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# Current and potential pharmacological treatment options for insomnia in patients with alcohol use disorder in recovery

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## Abstract

Alcohol use disorder (AUD) is characterized by dysfunction in motivational, mood-stress regulation, and sleep systems that interact in complex ways to heighten the risk of relapse during abstinence. Emerging data suggest that excessive and chronic alcohol use disrupts sleep homeostasis and, in abstinence, subjects with AUD are known to experience insomnia that may persist for weeks to years, which we propose to refer to as insomnia associated with alcohol cessation (IAAC). The purpose of this review is to provide an update of pharmacological approaches to therapy including compounds in development, to raise awareness of the prevalence of and unmet need in IAAC and highlight differences in treatment consideration for IAAC as compared to insomnia disorder. We performed a search of select electronic databases to identify studies of pharmacological agents used to treat sleep disturbances in abstinent or treatment-seeking patients with alcohol use disorder. The search, conducted in June 2019 and updated in December 2019, yielded 1,188 abstracts after duplicates were removed, of which 36 full-text articles were assessed for eligibility. Eighteen studies were included, 15 randomized controlled trials and three open-label studies. Several classes of medications including antidepressants, anticonvulsants, and antipsychotics have been evaluated for their effectiveness in treating sleep disturbances in abstinent or treatment-seeking patients with AUD. None of these medications are approved by the FDA for the treatment of IAAC, and the currently available evidence for these agents is limited. Randomized, controlled clinical trials are warranted to evaluate the efficacy and safety of medications in the treatment of IAAC.

**KEYWORDS**

alcohol cessation, alcohol use disorder, alcohol withdrawal, Insomnia, pharmacological treatment, treatment

## 1 | INTRODUCTION

The acute and chronic use of alcohol has been shown to cause disturbances in sleep patterns in humans. In patients with alcohol use disorder (AUD) in recovery, insomnia is characterized using polysomnography (PSG) as increased sleep-onset latency, sleep fragmentation, rapid eye movement (REM) sleep percentage, and reductions in sleep efficiency, the percentage of slow-wave sleep (SWS), and REM latency.[1,2] Insomnia commonly occurs in the acute withdrawal phase (1 to 2 weeks) and early recovery phase (2 to

8 weeks after detoxification). In the acute withdrawal phase, insomnia symptoms are variable and can improve over the detoxification period,[3] yet may continue into the sustained recovery phase (3 or more months after the detoxification phase). During the sustained recovery phase, sleep-related disturbances can continue for up to 3 years.[4–6]

From a clinical and pathophysiological perspective, it is currently controversial if insomnia in patients with AUD is distinct from insomnia disorder. This point is highlighted in the differing criteria within the two major insomnia nosology systems. The Diagnostic and Statistical Manual of Mental Disorders, 5th edition, separates substance/medication-induced sleep disorder (including that from alcohol) from insomnia disorder, the former being characterized as a prominent and severe disturbance in sleep causing clinically significant distress or impairment that developed during or soon after the substance intoxication or after withdrawal from exposure.[7] The International Classification of Sleep Disorders, 3rd edition, in a departure from its previous version, no longer promotes the concept that insomnia arises as a secondary form of sleep disturbance related to an underlying primary disorder such as substance use disorder, providing a single diagnosis of chronic insomnia disorder for all patients who have persistent and frequent insomnia.[8] However, when evaluating treatment options, and in particular pharmacological options, there is a clear need for differing considerations for patients with AUD in recovery with insomnia versus the general insomnia population. In patients with AUD in recovery, reducing the risk of alcohol relapse and concerns of abuse and addiction are of the utmost importance when evaluating treatment for insomnia. Therefore, we propose to refer to this disorder as insomnia associated with alcohol cessation (IAAC).

### 1.1 | Prevalence of IAAC

Sleep complaints are common among patients with AUD during both acute and sustained abstinence.[5] During the acute withdrawal phase, estimates of sleep disturbances based on surveys of treatment-seeking alcohol-dependent patients ranged from 57% to 92%.[9–11] Additionally, Brower and Perron, 2010[12] analyzed data from the 2001 to 2002 National Epidemiologic Survey on Alcohol and Related Conditions (N = 43 093 adults) and determined in participants with a lifetime diagnosis of alcohol dependence and acute alcohol withdrawal, the prevalence of self-reported acute alcohol withdrawal-related insomnia was 32%, and acute alcohol withdrawal-related sleep disturbance was 50% in this population.[12]

Sleep-related disturbances including insomnia may improve as detoxification progresses yet remain high during recovery and have been demonstrated to persist for up to 3 years.[6] The prevalence of self-reported insomnia symptoms in a sample of 164 patients undergoing alcohol detoxification in an inpatient clinical research setting was 90% upon admission (Day 2) and 51% by Day 28.[13] Additionally, in a prospective analysis of the Pittsburgh Sleep Quality Index (PSQI) administered to 119 alcohol-dependent patients who met the inclusion criteria in a 1-month residential treatment program, 69% of patients reported sleep disturbances upon admission, and 49% reported sleep disturbances upon discharge.[14] Furthermore, in a naturalistic, longitudinal outcomes study, alcohol-dependent patients were interviewed using the Sleep Problems Questionnaire, Time-Line Follow-Back Interview, and Brief Symptom Inventory. The interview results showed that 47% (n = 125) of 267 patients reported insomnia at baseline. Among all patients followed in the study, 62% (64/103) of those who had insomnia at baseline continued to have insomnia at 6 months.[15] In a recent study of 77 patients with alcohol dependence electively admitted to a hospital for detoxification, 70.1% had PSQI scores greater than five at admission which fell to 59.7% at discharge.[3] From the above analyses, it is clear that the incidence of insomnia associated with alcohol cessation both during and after detoxification is high.

### 1.2 | Effects of alcohol on sleep: progression to IAAC

Acutely, alcohol has several effects related to neurotransmitters that are involved in the control of normal sleep, including an increase in mesolimbic dopaminergic activity, alteration of serotonin receptor function, the facilitation of gamma-aminobutyric acid (GABA) inhibition, the inhibition of glutamate excitation, an increase in endogenous opioid synthesis and release, and the promotion of adenosine signaling[16,17]; with chronic intake, these effects become more exaggerated. As a result, the control of sleep and wake is altered in AUD.

Patients with AUD who are actively drinking commonly have an inability to initiate and maintain sleep and a disruption in the organization of sleep stages. These patients have increases in sleep-onset latency, REM sleep latency, and SWS, as well as a reduction and fragmentation in total sleep time and REM sleep suppression.[1,2,17,18]

With alcohol cessation in patients with AUD, a full complement of sleep dysfunction may emerge, including REM and non-REM (NREM) deficiencies, which are associated with an increased risk of alcohol relapse, and disruptions in sleep homeostasis, which, in preclinical sleep deprivation studies, have been associated with impairment of adenosine regulatory mechanisms.[1,19–21] Patients with AUD in the early recovery phase often experience increased sleep fragmentation, increased awakenings, especially in the second half of the night, frequent sleep-stage transitions, and body movements.[4,17] Compared with healthy controls, patients in early recovery have shown polysomnogram abnormalities, including reduced sleep efficiency, total sleep time, and SWS. Patients in early recovery also show shortened NREM to REM cycles, an increase in sleep-onset latency, an increase in REM sleep percentage, and reduced REM latency.[1,2,22] An increase in sleep-onset latency, a reduction in the percentage of SWS and REM latency, and a reduction in sleep efficiency are all predictors of alcohol relapse.[20]

## 1.3 | Underlying neurobiology of IAAC

Many sleep abnormalities including insomnia may improve with time for many patients after continued abstinence from alcohol.[23] However, chronic alcohol use in some patients may cause permanent neurologic and functional alterations to the sleep centers of the brain, leading to persistent symptoms that require independent treatment.[4,5] Researchers have developed several theories based on available data to explain the neurobiological mechanisms underlying the persistent sleep-wake disturbances experienced by patients with AUD, even after months to years of abstinence from alcohol.[1,24] Using studies conducted in animals, Thakkar et al[21] theorized that adenosine and the wake-promoting cholinergic neurons of the basal forebrain are important mediators of sleep homeostasis. Based on the results in preclinical studies, these researchers suggested that alcohol alters sleep homeostasis by down-regulation of the adenosine system and dysregulation of the cholinergic neurons in the basal forebrain.[21]

As yet, no studies have directly compared and contrasted the neuropathophysiology of insomnia disorder with that of IAAC. It is, therefore, controversial as to whether the neurobiological underpinnings of insomnia disorder and IAAC differ. It is also currently unclear why, in some individuals, IAAC resolves over time with continued abstinence while it persists in others. Furthermore, pre-existing insomnia prior to alcohol abuse further complicates the separation of these populations for study.

The sensitivity and responsiveness of the sleep homeostat can be assessed by challenges such as assessing response to auditory stimulation during sleep or recovery after sleep deprivation. Subjects with AUD relative to age-matched controls show a lower incidence and amplitude of evoked EEG K-complexes to tones presented during sleep.[25] In the Michigan Longitudinal Study, response to reduced sleep time, produced by a three-hour phase delay, was compared between healthy controls and abstinent AUD patients. In the control group, after recovery from reduced sleep, controls had enhanced slow-wave sleep and slow-wave activity (rebound). However, rebound was not present in abstinent AUD patients; that is, they do not recover.[26–28] Further research in this area is needed to advance understanding of the interaction between alcohol use disorder, abstinence, and insomnia.

## 1.4 | Correlations with relapse

Many researchers have concluded that untreated sleep disturbances can contribute to the risk of alcohol relapse after a period of abstinence and that disturbed sleep is an important predictor of relapse.[4,29] Subjective and objective indicators of sleep disturbances that have been evaluated in alcohol-dependent patients after the acute abstinence period, such as difficulty in falling asleep, decreased total sleep time and decreased sleep efficiency, predict the likelihood of relapse during longer periods of abstinence.[1,4,21,30,31]

In an early polysomnography study,[32] found 10 of 28 subjects with AUD had relapsed at three months of abstinence. Those relapsing had reduced REM latency, increased REM %, and in a replication cohort, the 6 of 17 who relapsed had a shortened REM latency and greater REM %.[20] extended this work showing that persistently abnormal recordings of eye movement density in REM sleep and REM latency in primary alcohol-dependent inpatients at 14 months were associated with alcohol relapse. Other relapse predictors in this study were an increase in sleep-onset latency, a reduction in the percentage of SWS, and a reduction in sleep efficiency. Similarly,[33] found 36 of 74 AUD patients relapsed at five months and that individuals who relapsed showed an increased sleep latency, reduced REM latency, and reduced NREM stage 4%. Researchers have also determined that persistent insomnia and sleep fragmentation after five months of abstinence predicted relapse over 12-14 months of sustained abstinence.[2,20] One study also suggests subjective impressions of sleep, sleep-onset latency, and wakefulness after sleep onset may be better predictors of relapse than PSG measures.[34] Lastly, a recent study established a link between craving in treatment-seeking patients with alcohol dependence and insomnia as measured using the Short Sleep Index.[31] Although insomnia and sleep-stage disturbance have been associated with craving and risk of relapse in alcohol-dependent patients, treatment of sleep disturbances for the prevention of relapse has not been adequately studied[31,35] and would be helpful in definitively establishing causality.

## 1.5 | Treatment of IAAC

Insomnia is an easily recognizable symptom in patients with alcohol use disorder in recovery, and if addressed, may improve treatment outcomes for this patient population.[2,4] Comprehensive management of insomnia in this population involves a wide array of treatments and interventions to reduce symptoms and increase functionality.

Nonpharmacological interventions used to treat IAAC in patients with AUD include sleep-hygiene education, cognitive-behavioral therapy (CBT) for insomnia, relaxation therapy, and bright-light therapy.[36] While a thorough review of these treatment modalities is outside the scope of the current review, these options are an important component of the armamentarium of the healthcare provider and demand mention. Three controlled studies[37–39] and one uncontrolled study[40] evaluated the efficacy of CBT in treating insomnia in abstinent patients with AUD. One controlled study evaluated the efficacy of progressive muscle relaxation,[41] and one uncontrolled study evaluated bright-light therapy[42] in treating insomnia in abstinent patients with AUD. All these interventions demonstrated efficacy in reducing self-reported symptoms of insomnia. However, studies that utilize PSG as a primary outcome are needed. Additionally, it is currently unclear if nonpharmacological treatments improve drinking outcomes such as relapse which highlights the need for further randomized controlled studies.[36,38,43]

While physicians may be reluctant to utilize medication in this group, there may be legitimate reasons to do so. In concert with non-pharmacological approaches, many patients with IAAC may benefit from consideration of pharmacological interventions, especially if sleep disturbances are accompanied by daytime dysfunction or psychological distress and persist beyond four weeks of alcohol cessation.[4,36] In a 2000 national survey of addiction-medicine physicians, only 22% of physicians (n = 311) offered pharmacological treatment to more than half of patients in early recovery from AUD who had sleep problems.[44] This highlights a key difference in treatment considerations from insomnia disorder, where pharmacological treatments are more prevalent.

Specific treatment goals for IAAC have not been thoroughly described in the published literature or clinical practice guidelines. Additionally, clinical practice guidelines regarding the treatment of IAAC are insufficient. However, the treatment goals for IAAC, in general, are to improve sleep, increase the ability to function during the day, and reduce the risk of alcohol relapse.[35] This article aims to review current and potential future pharmacological treatment options in patients with IAAC. Therefore, we identified and reviewed studies that evaluated the efficacy of pharmacological agents in the treatment of sleep disturbances in patients with alcohol use disorder who were abstaining from alcohol or were treatment-seeking.

## 2 | METHODS

We performed a search of the published literature in MEDLINE (Ovid and PubMed), EMBASE, and PsycINFO through June of 2019 by searching abstracts and titles using the following terms: alcoholism, "alcohol depen*," "alcohol withdrawal," or "alcohol use disorder" in conjunction with insomnia or "sleep*." The literature search was updated in December 2019 which did not result in the inclusion of any additional studies.

### 2.1 | Eligibility criteria and study selection

Studies that prospectively evaluated drug effects on insomnia-related sleep parameters and sampled subjects with alcohol use disorder who were treatment-seeking or abstinent at study entry were included. Review articles and meta-analyses were excluded yet reviewed to ensure all eligible published literature was captured; case reports were also excluded. We restricted results to those written in the English language and original, full-text published studies from the year 1990 and after. All resulting titles and abstracts were reviewed, and the full text was reviewed for any publication that was potentially relevant.

Additionally, we attempted to identify novel molecules in development that may be useful in the treatment of insomnia associated with alcohol cessation. We searched four databases, Cortellis for Competitive Intelligence (Clarivate Analytics), Pharmaprojects (Informa PLC), GlobalData (GlobalData PLC), and ClinicalTrials.gov through July of 2019 to identify any drugs in development targeting insomnia in the United States. We believe these four databases, taken together, provide a comprehensive record of drug products in development.

## 3 | RESULTS

The search of the published literature yielded 1,188 abstracts after duplicates were removed (Figure 1). Of these, 997 were excluded as they did not evaluate a pharmacological agent. Of the remaining 190 abstracts screened, 154 did not meet inclusion criteria and 36 full-text articles were assessed for eligibility. Of these, 15 did not assess insomnia or sleep parameters and in three articles, the subjects were not treatment-seeking or abstinent at study entry. Eighteen studies were included, 15 randomized controlled trials and three open-label studies.

Several classes of medications have been evaluated for their effectiveness in treating sleep disturbances in abstinent or treatment-seeking patients with AUD (eg, antidepressants, anticonvulsants, melatonin agonists, and antipsychotics) and are described here and summarized in Table 1.

### 3.1 | Sedative antidepressants

#### 3.1.1 | Trazodone

Trazodone 50-200 mg/day has been shown to improve sleep in two randomized, double-blind, placebo-controlled studies [45,46], and while it is not approved by the FDA for the treatment of insomnia, it is the most frequently prescribed medication for the treatment of IAAC.[36,44] However, one of these studies showed evidence of an increased risk for alcohol relapse with trazodone.[45]

Le Bon et al[46] evaluated the efficacy of trazodone (50-200 mg/day) administered before bedtime in increasing sleep efficiency in 18 patients (16 completers; trazodone, n = 8; placebo, n = 8) with AUD who had completed alcohol detoxification. Trazodone significantly improved sleep efficiency after sleep onset and reduced wake time after sleep onset compared with the placebo group (for which there was no benefit) on the first night of treatment and after four weeks of treatment in abstinent patients. Non-REM sleep was also significantly improved after the first night of treatment with trazodone.[46] Friedman et al[45] evaluated the efficacy of trazodone (50-150 mg) administered at bedtime for 12 weeks in 173 alcohol-dependent inpatients (who were discharged 3 to 5 days after detoxification). Some primary outcomes in the study were the proportion of days abstinent and the proportion of drinks per drinking day, and sleep quality was a secondary outcome. Although trazodone improved sleep quality at 12 weeks compared with baseline as measured by the PSQI (mean PSQI change = −3.02; 95% confidence interval [CI]: −3.38 to −2.67), sleep quality worsened in the trazodone group at 6 months with no significant differences noted compared with placebo. Furthermore,

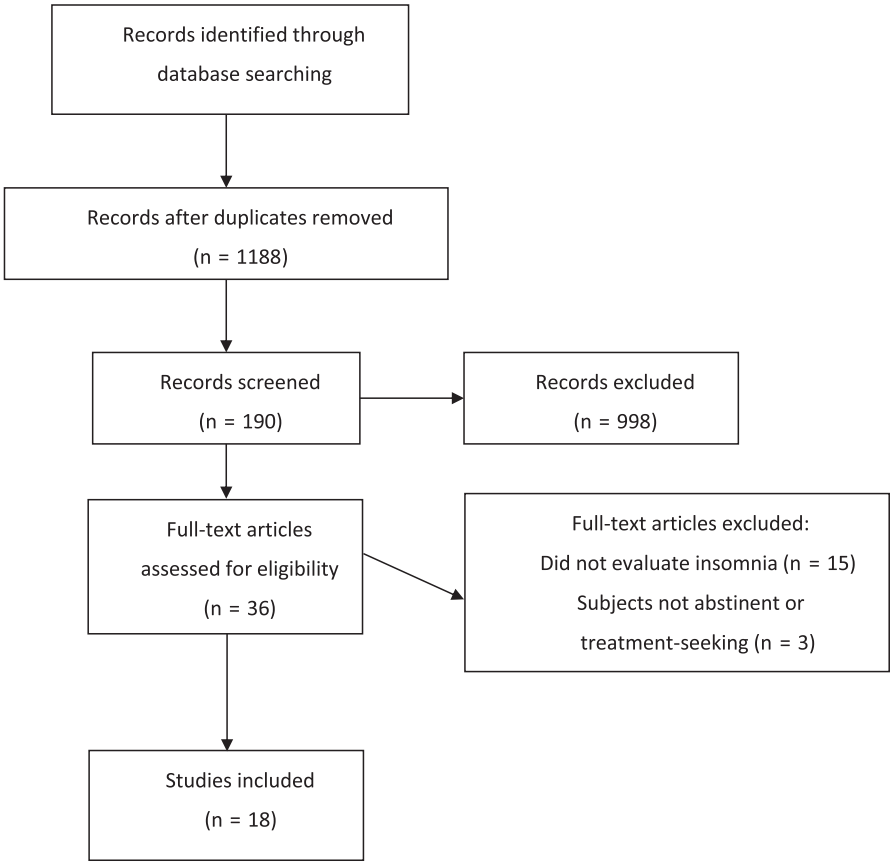


**FIGURE 1** Flow diagram of literature search

patients in the trazodone group had comparable or worse drinking outcomes versus placebo during and after treatment. At six months, placebo-treated patients had an increased percentage of abstinent days and fewer drinks per drinking day. At 6 months, 9% of trazodone-treated patients and 14% of placebo-treated patients had continuous abstinence.[45]

## 3.2 | Anticonvulsants

### 3.2.1 | Carbamazepine

One double-blind active-comparator trial randomized 136 patients with mild to moderate alcohol withdrawal to receive carbamazepine or lorazepam for five days on a fixed-dose tapering schedule. When adjusted for time since last drink, visual analog measures of sleep quality indicated a statistically significant main effect of medication on sleep that favored carbamazepine over lorazepam (adjusted mean = 62.1 vs 51.2 for lorazepam; $P = .0186$).[47]

### 3.2.2 | Gabapentin

Six randomized, double-blind, placebo-controlled or active-comparator studies have evaluated the efficacy of gabapentin 400-1800 mg/day in the treatment of individuals with IAAC.[48–53] Of the six studies, three showed significant improvements in sleep parameters,[50,51,53] and four of the six studies showed a positive effect on drinking outcomes.[48,50,51,53]

Malcolm et al,[52] in a double-blind, randomized controlled clinical study, evaluated the efficacy of gabapentin compared to lorazepam in improving sleep disturbances and daytime sleepiness in outpatients being treated for mild to moderate alcohol withdrawal. The patients received a 4-day fixed-dose taper of gabapentin (range = 400-1200 mg) or lorazepam (range = 4 mg [two doses of 2 mg] to 6 mg [three doses of 2 mg]) (n = 75) with an 8-day follow-up period (n = 68). In the early treatment period, self-reports of insomnia were lower while daytime sleepiness was higher with lorazepam than with gabapentin. In the follow-up period, patients previously taking lorazepam reported increased insomnia and daytime sleepiness while patients on gabapentin reported continued improvement in sleep measures. Gabapentin and lorazepam were similar in efficacy related to self-reports of sleep and sleepiness in patients with limited previous alcohol withdrawals. However, in patients with multiple previous alcohol withdrawals, gabapentin significantly reduced sleep disturbances and sleepiness compared with lorazepam.[52] Brower et al[48] evaluated the efficacy of gabapentin 1500 mg administered at bedtime for six weeks in the treatment of insomnia and prevention of relapse in 21 patients (gabapentin, n = 10; placebo, n = 11) with AUD whose insomnia persisted for at least one week of abstinence with no withdrawal symptoms. There were no significant differences between the gabapentin and placebo groups in subjective sleep reports and polysomnography; however, there was a nonsignificant trend for rebound insomnia with gabapentin.

**TABLE 1** Studies that evaluated the effect of pharmacological treatment on sleep outcomes in alcohol use cessation or treatment

| Citation | Medication | RCT | n | Daily dose | Duration of treatment | Sleep outcome measured | Results | Effect on alcohol use |
|---|---|---|---|---|---|---|---|---|
| *Antidepressants* | | | | | | | | |
| Le Bon (2003) | Trazodone | Yes | 18 | 50-200 mg | 4 wk | PSG | Sleep efficiency increase when calculated after sleep onset | NA |
| Friedmann (2008) | Trazodone | Yes | 173 | 50-150 mg | 12 wk | PSQI | Improved sleep quality during administration (mean change from baseline −3.02; 95% CI −3.38 to −2.67) | Reduction in abstinent days compared to placebo |
| *Anticonvulsants* | | | | | | | | |
| Malcolm (2002) | Carbamazepine/ lorazepam | Yes | 136 | 200-800 mg/2-8 mg | 5 days | Sleep Quality VAS | Significant effect of drug group on sleep quality that favored carbamazepine (adjusted mean 62.1 vs 51.2; $P = .0186$) | NA |
| Malcolm (2007) | Gabapentin/ Lorazepam | Yes | 75 | 400-1200/4-6 mg | 4 days | BDI and ESS | Those with multiple previous withdrawals reported reduced sleep disturbances and sleepiness in gabapentin compared to lorazepam group | No difference |
| Brower (2008) | Gabapentin | Yes | 21 | 1500 mg | 6 wk | SPQ and PSG | No effect | Significantly delayed the onset to heavy drinking |
| Trevisan (2008) | Gabapentin | Yes | 57 | 1200 mg | 4 wk | PSQI | No effect | No effect |
| Anton (2009) | Gabapentin/ flumazenil (IV) | Yes | 60 | Up to 1200 mg/2mg | 39 days | ISI and ESS | Decreased insomnia symptoms in those with low withdrawal symptoms on gabapentin vs placebo ($P = .015$)<br>Lower daytime sleepiness in gabapentin group vs placebo ($P < .004$) | Decreased alcohol use in patients with high withdrawal symptoms |
| Anton (2011) | Gabapentin/ Naltrexone | Yes | 146 | 1200 mg/50 mg | 6 wk | ISI | Gabapentin/Naltrexone group reported better sleep compared to placebo or naltrexone-only group ($P = .02$ and $P = .03$, respectively) | Gabapentin/ Naltrexone group had improvements in drinking outcomes over naltrexone alone |
| Mason (2014) | Gabapentin | Yes | 150 | 900 or 1800 mg | 12 wk | PSQI | Significant improvement in sleep compared to placebo ($P < .001$) | Significantly improved rates of abstinence and no heavy drinking compared to placebo |
| Karam-Hage (2003) | Gabapentin/ Trazodone | No | 50 | 300-1800 mg/50-300 mg | Up to 6 wk | SPQ | Both groups improved significantly, however, gabapentin group improved more than the trazodone group from baseline (8.8 vs 6.1, $P = .023$) | NA |

(Continues)

**TABLE 1** (Continued)

| Citation | Medication | RCT | n | Daily dose | Duration of treatment | Sleep outcome measured | Results | Effect on alcohol use |
|---|---|---|---|---|---|---|---|---|
| *Melatonin Agonists* | | | | | | | | |
| Brower (2011a) | Ramelteon | No | 5 | 8 mg | 4 wk | ISI | Significant improvement insomnia score from baseline (mean 17.6 to 9.8; Cohen's $d$ = 1.31) | NA |
| Grosshans (2014) | Agomelatine | No | 9 | 25-50 mg | 6 wk | PSQI | Significant improvement in insomnia score from baseline (mean 13.1 to 7.8, $P$ < .01) | NA |
| *Antipsychotics* | | | | | | | | |
| Litten (2012) | Quetiapine XR | Yes | 218 | Up to 400 mg | 12 wk | PSQI | Significant improvement in sleep compared to placebo ($P$ = .009) | No effect |
| Chakravorty (2014) | Quetiapine XR | Yes | 20 | Up to 400 mg | 8 wk | PSG | No effect on sleep efficiency yet a reduction in wake after sleep-onset time from baseline ($P$ = .03) | NA |
| *Other Agents* | | | | | | | | |
| Staner (2006) | Acamprosate | Yes | 24 | 1998 mg | 3 wk | PSG | Decreased wake time after sleep onset and increased stage 3 and REM sleep latency compared to placebo ($P$ < .05) | NA |
| Perney (2012) | Acamprosate | Yes | 592 | 2000 or 3000 mg | 24 wk | SSI | Percentage of mean change over baseline was significantly improved with compared with placebo ($P$ = .001) | NA |
| Irwin (2009) | Etanercept | Yes | 18 | 25 mg | Single dose, crossover | PSG | Significant decrease in amount and percentage of REM sleep compared to placebo | NA |
| Petrakis (2016) | Prazosin | Yes | 96 | 16 mg | 13 wk | PSQI | No effect | No effect |

Abbreviations: BDI, Beck Depression Inventory, Item 16; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; IV, intravenous; n, number of evaluated subjects; NA, not applicable, not investigated; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; RCT, randomized clinical trial; SPQ, Sleep Problems Questionnaire; SSI, Short Sleep Index; VAS, visual analog scale; XR, extended-release.

Gabapentin significantly delayed the onset of relapse at six weeks and 12 weeks. For the 14 patients who completed the study, there was a significant relationship between improvement in sleep and good drinking outcomes during the first six weeks.[48] Trevisan et al[49] evaluated the efficacy of gabapentin 1200 mg/day; valproic acid 1500 mg/day; and placebo in the treatment of acute alcohol withdrawal over five days and the prevention of relapse and symptoms of prolonged alcohol withdrawal (including psychiatric distress and sleep disturbances) over four weeks in 57 male veterans in an alcohol detoxification program. The three treatments had similar effects on drinking outcomes, relapse rates, and improved sleep.[49] Anton et al[50] evaluated the efficacy of the combination of flumazenil 2 mg administered intravenously for two consecutive days and gabapentin (up to 1200 mg nightly) administered orally for 39 days on drinking outcomes and sleep parameters in 60 alcohol-dependent patients who were required to be abstinent at least 72 hours before randomization. Upon randomization, 44 patients had low alcohol withdrawal symptoms, and 16 patients had high alcohol withdrawal symptoms. Patients with high alcohol withdrawal symptoms had better drinking outcomes after the combination of medications. Patients with lower withdrawal scores had better sleep with the combination of medications, as measured by the Insomnia Severity Index, and patients with high alcohol withdrawal symptoms had better sleep with placebo. There was no relationship between treatment effect on sleep and drinking outcomes.[50]

In a separate study, Anton et al[51] compared the efficacies of gabapentin titrated to 1200 mg/day (for 6 weeks) plus naltrexone titrated to 50 mg/day (for 16 weeks; n = 50), naltrexone 50 mg/day alone (for 16 weeks; n = 50), or placebo (n = 50) in the treatment of alcohol dependence in patients who were able to maintain abstinence for 4 days before randomization. Of the 150 randomized patients, four patients did not have drinking data available and, therefore, were not included in the analysis. For the first six weeks, the gabapentin-naltrexone group had a longer time to relapse, a lower percentage of heavy drinking days, and fewer drinks per drinking day than the group taking naltrexone alone. The gabapentin-naltrexone group had significantly better sleep than the naltrexone or placebo groups. Poor sleep quality was significantly related to relapse in the naltrexone group, but not in the gabapentin-naltrexone group.[51] Mason et al[53] evaluated the efficacy of gabapentin 900 mg/day and 1800 mg/day on measures including the rates of relapse and insomnia in 150 alcohol-dependent patients for 12 weeks who were abstinent from alcohol at least three days before randomization. Gabapentin significantly improved rates of both abstinence and no heavy drinking, as well as significantly reduced the PSQI total score compared with placebo in a linear dose-related manner.[53]

Additionally, one open-label study was conducted to evaluate gabapentin in patients experiencing insomnia after alcohol cessation. Karam-Hage and Brower[54] evaluated the efficacy of gabapentin (n = 34; range = 300-1800 mg) compared with trazodone (n = 16; range = 50-300 mg) at bedtime in alcohol-dependent outpatients with persisting insomnia despite 4 or more weeks of abstinence at baseline and up to 6 weeks in an open pilot study. Patients in the gabapentin group reported significant improvement in total SPQ scores compared with patients in the trazodone group ($P$ = .023). At follow-up, patients in the gabapentin group reported less initial insomnia and "feeling tired and worn out" compared with patients in the trazodone group.[54]

Gabapentin has some inherent advantages in clinical practice because it is not metabolized by the liver, does not lower the seizure threshold, and does not require frequent blood tests. However, gabapentin has been associated with abuse liability[55] and may increase suicidal thoughts and behavior, which may require careful risk assessment in the AUD patient population due to the high comorbidity with mood disorder in AUD.[36,48,49,53,56]

## 3.3 | Melatonin agonists

### 3.3.1 | Ramelteon and agomelatine

A small, open-label, 4-week study evaluated the efficacy of ramelteon 8 mg/night in treating insomnia in five patients with AUD and primary or alcohol-induced insomnia. Ramelteon improved Insomnia Severity Index scores from a mean (standard deviation [SD]) of 17.6 (3.6) to 9.8 (7.6), increased total sleep time from 5.0 (1.0) to 6.3 (1.6) hours, and decreased sleep-onset latency from 50.3 (20.9) to 23.5 (21.4) minutes.[57]

Subjective sleep quality was improved in a small, open-label, 6-week study that evaluated the efficacy of agomelatine 25-50 mg/day in treating insomnia in 9 abstinent patients with AUD. Treatment with agomelatine significantly decreased the PSQI total score from a mean (SD) of 13.1 (1.7) to 7.8 (1.7).[58] Agomelatine has some limitations in clinical practice because of its potential for causing hepatotoxicity, and it is not approved by the US Food and Drug Administration (FDA) for use in the United States.[36,58]

## 3.4 | Antipsychotics

### 3.4.1 | Quetiapine

Two randomized, double-blind, placebo-controlled studies demonstrated that quetiapine up to 400 mg/day significantly improved sleep parameters compared with those of placebo in patients with AUD.

In an 8-week study of 20 patients (quetiapine XR, n = 10; placebo, n = 10) with AUD in early recovery who complained of sleep-related disturbance, patients treated with quetiapine XR experienced significantly greater improvement in wake after sleep onset, as measured by polysomnography, and initial (although not sustained) improvements in insomnia symptoms, as measured by the Insomnia Severity Index. The effect of quetiapine on drinking outcomes was not evaluated. No significant differences in PSQI scores were noted between treatment groups.[59] In a 12-week study of 224 very heavy drinking patients with AUD (218

completers), sleep quality (as measured by the PSQI) improved with both groups but was greater with quetiapine (least-squares [LS] mean, 4.1, 95% CI: 3.6-4.6) as compared with placebo (LS mean, 5.1, 95% CI: 4.6-5.6). Quetiapine was not effective in improving the percentage of days of heavy drinking.[60]

Only modest improvements in sleep scores were noted, and these improvements were not sustained upon follow-up in the 8-week study.[59] Also, adverse effects (increased weight, increased triglyceride levels, dizziness, dry mouth, dyspepsia, increased appetite, sedation, and daytime somnolence) were more common with quetiapine than with placebo.[60] Another point of consideration for the AUD population is that there is a concern for misuse and abuse of quetiapine based on case reports in the published medical literature.[36,61,62]

## 3.5 | Other medications

### 3.5.1 | Acamprosate

Acamprosate is approved by the FDA for the maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation.[63] Two randomized, double-blind, placebo-controlled studies showed significant improvements in sleep parameters in patients with AUD during alcohol abstinence.

In a 3-week study (acamprosate, n = 12; placebo, n = 12), polysomnography data showed that acamprosate 666 mg administered three times daily (initiated 8 days before alcohol withdrawal and continued during the 15 days following alcohol withdrawal) significantly reduced wake time after sleep onset (11.5 ± 12.1 vs 13.9 ± 13.0) and increased Stage 3 sleep (6.2 ± 2.5 vs 4.4 ± 2.2) percent and REM latency (82.1 ± 23.5 vs 62.6 ± 34.9) minutes compared with placebo after two weeks of abstinence (all treatment effects, $P < .05$).[64] In a post hoc analysis of a 24-week study (n = 592; 292 completers), acamprosate 2000 or 3000 mg/day significantly reduced the percentage of alcohol-dependent patients who experienced subjective sleep disturbance symptoms at six months compared with placebo (from 40.2% at baseline for all patients to 19.5% with acamprosate and 26.1% with placebo; $P = .04$). The percentage of mean change over baseline in the Short Sleep Index score was significantly improved with acamprosate (−39.1%) compared with placebo (−2.6%) ($P = .001$) [65].

### 3.5.2 | Prazosin

Prazosin showed some promise in patients with post-traumatic stress disorder-without comorbid AUD[66,67] however, in a randomized, double-blind, placebo-controlled, 13-week study in 96 veterans with post-traumatic stress disorder and AUD (abstinent for two days before randomization), prazosin 16 mg/day did not significantly improve sleep parameters (including PSQI) or alcohol use compared with placebo.[68]

### 3.5.3 | Etanercept

Etanercept is a tumor necrosis factor-alpha (TNF-α) blocker indicated for the treatment of a variety of inflammatory diseases, such as rheumatoid arthritis and plaque psoriasis.[69] Circulating levels of TNF-α have been correlated with increases in REM sleep.[70] In a randomized, double-blind, placebo-controlled, crossover, single-dose study in 21 (18 completers) abstinent alcohol-dependent male patients, etanercept 25 mg significantly reduced the amount and percentage of REM sleep compared with placebo. The reduction in REM sleep reported with etanercept approached those values found in control subjects.[70]

These 19 studies evaluated patients at differing time points during abstinence, yet they did not uniformly measure drinking outcomes, a key limitation in the study designs. Additionally, most of these studies did not establish the temporal relationship between the subjects' sleep disturbances and alcohol use disorder. Furthermore, none of these medications are approved by the FDA for the treatment of insomnia in patients with AUD or IAAC and the currently available evidence for these agents is limited.

## 3.6 | Pharmacological treatments for insomnia disorder currently in development

Considering therapeutic targets in sleep research, our search identified eight novel compounds currently being studied for use in the United States. Three of these target the orexin system, a new pharmacological target for insomnia disorder, and recognized as a major addition to treatment armamentarium. The first dual orexin antagonist (DORA) approved by the FDA was Merck's suvorexant, which blocks both orexin-1 and orexin-2 receptors. A key differentiator for this class is the reduction of wakefulness, rather than increasing sleep drive.[71] DORAs that are being developed include lemborexant and daridorexant (previously referred to as nemorexant). A follow-on approach is to target only the orexin-2 receptors, which proponents argue will lead to an improved risk-benefit ratio.[72] One such molecule in development is seltorexant, which recently reported beneficial sleep onset and maintenance effects in a Phase 2 study of subjects with insomnia disorder.[72] Importantly the orexin antagonists, dual and selective, are currently targeted toward insomnia disorder rather than IAAC. We do note that suvorexant is currently listed on ClinicalTrials.gov as being studied in patients with comorbid sleep disorder and alcohol dependence (NCT03897062); however, preclinical work with suvorexant demonstrated that in the period following alcohol withdrawal orexin antagonism had sleep-promoting effect yet may exacerbate some aspects of sleep and EEG pathology,[73] leading the authors to suggest that the approach may not be best suited to this vulnerable population.

Other compounds in development for insomnia disorder target gamma-aminobutyric acid receptors (eg, EVT-201 and SAGE-217),[74,75] which may not be appropriate for IAAC as previously discussed. Piromelatine, a melatonin MT1/2/3 and serotonin

5-HT-1A/1D receptors agonist, is in development for sleep disorders and Alzheimer's disease.[76] Lumateperone is a serotonin 2a receptor antagonist which also modulates dopaminergic and glutaminergic systems from Intra-Cellular Therapies, Inc; it is currently being developed for schizophrenia and is also being studied in Phase 2 trials for *"sleep disorders associated with neuropsychiatric disorders"*.[77,78] Also, Imbrium Therapeutics has advanced a novel, potentially first-in-class small molecule nociceptin/orphanin-FQ receptor agonist to a randomized, double-blind, placebo-controlled, multi-center, parallel-group Phase 2 study (NCT04035200) to evaluate the compound's safety, efficacy, and tolerability in adults with moderate or severe AUD who are experiencing IAAC. Prior studies with this molecule in patients with insomnia disorder demonstrated increases in sleep efficiency over placebo, and reduction of sleep fragmentation throughout the night. Importantly, this treatment is minimally metabolized by the liver, increasing its suitability for use in patients with a history of significant alcohol use who are more likely to have impaired liver function.[79]

## 4 | DISCUSSION AND DIRECTIONS FOR FUTURE RESEARCH

The prevalence of insomnia associated with alcohol cessation in patients with AUD is high; however, limited prevalence data describe the persistence of sleep-related disorders for patients with AUD who are in a sustained abstinence period.[4,12] Patients with IAAC have been shown to experience increased sleep-onset latency, sleep fragmentation, and REM sleep percentage, as well as reductions in sleep efficiency, the percentage of SWS, and REM latency.[1,2] If these sleep disturbances go untreated, they are likely to contribute to lower quality of life and increase the risk of relapse in this patient population.[4,29] Further research is needed to provide prevalence data for IAAC and to fully characterize the physiology of sleep in patients with AUD in early and sustained recovery.[4]

Data from sleep studies suggest a progression of disturbance in sleep continuity to IAAC.[1,2,4,16–22,80] While currently controversial, emerging data are directed toward understanding the physiological differences between IAAC and insomnia disorder.[30,81] What is abundantly clear is that when employing treatment options, these two populations need to be considered differently.

Although sedative-hypnotic agents (eg, benzodiazepine receptor agonists, including Z drugs) are considered first-line treatment for insomnia, these agents have abuse liability and risk for overdose when combined with alcohol, both of which are significant concerns in the alcohol-dependent population.[36] Furthermore, the safety and efficacy of these medications have not been evaluated in controlled clinical trials for the management of insomnia in patients with AUD or IAAC. Additionally, clinicians are hesitant to prescribe sleep-inducing agents such as benzodiazepines because of concerns regarding abuse, overdose, and risk of alcohol relapse in this patient population.[44]

Currently available pharmacological interventions have shown some benefit in improving insomnia associated with alcohol cessation in patients with AUD; however, they have not been extensively studied in this patient population, are not approved by FDA for such use, and there are limitations to their use due to misuse and abuse potential, unfavorable safety profile, or risk of relapse.[35,36] The ideal pharmacological treatment for IAAC would have the following minimal attributes: efficacious with a low potential for abuse, low risk for adverse effects involving the respiratory system and favorable safety profile in hepatically compromised individuals.[35,36] In addition, pharmacological treatment should ideally reduce the risk of relapse and should be compatible with comorbid medical and psychiatric disorders often present in this patient population as well as with nonpharmacological treatment approaches. Most important, the efficacy and safety of any treatment should be supported by a substantial body of research consisting of controlled clinical trials with a methodological focus on the AUD population in early and sustained recovery.[4,36]

Other methodological considerations for future studies in this population should include the following: firstly, inclusion criteria with currently accepted definitions of insomnia (and excluding those with other sleep disorders), secondly the impact of insomnia-focused interventions on drinking outcomes, thirdly the role of medical and psychiatric comorbidities in predicting outcomes for insomnia treatments, and fourthly the efficacy of pharmacological and nonpharmacological monotherapy versus combination therapy.[4,35,36]

Looking toward future possible novel treatment options, we are aware of eight novel compounds in development for the treatment of insomnia in the United States, one of which specifically targeting IAAC. With an increasing awareness of the importance of IAAC and a move toward studying therapeutic approaches for niche sleep indications, we are hopeful that efficacious and safe treatment options for this vulnerable patient population appropriate for use in early and sustained recovery will become available.

### CONFLICT OF INTEREST

TAR has received compensated consultation support from Purdue Pharma LP for this work. JA and JT are former employees of Purdue Pharma LP GW is a current employee of Imbrium Therapeutics, a subsidiary of Purdue Pharma LP This work was funded by Purdue Pharma LP

### AUTHOR CONTRIBUTIONS

Timothy A. Roehrs, PhD, Jessica Auciello, PharmD, MPH, Jack Tseng, PhD and Garth Whiteside, PhD have read and approved the final version of the manuscript for submission to Neuropsychopharmacology Reports and agree to be accountable for all aspects of the work; each has made a substantial contribution to the conception, design, gathering, analysis and/or interpretation of data and a substantial contribution to the writing and intellectual content of the article; and acknowledge that they have exercised due care in ensuring the integrity of the work. As such, all authors meet criteria for authorship as defined by Neuropsychopharmacology Reports.

### DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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