and epidemiological research evaluating the effects of poor sleep on pain. We will also review how sleep may be altered by opioid analgesic use.

Poor Sleep and Hyperalgesia

Reported Poor Sleep and Pain Response to Noxious Stimulation

In general, people exhibit increased pain response to experimentally induced noxious stimulation following poor sleep. Patients with rheumatoid arthritis showed a significant relationship between self-rated poor sleep and lower pressure pain thresholds both in joint and non-joint sites [11]. Similarly, TMD patients with primary insomnia have been shown to exhibit reduced pain thresholds to mechanical stimulations in the affected and distal areas [6].

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In a recent laboratory study by Campbell et al. [12], 28 healthy people were tested under two conditions; the heat-capsaicin nociceptive test and the same test with distracting game playing. The subjects who reported chronically short sleep duration (<6.5 h per night on average) exhibited greater secondary hyperalgesia to the heat-capsaicin test. Secondary hyperalgesia in this case is expressed as increased pain sensitivity to mechanical stimulation in the surrounding, but not including, region of the capsaicin-treated skin. Since secondary hyperalgesia implicates hyperexcitability of dorsal horn interneurons [13], the results suggest the possibility that sleep deprivation has adverse nociceptive effects at the spinal level. They also showed significantly attenuated analgesic benefit from distraction with game playing, even though the groups did not differ in the degree of attention to and focus on the game playing task. Reduced benefit from distraction also suggests a possibility that sleep-deprived people may have trouble disengaging themselves from pain.

Past research has implicated that distraction analgesia may result from the activation of the endogenous opioid system [14]. Attenuated distraction analgesia in people with poor sleep suggests that poor sleep may interfere with this activation thereby reducing the analgesic benefit from the distraction technique. As we review in the next section, animal research also suggests that sleep deprivation interferes with opioid-mediated analgesia. Based upon these results, we may speculate that disordered sleep may attenuate the analgesic effects of certain behavioral coping strategies (e.g., distraction) via compromised endogenous opioid activation and effect. As noted, poor sleep is prevalent in chronic pain patients. Clinicians may need to be aware of the possibility of adverse effects of insomnia on distraction-based techniques.

Effects of Sleep Deprivation on Pain Response to Noxious Stimulation

In general, pain response to noxious stimulation seems to increase following poor sleep.

Animal Data: Effects of REM Deprivation on Pain Behavior

Because of the methodological constraints of animal model (i.e., no self-report data), poor sleep has to be experimentally defined by manipulating the quantity of sleep. Most commonly, the deprivation of rapid eye movement (REM) sleep is used in animals as a sleep measure of poor sleep and behavioral indication of response to noxious stimulations as an outcome. REM deprivation is typically achieved by utilizing a platform placed in shallow water, and when muscle atonia occurs in REM, the animal's limb or entire body falls into the water and it awakens. As reviewed extensively in Kundermann et al. [15], the animal studies showed consistent hypersensitivity with REM deprivation using a range of noxious stimulation modalities. A recent study [16], using the thermal preference apparatus, showed that REM deprivation may impact differentially on the nociceptive sensitivity to different types of noxious stimuli. When the animals had a choice of either staying on the hot plate or cold plate, their occupancy time did not differ between the two plates following a non-deprived sleep, whereas following the REM-deprived night, they stayed significantly longer on the hot plate than the cold plate. Although one often assumes the thermal pain of cold-hot sensations to be on one spectrum, evidence suggests that they do employ somewhat different processes [17]. Mechanisms underlying cold hyperalgesia/allodynia are not very well understood at this time, but likely involve multiple pathways. The results suggest that REM deprivation may more greatly augment sensitivity to cold and heat pain should further be studied to examine whether sleep deprivation differentially affects various thermal pain afferent pathways.

Animal Data: Effects of REM Deprivation on Analgesics

There are a few studies that suggest the possibility of REM deprivation interfering with the antinociceptive efficacy of pharmacologic interventions. Rats undergoing REM deprivation showed attenuated analgesia with morphine administration (2.5, 5 mg/kg) in response to the hot-plate

test unless the dosage was very high (10 mg/kg) compared to control rats [18]. Recently, Skinner et al. [19] replicated the results with an interesting supposition that the slowing of paw withdrawal response to heat at the high-dose morphine (10 mg/kg) may not reflect the analgesic effects of opioids but rather it is due to decreased locomotor activity from the high-dose opioid.

It has been suggested [10] that sleep deprivation may reduce opioid binding and/or inhibit opioid protein synthesis, thereby reducing opioid analgesic effects on noxious stimulation. However, the autoradiographical analyses of receptor binding in the aforementioned study [18] showed no difference in the binding of [3H] DAMGO, a highly selective ligand for μ-opiate receptors, to mu receptors in REM-deprived rats compared to control rats. Thus, it is reasonable to assume that attenuated opioid analgesia in sleep-deprived animals do not result from the reduced affinity of mu receptor, although we cannot rule out the involvement of other opioid systems.

Damasceno et al. [20] tested the effects of REM deprivation on analgesic response with tricyclics. They divided rats into two groups: one group underwent REM deprivation whereas the other did not have any restriction of sleep. In each group, rats were given either saline or one of three dose levels of amitriptyline (3, 10 and 30 mg/kg) for 11 days prior to the testing. The REM-deprived rats consistently showed higher sensitivity to nociceptive testing with all doses; the difference was greatest at the highest amitriptyline dose (30 mg/kg) where the control rats showed significant analgesia while such effects were blunted in the REM-deprived rats.

Wei et al. [21] intrathecally administered specific 5-HT receptor subtype antagonists to REM-deprived rats and non-sleep-deprived rats. Compared to non-sleep-deprived rats, REM-deprived rats showed significantly increased pain responses to noxious mechanical stimuli. The effects of spinal 5-HT receptor antagonists are harder to interpret, as there was no effects of 5-HT(3) receptor antagonists, whereas 5-HT(1A) and 5-HT(2C) receptor antagonists had comparable analgesic effects for both REM-deprived and control animals. The results suggest that although some spinally administrated 5-HT receptor antagonists have analgesic effects in general, the effects do not interact with sleep deprivation. This seems at variance with the amitriptyline trial on REM-deprived rats [20] that showed analgesia only for their control subjects. Further studies are needed to clarity the interactive effects between the serotonergic system and sleep deprivation on pain.

Human Data

Experimental deprivation of sleep in humans involves several targets. It may simply reduce the duration of sleep or selectively target three areas: REM deprivation, total sleep deprivation (i.e., subject stays up all night), or deprivation of slow wave sleep (N3 sleep).

Reduced Sleep Duration

Tiede et al. [22] tested heat pain sensitivity in healthy volunteers twice, once after undergoing normal sleep and once after 4 h sleep regimens. The subjects showed significantly increased pain sensitivity to heat stimuli following the deprivation compared to normal sleep. The sleep duration for each phase was confirmed by the use of actigraph; however, how the sleep reduction altered the durations and proportions of each sleep stage could not be ascertained using actigraphy. Interestingly, the study also found that the pain-related-evoked potentials in response to the stimuli were reduced following sleep deprivation. The results appear contradictory; however, the authors argue that this dissociation may present a key to understand the sleep–pain connection in that it reflects an intracortical amplification process, resulting from reduced top-down control of the pain processing accompanied by reduced attentional resource allocation.

Deprivation of Total Sleep or Selective Sleep Stages

In the early uncontrolled study by Moldofsky et al. [23], six healthy young males underwent three consecutive nights of stage IV sleep deprivation. During the deprivation period, their pain sensitivity to pressure stimulation was significantly elevated. Acoustic disruption of N3 sleep

without decreasing sleep duration also reduced pressure pain thresholds by 24 % in middle age, sedentary healthy females on next day [24]. However, not all studies found the pain altering effects of selective N3 sleep deprivation. In the study by Older et al. [25], 13 healthy people underwent 3 nights of selective N3 sleep disturbance. Their pressure pain thresholds were unchanged as a function of the N3 sleep disturbance. Similar results were obtained by Arima et al. [26] who found that ten healthy men did not show changes in pressure pain thresholds following 3 nights of N3 sleep disruption. The variance of the results is difficult to explain. Differences in the methods, sample characteristics, and the levels of interruptions may contribute to the inconsistent results. Additionally, it is possible that hyperalgesic response may not occur as a function of N3 sleep deprivation alone, but as a result of interaction between N3 sleep deprivation and other factors. Further studies are warranted to clarify this point.

Other studies have shown that the effects of sleep disturbance on pain may not be limited to N3 sleep deprivation. Onen et al. [27] tested the pain tolerance following three types of sleep deprivation: Total sleep deprivation, REM deprivation, and N3 sleep deprivation. All three types of deprivation produced decreases in pain tolerance to mechanical stimuli with the total sleep deprivation showing the greatest effect. The level of pain tolerance was restored following recovery sleep. Similarly Roehrs et al. [28] demonstrated that healthy people showed significantly greater pain response following REM deprivation or reduction in sleep duration (4 h). In her editorial comment, Baghdoyan [29] speculates that the modulation of acetylcholine release in the reticular formation (RF) may play an important role in the relationship between REM deprivation and pain, given the demonstrated linear relations between release of acetylcholine in the RF and duration of REM sleep. However, not all studies showed the hyperalgesic effects of REM deprivation. Moldofsky et al. [30] failed to demonstrate changes in pain sensitivity after 3 nights of REM deprivation. Similarly, a recent study [31] showed significant increase in pain sensitivity after 2 nights of total sleep deprivation, but pain sensitivity was unchanged after 4 nights of REM deprivation in healthy males.

Kundermann et al. [32] assigned 24 healthy people either to 2 nights of total sleep deprivation (i.e., no sleep) with a recovery sleep night in between, or control condition (no sleep deprivation). The subjects who had been sleep-deprived showed significant decreases in heat pain thresholds that were normalized after the restored sleep. On the other hand, 1 night of total deprivation in healthy people did not alter pain threshold or tolerance to mechanical and thermal stimuli [33]. Similarly, 1 night total sleep deprivation (about 39 h continuous waking) in patients with chronic pain of unknown origin resulted in increased clinical pain report but not alteration in pain thresholds in heat, cold, and pressure stimuli [34].

To summarize, research evaluating the effects of various types of sleep deprivation on pain response shows inconsistent results. The discrepancy is difficult to explain. Many of the studies are well controlled; selective deprivation studies typically show the polysomnographic data to ascertain the effects of deprivation (i.e., deprivation was selectively conducted). It is possible that the relationship between sleep deprivation and pain is not linear and other moderators and mediators are at work to make the effects variable. Human pain perception is known to be influenced by a range of cognitive, emotional, behavioral, and environmental factors [35]. For example, experimental studies have shown that pain-related self-efficacy is associated with greater pain sensitivity in response to noxious stimulation [36–38]. Improvement in self-efficacy reduces pain sensitivity but the effects may be attenuated by a use of naloxone [39], suggesting the involvement of endogenous opioid system in the self-efficacy belief. Other cognitive factors, such as belief that there is nothing one can do to reduce pain, has shown to lead greater neural activation in the pain-perception areas of the brain [40]. Some of those factors may override the adverse hyperalgesic effects of sleep deprivation. Identification of such factors will be helpful in treatment planning for those whose insomnia is particularly recalcitrant.

Another important point to keep in mind is the possibility that acute deprivation of sleep in a laboratory setting can be quite different from chronic insomnia chronic pain patients typically present. We will now review the effects of poor sleep on pain reports. However, it should be noted that unfortunately, research evaluating the effect of chronic insomnia on pain sensitivity is scarce and not well understood.

Cross-Sectional Associations Between Poor Sleep and Clinical Pain

A significant relationship between self-reported poor sleep and pain severity has been reported in people with a range of pain/medical conditions including advanced cancer [41], burn injuries [42], and rheumatoid arthritis [43]. For migraine patients, self-reported poor sleep is associated with the severity of allodynia [44]. O'Brien and colleagues [45] examined 292 patients with chronic facial pain, back pain, and fibromyalgia and found a significant relationship between poor sleep and pain, although emotional distress may also have mediated the relationship. In pediatric patients with headache, severe migraine headaches were associated with more severe sleep disturbance compared to milder headaches [46].

Research provides overwhelming support for the cross-sectional association between self-reported poor sleep and pain. Conditions with high likelihood of sleep disturbance and pain tend to show significant relationship between the two. Similarly, chronic pain patients who report high pain levels also report high degree of sleep disturbance. However, the cross-sectional nature of these studies does not allow us to make an inference for any causal relationship between sleep disturbance and pain.

Furthermore, when sleep is measured objectively, the relationship may become more tenuous. In our recent study [47], self-reported poor sleep (number of times awake during night and how refreshed patients felt upon wakening) was significantly correlated to reported pain severity, whereas the relationship was not present for the objective (actigraphically obtained) sleep measures.

Several studies investigated the possibility that disturbances in specific sleep architecture are related to pain conditions. In the aforementioned study with migrainous children [46], subjects with severe headaches had significantly lowered percents of N3 sleep and REM sleep. Earlier studies [48–50] suggested that fibromyalgia may be associated with greater alpha intrusion to sleep relative to healthy people. However, alpha intrusion does not seem to be present in all fibromyalgia patients and its relationship to symptoms is unclear [51]. Furthermore, a recent study [52] showed that the sleep architecture did not differ between fibromyalgia patients and healthy controls. In contrast, in another study [53], fibromyalgia patients exhibited shorter duration of Stage II, not N3 sleep, than did the matched healthy subjects, with an inverse relationship between daily pain scores and duration of Stage II.

The Relationship Between Poor Sleep and Pain Complaints

Nonclinical Samples

Increased pain complaints seem to follow nights of poor sleep even for healthy individuals, who are typically free of pain problems. In Haack's study [54], 40 healthy adults were asked either to reduce sleep to 50 % of their normal duration or to maintain their normal sleep for 12 consecutive nights. Those with sleep restriction reported greater pain complaints, generalized body pain, back pain, and stomach pain, across days. Other research suggests that not just insomnia but also hypersomnia may result in greater pain. Daily assessment of sleep and pain in a large sample of individuals in the general population showed that shorter (<6 h) or longer (>9 h) sleep duration was followed by increased pain in the next day [55].

Clinical Samples

The sequential relationship seems to hold in the clinical pain populations as well. Affleck et al. [56] followed fibromyalgia patients for 30 days using the temporally sequential analyses of sleep

and pain and found that greater pain followed poorer sleep. Similarly, sequential analyses of sleep and pain over 10 days in adolescents with chronic pain [57] revealed that longer sleep duration and higher sleep interruption predicted the pain level in the next day. In a comprehensive study evaluating the two-way relationship between sleep and pain, Tang et al. [58] assessed sleep, pain, mood, and presleep arousal in 119 patients with various chronic pain conditions for 1 week. The results overall showed that no consistent relationship between sleep quality and pain. Presleep pain level was not a reliable predictor of sleep quality, whereas presleep cognitive and physiological arousal level did relate to the quality of sleep that night. Sleep quality seemed to have modest relation to pain next day although the effects are short-lived; the relationship only holds with pain reports taken in the earlier part of the day.

The sequential relationship seems less obvious when the objective measures of sleep are employed. In a recent report, 22 women with chronic pain underwent a 2-week assessment of pain and sleep, both self-report and actigraphic monitoring. Subjectively reported poor sleep, but not the actigraphically obtained sleep measures, was related to increased pain in the next day [59]. Another study using actigraphy [60] compared sleep patterns from ten consecutive nights between 61 teens with chronic pain and 60 healthy controls. Although the two groups were comparable in the sleep patterns of night time sleep, chronic pain teens had significantly greater daytime sleep, which was associated with greater functional limitation.

Sequential analyses between sleep and next day pain generally demonstrate that subjectively determined poor sleep, either insomnia or hypersomnia, seems to adversely impact pain at the later time. However, as in the cross-sectional analyses, the relationship may not hold when the quantity and quality of sleep are measured objectively.

The mismatch between subjectively reported and objectively measured sleep does not represent a pain-specific condition and is fairly common. Such discrepancy has been found in people with sleep disorders [61], depressed patients [62, 63], and community sample [64]. In our study of chronic pain patients whose sleep was measured seven consecutive nights, the average discrepancy between subjective and objective sleep was ±73 min per night, with greater discrepancy associated with restless sleep [47]. At this time, mechanisms underlying the discrepancy are not understood. The results raises an interesting question as to whether some of these discrepancies may reflect a form of sleep misperception ("paradoxical insomnia") in which a person complains of insomnia without any objective signs of sleep deprivation [65]. The misperception can go either direction, under-, or overestimation of the duration of sleep [66]. Future research needs to delineate how the discrepancy may be associated with various aspects of pain and wellness in general.

Effects of Poor Sleep on the Development of Chronic Pain

Research with prospective follow-up evaluation typically suggests that sleep disturbance is one of the contributors to the development of chronic pain. A study that followed 112 children with neck pain showed poor sleep and mood predicted the development of widespread body pain 1 year later [67]. Similarly, a study followed 394 high school students found that sleep disturbance and fatigue are significant predictors for the presence of weekly neck pain at age 22–25 [22–25, 68].

Sleep also seems to predict the development of chronic pain in adults. In a population study with 3,171 people, Gupta et al. [69] found that 324 people developed a new chronic widespread pain (CWP) 15 months later. Poor sleep at the baseline was a significant predictor, with an adjusted odds ratio of 2.7. Kaila-Kangas et al. [70] followed 902 metal workers for 28 years and found that the baseline sleep disturbance was a significant predictor for later hospitalization for back-related problems. Even when the workers with chronic or recurrent back pain at the baseline were excluded, the hazard ratio was 2.1 for those reported with the sleep latency disturbance and 2.9 for those with the latency problem and

the multiple wakening. Sleep may also be a factor for facilitating the development of chronic pain in people with a history of severe injury. Castillo et al. [71] found that for those who had severe lower extremity injuries with sleep disturbance at the 3 months post-discharge are more likely to report chronic pain 7 years later.

The development of chronic pain is complex and multifactorial. Research consistently shows that sleep is a significant predictor, albeit the reported ORs suggest modest predictive power. It is reasonable to assume that sleep disturbance is just one of the contributors to the onset of chronic pain. A number of variables, including the pain parameters at onset, disease/injury severity, and other psychological variables, are likely to contribute to the development of chronic pain. However, it is clear although those with a history of pain or injuries are clearly high risk for later development of chronic pain, sleep disturbance seems to further facilitate such development. Assessment and therapy addressing sleep problems may be critical for the secondary prevention of chronic pain for those who are vulnerable.

Effects of Opioid Analgesics on Sleep

We have thus far reviewed the effects of poor sleep on pain. We would like to shift the direction here to discuss how opioid medications may influence sleep. Opioid medications are one of the most commonly prescribed medications [72]. Based upon a population survey [73], it is estimated that over 43 million adult Americans regularly use opioid medications.

Acute administration of opioid to opioid naïve subjects has a significant disrupting impact on sleep architecture. For example, acute administration of 5 mg methadone or 15 mg sustained-release morphine sulfate by month to opioid naïve, healthy people decreased N3 sleep and increased the duration of Stage II [74]. The same results were obtained with an acute administration of IV morphine (0.1 mg/kg) compared to saline IV in healthy individuals. Cronin et al. [75] compared the effects of two types of intraoperative and postoperative epidural analgesia (fentanyl vs. bupivacaine) on sleep in women undergoing a surgery requiring a low abdominal incision. Only the fentanyl group showed significantly reduced N3 sleep percent in the early postoperative phase.

Research is relatively scarce in the investigation of the relationship between chronic opioid therapy and sleep architecture. As reviewed by Wang and Teichtahl [76], the effects of opioids on sleep differ as a function of opioid phasing: Initiation, maintenance, acute abstinence, and prolonged abstinence. In an early study with six healthy men in a federal prison, Martin et al. [77] examined the effects of methadone at these four phases on sleep. They observed an increase in the total sleep duration during the ascending and stabilization weeks; there was a significantly increased duration of N3 sleep and REM 10 weeks after terminating the opioids. On the other hand, the comparisons between methadone maintenance patients (for opioid addiction, not for pain: 2–10 years of therapy) and healthy people showed that the patient group had significantly shorter N3 sleep, less wake after sleep onset, and fewer arousals during sleep than did the healthy controls [78]. Another study [79] also showed that methadone maintenance patients showed longer Stage II and shorter REM durations.

The implications of these studies are difficult to apply to clinical pain populations. It is likely that pain patients may experience significant sleep disturbance with the initiation of opioid treatment, as the studies of acute opioid administration to naïve subjects would imply. Less clear, however, is how chronic opioid therapy would influence sleep architecture in patients with chronic pain. Paradoxical results of both analgesia and pro-nociceptive effects via sleep disturbance may be co-present with prolonged opioid use. Anecdotally, we have observed that some of our patients with short acting opioids complain of waking at night with pain and unable to fall back asleep. The problem tends to resolve when the medication is switched to a long acting one. It is possible that these with short acting treatment may be experiencing nightly micro-withdrawal, thereby disturbing sleep. Further research in this area is urgently needed.

Another important consequence of opioid use is sleep-disordered breathing. Research evaluating the acute administration of opioids is limited to healthy subjects. The results are variable; one study shows decreased ventilatory response to hypoxia [80], whereas others decreased ventilatory response to hyperoxia, or no alteration in respiration during sleep [76, 81]. In contrast, growing evidence suggests that chronic opioid use increases the risk of central sleep apnea. The comparison between methadone maintenance patients and healthy controls [82] revealed significantly reduced hypercapnic ventilatory response and increased hypoxic ventilatory response in methadone maintenance patients relative to healthy controls. Thirty percent of the methadone maintenance patients had the central apnea index of greater than 5, whereas the highest index for the healthy controls was 1. No group difference was found on the obstructive sleep apnea index.

Similarly, an observational investigation of 140 chronic pain patients on chronic opioids [83] revealed that sleep apnea is common in these patients, with 39 % with obstructive sleep apnea and 24 % with the central sleep apnea. The daily doses of methadone and benzodiazepines were linearly related to central apnea index. In a study with people referred for a sleep study [84], patients taking chronic opioids exhibited significantly greater central apnea index than those without opioid medications, although the group did not differ on the obstructive sleep apnea index. The results are replicated by a recent multicenter study with a group of chronic pain patients on chronic opioids ($n=61$), chronic pain patients without opioids ($n=187$), and pain-free control ($n=170$) [85], showing the significantly greater central sleep apnea index in those with chronic opioids compared to the others. The risk of central sleep apnea seems to be related to opioid dose. The regressive analysis estimated 2.8 central apnea events increase per hour, per 100 mg morphine equivalent opioids.

Overall, research suggests that people using chronic opioids are at higher risk of developing central sleep apnea. Given the increasing trend of opioid-related mortality [86], better understanding of the nature of the relationship between central sleep apnea and chronic opioid use is essential. Recently, the use of adaptive servo-ventilation, a form of closed-loop mechanical ventilation, has been shown to improve central apnea related to chronic opioid use [87]. Another important point to keep in mind is that those who are using chronic opioids also tend to use other centrally depressive drugs, such as benzodiazepine which potentiate the ventilatory changes with opioids [88]. How the polypharmacy contributes to mortality, and the extent to which this risk is attributable to the sleep effects, remains to be elucidated.

Effects of Improved Sleep on Pain

An epidemiological follow-up study by Davies et al. [89] suggests that good sleeping habits may be critical in later resolution of chronic pain. In this study, the investigators followed 679 people in the general population with CWP of at least 3-month duration and reassessed 15 months later. Approximately 44 % reported the resolution of their CWP at follow-up. Three parameters of sleep quality at the baseline, short sleep latency, absence of early wakening, and restorative quality of sleep, predicted the resolution of CWP at the follow-up assessment [89].

As noted, disturbed breathing during sleep is common in chronic pain [83]. Resolution of this problem may have an important therapeutic effect. A recent small, randomized controlled trial [90] treated elderly patients with obstructive sleep apnea either with low (4 cmH_2O pressure) or high (5–10 cmH_2O pressure auto-adjusted) capacity continuous positive airway pressure (CPAP) therapy. Although both groups showed improved respiratory functions, only those in the high CPAP group showed significantly increased tolerance to electric stimulation, a return of pain threshold towards normal.

Unfortunately, many trials testing the efficacy of treatments for managing chronic pain tend to focus on pain as a primary outcome and often do not include sleep measures. However, clinical trials on fibromyalgia tend to include sleep as one

of the outcomes probably because the adverse impact of poor sleep on the disorder is well recognized. A review of treatment efficacy for fibromyalgia suggests that both the use of amitriptyline and multimodal therapy approaches seems to help sleep and pain, although whether the sleep improvements are correlated with pain reduction is not known [91]. Application of cognitive-behavioral therapy for insomnia to fibromyalgia patients shows strong evidence for improvement in sleep but relatively small effects for pain reduction [92, 93]. In one study [92], however, the post-hoc analyses showed a moderate, though significant, correlation between the improvement in reported pain scores and the improvement in sleep quality (total waking time during night).

The lack of strong effect of better sleep influencing pain with the cognitive-behavioral approach is somewhat surprising as cognitive-behavioral therapy is typically shown to be efficacious for treating fibromyalgia [91]. Both studies, however, provided fairly brief intervention time (6 weeks). Given that the approach requires patients to learn the skills and practice, a longer duration may be needed to significantly impact pain severity. Furthermore, patients in the cognitive-behavioral treatment studies typically take multiple medications, unlike those in the pharmacotherapy trials. The potential confounding effects of those drugs may need to be considered. Having said that, however, this presents an interesting, yet familiar, dilemma. Washing out all the medications is needed to achieve an optimal level of internal validity for the study. On the other hand, the clinical reality is that many chronic pain patients have been taking multiple medications to address not just pain, but also sleep, mood, and function. How to apply the results from a well-controlled study to the actual patient population (that is, external validity) has always been a challenge in pain medicine.

A recent large multicenter, phase III clinical study with the randomized, double-blind, placebo-controlled design evaluated the efficacy of sodium oxybate in fibromyalgia patients [94]. Sodium oxybate is FDA-approved to treat narcolepsy, but the application for the use to treat fibromyalgia was rejected in 2010 for the safety concerns, mostly on the potential misuse and abuse potential of the drug. An earlier, open trial [95] showed that the use of sodium oxybate could normalize N3 sleep disturbance in fibromyalgia. In the multicenter study, 548 highly selected patients were randomized into placebo, sodium oxybate 4.5 or 6 g a day. The study had a high attrition (39 %), with the majority of dropouts being resulted from side effects and lack of efficacy. The series of intent-to-treat analyses revealed that the two sodium oxybate groups showed significant improvement in self-reported sleep quality and pain, as well as, to the lesser degree, tender point sensitivity.

Although clinical studies typically show the correlation of sleep improvement and pain reduction in chronic pain patients, it is still difficult to interpret the causal-effect relationship. Future research should evaluate the relationships; whether decreased pain improves sleep; whether improved sleep reduces pain; or whether other factors affect both sleep and pain.

Conclusion

We have reviewed several areas of research investigating the relationship between poor sleep and pain. Although there is some inconsistency in the results, overall, evidence seems to point to the relationship where poor sleep increases pan sensitivity to experimentally produced stimuli and is related to higher clinical pain report. Furthermore, the animal data suggests the potential interfering effects of poor sleep on the efficacy of analgesic pharmacotherapy. Similarly, the human data suggests that poor sleep may also attenuate the benefit of the behavioral approach to pain management.

In order to provide the other perspectives on the topic, we have reviewed the literature suggesting the possible adverse effects of opioid use on sleep. The area is fairly new but the accumulating evidence certainly suggests the importance of better understanding of how sleep is impacted by opioid analgesics, particularly chronic use, and how sleep disturbance from the opioid use,

one of the most widely used pain treatment, may adversely impact the pain condition as a whole.

Treatment of sleep problems in chronic pain is not an easy task, given the likely bidirectional relationship between sleep and pain and its complicated relation to mood and function. Nonetheless, available evidence suggests that sleep is an important treatment target in chronic pain management. Improvement of sleep is essential, if not necessary, for recovery from pain and disability. Thus, better understanding of the sleep–pain relationship is imperative for developing effective sleep management for pain patients.

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