# Assessing and Managing Sleep Disturbance in Patients with Chronic Pain

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**KEYWORDS**

- Chronic pain • Insomnia • Cognitive behavior therapy • Sleep-disordered breathing
- Pharmacotherapy

**KEY POINTS**

- Sleep disturbance is common in patients with chronic pain (CP).
- Sleep and pain are bidirectional; pain can interfere with sleep and sleep disturbance can exacerbate pain.
- The presence of sleep-disordered breathing, including obstructive sleep apnea and central sleep apnea, increases the risk of significant harm associated with the use of opioids and other centrally sedating medications.
- Cognitive behavior therapy (CBT) has the potential to improve both pain and sleep quality.
- There are several pharmacologic agents used to improve sleep disturbance in the CP population.

## INTRODUCTION

Patients with CP often present to clinicians with numerous medical and psychological comorbidities, including mood and anxiety disorders, secondary medical problems related to inactivity and weight gain, and sleep disturbance. Insomnia can be generally defined as the inability to acquire adequate sleep to feel rested in the morning. Insomnia can be due to difficulties initiating or maintaining sleep or both. Chronic insomnia (occurring at least 3 times per week for at least 3 months) usually leads to daytime consequences, such as fatigue, reduced mental acuity, and so forth.

It has been estimated that the prevalence of sleep disturbance in patients with CP ranges between 50% and 80%.[1–5] For example, Tang and colleagues[1] evaluated 70 patients with chronic back pain and compared them to 70 gender-matched and age-matched pain-free control patients, measuring sleep disturbance, pain, and a variety of psychological variables, including health status anxiety and depression. Results indicated that 53% of the patients with CP demonstrated evidence of clinical insomnia, with only 3% of the pain-free controls meeting criteria for insomnia. Furthermore, insomnia severity was positively associated with pain intensity, sensory pain ratings, affective pain ratings, general anxiety, general depression, and health anxiety. Affective pain ratings and health status anxiety were the best predictors of insomnia severity, which suggests that emotional distress is strongly linked to sleep disturbance. In another study by McCracken and colleagues,[2] 159 patients undergoing evaluation at a pain management center were assessed for history of sleep disturbance. In this cohort, 79% met criteria for significant insomnia based on self-reported symptoms.

There is persuasive evidence to support the hypothesis that the association between pain and sleep are bidirectional in nature.[6,7] Sivertsen and colleagues[7] collected data on CP and sleep and assessed experimental pain sensitivity via cold pressor testing in 10,412 adults in Norway. The results of this study revealed that insomnia frequency and severity, sleep-onset problems, and sleep efficiency were positively associated with pain sensitivity. Results also revealed that pain tolerance was reduced further in a synergistic fashion in subjects who reported both CP and insomnia. Clinical studies have proved that CP patients who reported sleep disturbance also note increased pain, more fatigue, poor mood, and generally higher levels of stress and disability.[8,9] Experimental studies in healthy controls demonstrate that sleep deprivation or disruption leads to an increase in pain via an increase in the release of proinflammatory cytokines[10] and a decrease in pain tolerance.[11] There has also been some speculation that pain, sleep, and depression share underlying neurobiological mechanisms.[12]

Despite the burgeoning evidence for the bidirectional association between pain and sleep and the deleterious effects of sleep deprivation on mood, pain sensitivity, and disability, addressing sleep disturbance in patients with CP is often overlooked in the clinical encounter due to the many competing concerns. The aim of this article is to provide clinicians with a basic understanding of assessing sleep disturbance and the use of nonpharmacologic and pharmacologic treatment strategies to improve sleep quality in patients with CP. This article does not include a discussion of other sleep disorders, in particular, sleep-disordered breathing (obstructive sleep apnea and central sleep apnea). It is critical to assess and monitor obstructive sleep apnea and central sleep apnea in patients considered for opioid therapy or who are receiving opioids, because a significant percentage of patients on opioid therapy has sleep-disordered breathing. A recently published article by Cheatle and Webster[13]

specifically addresses the topic of sleep-disordered breathing and opioids in patients with CP.

## ASSESSMENT OF SLEEP DISTURBANCE

Polysomnography (PSG) and self-report measures of sleep disturbance are standard approaches used in insomnia research. More recently, actigraphy has been used as an objective measure of sleep quality in sleep research. There are also several commercially available activity-sleep monitors that can be used clinically in assessing and monitoring sleep duration. Self-report questionnaires are more commonly used because they

1. Are inexpensive
2. Are the primary assessment tool used by clinicians treating insomnia
3. Standardize methods across research studies given the lack of a biomarker for insomnia and a universally accepted definition of insomnia[14]

The selection of a self-report measure depends on a clinician's goals. These goals may vary from screening and diagnosis to monitoring of previously identified sleep disturbances to evaluating the efficacy of treatment interventions. There are several sleep assessment scales that evaluate multiple dimensions of sleep, including sleep quality, sleep onset, postsleep evaluation, and generic outcomes. Of these, sleep quality and postsleep evaluation measures are the most commonly used. Examples of various sleep instruments are outlined in **Table 1**.[15–20] Moul and colleagues[14] also provide a comprehensive review of the different sleep scales.

Each measure has varying degrees of utility depending on the nature of the sleep disturbance, the level of severity, and the specific characteristics of sleep a

| Table 1 Self-report measures for assessment of insomnia | | | | |
|---|---|---|---|---|
| Domain | Scale | Time Frame | No. of Items | Comments |
| Postsleep evaluation | Wolff's Morning Questions[14] | Today | 8 | Yes/no questions detailing morning restedness, presence of bedpartner, etc. |
| Postsleep evaluation | Kryger's Subjective Measurements[15] | Today | 9 | Mixed format questions detailing sleep onset, sleep latency, etc. |
| Postsleep evaluation | Morning Sleep Questionnaire[16] | Today | 4 | Mixed format questions evaluating sleep goodness and other factors |
| Sleep quality | Pittsburgh Sleep Quality Index[17] | Past month | 24 | Mixed format questions and household-related questions that use an algorithm to score sleep disturbance |
| Sleep quality | Sleep Questionnaire[18] | Indefinite | 59 | Questions use Likert-type scale responses ranging from sleep depth to dream recall/vividness |
| Sleep quality | Sleep Disturbance Questionnaire[19] | Indefinite | 12 | Questions use Likert-type scale responses that assess mental anxiety and physical tension |

*Data from* Refs.[14–19]

clinician seeks to assess. It is important to select a sleep instrument that fits the dynamics of the clinical setting, such as time constraints, patient burden, and staff resources.

## NONPHARMACOLOGIC INTERVENTIONS
### Cognitive Behavior Therapy for Pain and Sleep

Medications are commonly used to manage both pain and insomnia; however, the use of medications can result in adverse effects, dependence, and poor treatment efficacy. The use of nonpharmacologic approaches for pain and insomnia may mitigate these negative effects, but clinicians seldom implement psychological strategies. Evidence-based CBT approaches for pain (CBT-P) and for insomnia (CBT-I) are well developed, efficacious, and cost effective and may improve clinical outcomes and treatment response for different subpopulations with varied pain conditions. Many clinicians lack training in the effective use of CBT techniques, however, or there is poor access to these services.

#### Cognitive behavior therapy for pain

A variety of psychological and behavioral strategies are effective for CP management, including CBT, acceptance and commitment therapy, mindfulness-based stress reduction, progressive muscle relaxation training, motivational interviewing, and goal setting to increase behavioral activation.[21–23] CBT may incorporate any of these specific components. CBT techniques usually involve the identification of maladaptive or dysfunctional thoughts and behaviors that may worsen patient adjustment to CP and disability. The evaluation and modification of negative thought patterns and their substitution with more rational cognitions can reframe patients' interpretations that contribute to feelings of suffering, demoralization, and helplessness. CBT may assist patients in developing and implementing specific strategies, such as progressive muscle relaxation train, activity pacing, distraction techniques, and positive self-talk, to help them cope with negative affect caused by pain and disability.

CBT-P has been shown highly effective at reducing patient distress in a variety of pain disorders.[24–27] It might be expected that improved pain would translate into improved sleep for patients. It is difficult, however, to make this conclusion because few studies evaluating the efficacy of CBT-P in a CP population have examined sleep. Although the data are inconclusive, the few studies that included sleep measures suggested minimal improvement in sleep after CBT-P.[28,29] Based on this observation, CP patients suffering from insomnia may achieve the most improvement in sleep from interventions that specifically target sleep disturbance.

#### Cognitive behavior therapy for insomnia

In studies of patients with chronic primary insomnia, CBT-I has been shown equally effective or even superior to pharmacotherapy in multiple outcomes. Sivertsen and colleagues[30] compared CBT-I to standard therapy with eszopiclone and found that the CBT-I treatment group had increased time spent in slow-wave restorative sleep and improved sleep efficiency (proportion of time spent in bed actually sleeping).

A course of CBT-I typically consists of

- Psychoeducation about sleep and insomnia
- Stimulus control
- Sleep restriction
- Sleep hygiene
- Relaxation training
- Cognitive therapy

Stimulus control strengthens a patient's association of the bed with rapid-onset sleep, by teaching the patient to limit the use of bed to sex and sleep, avoid daytime naps, maintain a regular sleep/wake time, go to bed only when sleepy, and get out of bed if not asleep within 15 to 20 minutes. Sleep restriction limits the amount of time a patient spends in bed to the actual time asleep, so, for example, if a patient spends 8 hours in bed but only 4 hours total asleep, the patient is instructed to spend only 4 hours in bed. This leads initially to a mild sleep deprivation, which increases the patient's drive to sleep and leads to more consolidated, restful sleep and greater sleep efficiency. Over time, as sleep efficiency improves, the patient gradually increases time in bed. Sleep hygiene increases patients' awareness of behavioral and environmental factors that have an impact on sleep, such as how caffeine, alcohol, periods of intense exercise, bright lights, and use of electronic devices before bed may be detrimental to sleep, as well as education on the benefits of a restful bedroom environment. Relaxation training reduces cognitive and physical tension close to bedtime and involves techniques, such as hypnosis, meditation, and guided imagery. Cognitive therapy helps patients explore how beliefs and attitudes toward sleep affect sleep behaviors. Patients learn to identify maladaptive or distorted thoughts and replace them with more adaptive substitutes, thereby helping to alleviate worrying or rumination about insomnia.

CBT-I has been shown in several studies to improve sleep in patients with CP. For example, Jungquist and colleagues,[31] in a study of 28 patients with chronic back and neck pain, found that those patients who received CBT-I had significantly improved sleep and maintained improvements in total sleep time at 6 months post-treatment completion, despite the persistence of moderate to severe pain.

### Combined treatment of pain and sleep

Given the effectiveness of CBT-I and of CBT-P, there has been growing interest in the feasibility of combining CBT-I with CBT-P. In a small pilot study of 20 patients with CP, Tang and colleagues[32] found that a hybrid CBT-I/CBT-P intervention was associated with greater improvement in sleep at post-treatment. Although pain intensity did not change, the hybrid group reported greater reductions in pain interference, fatigue, and depression than the controls, and overall changes were clinically significant and durable at 1-month and 6-month follow-ups. Thus current evidence suggests that CBT is an important treatment that should be used in the treatment of insomnia in CP patients.

## PHARMACOTHERAPY

For many patients with CP, uncontrolled pain precipitates sleep and mood disturbance, so naturally clinicians often first focus exclusively on treating pain.[33] Due to the reciprocal relationship between pain and sleep, however, it is important to concurrently treat sleep disorders; pharmacologic treatments aimed at improvements in sleep have been shown to decrease pain intensity.[34,35] Given the complex presentation of patients with CP and sleep disturbance, clinicians usually tailor pharmacologic therapy for insomnia based on a patients pain pathophysiology and comorbid conditions. The most commonly used medications for insomnia are reviewed and their role for patients with CP and sleep disturbance highlighted. An overview of pharmacologic sleep agents, dosing, and adverse effects is in Table 2.

### Opioid Analgesics

Several studies have shown that opioid medications may improve subjective quality of sleep; for example, 1 study in patients with osteoarthritis found that extended-release

**Table 2**
**Pharmacologic sleep agents, dosing, and adverse effects**

| Agent | Dose | Adverse Effects | Comments |
|---|---|---|---|
| Amitriptyline | 10–100 mg | Orthostatic hypotension, daytime sedation, anticholinergic effects, cardiac conduction abnormality, sexual dysfunction, weight gain | Used for neuropathic pain, tension headaches, and fibromyalgia |
| Doxepin | 3–6 mg proprietary, 10–100 mg generic | Minimal anticholinergic side effects at hypnotic doses | FDA approved for insomnia |
| Mirtazapine | 7.5–30 mg | Increased appetite, weight gain, anticholinergic effects | Excellent for patients with poor appetite, mood and sleep disturbance |
| Trazodone | 25–100 mg | Dizziness, anticholinergic effects, daytime sedation, priapism, neuropathic pain | May be helpful in diabetic neuropathy and fibromyalgia |
| Temazepam | 15–50 mg | Sedation, fatigue, depression, dizziness, ataxia, confusion | FDA approved for insomnia; no evidence for long-term use |
| Clonazepam | 0.5–3 mg | Sedation, fatigue, depression, dizziness, ataxia, confusion | Used for restless leg syndrome, anxiety, muscle spasm, anticonvulsant activity. May be beneficial for patients with neuropathic pain; no evidence or long-term use for sleep |
| Zolpidem | 5–10 mg (immediate release) 6.25–12.5 mg (extended release) | Aberrant sleep-related behaviors | Most prescribed hypnotic |
| Zaleplon | 5–20 mg | — | Shortest active BzRA; useful for patients with nocturnal awakenings |
| Eszopiclone | 1–03 mg | Unpleasant taste, sedation, dizziness | Well tolerated; may boost antidepressant and anxiolytic efficacy |
| Melatonin | 0.5–3 mg | — | Well tolerated; over-the-counter no FDA approval; useful for shift workers/delayed sleep phase |

(*continued on next page*)

**Table 2**
**(continued)**

| Agent | Dose | Adverse Effects | Comments |
|-------|------|-----------------|----------|
| Ramelteon | 8 mg | — | FDA approved; few adverse effects other than sedation, main effect on sleep latency |
| Quetiapine | 25–50 mg | Dry mouth, weight gain, metabolic syndromes, orthostatic hypotension rare dystonias | Effective in anxiety disorders |
| Gabapentin | 100–900 mg | Dizziness, ataxia, fatigue, weight gain, lower extremity swelling | Used for neuropathic pain, fibromyalgia with comorbid sleep disturbance |
| Diphenhydramine | 25–50 mg | Anticholinergic side effects | Caution with elderly, no literature to support chronic use, no evidence for pain control |

morphine sulfate was associated with improvements in objective sleep measures of PSG, including sleep efficiency.[36] In contrast, there have also been studies that demonstrate that opioids can inhibit both rapid eye movement and non–rapid eye movement sleep, contributing to an exacerbation of pain.[37,38] There is also compelling evidence that long-term use of opioid analgesics may lead to adverse effects, including sleep-disordered breathing, opioid-induced hyperalgesia, tolerance, and dependence in populations at risk.[39] Therefore, although opioids may be effective in carefully selected patients for the treatment of pain, opioids should never be used to treat insomnia.

### Benzodiazepine Receptor Agonists

Benzodiazepine receptor agonists (BzRAS) include benzodiazepines (eg, temazepam and triazolam) and the newer class of nonbenzodiazepine drugs (eg, zolpidem and eszopiclone). This class of drugs binds to $\gamma$-aminobutyric acid (GABA)-A receptors and induces sedative/hypnotic, amnestic, anxiolytic, muscle relaxant, and anticonvulsant effects.[40,41] Many short-term clinical trials show that BzRAs improve sleep quality, sleep latency, wakefulness after sleep onset, and total sleep time.[40] Most benzodiazepines (excluding triazolam) have intermediate to long half-lives and, therefore, may help patients fall asleep and stay asleep.

Food and Drug Administration (FDA)-approved benzodiazepines for insomnia include temazepam, triazolam, estazolam, quazepam, and flurazepam.[42] Lorazepam, alprazolam, and clonazepam are anxiolytics that are often used off-label for sleep. For patients with CP, short-term use of benzodiazepines may be useful in improving muscle tension, anxiety, and neuropathic pain as well as sleep.[43,44] One early study found, however, that with long-term use (>1 year), pain patients using benzodiazepines reported no significant clinical improvements in sleep.[45]

Although the benzodiazepines may work well in short-term efficacy trials, few data are available on long-term use, and there are many documented adverse effects. In the elderly, standard doses may lead to ataxia and psychomotor impairment, which

may increase the risk of falls and hip fractures.[46] All BzRAs can cause cognitive impairment and decreased attention, specifically anterograde amnesia.[47] Long-term use of benzodiazepines may increase depressive symptomatology, with cognitive and psychomotor slowing.[45] In addition, abruptly stopping the drug may lead to rebound insomnia and seizures. There is also a concern of tolerance and dependence, especially in patients with a history of sedative or alcohol abuse.[48]

Care should be taken to not use more than 1 benzodiazepine at once (for example, temazepam for sleep and clonazepam for muscle relaxation), because many drugs in this class have active metabolites that can combine and lead to delayed sedation.[40] Also, the use of benzodiazepines in combination with opioids presents increased risk of harm to patients, especially those patients with sleep-disordered breathing. In addition, combining opioids with benzodiazepines should be avoided in patients with depression, especially in those patients with suicidal ideation.

### Nonbenzodiazepine Benzodiazepine Receptor Agonists

The nonbenzodiazepine BzRAs (NBzRAs), zolpidem, zaleplon, and eszopiclone, are the newest class of FDA-approved hypnotics used for insomnia. They universally improve sleep latency and have the potential for fewer daytime side effects give their shorter half-lives and receptor binding profile. Long-term efficacy trials have supported their use.[49,50]

Zolpidem is currently the most widely prescribed drug for insomnia. In contrast to the benzodiazepines, 1 double-blind, placebo-controlled study showed that nightly use of zolpidem remained effective after 8 months of nightly use with no evidence of tolerance or rebound effects.[50]

Eszopiclone was approved by the FDA for the treatment of insomnia with no short-term restrictions on use. Similar to zolpidem, studies suggest that eszopiclone is effective for 6 to 12 months of long-term use.[51] In addition, eszopiclone augments the effects of antidepressants and anxiolytics in patients who have insomnia and co-morbid depression or anxiety.[49]

The use of both zolpidem and eszopiclone is associated with improved sleep and quality of life in fibromyalgia and rheumatoid arthritis patients.[44,52,53] In terms of safety, similar to triazolam, zolpidem and zaleplon are associated with sleep-related behaviors, including sleep eating, sleep walking, and sleep driving.[40] For zolpidem, recent data on cognitive function and drug blood levels have prompted the FDA to lower the recommended daily dose for women.[40] In contrast to studies of typical benzodiazepines, recent studies of zolpidem, zaleplon, and eszoplicone have not noted tolerance or discontinuation effects. Although there are limited and conflicting data on the potential risk of this class of medications on sleep-disordered breathing[54] there is some evidence that NBzRAS have contributed to deaths, typically in combination with other central nervous system depressants, including opioids.[55] Clinicians should consider the potential added risk of prescribing NBzRAS to patients with CP receiving opioids and alternatively use medications for insomnia with a lower risk profile.

### Antidepressants

Sedative antidepressants, such as tricyclic antidepressants (TCAs), mirtazapine, and trazodone, are useful in treating CP patients with insomnia by helping to relieve

1. Insomnia
2. Depressive symptoms that likely enhance pain perception
3. The pain condition itself[33]

TCAs (amitriptyline, nortriptyline, desipramine, clomipramine, imipramine, trimipramine, and doxepin) have proserotonergic, noradrenergic, dopaminergic, and sodium-channel blocking effects that may account for their efficacy in pain and depression, along with anticholinergic and antihistaminic effects that lead to sedation. At standard doses, all TCAs have shown equal efficacy in treating neuropathic pain; however, they are not all equal in promoting sleep.[56,57] For example, desipramine and imipramine are less sedating and may disrupt sleep.[58,59] Amitriptyline, nortriptyline, trimipramine, and doxepin, on the other hand, may decrease sleep latency, increase sleep efficiency, and increase total sleep time.[56,60]

Amitriptyline is probably the best studied TCA for improving sleep in patients with comorbid pain, especially headache, fibromyalgia, and neuropathic pain.[61–63] It may be poorly tolerated, however, due to anticholinergic side effects. Nortriptyline, a metabolite of amitriptyline, may cause less sedation but may also have fewer side effects, including less daytime drowsiness.[64]

Doxepin, the only TCA approved by the FDA for the treatment of insomnia, has a hypnotic dose of 1 mg to 6 mg as opposed to 150 mg to 300 mg when used as an antidepressant. At the lower doses, doxepin is selective for histamine type 1 receptors, which may explain its sedative effects without typical anticholinergic adverse effects. Safety and efficacy studies revealed reduced wakefulness after sleep onset, increased sleep efficiency, and total sleep time without next-day sedation or anticholinergic effects.[65] At these doses, doxepin has not been formally studied for an analgesic or antidepressant effect, although it may be titrated as tolerated to improve pain syndromes.[41]

Adverse effects of TCAs, due to anti–$\alpha$-adrenergic and anticholinergic effects, include orthostatic hypotension, dry mouth and eyes, constipation, and cardiac conduction delays. In addition, TCAs may prolong the QT interval, leading to increased risk for serious cardiac arrhythmias. Risks of cardiac-related adverse effects, including orthostatic hypotension, increase with increased age. The blood levels of TCAs can be increased by the concurrent use of several medications, including selective serotonin reuptake inhibitors. Because the risk for serious adverse events is increased with increased TCA blood levels, care must be taken to carefully consider concurrent medications and make appropriate dose adjustments when indicated. Clinicians must also be cautious when prescribing TCAs to depressed and suicidal patients, because they are extremely lethal in overdose (lethality may occur with as little as 1 g).[66]

Trazodone is an antagonist of serotonin type 2, histamine, and $\alpha_1$-adrenergic receptors, and mildly inhibits serotonin reuptake. Similar to the other antidepressants, trazodone exerts most of its hypnotic effects at low doses and has antidepressant effects at higher doses. Several studies show that trazodone improves sleep in the elderly, depressed patients, and patients with anxiety disorders and posttraumatic stress disorder.[67] Trazodone has also been studied in patients with various pain syndromes, including fibromyalgia and diabetic neuropathy, where it was associated with both improved pain and sleep quality.[68,69] There is also some evidence for adjunctive effects when used with pregabalin for CP patients.[67] There are concerns about tolerance with this drug, however; in 1 study trazodone was shown as effective as zolpidem on sleep latency and total sleep time but only during the first 2 weeks of therapy.[70] Side effects include next-day drowsiness, rebound insomnia, orthostatic hypotension, dry mouth, and, rarely, priapism.

Mirtazapine is an antidepressant with sedating qualities due to the antagonism of type 1 histaminergic and serotonin type 2 receptors. At doses of 15 mg to 30 mg, it improves sleep latency, total sleep time, and sleep efficiency and decreases

frequency of night awakenings.[56] It has been shown to improve sleep, pain, appetite, and mood in cancer patients.[71] In addition, several studies have suggested that mirtazapine is useful for the treatment of pain caused by recurrent headache and postherpetic neuralgia.[72–74]

Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors (SNRIs), although effective for depression and pain, have been shown to disrupt and fragment sleep.[60] Duloxetine, an SNRI, is often used to treat neuropathic pain and comorbid mood but has been shown to decrease sleep efficiency.[33,61] Dosing of the SNRI during the day and avoiding SNRI use in the evening hours may help to mitigate this adverse effect.

### Antipsychotics

Two of the newer atypical antipsychotic medications, quetiapine and olanzapine, are used off-label for the treatment of insomnia. Self-reported outcomes and PSG data suggest efficacy in increasing total sleep time and slow wave restorative sleep and in decreasing sleep latency.[64,75] At low doses, quetiapine primarily has antihistiminergic properties and is weakly proserotonergic. It has been shown to decrease anxiety and enhance the effects of antidepressant medication.[64] In addition, several case reports and open-label studies show that quetiapine and olanzapine have analgesic properties, especially for fibromyalgia and migraine disorders.[75,76] These medications may cause significant weight gain (olanzapine more so than quetiapine), however. Cardiac conduction abnormalities (such as prolonged QT interval) should be monitored in patients using these drugs. In addition, there is a small risk of movement disorders, such as akathisia and tardive dyskinesia. If atypical antipsychotics are considered, it is advisable to do so in consultation with a psychiatrist.

### Anticonvulsants

Gabapentin and pregabalin are GABA analogs often used to treat CP conditions with comorbid insomnia.[33] Across multiple studies of patients with neuropathic pain and fibromyalgia, self-reported sleep outcomes suggest positive effects on sleep latency and wakefulness after sleep onset as well as increased deep sleep.[33,77,78] Both drugs also have adjunctive effects on depression and anxiety.[79] A recent study showed that pregabalin was more effective in improving sleep among patients with diabetic neuropathy compared with amitriptyline.[61] Common adverse effects include dizziness, next-day sedation, gastrointestinal symptoms, and peripheral edema.

### Over-the-Counter Medications

Melatonin receptor agonists include the natural ligand melatonin as well as nonmelatonin drugs such as ramelteon. Melatonin has been shown to induce sleep by attenuating the wake-promoting impulses in the suprachiasmatic nucleus of the hypothalamus. Melatonin is available over the counter and is not FDA approved. In 2005, the FDA approved ramelteon, a melatonin receptor agonist, for the treatment of sleep-onset insomnia. Both melatonin and ramelteon have mild efficacy for reducing sleep latency, especially in patients who have delayed sleep phases (sleep and wake times shifted later).[80] This population frequently includes older adults and shift workers. There is some evidence that melatonin may have analgesic effects in patients with fibromyalgia, irritable bowel syndrome, and migraine disorders.[81]

Most other over-the-counter sleep agents contain first-generation antihistamines, such as diphenhydramine and doxylamine, which also have anticholinergic effects. Diphenhydramine is the most commonly used nonprescription sleep aid. Patients, however, may quickly develop tolerance. To date there are no controlled trials that

demonstrate the efficacy of diphenhydramine for greater than 3 weeks in the treatment of insomnia. Antihistamines can cause next-day sedation and impair cognitive function and should be used with caution in the elderly.

## SUMMARY

Sleep disturbance commonly occurs in patients with CP and can cause additional distress and fatigue and may exacerbate pain. There is persuasive evidence that pain and sleep have a bidirectional relationship; pain can cause sleep disturbance and sleep disturbance can increase pain. Typically, sleep disturbance is not systematically evaluated, treated, and monitored in busy pain care settings. There are multiple evidenced-based nonpharmacologic and pharmacologic approaches that can significantly improve both sleep disturbance and co-occurring pain, and some may reduce the use of opioids in specific patients on long-term opioid therapy. The assessment of the multiple dimensions of sleep and basic treatment strategies should be incorporated into the routine care of patients with CP and included in pain education and training for professionals.

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