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Exploring the Relationship Between Sleep and Pain

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Disturbed sleep is a common comorbidity of patients who experience pain. Between 50% and 88% of patients with chronic pain also demonstrate sleep disturbances.[1,2] Patients experiencing high levels of pain tend to report less sleep time, more delayed sleep onset, and increased nighttime awakenings, which in turn can further increase pain intensity and sleep disturbances.[3] In a community study of 5 European countries, more than 40% of patients with insomnia reported the occurrence of at least one chronic painful physical condition.[4] Insomnia with chronic pain was found to be associated with significantly increased difficulties with various sleep symptoms, including initiation of sleep, sleep disruption, early morning awakenings, nonrestorative sleep, observance of insomnia symptoms, and dissatisfaction with sleep quality.[4]

The relationship between sleep and pain is complex.[5] Pain may be considered a state of hypervigilance, and in contrast, sleep may be considered a state of hypovigilance. A study of healthy, pain-free sleepers looked at the effects of the loss of 4 hours of sleep and at the specific loss of rapid eye movement (REM) sleep and found that both had a hyperalgesic effect.[6] In another study, total sleep deprivation was found to be associated with significantly decreased pain thresholds, and on subsequent nights, REM and slow-wave sleep (SWS) interruptions were associated with a trend for decreased pain thresholds.[7] During the following night, recovery sleep following SWS interruption, but not REM interruption, resulted in increased pain thresholds, demonstrating that the amount of SWS could be correlated to pain tolerance levels.

Normal, healthy patterns of sleep have been well-described.[8] In brief, the early patterns of sleep are designated to be non-REM sleep and include stages 1, 2, 3, and 4 sleep. Stages 3 and 4 are further characterized as deep sleep or SWS. Cycles of light sleep and REM sleep occur throughout the night. Changes in the sleep architecture of patients experiencing pain include longer periods of light sleep and less deep or SWS.[9] The exact physiologic mechanism of

the relationship of sleep and pain is not well understood. One explanation could be the complex nature of the neurochemical pathways that play a role in both the perception of pain and sleep maintenance. Also, it has been suggested that the occurrence of alpha wave intrusion into non-REM sleep could be related to sleep disturbances in patients with chronic pain.[9,10]

A diverse array of conditions exist in association with chronic pain that result in significant sleep disturbances. Patients with tension headaches generally experience low sleep efficiency, frequent awakenings, and reduced SWS.[10] The story is likely to be more complicated for patients with migraines, as studies do not consistently report polysomnographic changes, although some studies do show increased REM and REM latency.[9] Patients with neuropathic pain disorders have been shown to have decreased SWS and REM sleep, and as a result experience lower sleep efficiencies and fragmented sleep.[10] Musculoskeletal pain can manifest as many different conditions, including osteoarthritis, rheumatoid arthritis, and fibromyalgia. Patients with these disorders have, as a whole, been observed to demonstrate disrupted and fragmented sleep with an increased prevalence for underlying primary sleep disorders (eg, apnea or periodic leg movements).[10] In particular, fibromyalgia, and to some extent rheumatoid arthritis, have been found to be associated with the intrusion of alpha waves into SWS, which correlates positively with the occurrence of pain and psychological distress.[9] The timing of many of these conditions has been observed to be associated with a circadian pattern of pain. For example, pain intensity seems to be increased in the morning hours for patients with rheumatoid arthritis and sleep-related headaches, while fibromyalgia and neuropathic pain increase in the midafternoon to evening.[11,12] In one study, 3 factors were identified that appeared to predict the occurrence of pain lasting 7 years. A self-reporting survey of patients who had sustained trauma to their lower extremities reported that, at 3 months posttrauma, the presence of severe pain, high levels of sleep and rest dysfunction, and greater amounts of depression and anxiety predicted persistent pain at 7 years.[13] Thus, timing of pain intensity and the type of sleep pattern that is affected in each condition should be taken into consideration when examining treatment options.

In most cases it is very difficult to determine whether the pain or the sleep disturbances occurred first, so combination therapy for both conditions should be considered. A thorough medical history is the first step in determining any link between the sleep and pain conditions, which will suggest different treatment choices. Overall, it is critical to determine which treatment will provide restorative sleep because this may help improve the effectiveness of chronic pain management.

Nonpharmacologic Treatment

Cognitive behavioral therapy (CBT) has been established as a safe and effective treatment for chronic insomnia. CBT strategies for insomnia include stimulus control, sleep restriction, relaxation, cognitive therapy, and sleep hygiene education.[14] In both case study reports and a randomized clinical trial, improvements in sleep-onset latency, wake time after sleep onset, sleep efficiency, and sleep quality were observed with CBT according to objective and subjective measures, with a trend for a greater reduction in pain severity for patients who were treated with CBT in the clinical trial.[1] CBT for pain management has also been explored. CBT for pain includes incorporation of strategies to encourage behavior that may help relieve chronic pain, such as relaxation, exercise, and activity pacing.[15] In a review of clinical studies related to CBT for patients experiencing chronic pain, many studies indicate that CBT for pain management can help reduce pain severity, although methodologic problems frequently confounded the conclusions.[5,15]

Pharmacologic Treatment

Primary strategies for pain management involve pharmacologic treatment options. Some common drugs used in the United States include analgesics, including nonsteroidal anti-inflammatory drugs and acetaminophen; opioids, including morphine, methadone, codeine, fentanyl, buprenorphine, hydromorphone, dextropropoxyphene, and pentazocine; antidepressants such as amitriptyline, duloxetine, paroxetine, and mirtazapine; as well as hypnotics, including benzodiazepines (BZDs) such as clonazepam and non-BZDs such as zolpidem, zaleplon, and

eszopiclone.[9,16]

The optimal approach for controlling pain would also include consideration of any sleep disturbances experienced by the patient. Many of the pharmacologic treatment options for pain management have been shown to cause effects on sleep architecture, sleep restoration, pain threshold levels, as well as other adverse effects. In the class of opioids, morphine has demonstrated the ability to reduce SWS (by 75%) and REM sleep while increasing stage 2 sleep.[17] However, significant differences were not observed in sleep variables such as awakenings, electroencephalogram arousals, and wake after sleep onset. In another study, morphine and methadone were both shown to increase stage 2 sleep and significantly decrease stage 3 and 4 sleep ($P < .001$).[18] Similar effects on sleep architecture were observed with an atypical opioid drug, tramadol, and at higher doses, this agent was shown to markedly reduce REM sleep.[19] In contrast, a study of patients with chronic osteoarthritic pain complaining of sleep disturbances demonstrated significantly improved pain scores from baseline following treatment with a morphine sulfate product.[20] Improvements in sleep were also noted, including significant increases in total sleep time and sleep efficiency, while latency to persistent sleep and wake after sleep onset demonstrated decreasing trends. Whereas the effects of opioids on sleep architecture appear relatively consistent, the clinical effects require further research.

Tricyclic antidepressants (TCAs) are commonly administered for chronic pain, especially for neuropathic disorders. A meta-analysis of 61 clinical trials found that TCAs have demonstrated effectiveness for treatment of diabetic neuralgia and postherpetic neuralgia, and have shown some effectiveness for central pain, atypical facial pain, and postoperative pain after breast cancer treatments.[21] The advantage of using this class of drugs is that they also address symptoms of insomnia and depression that may influence the perception of pain.[2]

Traditionally, BZDs are used in the management of sleep disorders; however, when sleep disturbances are complicated by pain, the efficacy of BZD treatment is not clear. Some studies have demonstrated improvements in sleep outcomes such as decreased sleep latency, awakenings, and increased total sleep time, but many studies have demonstrated either no effect or high levels of pain associated with treatment compared with controls.[9] Some reports have indicated that the newer BZDs and the non-BZDs may be safer and more efficacious in terms of affecting sleep outcomes, but only limited data are available regarding improvement in pain management.[9,10]

Pharmacologic agents used for the management of sleep and pain have been associated with several adverse effects. For example, opioids, and methadone in particular, have been found to be associated with a high rate (75%) of obstructed breathing and sleep apnea in patients with chronic pain.[22] In another study, the prevalence of central sleep apnea (as measured by a central apnea index value > 5 [number of central apnea events per total sleep time (in hours) was found to be 30% in patients undergoing methadone maintenance treatment, whereas central sleep apnea is uncommon in the general population.[23] A significant additive effect on methadone-related sleep apnea was observed with concomitant BZD administration.[22] TCAs are associated with a variety of adverse effects, including drowsiness, dry mouth, blurred vision, constipation, urinary retention, and more serious heart-related conditions.[21] Therefore, patients who are being managed for sleep disturbances and pain should be monitored closely for medication-related effects on sleep pathology and pain sensitivity.

Because of the bidirectional relationship of pain and sleep disturbances, achievement of restorative sleep in patients with pain is a significant challenge. Many different conditions associated with pain have demonstrated disrupted patterns in the sleep architecture, which can then manifest as various sleep disturbances, including delayed initiation of sleep, early morning awakenings, nonrestorative sleep, insomnia symptoms, and overall poor sleep quality. Both sleep disturbances and painful conditions must be treated to provide optimal health benefits. To advance the most comprehensive treatment plan for the management of pain complicated by sleep disturbances, appropriate pharmacologic treatment options should be used in combination with CBT.

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