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REVIEW

Neuropathic Pain and Sleep: A Review

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ABSTRACT

Neuropathic pain is associated with sleep disturbances, and inturn poor sleep quality leads to increased pain sensitivity, so it is essential to assess sleep alongside neuropathic pain. Responses to drugs are inconsistent and identifying the best treatment option that will reduce pain and improve sleep quality remains challenging for clinicians. Anticonvulsants such as pregabalin and gabapentin improve neuropathic pain and have a positive effect on comorbid sleep disturbances. Opioids and antidepressants are effective in reducing pain but can exacerbate sleep disturbances.
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Keywords: Anticonvulsants; Antidepressants; Neuropathic pain; Opioids; Sleep disturbances; Sleep quality

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INTRODUCTION

The prevalence of sleep disturbance in patients with chronic pain ranges from 50% to 80%, and the severity of sleep disturbance is related to pain intensity [1]. As neuropathic pain and sleep disturbance have a bidirectional relationship, they should be treated concurrently [1]. However, clinicians tend to focus on the pain, even though reducing sleep disturbance decreases pain intensity [1]. This report describes sleep disturbances associated with neuropathic pain, their relationship, and available treatments.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by the author.

SLEEP DISTURBANCES IN PATIENTS WITH NEUROPATHIC PAIN

Healthy sleep is composed of two repeated phases with different neocortex firing patterns: the non-rapid eye movement (NREM) phase, comprising four stages, and the rapid eye movement (REM) phase [2]. The first stage of the NREM phase (decrease of alpha waves) initiates sleep and is followed by the second stage

(spindles and K complexes) and the third and fourth stages or deep sleep (slow-wave). The REM phase consists of desynchronized brain wave activity, dreaming, and muscle atonia [2].

The effects of neuropathic pain on sleep quality have been examined directly [3]. One study revealed that 68% of patients with neuropathic pain had "strongly" or "mostly" disturbed sleep [4]. Patients with post-herpetic trigeminal neuropathy (unilateral head/facial pain caused by herpes zoster) have reduced sleep efficiency with shorter REM and NREM stages 3 and 4 [5]. Trigeminal nerve dysfunction following trauma (trigeminal neuropathy) is also characterized by unilateral facial or oral pain, and patients are four times more likely to wake up during sleep than subjects without trigeminal neuropathy [6]. Nearly two-thirds of patients with trigeminal neuralgia (extreme, sporadic, sudden burning or shock-like facial pain) report at least occasional awakenings due to innocuous stimuli at the trigger points [7] whilst 22.6% report pain-related awakening [6]. Neuropathic pain occurs in about 15–20% of patients with diabetes and is also associated with mood and sleep disturbances [8].

RELATIONSHIP BETWEEN SLEEP DISTURBANCES AND NEUROPATHIC PAIN

The relationship between neuropathic pain and sleep disturbances is bidirectional [1, 9]. Patients with neuropathic pain are more likely to develop sleep disorders and in turn pain is exacerbated by the lack and/or poor quality of sleep [1]. A positive association between pain sensitivity and the frequency/severity of insomnia and a synergistic reduction of pain tolerance in patients with both chronic pain and insomnia have been reported [10]. A clinical evaluation of neuropathic pain following spinal cord injury should include a sleep assessment [11].

PHARMACOLOGIC AGENTS

Reducing pain improves sleep [9]; however, it is difficult for clinicians to prescribe the most adequate treatment for neuropathic pain as the response to most drugs remains unpredictable [12]. Treatments for neuropathic pain include antidepressants, anticonvulsants, tramadol, opioids and topical analgesics [12]. The Special Interest Group on Neuropathic Pain (NeuPSIG) of the International Association for the Study of Pain (IASP) carried out a systematic review and meta-analysis of double-blind studies of oral and topical therapies for neuropathic pain [13]. Their findings support a revision of the NeuPSIG recommendations for the pharmacotherapy of neuropathic pain and include a strong recommendation for the use of tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors, pregabalin, and gabapentin as first-line treatments and a weak recommendation for the use of lidocaine patches, capsaicin high-concentration patches, and tramadol as second-line treatments [13].

Novel anticonvulsants such as pregabalin and gabapentin represent an attractive treatment strategy as they are efficient in improving neuropathic pain and have a positive effect on comorbid sleep disturbances [5, 14]. Ameliorations in sleep latency and wakefulness after sleep onset, increased deep sleep, and adjunctive effects on depression and anxiety have been reported by patients with neuropathic pain treated with gabapentin or pregabalin [14–16]. Pregabalin significantly reduces pain score and pain-related sleep interference score in patients with neuropathic pain [17], regardless of previous treatment with gabapentin; it can therefore be administered to patients intolerant or refractory to gabapentin [18]. Quality of sleep was "mostly" or "strongly" improved in 77% of patients with neuropathic pain treated with pregabalin as monotherapy or add-on therapy [4]. Anticonvulsants including oxcarbazepine, lamotrigine, gabapentin, and pregabalin as well as baclofen (muscle relaxer and an antispastic agent) may be used as second-line therapy [3].

Post-herpetic neuralgia may be first treated with tricyclic antidepressants, gabapentin, pregabalin, and topical lidocaine (local anesthetic); second- and third-line treatment may include opioids, topical capsaicin (analgesic), and tramadol (narcotic-like pain reliever) [3]. Two meta-analyses found that patients with

post-herpetic neuralgia treated with daily gabapentin reported a significant improvement in sleep rating scores compared with patients who had received placebo; however, treatment was associated with somnolence, dizziness, peripheral edema, ataxia, or gait disturbance and diarrhea [19, 20]. A drug evaluation review reported significant improvements in pain relief and pain-related sleep interference in patients treated with pregabalin compared with those who had received placebo [21].

Carbamazepine (anticonvulsant) is recommended as first-line therapy for trigeminal neuralgia [22]. Pregabalin, gabapentin, venlafaxine, duloxetine, tricyclic antidepressants, and opioids are the drugs with the best evidence to support their use for painful diabetic neuropathy [12, 23–25]. The opioid tapentadol has also received FDA approval for painful diabetic neuropathy. Benzodiazepines have been approved for insomnia by the US FDA and their short-term use also relieves neuropathic pain [1].

Opioids must be administered with caution to relieve pain but cannot be used to treat insomnia. Moreover, chronic opioid use has been associated with the development of sleep-disordered breathing, such as central sleep apnea (CSA). Studies indicate that the overall prevalence of CSA in patients taking chronic opioids is about 24% [26]. Older age, lower BMI, male gender, higher pain levels, higher benzodiazepine doses, and higher opioid doses were all predictors for CSA [27].

In another situation, opioid receptor agonists provide symptomatic relief from dysesthesias and pain in patients with severe restless legs syndrome (RLS), a condition that may have prolonged sleep induction or sleep fragmentation [28]. Antidepressants can reduce pain-related sleep disturbances and reduce chronic pain in both depressed and non-depressed patients [29]. However, many antidepressants, including tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, and serotonin-specific reuptake inhibitors, may exacerbate RLS [30].

A polysomnography study in subjects with insomnia and epilepsy reported a significant relative increase in slow-wave sleep and a decrease of stage 1 sleep in patients treated with pregabalin versus placebo [31]. A systematic review on the effects of epilepsy treatments on sleep architecture concluded that epilepsy drugs including gabapentin and pregabalin reduce sleep latency and/or improve sleep efficiency [32]. Although their pain-relieving efficacy is comparable, antidepressant drugs and opioids tend to worsen sleep quality whilst the anticonvulsants pregabalin and gabapentin improve it.

Both antidepressants and cannabis have been shown to improve sleep in patients with pain [33, 34]. However, amitriptyline can favor RLS and periodic legs movements (PLM); duloxetine can promote bruxism [35]. Additionally, antidepressants have a suppressant effect on REM sleep [34] and for this effect experts in sleep medicine are reluctant to prescribe them. The use of cannabis for sleep disorders has been extensively reviewed recently by Babson and colleagues [33]. While cannabis has been shown to improve sleep in subjects with pain, the authors do note that "research on cannabis and sleep is in its infancy and has yielded mixed results". They suggest that further controlled and longitudinal research should be conducted to "advance our understanding" about the clinical implications of using cannabis to improve sleep [33].

BEHAVIORAL INTERVENTIONS

Insomnia may be treated with relaxation, sleep restriction, cognitive, and cognitive behavioral therapies [3]. Although cognitive behavioral therapies for pain and for insomnia are well developed, efficacious, and cost-effective, most clinicians are not trained to use them effectively and access remains limited [1].

CONCLUSION

Neuropathic pain is associated with sleep disturbances in a reciprocal manner, and it is essential for clinicians to consider both aspects of treatment. Anticonvulsants such as pregabalin and gabapentin and antidepressants are

good candidates for pain relief, and the effects of anticonvulsants on sleep are preferable to those of antidepressants.

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