Insomnia in patients with a substance use disorder

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INTRODUCTION

Insomnia is one of most common complaints among patients in recovery from a substance use disorder and persists in many patients for months or even years despite continued abstinence. Important aspects of the intersection between insomnia and substance use disorders include the following:

- All substances of abuse directly and differentially impact sleep during active use, acute withdrawal, and with sustained abstinence; thus, differentiating insomnia that relates directly to substance use or to acute withdrawal from insomnia that is likely to persist and require independent treatment can be challenging.
- Insomnia has been linked to the initial development of substance use disorders and to relapse.
- Certain conventional treatments for insomnia should be avoided in patients with a history of substance misuse.

This topic will review the prevalence, pathophysiology, clinical features, diagnosis, and management of insomnia in patients with a substance use disorder. Insomnia in the general population is reviewed elsewhere. (See "Risk factors, comorbidities, and consequences of insomnia in adults" and "Evaluation and diagnosis of insomnia in adults" and "Overview of the treatment of insomnia in adults" and "Cognitive behavioral therapy for insomnia in adults" and "Pharmacotherapy for insomnia in adults".)

EPIDEMIOLOGY

Prevalence and risk factors — Insomnia is very common in patients with substance use disorders across a range of substances and phases of illness.

- **Alcohol** – In patients with alcohol use disorder, the prevalence of insomnia during active drinking is as high as 75 percent [1,2]. 50 to 90 percent of inpatients and about one-third of community-dwelling individuals report difficulties with sleep initiation, sleep maintenance, or overall sleep quality during alcohol withdrawal [2-5]. During early recovery (two to eight weeks following acute withdrawal), 65 to 88 percent of treatment-seeking patients with alcohol use disorder report insomnia [6,7].

- **Opioids** – A study of 225 patients on methadone maintenance found that 84 percent had scores of 6 or higher on the Pittsburgh Sleep Quality Index (PSQI), consistent with clinically significant sleep disturbance [8].

- **Cannabis** – In a cohort study of more than 800 patients seeking medical cannabis, 50 percent reported difficulties falling and/or staying asleep at least two times/week, and 25 percent reported nightly insomnia symptoms [9]. In addition, rates of insomnia as high as 75 percent have been reported among daily cannabis users during acute withdrawal [10]. More than three-fourths of cannabis users in recovery who experience sleep disturbances report using tranquilizers, alcohol, or relapsing to cannabis to improve sleep quality [11].

The most consistently identified risk factors for insomnia among patients with substance use disorders include:

- More severe addiction (eg, greater self-reported quantity and frequency of drinking or higher gamma-glutamyltransferase levels) [12-14]

- Frequent use of alcohol specifically for sleep [3]

- Concomitant drug use [8,15,16]

- Psychiatric comorbidity, particularly depression and anxiety [8,12-14,17,18]

Bidirectional relationships — There are bidirectional relationships between insomnia and substance use disorders. Alcohol is regularly used by more than 10 percent of the population to help with sleep [19], and individuals with insomnia are more likely to choose alcohol before bed than individuals without insomnia [20]. Insomnia also increases the risk of developing a

substance use disorder, independent of other mental health disorders [21]. More than half of patients report that insomnia predated the onset of drinking by more than 10 years [3,22].

Longitudinal studies have found that sleep problems and insomnia in childhood and adolescence are associated with early initiation of alcohol, cannabis, and other illicit drugs and greater alcohol and drug misuse [23-25]. By contrast, higher rhythmicity of sleep and less frequent sleep difficulties have been associated with higher behavioral control and resilience in adolescent children of adults with alcohol use disorder [26]. Among a sample of military service members, baseline insomnia prospectively predicted heavy drinking and alcohol-related problems at six-month follow-up, but alcohol variables were not predictive of insomnia [27]. In a longitudinal study that followed community-dwelling older adults for 30 years, however, men who exhibited sustained hazardous drinking had worse sleep profiles than men who drank moderately; associations between drinking and sleep were less clear among older women [28]. Persistent misuse of substances can directly disrupt neurobiological systems that regulate sleep and wakefulness, potentially leading to insomnia [29].

Association with relapse — Sleep disturbances are an important risk factor for relapse in patients with alcohol use disorder. Among subjective symptoms, difficulty falling asleep is the most consistent indicator of increased relapse risk in the first six months following treatment [30-32]. These findings have been replicated in studies using objective polysomnography or wrist actigraphy with follow-up periods ranging from 1 to 27 months [30,33,34]. Night-to-night variability, rather than average sleep patterns, may be more strongly associated with relapse [35]. Abnormalities in rapid eye movement (REM) sleep at the time of inpatient treatment that are consistent with increased REM pressure (eg, shorter REM latency, increased REM percent, and increased REM density) have also been associated with greater likelihood of relapse to drinking within three to six months after discharge [36,37].

Sleep disturbances may also predict relapse to substances other than alcohol, but data are less consistent and prospective studies are lacking [38-40]. One study in cocaine-dependent patients found that more REM sleep and a greater increase in deep slow wave sleep over two weeks of abstinence were positively associated with abstinence over the next six weeks [41]. Another study found that individuals with opioid misuse who relapsed by six months had more light stage N1 sleep and a higher arousal index at detoxification compared with those who remained abstinent [42]. Other studies have found an association between certain quantitative electroencephalography (EEG) findings, such as high frequency beta activity during wakefulness, and relapse among individuals in a residential substance recovery program [43].

PATHOPHYSIOLOGY

Substances of abuse directly alter the homeostatic balance of several neurotransmitter systems that are intimately involved in the regulation of sleep and wakefulness, including acetylcholine, gamma-aminobutyric acid (GABA), dopamine, glutamate, norepinephrine, adenosine, and orexin [29,44].

The pathophysiology of insomnia in patients recovering from substance use disorders is multifactorial, and studies have focused on several potential mechanisms:

- **Central nervous system (CNS) hyperarousal** – Patients recovering from alcohol dependence exhibit nighttime electroencephalography (EEG) patterns that are consistent with abnormal arousal levels. Beta EEG activity during sleep, a marker of CNS hyperarousal, is more prominent in abstinent patients with a history of alcohol dependence than in controls [45,46] and is higher in patients who subsequently relapse compared with those who remain abstinent [45].

- **Genetic polymorphisms** – A specific polymorphism of *PER3*, a gene involved in sleep regulation, has been associated with insomnia in patients with alcohol use disorder. In one study, patients who were homozygous for the four-repeat allele of *PER3*, associated with evening circadian preference, had worse insomnia symptom severity than patients homozygous for the morning circadian preference five-repeat allele [47].

- **Circadian rhythm abnormalities** – Melatonin and cortisol, which are the primary neurohormones of the circadian system, have been shown to be disrupted in patients with alcohol dependence [48]. Reduced melatonin levels are evident during acute withdrawal from alcohol [49] and with continued abstinence [50]. In a controlled laboratory study, abstinent men had reduced melatonin levels at the beginning of the night and a 90-minute delay in peak melatonin secretion compared with healthy sleepers [51]. They also showed abnormal nighttime cortisol profiles compared with controls, with lower cortisol levels early in the night and higher levels later in the night. Among adolescents, circadian rhythm variables (greater eveningness and later weekday and weekend bedtimes) have been associated with an increased likelihood of risky alcohol behaviors and marijuana use [52]. Chronic substance misuse also changes clock gene expression in brain areas related to drug reward, drug seeking, and relapse [53].

- **Homeostatic system abnormalities** – Other research has focused on the homeostatic sleep regulatory system, which reflects the biological sleep drive. Disruptions to the homeostatic sleep system have been directly implicated in alcohol-related sleep disturbances [54]. Compared with healthy controls, abstinent men with a history of alcohol dependence have reduced deep slow wave (delta) EEG activity over the whole night and

during the first non-rapid eye movement (NREM) period, when delta activity is typically highest [55]. Delta sleep deficits have also been identified in healthy sleeping children with a parental history of alcohol use disorder, conferring increased risk for sleep disruption later in life [56]. When sleep deprived, patients with alcohol dependence fail to respond with an appropriate increase in slow wave sleep or delta power [46]. Instead, these patients show a blunted slow wave activity response when bedtime is delayed compared with healthy controls [57]. Dysregulation of the homeostatic sleep system has also been posited as a cause of sleep disturbances in patients who misuse cocaine and in patients with opioid use disorder on methadone maintenance [58-60].

CLINICAL FEATURES

The clinical characteristics of insomnia in patients with substance use disorders vary based on the specific substance of abuse and whether an individual is actively using, in acute withdrawal, or in abstinence.

Alcohol — The most common sleep complaints associated with both chronic use of alcohol and abstinence from alcohol are difficulties falling asleep, staying asleep, or a combination of the two (so-called mixed insomnia) [3,12]. In many cases, symptoms are longstanding and persistent [17,22]. More than half of patients report that insomnia predated the onset of drinking by more than 10 years [3,22].

The normal circadian pattern of sleep and wakefulness can also be disrupted in patients who are actively using alcohol. Polyphasic sleep-wake cycles can occur in some patients, characterized by multiple brief bouts of binge drinking-induced sleep followed by brief periods of wakefulness.

Patients with alcohol use disorder who are in the first year of recovery show longer sleep latencies on wrist actigraphy than individuals with insomnia and chronic pain [22]. In the first few months of recovery, polysomnography demonstrates increased sleep latency and light stage N1 sleep, decreased slow wave sleep, sleep efficiency, and total sleep time, and more abnormalities in rapid eye movement (REM) sleep compared with healthy controls [61-63]. Objective sleep disturbances during this period are more severe in patients with comorbid depression [61] and in those who are older [64] or African-American [55].

Longitudinal studies have found that sleep latency, total sleep time, and sleep efficiency recover to healthy levels during the first year of abstinence from alcohol, but abnormalities in REM sleep persist [33,65].

Cannabis — Patients who use cannabis (marijuana) are likely to report that it reduces sleep latency, with less consistent positive effects on awakenings during the night, total sleep time, and satisfaction with sleep [66]. Objective changes in sleep are not well characterized.

In contrast, withdrawal from cannabis is reliably associated with sleep complaints, most commonly difficulty falling asleep. One large study of 469 non-treatment-seeking cannabis smokers found that more than 33 percent reported insomnia symptoms upon quitting cannabis, including trouble falling asleep, staying asleep, waking up earlier than desired, and sleeping less than usual. Symptoms began within five days of quitting and persisted for as long as two years, the longest of any self-reported withdrawal symptom [67].

A polysomnographic study in chronic heavy cannabis users demonstrated similar findings [68]. Compared with baseline, the first two days of withdrawal were associated with lower total sleep time, worse sleep efficiency, longer sleep latency, shorter REM latency, and lower slow wave sleep. The effects were not related to the amount or duration of cannabis use, severity of withdrawal symptoms, amount of craving, or mood. Total sleep time, sleep efficiency, and REM sleep continued to decline across 14 days of abstinence, while wakefulness during the night and periodic limb movements in sleep increased [69]. Periodic limb movement frequency correlated with both quantity and duration of cannabis use.

Cocaine — As with other stimulants, acute cocaine intoxication is associated with difficulty sleeping [70]. When taken intranasally before bed, cocaine objectively increases sleep latency and REM sleep latency and decreases sleep efficiency and REM sleep [59,71].

During acute withdrawal from cocaine, patients report sleep disturbances, hypersomnia, and unpleasant dreams [71,72]. Reports of subjective sleep quality improve steadily during the first few weeks of abstinence, which contrasts with an objective worsening of sleep latency, sleep efficiency, REM latency, and both total and REM sleep time [59,73,74]. This paradox, which may relate to increases in delta spectral power during early abstinence [59], has also been found in patients with alcohol dependence and insomnia [32].

Opioids — Although opioids are perceived as sedating, chronic opioid use can be disruptive to sleep quality. In a sample of 62 patients on methadone maintenance therapy who reported disturbed sleep, total sleep time as measured by daily sleep diaries for one week was less than six hours, and polysomnography confirmed poor sleep efficiency and decreased total sleep time that correlated with scores on the Pittsburgh Sleep Quality Index (PSQI) [75]. In another study, patients on chronic methadone maintenance had increased nighttime wakefulness and reduced total sleep time, sleep efficiency, and REM sleep compared with normative values [76].

Sleep disturbances may persist long after discontinuation of opioids. One prospective study found that reductions in total sleep time, REM sleep, and slow wave sleep had not recovered to normal levels up to 12 months following treatment [77].

Other studies have identified an increased prevalence of sleep-related breathing disorders and irregular breathing patterns in patients who use opioids both acutely and chronically. These breathing disturbances may further disrupt sleep. (See "Sleep-disordered breathing in patients chronically using opioids".)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of insomnia in patients with substance use disorders is similar to that in the general population and includes short sleep duration, delayed sleep-wake phase disorder, and chronic volitional sleep restriction. These can generally be distinguished from insomnia by clinical history and review of collateral clinical information, such as daily sleep-wake diaries. (See "Evaluation and diagnosis of insomnia in adults", section on 'Differential diagnosis'.)

Fragmented sleep due to other or comorbid sleep disorders should also be considered in patients who complain of difficulty with sleep initiation or maintenance. In particular, patients with substance use disorders have an increased prevalence of sleep-related breathing disorders and periodic limb movements during sleep compared with healthy individuals [78-80]. (See "Sleep-disordered breathing in patients chronically using opioids", section on 'Prevalence'.)

- Sleep-related breathing disorders (eg, obstructive sleep apnea, central sleep apnea) cannot be reliably diagnosed by history alone, and polysomnography is required to make the diagnosis. (See 'Polysomnography' below.)

- Restless legs syndrome (RLS) can manifest with sleep-onset or maintenance difficulties due to an unpleasant or uncomfortable urge to move the legs while at rest, particularly in the evenings. An effective single screening question for RLS is "When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?" [81]. RLS is important to distinguish from insomnia, as treatment strategies differ. (See "Clinical features and diagnosis of restless legs syndrome and periodic limb movement disorder in adults" and "Management of restless legs syndrome and periodic limb movement disorder in adults".)

EVALUATION

Deciding when to initiate independent evaluation and treatment for insomnia in patients with a substance use disorder is challenging. While patients who are actively abusing substances should be referred for substance treatment first, insomnia persists in up to two-thirds of patients in recovery, even with abstinence or a significant reduction in substance use [17]. Thus, clinicians should not assume that substances of abuse are the sole or even the primary cause of insomnia during recovery.

A multidimensional evaluation of insomnia can begin early in the recovery process, with specific attention devoted to assessing the onset and course of the insomnia in relation to the pattern of substance use.

Sleep history — A thorough sleep history includes key clinical questions to assess the relationship between the insomnia complaints and the substance use disorder. Key clinical questions to establish whether insomnia requires independent treatment include:

- Did the insomnia precede the onset of substance use disorder?
- Did insomnia persist during previous periods of abstinence?
- Is the substance being used specifically as a sleep aid?
- Are there perpetuating cognitive or behavioral factors (eg, conditioned arousal, sleep-disruptive habits, negative sleep expectations)?

Positive responses to these questions increase the likelihood that insomnia will need to be addressed independently.

Sleep-wake diary — Patients should be asked to complete daily sleep-wake diaries (table 1 and table 2). The diary can be easily modified for this patient population to track salient symptoms (eg, craving) and outcomes (eg, concomitant substance use). Sleep-wake diaries help to better characterize the insomnia complaint while also engaging the patient in the treatment process.

Clinical questionnaires — Insomnia scales or questionnaires can help define the severity of the complaint and response to treatment. While not validated specifically in patients with substance use disorders, the Sleep Problems Questionnaire has been used in research studies with this population and can be easily administered and followed over time (calculator 1) [17]. Total scores range from 0 to 20, with higher scores indicating more severe sleep disturbances, and scores of 4 or 5 on any single item indicative of clinically significant sleep disturbance. Other commonly used questionnaires include the Pittsburgh Sleep Quality Index (PSQI) (table 3 and table 4) [82] and the Insomnia Severity Index [83]. The Insomnia Severity Index is widely used with other insomnia populations and has validated criteria to define both treatment response and treatment remission [84,85]. The Short Sleep Index, a four-item

insomnia symptom scale derived from the Hamilton Anxiety and Depression Scales, has been found to be as reliable as the PSQI in detecting insomnia in patients with alcohol use disorder, but simpler to administer [2,14].

Use of questionnaires to assess concomitant substance use and psychiatric comorbidity is also recommended to supplement the history. Patients who indicate active substance misuse should be referred for treatment before initiating insomnia-focused treatment. Examples of validated questionnaires include:

- **Alcohol** – Alcohol Use Disorders Identification Test (AUDIT) (figure 1) (see "Screening for unhealthy use of alcohol and other drugs in primary care")
- **Other substances** – Drug Abuse Screening Test (DAST) [86] (see "Cannabis use disorder: Clinical features, screening, diagnosis, and treatment" and "Opioid use disorder: Epidemiology, clinical features, health consequences, screening, and assessment", section on 'Assessment')
- **Anxiety** – Generalized Anxiety Disorder seven-item (GAD-7) scale (table 5) (see "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis", section on 'Screening, assessment, and diagnosis')
- **Depression** – PHQ-9 (table 6) (calculator 2) (see "Screening for depression in adults")

Polysomnography — Polysomnography is not routinely indicated for the evaluation of insomnia in the general population [87]. However, patients with substance use disorders are at increased risk for sleep-related breathing disorders, which may contribute to sleep complaints and require independent treatment.

In general, signs and symptoms consistent with a sleep-related breathing disorder on the sleep history (eg, snoring, witnessed pauses in breathing during sleep, waking up gasping or choking) warrant diagnostic polysomnography. Polysomnography should also be considered in patients with opioid use disorder, even if asymptomatic, because of the increased risk for central sleep apnea. (See "Sleep-disordered breathing in patients chronically using opioids", section on 'Diagnosis'.)

Insomnia treatment can proceed concomitantly with work-up for other suspected sleep disorders as long as the other sleep disorder is not judged to be the sole cause of insomnia.

DIAGNOSIS

The International Classification of Sleep Disorders, Third Edition (ICSD-3), recognizes three insomnia diagnoses: chronic insomnia disorder, short-term insomnia disorder, and other insomnia disorder [88]. (See "Evaluation and diagnosis of insomnia in adults", section on 'Diagnostic criteria'.)

Specific diagnostic considerations in patients with a substance use disorder include the following:

- Patients with a substance use disorder who report insomnia may also meet criteria for a chronic insomnia disorder if they report nighttime insomnia symptoms and associated daytime impairment on three or more nights per week for three months or longer.
- As insomnia commonly occurs in the context of a substance use disorder, a separate insomnia diagnosis should only be considered if the insomnia is judged to be related to factors in addition to the substance, of sufficient severity to warrant independent treatment, and/or the patient reports that it independently causes clinical distress or impairment in functioning.
- As some substances can have protracted periods of withdrawal and/or very long half-lives, the onset of insomnia may occur two to four weeks after substance discontinuation. Patients who warrant a separate insomnia diagnosis are more likely to report being dependent on the substance for sleep and/or being concerned about being able to sleep without it. In addition, a diagnosis of insomnia should be considered only if symptoms persist beyond one month following discontinuation of the substance.

MANAGEMENT

General approach — Independent insomnia treatment should generally be initiated during recovery from substance misuse; patients who are actively misusing substances should be referred for substance treatment first. At least one month should pass after substance cessation to eliminate acute withdrawal as the primary cause of insomnia symptoms.

Insomnia treatments, both nonpharmacologic and pharmacologic, have been evaluated primarily in adults without substance use disorders, and objective evidence of their efficacy and safety profile in patients with substance use disorders is limited. The two modalities have not been compared head-to-head, but the safety profile favors nonpharmacologic treatments as a first-line approach in this patient population.

Initial management of insomnia in patients with a substance use disorder should include evaluating causes and contributors to insomnia and emphasizing the importance of good sleep hygiene. Sleep-focused treatment should be initiated if insomnia complaints persist for longer than one to three months and are accompanied by daytime distress and impairment [89].

Specialists in addiction medicine are reluctant to prescribe sleep medications in patients with a substance use disorder [90], and there is no single best drug or class of drugs. The available data and safety considerations for some of the more commonly considered agents are reviewed below.

Nonpharmacologic therapies — Nonpharmacologic insomnia treatments are the preferred first-line therapy for patients with a substance use disorder, in conjunction with addiction-focused therapies. Most of the evidence derives from patients with alcohol use disorder; studies in patients who misuse other substances are limited.

As in the general population, good sleep hygiene should be reviewed in all patients (table 7), both as part of a broader cognitive behavioral therapy approach and in patients who are treated with pharmacotherapy.

Cognitive behavioral therapy for insomnia (CBT-I) is delivered over multiple sessions and incorporates several components, including sleep hygiene education, relaxation, stimulus control, sleep restriction, and cognitive therapy. (See "Cognitive behavioral therapy for insomnia in adults".)

CBT-I has been established as an effective therapy for chronic insomnia in the general population [91-94], and more limited data also support its utility in patients with substance use disorders [83,95,96]. In three randomized trials in alcohol-dependent patients with insomnia, CBT-I was well tolerated and superior to placebo on subjective measures of insomnia, including sleep latency, sleep efficiency, and number of awakenings, and on daytime symptoms, such as tiredness, fatigue, and unhelpful sleep-related thoughts [83,95,96]. Drinking outcomes were unchanged. Improvements in insomnia symptoms persisted through three- and six-month follow-up [95,96]. Larger randomized controlled trials in veterans and civilians with alcohol use disorder and insomnia are underway to evaluate the impact of CBT-I on sleep and drinking outcomes [97].

Other nonpharmacologic therapies require further study. One small, randomized trial found that progressive relaxation training improved subjective sleep quality more than no treatment in inpatient men with alcohol dependence [98]. Another pilot study found that insomnia, craving, and cannabis-related problems, but not cannabis use, were reduced in trauma-exposed young adults with problematic cannabis use who received brief behavioral treatment for

insomnia (BBTI), which is a brief version of CBT-I that includes only behavioral treatment components [99].

Light therapy could also theoretically target circadian disruption in patients with substance use disorders. One study administered bright light therapy (3000 lux) to 10 patients with alcohol dependence on day 3 of alcohol withdrawal from 7:00 AM to 9:00 AM and from 5:00 PM to 9:00 PM [100]. Subjective sleep, objective sleep consolidation, and rapid eye movement (REM) sleep percentage improved on the night following light administration. Dawn simulation, a low-level light that gradually increases in intensity prior to awakening, is another form of light therapy that was found to improve sleep and mood in one study of abstinent patients with a history of alcohol dependence [101], but the effects on insomnia require further evaluation. A randomized controlled trial is ongoing to evaluate the efficacy of a personalized circadian-focused intervention adjunctive to alcohol use disorder treatment [102].

Pharmacologic treatments — Medication classes that have been evaluated specifically for insomnia in patients with substance use disorders include sedating antidepressants, anticonvulsants, melatonin agonists, and antipsychotics. The available data in patients with substance use disorders are reviewed below; the use of these medications for insomnia in the general population is reviewed in more detail separately. (See "Overview of the treatment of insomnia in adults" and "Pharmacotherapy for insomnia in adults".)

Benzodiazepine receptor agonists (BZRAs; includes benzodiazepines and nonbenzodiazepine BZRAs such as zolpidem) should be avoided in patients with a substance use disorder because of the increased likelihood of abuse and potential for overdose when combined with alcohol, opioids, and other central nervous system depressants [103-106].

Trazodone — Among sedating antidepressants, trazodone is the best studied option for insomnia in patients with a substance use disorder and the most commonly prescribed drug for this purpose among specialists in addiction medicine [90]. It has the potential advantages of being nonaddictive, available as a generic, and not associated with abuse liability, high overdose risk, or life-threatening withdrawal symptoms. Results of randomized trials have been mixed, however, and close monitoring of drinking is indicated when trazodone is used in patients with alcohol use disorder.

In a randomized trial of 173 patients in an alcohol detoxification program who reported sleep disturbance, trazodone 50 to 150 mg at bedtime for 12 weeks improved subjective sleep quality more than placebo, but drinking outcomes improved less than placebo [107]. Three months after trazodone was discontinued, sleep quality returned to placebo levels and drinking outcomes were worse than placebo. In a smaller randomized trial, trazodone 50 to 200 mg at

bedtime objectively reduced wakefulness during the night and improved sleep efficiency and total sleep time compared with placebo in 16 patients with alcohol dependence in early withdrawal, but tolerance developed over four weeks of treatment [108]. Of note, a large retrospective study following residential treatment of 283 patients with alcohol use disorder did not find associations between trazodone use at discharge and relapse at six-month follow-up [109].

Trazodone does not appear to be as useful in patients with opioid use disorder. A multicenter randomized trial in 137 patients on methadone maintenance with sleep complaints found that trazodone 50 mg taken over three months did not improve subjective or objective sleep measures and had no effect on illicit drug use compared with placebo [110].

Common side effects of trazodone include dizziness, dry mouth, and nausea. Rare but serious side effects include priapism and cardiac arrhythmias. (See "Serotonin modulators: Pharmacology, administration, and side effects", section on 'Trazodone'.)

Mirtazapine — Mirtazapine, an antidepressant with sedative and anxiolytic properties, is reasonable to consider in patients with substance use disorder who have both depression and insomnia. It is thought that low doses of mirtazapine (eg, 7.5 to 15 mg nightly) are more sedating than the therapeutic range for depression (eg, 15 to 45 mg), although this is not well documented in clinical trials, and the therapeutic range should be targeted when treating depression.

Small studies in patients with substance use disorders have primarily enrolled patients with comorbid major depression and measured sleep symptoms as a secondary outcome. In a small open-label study in 12 adults with alcohol use disorder and comorbid major depression, patients were treated with mirtazapine 15 mg daily for the first two weeks and then 30 mg daily for six weeks [111]. Insomnia symptoms were reduced at eight weeks as measured by the Hamilton Rating Scale for Depression, and these improvements were maintained at two-year follow-up [112]. Depression scores and alcohol use also improved at both time points [111-113]. A 12-week randomized trial of mirtazapine 45 mg versus placebo in 24 people with cocaine dependence and depression found reductions in sleep latency over the first month, but these did not persist [113]. No differences in depression or substance use were observed.

Gabapentin — Gabapentin has been considered as a treatment for insomnia in patients with substance use disorders because it has sedative effects, is not metabolized in the liver, does not lower the seizure threshold, and does not require ongoing blood monitoring. It has not been well studied outside of the context of early recovery from alcohol use disorder, however, and

there are some concerns about its abuse potential. (See "Alcohol use disorder: Pharmacologic management", section on 'Gabapentin'.)

One randomized trial in 21 patients with alcohol dependence and insomnia found that 1500 mg of gabapentin at bedtime reduced relapse but did not alter subjective measures of insomnia or polysomnographic parameters compared with placebo [114]. Two subsequent studies in a total of 300 patients found that gabapentin 900 to 1800 mg daily, with or without naltrexone 50 mg, improved both drinking outcomes and subjective sleep measures in alcohol-dependent patients in early recovery [115,116]. These benefits were not replicated in a randomized controlled trial of gabapentin enacarbil (extended-release gabapentin) [117].

A typical starting dose of gabapentin for insomnia is 300 mg at bedtime. Common side effects of gabapentin include dizziness, ataxia, fatigue, and weight gain. Neuropsychiatric side effects, including emotional lability and hostility, have been described primarily in children. Antiseizure drugs as a class have been associated with an increased risk of suicidal thoughts and behavior.

Melatonin agonists — Melatonin agonists show potential as an insomnia medication for patients with substance use disorders, particularly those with alcohol use disorder, although current data are quite limited.

Both ramelteon, a melatonin receptor agonist, and agomelatine, an analog of melatonin that is available outside the United States as an atypical antidepressant, could theoretically target the disrupted circadian system of patients with substance use disorders and thereby improve sleep. These medications are generally well tolerated with no evidence of abuse potential, but agomelatine is metabolized in the liver by the P450 enzyme CYP1A2 and can be hepatotoxic.

In a case series of five recovering alcohol-dependent patients with insomnia, four weeks of nightly ramelteon (8 mg) improved insomnia scores, increased estimates of sleep duration by more than one hour, and reduced subjective sleep latency by more than 50 percent [118]. No drug-related adverse events were reported. However, a randomized controlled trial of melatonin 5 mg versus placebo for four weeks in 60 treatment-seeking individuals with alcohol use disorder found no differences in Pittsburgh Sleep Quality Index (PSQI) scores between groups [119]. In another case series, nightly agomelatine 25 to 50 mg for six weeks improved PSQI scores from 13 to 8 in nine alcohol-dependent outpatients; there were no cases of hepatotoxicity [120]. None of these studies evaluated medication-related changes in circadian markers (eg, melatonin) or effects on drinking outcomes; thus, more studies are needed.

Quetiapine — Although quetiapine is widely used in addiction treatment centers for insomnia and to manage depressed mood and agitation during substance withdrawal, using it as a first-

line pharmacotherapy for insomnia is discouraged because there is limited evidence that it is beneficial and there are substantial risks of adverse side effects.

In an eight-week randomized trial in 20 recovering alcohol-dependent patients, bedtime quetiapine 50 to 400 mg reduced wakefulness during the night and improved insomnia ratings over the first three weeks of treatment compared with placebo, although this effect was not sustained at eight weeks [121]. Dry mouth and daytime somnolence were reported more commonly by patients treated with quetiapine. In a larger trial of 224 alcohol-dependent patients with very heavy drinking (10 or more drinks/day for men, 8 or more drinks/day for women), quetiapine 400 mg/day improved sleep quality ratings over 12 weeks more than placebo, but the magnitude of the effect was small and it had no positive effect on drinking measures [122]. Patients in the quetiapine group also gained more weight, had larger increases in triglycerides with smaller reductions in cholesterol, and were more likely to report dizziness, dry mouth, dyspepsia, increased appetite, sedation, and somnolence compared with the placebo group.

If quetiapine is used for insomnia, it should be given at the lowest effect dose with frequent reassessments of the clinical response and need for ongoing use.

Other agents

- **Dual orexin receptor antagonists (DORAs)** – Daridorexant, lemborexant, and suvorexant are oral dual orexin receptor antagonists that are approved by the US Food and Drug Administration (FDA) for treatment of insomnia in adults. They are Schedule IV controlled substances but are not known to be associated with physiologic dependence or withdrawal; they are classified as controlled substances due to likeability ratings among sedative-using subjects in clinical studies. DORAs are under investigation as therapeutic agents in people with substance use disorders; pending published data, however, we do not yet generally prescribe DORAs for insomnia in this population.

- **Modafinil** – Modafinil, a wake-promoting agent with effects on dopamine neurotransmission, has been evaluated as a potential treatment for stimulant dependence. Increasing evidence suggests that modafinil might mitigate sleep abnormalities and daytime sleepiness associated with cocaine during early withdrawal [41,123,124]. (See "Stimulant use disorder: Treatment overview", section on 'Other agents with limited supporting data' and "Stimulant use disorder: Treatment overview".)

  In a randomized trial of 57 cocaine-dependent patients, modafinil 400 mg or placebo was taken daily in the morning during a 12-day inpatient treatment and continued during six weeks of outpatient therapy [124]. Patients receiving modafinil had a higher mean

percentage of cocaine-free urine screens (52 versus 26 percent). In addition, polysomnography showed significant increases in non-rapid eye movement (NREM) stage N3 sleep time in the modafinil group.

FOLLOW-UP AND MONITORING

Insomnia in patients with substance use disorders is often longstanding and persistent. Long-term management therefore often requires collaboration among addiction treatment providers and other members of the care team. Engagement of significant others or family members may also be useful. Ideally, insomnia treatment is integrated into the addiction treatment setting.

Goals of therapy are improvement in subjective sleep quality as well as ongoing control of the comorbid substance use disorder. Sleep quality and substance use can be followed on a simple calendar or by modifying sleep instruments (table 1 and table 2) to collect collateral information (eg, monitoring drinking quantity and frequency on the sleep-wake diary). (See 'Clinical questionnaires' above.)

Since the rate of polysubstance use is high in patients with substance use disorders, clinicians may need to monitor use of multiple substances during insomnia treatment. Under certain circumstances, drug or alcohol testing may need to be conducted routinely prior to insomnia treatment visits.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Insomnia in adults" and "Society guideline links: Opioid use disorder and withdrawal" and "Society guideline links: Benzodiazepine use disorder and withdrawal" and "Society guideline links: Alcohol use disorders and withdrawal" and "Society guideline links: Stimulant use disorder and withdrawal" and "Society guideline links: Cannabis use disorder and withdrawal".)

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – Insomnia and sleep disturbances are exceedingly common in patients with substance use disorders. Sleep problems may contribute to the initial development of a substance use disorder, are exacerbated by chronic substance use, and frequently persist well into abstinence. (See 'Epidemiology' above.)

- **Clinical features** – Insomnia during recovery has been consistently linked with relapse, thus close attention should be paid to insomnia during recovery. Although sleep improves with abstinence and with significant reductions in substance use, most patients will continue to experience insomnia that often requires independent treatment. (See 'Clinical features' above.)

- **Evaluation** – Patients should be evaluated for causes and contributors to insomnia early in the recovery process. A sleep history and review of sleep/wake diaries are the core components of the evaluation. Polysomnography is not routinely indicated unless there are signs or symptoms of a sleep-related breathing disorder. (See 'Evaluation' above.)

- **Diagnosis** – Independent insomnia treatment should generally be initiated during recovery from a substance use disorder; patients who are actively misusing substances should be referred for substance treatment first. An insomnia diagnosis can be made when insomnia symptoms occur at least three times per week, persist beyond one month of abstinence, and are accompanied by daytime impairments and/or psychological distress. (See 'Diagnosis' above.)

- **Management** – Initial management of insomnia should include evaluating causes and contributors to insomnia and emphasizing the importance of good sleep hygiene (table 7). (See 'General approach' above.)

  - **First-line therapy** – For patients with persistent insomnia symptoms during recovery, we recommend cognitive behavioral therapy for insomnia (CBT-I) rather than drug therapy as a first-line approach (**Grade 1B**). CBT-I has established efficacy for insomnia in the general population and is the best-studied nonpharmacologic approach in patients with substance use disorders. (See 'Nonpharmacologic therapies' above.)

  - **Medication options** – Benzodiazepine receptor agonist medications should be avoided in patients with a substance use disorder because of the increased likelihood of abuse and potential for overdose when mixed with alcohol or other substances. Safer alternatives, albeit with limited evidence of efficacy, include trazodone, mirtazapine, gabapentin, and melatonin agonists. Modafinil may be specifically effective in patients with cocaine use disorder. (See 'Pharmacologic treatments' above.)

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