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ALCOHOL (RF LEEMAN, SECTION EDITOR)

Assessing and Treating Insomnia Related to Alcohol Use Disorders

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Abstract Insomnia is a frequent complaint and may persist despite abstinence in patients with alcohol use disorders (AUDs). The association of insomnia with relapse and suicidal behaviors underlies the importance of proper assessment and treatment, which is the focus of this review. Contributory factors to insomnia in AUD patients include premorbid insomnia; effects of alcohol on sleep regulatory systems; co-occurring medical, psychiatric, and other sleep disorders; other substances and medications; stress; environmental factors: and suboptimal sleep hygiene. Polysomnography is recommended to rule out other sleep disorders (e.g., sleep apnea and periodic limb movement disorder) when suggested by history or treatment-resistant insomnia. Sleep will improve in most patients with sobriety, which remains the first line of treatment. Nevertheless, insomnia may also be thought of as a comorbid disorder with AUDs, requiring its own treatment for many patients. Randomized controlled studies support efficacy with behavioral therapies and medications. Melatonin agonists as well as sedating antidepressants, anticonvulsants, and antipsychotics are potentially effective and non-addictive.

Keywords Sleep disorders · Drinking · Review · Pharmacotherapy · Behavioral therapy

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Introduction

Insomnia is a common and persistent symptom, which has been associated with both relapse and suicidal thoughts in adult patients with moderate-to-severe alcohol use disorders (AUDs).[1] Consequently, this article focuses on assessing and treating patients with AUDs and comorbid insomnia, after a brief review of definitions, prevalence, persistence, and associations with relapse and suicidal thoughts.

In this paper, insomnia refers to a symptom involving trouble falling or staying sleep, early morning awakening, and/or non-restorative or poor quality sleep as reported by the patient. Insomnia as a disorder is defined in DSM-5 as dissatisfaction with sleep quantity or quality characterized by difficulty initiating sleep, maintaining sleep, or early morning awakening that causes distress or daytime impairment and occurs at least three times a week for at least 3 months [1]. DSM-5 also supports the clinical notion that persistent insomnia in AUD patients is a comorbid disorder deserving its own treatment when not simply attributable to the physiological effects of alcohol.

A mean of 60 % (range 36–91 %) of adult patients with AUDs report symptoms of insomnia, depending on sample differences and how insomnia was defined or measured [2, 3]. Measures of drinking severity and psychiatric severity are replicated and independent correlates of insomnia across studies [2, 4]. Biological mechanisms underlying alcohol-associated insomnia may include genetic polymorphisms [5], reductions in the biological drive for sleep [6, 7], and dysregulation in circadian rhythms [8].

[1] Moderate-to-severe AUD is a DSM-5 diagnosis roughly equivalent to DSM-IV alcohol dependence. AUD will be used in this article to denote both moderate-to-severe AUD and DSM-IV alcohol dependence as most studies were conducted prior to DSM-5.

Insomnia may begin in childhood prior to the onset of drinking (premorbid insomnia) [9], during periods of heavy drinking [10], or during acute and protracted alcohol withdrawal among individuals with AUDs [11, 12]. In one study, 25 % of 103 individuals with AUDs had persistent insomnia at a 6-month follow-up despite no drinking for the 3 months prior to follow-up [13]. Abnormal sleep parameters as measured by polysomnography (PSG) in prospective studies—including increased rapid eye movement (REM) sleep and decreased slow wave sleep (SWS)—can persist for 21 to 27 months [14]. PSG-measured correlates of insomnia, such as sleep onset latency (time to fall asleep), sleep efficiency (percentage of time in bed spent sleeping), and total sleep time, can take 5 to 14 months to normalize [14, 15].

Subjective reports of insomnia as well as objective sleep correlates (measured by PSG and actigraphy) have been associated in prospective studies with relapse or return to drinking in patients with AUDs [16••, 17–20]. However, not all studies have found an association between insomnia and relapse [21], likely because of the wide range of factors influencing relapse, which are difficult to measure in a single study. Potential mechanisms through which insomnia could influence relapse include self-medication [21], impaired cognitive [22] and executive functioning (e.g., impulse control, judgment, decision making), negative affect, and enhanced sensitivity to stress.

Across different populations, including alcohol-dependent patients [23] and veterans who misuse alcohol [24], sleep problems have been associated with suicidal thoughts and behaviors [25]. Moreover, insomnia may mediate the relationship between drinking severity and suicidal thoughts [26]. Therefore, attending to insomnia in the clinical arena is important.

Assessment

A good screening question is, "Are you satisfied with your sleep?" If the answer is no, then ask about the following:

- How long it takes to fall asleep (>30 min is frequently problematic).
- How often one awakens during the night, possible causes for waking up (e.g., nightmares), and how long it takes to fall back asleep (>30 min of awake time after falling asleep is generally problematic).
- Awakening earlier than desired and at what time (not as common as trouble falling and staying asleep in AUD patients [27, 28]).
- Total hours of sleep per night (<6–7 h per night has been associated with cognitive dysfunction, at least in older adults and premature mortality, although not all studies agree) [29–32].
- Are bedtimes and wake times consistent or variable across nights?
- Is daytime functioning impaired (usual responsibilities, cognitive functioning, interpersonal relationships, and emotional responses) because of sleep problems?
- How often (nights per week) and for how long have insomnia symptoms been present?
- How are drinking and insomnia related in terms of the patient's view? Self-medication of insomnia with alcohol is common [33] although ineffective. Insomnia that developed prior to the onset of drinking and/or persisted during prior sober periods of 1–3 months are evidence of an independent, co-occurring disorder.

Persistent insomnia despite 1 to 3 months of abstinence may be due to the following:

1. *Premorbid insomnia*. In one study, more than 50 % of alcohol-dependent patients reported that their insomnia preceded their drinking problems [27] and insomnia is considered to be a risk factor for new-onset alcohol use disorders [34, 35, 36•].
2. *Comorbid or co-occurring disorders*.

    - Medical problems such as chronic pain, hyperthyroidism, nocturia, gastroesophageal reflux disease, and chronic obstructive pulmonary disease [37].
    - Mental disorders, particularly mood disorders, anxiety disorders, and trauma-related disorders. Both nightmares and hyperarousal can disrupt sleep in patients with post-traumatic stress disorder. In one study, childhood trauma significantly predicted insomnia in patients with AUDs after controlling for other variables [28].
    - Sleep disorders, such as obstructive sleep apnea (OSA) and periodic limb movement disorder (PLMD), are not uncommon in AUD patients [38, 39] and can only be diagnosed with PSG. Loud snoring and either breathing cessation or gasping for air during sleep suggests OSA, while kicking or jerking movements suggest PLMD. Patients may complain of daytime sleepiness, which can be measured with the Epworth Sleepiness Scale [40]. Restless legs syndrome, driven by distressing, uncomfortable sensations in the legs, causes difficulty falling asleep and is highly comorbid with PLMD. Bed partners may also observe nocturnal wandering, including sleepwalking (a non-REM sleep disorder), which occurs more commonly in those with than without AUDs [41]. In REM sleep behavior disorder, patients may dangerously act out their dreams. Circadian rhythm sleep-wake disorders include delayed and advanced sleep phase types. People with delayed sleep

phase have difficulty falling asleep until later in the night than most people and likewise sleep later into the morning. The opposite is true of those with advanced sleep phase type. Sleep diaries [42] and chronotype questionnaires [43] can help to characterize these diurnal preferences.

3. *Substance- or medication-induced insomnia*. Stimulants including caffeine and withdrawal from cannabis, opioids, sedative-hypnotics, and tobacco are all associated with insomnia and related PSG changes [44, 45]. Stimulating antidepressants (e.g., bupropion), thyroid medication, and bronchodilators can also induce insomnia [46]. Serotonin-selective reuptake inhibitors (SSRIs), even as they improve mood and anxiety disorders, can disrupt PSG-measured sleep parameters and increase periodic limb movements during sleep [47, 48].
4. *Stressful events* are a common reason for seeking treatment, and insomnia is associated with greater psychosocial severity in AUD patients [49]. Stress is associated with neurophysiological hyperarousal, which contributes to insomnia [50].
5. *Inadequate sleep hygiene and environmental factors*. Daytime naps, irregular sleep schedules, or "voluntary sleep deprivation" (i.e., deliberately staying up late for work or pleasure despite needing to get up early) can perpetuate insomnia [27]. Environmental disruptions include a bed partner who snores or kicks, small children who awaken at night, pets, noise, uncomfortable room temperature, viewing television or electronic screens before bedtime (which suppress melatonin), stimulating bedtime activities, and/or an uncomfortable mattress or pillow.

Measurement-Based Care

A number of self-administered scales measure symptoms of insomnia and daytime sleepiness, all of which have been utilized in the studies of AUD patients [40, 51–53]. They can be used during the initial assessment to quantify symptom severity and over time to measure response to treatment. Sleep diaries are an excellent way to assess night-to-night sleep patterns and variability in sleep parameters [42]. Some patients who are unwilling to complete a sleep diary may be intent only on obtaining pills.

Treatment

The evidence base for treating insomnia in patients with AUDs is growing but limited. The evidence that treating insomnia will reduce relapse to drinking is also limited, despite the association between insomnia and relapse [54]. Nevertheless, improving sleep has its own benefits in terms of symptom relief and daytime functioning, which can support recovery, even if not sufficient to prevent relapse. AUD and persisting insomnia may best be conceptualized as co-occurring (and likely interacting) disorders with each disorder warranting its own treatment. Still, it is difficult to assess the contribution of drinking to insomnia unless the patient abstains. Therefore, abstinence from alcohol is always the first line treatment for alcohol-related insomnia. Even when abstinence is not sufficient by itself, partial improvement in insomnia can happen relatively quickly within a few weeks or months.

Education and Behavioral Therapies

Principles of good sleep hygiene should be reviewed with all patients [55]. These include making the sleep room as comfortable as possible; using earplugs or eye masks and replacing pillows when helpful; regular bedtimes and wake times within 1 h daily; no napping during the day (although brief naps of 10–20 min may help to reduce sleepiness when attention is required); creating a relaxing bedtime routine to prepare for sleep; avoiding lights that can suppress melatonin secretion, including televisions and electronic screens prior to bed time; abstaining from alcohol, caffeine, and other drugs, which disrupt sleep; and limiting fluid intake and heavy meals prior to bedtime. These principles establish a foundation for good sleep and work best when combined with other therapies. If patients report that they have tried these things without benefit, then clinicians can emphasize that sleep hygiene is optimal only if practiced consistently over several weeks to become habits.

Behavioral therapies for insomnia in AUD patients have been reviewed previously [2, 44, 56••, 57]. Cognitive-behavioral therapy for insomnia (CBT-I) is generally recommended as the first-line treatment in most patients with insomnia in general medical care [58]. While medication works faster, CBT-I is highly effective and longer lasting than medications [59], which work only as long as they are taken [60]. Moreover, medications for insomnia may inadvertently reinforce an already entrenched mindset in AUD patients that distressing symptoms are best managed by using external chemicals. While CBT-I is best studied in patients without AUDs or comorbid disorders [58], two randomized controlled trials (RCTs) support its use in AUD patients [61, 62]. Although sleep improved in both studies, no differences in drinking outcomes were found between the CBT-I and control groups. Improvement in the sleep of these patients was evident by five sessions. Spielman's three-part model of insomnia [63] helps to explain why behavioral therapy is effective, even when a chemical substance like alcohol is involved. According to this model, insomnia results from predisposing factors (e.g., childhood trauma, family history, genetics), precipitating factors (often stressful events), and perpetuating factors (poor sleep hygiene, conditioned responses, decreased

sleep drive, and alcohol). Alcohol-specific treatment addresses one perpetuating factor (alcohol) via the initiation of abstinence. CBT-I addresses many of the other perpetuating factors.

The components of CBT-I are sleep hygiene, stimulus control, sleep restriction, and cognitive therapy [62]. Stimulus control confines bed use to sleep and sex only. Other activities such as watching television or staying awake worrying are discouraged. If patients are unable to fall sleep after 15–20 min, then they are instructed to get out of bed and engage in a quiet and relaxing activity until they feel sleepy or ready for bed again. The goal is to extinguish any conditioning that has resulted in the bed acting as a cue for not sleeping. Sleep restriction is complementary in that the patient's current total sleep time is consolidated into a single period. The rationale for sleep restriction is to increase sleep drive or pressure to sleep for patients who have difficulty falling asleep. The longer one stays up, the greater the sleep drive. By keeping a sleep diary for at least a week, the patient's usual bed times (e.g., 11:30 p.m.) and wake times (e.g., 6:30 a.m.) can be averaged to derive the average time spent in bed (e.g., 7 h). From the sleep diary, the average sleep duration across nights can also be estimated (e.g., 5 h). By subtraction, the patient spends 2 h awake on average. Thus, the patient is next encouraged to set their wake at 6:30 a.m., while delaying their bedtime by 1 to 2 h, allowing only 5 to 6 h in bed, depending on the clinical judgment of the clinician. Gradually, the bed time is adjusted to be earlier in the night in increments of 15 to 30 min weekly which allows more time for sleep. Cognitive therapy provides education about sleep and addresses dysfunctional beliefs about sleep. An alcohol-specific example is thinking that alcohol is a good solution to sleep. One study paradoxically found, however, that some dysfunctional beliefs were protective of relapse to drinking [64].

Progressive relaxation therapy is another behavioral therapy for insomnia, with one small RCT showing benefit to inpatients with AUDs [65]. Post-hospitalization outcomes were not included in this study.

Pharmacotherapy

Recent reviews of medications to treat insomnia in AUD have been published [2, 66•, 67]. Controlled trials, especially randomized, double-blind placebo-controlled trials (DB-RCTs), will be emphasized here (Table 1). Uncontrolled and open label studies will be discussed only in the absence of RCTs or when they contribute unique information. Medications reviewed below include those approved by the United States Food and Drug Administration (FDA) for the treatment of insomnia, including the benzodiazepine receptor agonists (BzRAs), ramelteon [80], doxepin, and suvorexant [81]. Of note, the BzRAs and suvorexant are Schedule IV controlled substances in the USA because of their abuse potential, although not fully established for suvorexant. Prescription medications that have been used off-label for insomnia in AUD patients include sedating antidepressants, anticonvulsants, and antipsychotics [82]. Some medications used for relapse prevention (acamprosate, topiramate) may also benefit sleep. Prazosin, an antihypertensive drug used to treat nightmares, may also have relapse prevention properties. Prescriptions for zopiclone, agomelatine, and prolonged release melatonin are available in countries other than the USA. "Off-the-shelf" (or so-called "over-the-counter" [OTC]) substances sold without a prescription are also used by patients. Herbal remedies such as valerian, chamomile, and kava have not been shown to be more effective than placebo [83] and will not be discussed further.

BzRAs (FDA-Approved to Treat Insomnia)

This group is comprised of the structural benzodiazepines (estazolam, flurazepam, quazepam, temazepam, triazolam) and the non-benzodiazepine, alpha-1-selective BzRAs (eszopiclone, zaleplon, zolpidem). Zopiclone, while not FDA-approved in the USA for any purpose, is available in other countries. The alpha-1-selective BzRAs have largely supplanted the traditional BzRAs for sleep. BzRAs work by facilitating the action of GABA, the major inhibitory neurotransmitter in the brain. Benzodiazepines are the medications of choice to treat alcohol withdrawal, but addiction physicians generally avoid them in the post-withdrawal phase due to their abuse potential [84] and overdose risk when combined with alcohol. BzRAs may have beneficial effects on sleep during acute, uncomplicated alcohol withdrawal, but no controlled trials have investigated their safety and efficacy to treat persistent insomnia in abstinent AUD patients. Given that medications for chronic insomnia are effective only as long as taken, BzRAs are not good first-line medications, despite their known safety and efficacy for insomnia in patients without AUDs [85]. Nevertheless, long-term use of benzodiazepines does not necessarily increase the risk for relapse [86]. In weighing the risks and benefits of using BzRAs to treat chronic persisting insomnia in AUD patients, the following factors may be considered to increase risk: (1) prior history of a sedative-hypnotic use disorder or polysubstance dependence; (2) prior history of intentional or unintentional drug overdose, especially involving sedative-hypnotics; (3) high risk for suicide; (4) history of drinking while taking sedative-hypnotics; (5) State prescription drug monitoring report reveals undisclosed medication or doctor shopping; (6) refusal to submit a urine sample for drug screen or undisclosed drugs on drug screen; (7) a pattern of missed visits; (8) risk for falling or memory impairment (e.g., older age); (9) tentative or unstable physician-patient alliance; (10) refusal to try other therapies for insomnia or noncompliance with other treatment recommendations; and (11) refusal to sign a controlled substance agreement specifying benefits, risks, and conditions for receiving prescriptions (e.g., urine drug screens, single prescriber and pharmacy, early refill policy,

Table 1 Double-blind, randomized controlled trials with insomnia outcomes in patients with AUDs

Authors (ref)	*N*	Daily dose[a]	Selected for insomnia	Objective sleep measure	Treatment duration	Effect on insomnia	Effect on drinking
Gabapentin							
Brower et al. [68]	21	1500 mg qhs	Yes	PSG	6 weeks	NS	↓
Trevisan et al. [69]	57	400 mg TID	No	None	4 weeks	NS	NS
Anton et al. [70]	60	1200 mg qhs	No	None	39 days	↓[b]	↓[b]
Anton et al. [71][c]	150	300-300-600 mg[d]	No	None	6 weeks	↓	↓
Mason et al. [72]	150	300 or 600 TID	No	None	12 weeks	↓	↓
Trazodone							
Le Bon et al. [73]	18	150–200 mg qhs	Yes	PSG	4 weeks	↓	NA
Friedmann et al. [60]	173	50–150 mg qhs	Yes	None	12 weeks	↓	↑
Quetiapine							
Litten et al. [74]	224	400 mg (XR)	No	None	12 weeks	↓	NS
Chakravorty et al. [75]	20	400 mg	Yes	PSG	8 weeks	↓	NA
Acamprosate							
Staner et al. [76]	24	666 mg TID	No	PSG	23 days[e]	NS[f]	+/–[f]
Perney et al. [77]	592	2 or 3 g[d]	No	No	24 weeks	↓	NS[g]
Topiramate							
Johnson et al. [78]	371	100–200 mg	No	None	14 weeks	↓	↓
Prazosin							
Simpson et al. [79]	30	4-4-8 mg[a,d]	No[h]	None	6 weeks	NS[h]	↓

NA not applicable because not studied, *NS* not significant, *PSG* polysomnography, *TID* three times daily, *qhs* at bedtime, *XR* extended release

[a] Target doses. Follow manufacturers' recommendations for titration

[b] Sleep improved only for patients who had lower than study threshold withdrawal scores during detoxification, whereas drinking decreased only for patients who had higher than study threshold withdrawal scores during detoxification

[c] A comparison of gabapentin + naltrexone, naltrexone + placebo, and double placebo

[d] Divided doses

[e] Included 8 days while drinking

[f] PSG data were collected on days 2 and 14 of abstinence. A positive treatment effect for acamprosate was found (+), but the time X group interaction was not significant (−)

[g] Previously published data referenced by the secondary data analysis of sleep outcomes

[h] Patients had comorbid AUD and post-traumatic stress disorder. Only one sleep item included, which assessed disturbing dreams

and indications for tapering or stopping). If alternative insomnia-specific treatments in combination with abstinence have been tried and failed, then PSG should be considered to rule out other sleep disorders.

Melatonin Agonists (Melatonin, Ramelteon, and Agomelatine)

Melatonin is a hormone that is synthesized and secreted by the pineal gland in the brain when darkness pervades the nighttime. It signals that it is time for sleep. Light suppresses melatonin secretion, regardless of the time of day. Classified in the USA as a food supplement, it is available OTC without a prescription and not regulated in terms of its contents. The dosage listed on the label, therefore, may not accurately represent its contents. It is used mainly in small doses as a chronobiotic to advance or delay the circadian phase of the sleep cycle, such as for jet lag. It may also have modest effects on sleep induction without regard to circadian phase [87]. The use of melatonin in AUD patients with insomnia is suggested by the evidence of circadian dysregulation and decreased or delayed melatonin levels in AUD patients [8, 88••]. However, no controlled studies have been conducted in AUD patients, so optimal dosing and timing of melatonin administration are not well established. Ramelteon is a melatonin agonist available by prescription and approved by the FDA to treat sleep-onset insomnia [80]. Five AUD patients participated in a 4-week open label study of ramelteon 8 mg taken 30 min before bedtime and had improvements in insomnia [89]. Agomelatine is an antidepressant with melatonin agonist properties that is approved for use in the European Union. In a 6-week open label study of nine AUD outpatients with insomnia, 25 to 50 mg of agomelatine at bedtime improved sleep [90]. Hepatotoxicity may be a limiting factor for agomelatine in AUD patients [91].

Doxepin and Other Sedating Antidepressants (Trazodone and Mirtazapine)

Doxepin, which is approved in the USA to treat sleep-maintenance insomnia (in doses of 3 and 6 mg at bedtime), is a sedating tricyclic antidepressant with antihistaminic effects [92]. Histamine is a wake-promoting neurotransmitter, so inhibiting its action causes sleepiness. No studies of its use in AUD patients have been published. Mirtazapine has positive effects on sleep in depressed patients, likely due to its antihistaminic effects and blockade of serotonin type 2 receptors, but it is poorly studied in patients with AUDs [93]. Of the three antidepressants discussed here, however, its antidepressant dose overlaps with its use for sleep, so it may find a place for AUD patients with comorbid major depression [94].

Among the antidepressants, only trazodone has specifically been studied for its effects on sleep in AUD patients and it was (and may still be) the most commonly prescribed sleep aid by addiction specialists [95]. Its exact mechanism of action for promoting sleep is unknown, although it has some antihistamine effects and blocks both type 2 serotonin and alpha-1-adrenergic receptors. It also increases slow wave sleep in some studies. Four studies, including RCTs and two retrospectively controlled trials that were previously reviewed in detail [2], are briefly summarized here and in Table 1. A small study of 18 AUD patients with insomnia were randomized to 4 weeks of trazodone (titrated up to 200 mg nightly) vs. placebo and outcomes were measured with PSG [73]. The trazodone group spent less time awake during the night and more time in bed spent when compared to placebo. Drinking outcomes were not reported.

The second DB-RCT involved 173 AUD patients (>90 % male), admitted for 3 to 5 days of inpatient detoxification at a single Veterans Affairs facility [60]. They were randomized to 12 weeks of either placebo or trazodone 50 to 150 mg as tolerated, taken 1 h nightly before bedtime and followed for an additional 12 weeks. Subjective sleep improved markedly in the trazodone group during the 12 weeks of study medication, but no differences were seen at 12 weeks after stopping the medication. No significant difference between groups was observed for continuous abstinence at 24 weeks (9.1 vs. 14.1 %, respectively); however, the placebo group had more abstinent days at 12 and 24 weeks and fewer heavy drinking days through the first 12 weeks. Taken together, the trazodone-treated group had superior self-reported sleep outcomes that lasted only as long as the medication was taken and similarly low rates of continuous abstinence, but otherwise worse drinking outcomes than the placebo group. The reason for worse drinking outcomes remains unexplained, but m-chlorophenylpiperazine, an active metabolite of trazodone, has been shown to increase craving, anxiety, and cortisol levels in AUD individuals under controlled laboratory conditions [96]. Another reason may be that the sedative effects of trazodone acted as a cue for drinking. It is also important to note that only 25 % of the sample had formal treatment for AUDs after completing inpatient detoxification.

A retrospective study conducted with a US veterans population examined 14,443 episodes of hospitalization for alcohol dependence without psychosis [97] and compared four subgroups, based on medications received within 45 days of discharge. Two of the groups received at least two fills of either trazodone alone or quetiapine alone, and two of the groups received either trazadone or quetiapine in combination with other psychiatric/addiction medications (antidepressants, antipsychotics, anitconvulsants, or naltrexone/disulfiram). Using the trazodone combination group as the reference group and adjusting for covariates, time to rehospitalization for alcohol dependence was shorter in the trazodone alone and quetiapine alone groups than in the trazodone combination group. The quetiapine combination group did not differ from the trazodone combination group. The second retrospective study compared 283 residential-treated (not simply detoxification) AUD patients who were (30 %) and were not prescribed trazodone at the time of discharge and followed for 6 months [98]. About 50 % of the sample was also prescribed relapse prevention medication for AUD. No differences between groups were found in relapse to alcohol use. While these studies are not directly comparable in design, sample, or treatment characteristics to the RCT, they suggest that supplementing trazodone with other medications as indicated may help delay relapse and/or hospitalization.

In conclusion, trazodone may worsen drinking outcomes for unknown reasons when used to treat comorbid AUD and insomnia. Therefore, patients who relapse to drinking while taking trazodone should be tried on alternative sleep therapies and/or have their alcohol-specific treatment intensified. As with any medication, the risks and benefits of trazodone for a given AUD patient should be weighed in light of these studies.

Suvorexant

Suvorexant, a novel orexin antagonist, was FDA-approved in 2014 to treat insomnia in doses ranging from 5 to 20 mg at bedtime [81]. Orexin is a neurochemical involved in maintaining wakefulness and patients with narcolepsy have a deficiency of it. Thus, medication that blocks the action of orexin at its receptor will produce sleepiness. As with other sedative-hypnotics, daytime somnolence is not uncommon, especially at higher doses. Suvorexant is currently classified as a Schedule IV controlled substance, the same category as BzRAs. The extent of its abuse potential is unknown at this time, because patients with substance use disorders were excluded from clinical trials. Although the orexin system has been implicated in addiction, orexin antagonists could be protective theoretically as they are in some animal models [99]. Until further research is conducted and data from post-marketing surveillance accrues, suvorexant cannot be recommended for use in patients with AUDs.

Anticonvulsants (Gabapentin, Topiramate, and Valproic Acid)

Gabapentin binds to the alpha-2-delta subunit of voltage-dependent calcium channels and closes them, which may promote sedation by facilitating cerebral GABA activity. Of five DB-RCTs of gabapentin vs. placebo, three of five showed positive effects on sleep and four of five showed positive effects on dinking (see Table 1). Anton and colleagues reported that only patients who had low threshold withdrawal scores during detoxification had improved sleep with gabapentin [70]. Thus, it may be that the particular subgroups of AUD patients have benefit for insomnia with gabapentin. Like gabapentin, topiramate also facilitates the activity of GABA. Among its other effects, topiramate may also produce sedation by antagonizing AMPA/kainite-type receptors for glutamate, the major excitatory neurotransmitter in the brain. Topiramate, titrated over 5 weeks to 300 mg daily in two divided doses, was associated with both improved drinking outcomes and sleep in a 14-week, multi-site DB-RCT of 371 outpatients [78]. Valproic acid showed no benefit over either placebo or gabapentin in either drinking or sleep outcomes in a 4-week RCT of 57 patients [69].

Sedating Antipsychotics (Quetiapine)

All of the atypical antipsychotic medications block dopamine and type 2 serotonin receptors; however, quetiapine also has antihistaminic activity. Quetiapine is the only antipsychotic medication that has been studied with DB-RCTs for its effects on sleep in AUD patients. The two studies found improved sleep with a 400 mg dose, although quetiapine did not differ from placebo in terms of drinking [74] or craving [75]. These doses may be higher than needed, especially with side effects such as weight gain and abuse potential [100]. In the author's experience, doses can start at 25 to 50 mg at bedtime and usually do not need to exceed 100 to 150 mg nightly in the absence of major psychiatric comorbidity such as bipolar disorder or psychosis.

Other Prescription Medications (Acamprosate, Prazosin)

Acamprosate, a relapse prevention medication for AUD, may decrease hyperarousal via its action of modulating glutamate receptors, although its precise mechanism of action remains unknown [101]. Acamprosate was investigated in a 22-day DB-RCT of 24 men with AUD using PSG. Subjects had PSG recordings on day 2 of alcohol withdrawal and day 14 of abstinence after starting acamprosate (666 mg TID) 8 days prior to withdrawal [76]. Analyses included treatment effects, time effects, and treatment by time interactions. When day 2 and day 14 data were combined, acamprosate was associated with significantly decreased wake time after sleep onset, increased stage 3 percentage (a component of slow wave sleep), and reduced REM sleep latency as compared to the placebo group. However, no significant time by treatment group interactions was found, making the results difficult to interpret. After stopping alcohol, both groups maintained sobriety for the 14 days. A secondary analysis of a 26-week DB-RCT of 592 outpatients showed no benefit of acamprosate vs. placebo on drinking outcomes, but found a positive effect on sleep [77] .

Post-traumatic stress disorder, characterized by nightmares and poor sleep quality, is highly comorbid with AUDs. A meta-analysis of five RCTs found that prazosin, an alpha-1-adrenergic antagonist, has a salutary effect on increasing sleep quality and reducing both nightmares and other PTSD symptoms [102]; however, its effects on sleep in AUD patients are poorly studied. One RCT of 30 patients with comorbid alcohol dependence and PTSD failed to find an effect of prazosin on disturbing dreams as measured by a single item; but did find improvement in drinking outcomes [79]. Two other small RCTs in AUD patients without PTSD did not report on any sleep measures, but respectively showed either decreased craving in response to stress [103] or improved drinking outcomes relative to placebo [104]. Further study of prazosin on sleep and drinking outcomes is warranted.

Summary and Conclusions

Assessment and treatment of insomnia is important in patients with AUDs because it is common, persistent, and associated with relapse and suicidal thoughts. When conducting an assessment, one can assume that alcohol is causative, especially during the first month of sobriety, due to mechanisms such as withdrawal-induced hyperarousal, impaired sleep homeostasis, and circadian rhythm dysfunction. Due to the multifactorial nature of persistent insomnia, however, alcohol will unlikely be the only cause. Clinicians can assess for other causes and factors during the first few weeks of sobriety if insomnia persists or if the risk for relapse is high. These factors include co-occurring substance use and medical, psychiatric, and sleep disorders; stress; prescription medications; poor sleep hygiene, and non-conducive sleep environments. When available, a bed partner can help identify breathing difficulties or snoring, kicking movements, or parasomnias such as REM sleep behavioral disorder. Sleep diaries for 1–2 weeks can engage patients in their own self-care, delay premature prescribing during the assessment period, and assess night-to-night sleep patterns and variability. Rating scales can assess the nature and severity of insomnia and daytime sleepiness, and track outcomes over time, consistent with measurement-based care. Referral to a sleep clinic for PSG is essential to diagnose sleep disorders such as sleep apnea and periodic leg movement disorder.

Treatment begins with sobriety, which will decrease insomnia symptoms in most patients and eliminate acute alcohol effects while assessing for other causes. Patients who use alcohol to self-

medicate insomnia can benefit from education about (a) healthy sleep, (b) how alcohol interferes with sleep and potentially harms those parts of the brain that regulate sleep, and (c) therapeutic alternatives for insomnia based on a thorough assessment. Although insomnia is associated with relapse to drinking, there is insufficient evidence to conclude that insomnia treatment will prevent relapse. Indeed, there is evidence for a dissociation between sleep and drinking outcomes (Table 1), most likely because of the complexity of factors underlying relapse. Therefore, persistent insomnia and AUDs are best treated as co-occurring disorders, without expectation that treatment of one disorder will be sufficient treatment for the other.

Once assessment is complete and other factors have been identified and managed, CBT-I is the treatment of choice for insomnia in most AUD patients. Its advantages include long-term benefits without worsening of drinking outcomes and non-reliance on external substances in a population prone to do so. The disadvantage of CBT-I is it can take up to five sessions or weeks before benefit is observed. In addition, some techniques such as sleep restriction may need to be modified in patients with bipolar disorder to prevent activation of mania. Medications can be considered during the early phases of CBT-I if a patient's distress from insomnia threatens sobriety. They can also be used as primary treatment for insomnia when CBT-I is not readily available or when the patient is unwilling or unable. Medications have the advantage of working more quickly, but insomnia returns when they are stopped (in the absence of CBT-I). Their potential side effects—including relapse in the case of trazodone, abuse potential with the BzRAs and suvorexant, weight gain with mirtazapine and quetiapine, and daytime somnolence with all of them—need to be weighed against their benefits using clinical judgment.

Selecting which medications to use or start with is an empirical process, meaning there is some element of trial and error as with most medications. The process is guided by the evidence base from research (Table 1), prior history of response, co-occurring disorders, tolerance for side effects, and likelihood of adherence. Medications that may have benefit for relapse prevention such as acamprosate, topiramate, or gabapentin might be considered first. FDA-approved medications for insomnia without abuse potential such as low-dose doxepin (3–10 mg/day) and ramelteon should be considered next. Medications that can treat insomnia and a co-occurring disorder may suggest using mirtazapine with major depression, quetiapine with bipolar disorder, or gabapentin with anxiety or pain. Trazodone is effective for sleep in AUD patients, but given the possibility of relapse, may need to be combined with naltrexone or acamprosate and discontinued if relapse occurs. First-generation antihistamines (H1 blockers), some of which are available OTC such as diphenhydramine and doxylamine, may work for some patients if they have not already tried them. Antihistamine effects, for example, may contribute to the mechanism of action for doxepin and quetiapine. OTC melatonin may be tried as a lower-cost alternative to ramelteon, but unfortunately is unregulated in the USA in terms of labeling and contents. In cases of insomnia that is not responsive to these treatment alternatives despite sobriety, referral to a sleep clinic or for PSG is recommended.

BzRAs and suvorexant are currently medications of last resort, due to their known and unknown abuse potential, respectively. Mixing BzRAs and alcohol can lead to lethal overdoses. Their judicious use might best be reserved for treatment-resistant insomnia, confirmed by a sleep medicine specialist, which threatens sobriety or seriously compromises daytime functioning. Before prescribing them, the patient's history of risk for misuse, abuse, or addiction (detailed above) should be assessed. If these medications are used, then monitoring precautions, standard to most controlled substance agreements, are recommended to minimize their risks.

Treatment for comorbid insomnia in AUD patients is now understood to be an important area for clinical care and research. No longer is it reasonable to assume that insomnia will automatically reverse with abstinence or that patients should simply learn to live with it. The risks of untreated insomnia can threaten sobriety and diminish quality of life. The suggestions for assessment and treatment in this article may help patients of today, while awaiting future research to guide practice further.

Compliance with Ethical Standards All cited references to studies conducted by Dr. Brower were approved by the appropriate Institutional Review Board(s) and complied with ethics guidelines.

Conflict of Interest Dr. Brower reports grants from NIH, outside the submitted work.

Human and Animal Rights and Informed Consent All cited references to studies conducted by Dr. Brower were approved by the appropriate Institutional Review Board(s), and written and signed informed consent was included for voluntary participation.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. American Psychiatric Association. DSM-5: diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
2. Brower KJ. Assessment and treatment of insomnia in adult patients with alcohol use disorders. Alcohol. 2015;49(4):417–27.
3. Wallen GR, Brooks AT, Whiting B, et al. The prevalence of sleep disturbance in alcoholics admitted for treatment: a target for chronic disease management. Family Commun Health. 2014;37(4):288–97.

4. Hartwell EE, Bujarski S, Glasner-Edwards S, Ray LA. The association of alcohol severity and sleep quality in problem drinkers. Alcohol Alcohol. 2015;50(5):536–41.
5. Brower KJ, Wojnar M, Sliwerska E, Armitage R, Burmeister M. PER3 polymorphism and insomnia severity in alcohol dependence. Sleep. 2012;35(4):571–7.
6. Armitage R, Hoffmann R, Conroy DA, Arnedt JT, Brower KJ. Effects of a 3-hour sleep delay on sleep homeostasis in alcohol dependent adults. Sleep. 2012;35(2):273–8.
7. Thakkar MM, Sharma R, Sahota P. Alcohol disrupts sleep homeostasis. Alcohol. 2015;49(4):299–310.
8. Conroy DA, Hairston IS, Arnedt JT, Hoffmann RF, Armitage R, Brower KJ. Dim light melatonin onset in alcohol-dependent men and women compared with healthy controls. Chronobiol Int. 2012;29(1):35–42.
9. Wong MM, Brower KJ, Fitzgerald HE, Zucker RA. Sleep problems in early childhood and early onset of alcohol and other drug use in adolescence. Alcoholism Clin Exp Res. 2004;28(4):578–87.
10. Brower KJ. Alcohol's effects on sleep in alcoholics. Alcohol Res Health. 2001;25:110–25.
11. Brower KJ, Perron BE. Prevalence and correlates of withdrawal-related insomnia among adults with alcohol dependence: results from a national survey. Am J Addict. 2010;19(3):238–44.
12. Heilig M, Egli M, Crabbe JC, Becker HC. Acute withdrawal, protracted abstinence and negative affect in alcoholism: are they linked? Addict Biol. 2010;15(2):169–84.
13. Brower KJ, Krentzman A, Robinson EA. Persistent insomnia, abstinence, and moderate drinking in alcohol-dependent individuals. Am J Addict. 2011;20(5):435–40.
14. Drummond SP, Gillin JC, Smith TL, DeModena A. The sleep of abstinent pure primary alcoholic patients: natural course and relationship to relapse. Alcohol Clin Exp Res. 1998;22(8):1796–802.
15. Williams HL, Rundell OH. Altered sleep physiology in chronic alcoholics: reversal with abstinence. Alcohol Clin Exp Res. 1981;2:318–25.
16.•• Brower KJ. Insomnia, alcoholism and relapse. Sleep Med Rev. 2003;7(6):523–39. **A review of the prevalence and correlates of comorbid insomnia and alcohol use disorders as well as an in-depth review of studies linking insomnia to relapse as known at that time**.
17. Conroy DA, Arnedt JT, Brower KJ, et al. Perception of sleep in recovering alcohol-dependent patients with insomnia: relationship with future drinking. Alcohol Clin Exp Res. 2006;30(12):1992–9.
18. Feige B, Scaal S, Hornyak M, Gann H, Riemann D. Sleep electroencephalographic spectral power after withdrawal from alcohol in alcohol-dependent patients. Alcohol Clin Exp Res. 2007;31(1):19–27.
19. Malcolm R, Myrick LH, Veatch LM, Boyle E, Randall PK. Self-reported sleep, sleepiness, and repeated alcohol withdrawals: a randomized, double blind, controlled comparison of lorazepam vs gabapentin. J Clin Sleep Med. 2007;3(1):24–32.
20. Smith N, Hill R, Marshall J, Keaney F, Wanigaratne S. Sleep related beliefs and their association with alcohol relapse following residential alcohol detoxification treatment. Behav Cogn Psychother. 2014;42(5):593–604.
21. Kolla BP, Schneekloth T, Mansukhani MP, et al. The association between sleep disturbances and alcohol relapse: a 12-month observational cohort study. Am J Addict. 2015;24(4):362–7.
22. Fortier-Brochu E, Morin CM. Cognitive impairment in individuals with insomnia: clinical significance and correlates. Sleep. 2014;37(11):1787–98.
23. Klimkiewicz A, Bohnert AS, Jakubczyk A, Ilgen MA, Wojnar M, Brower K. The association between insomnia and suicidal thoughts in adults treated for alcohol dependence in Poland. Drug Alcohol Depend. 2012;122(1–2):160–3.
24. Chakravorty S, Grandner MA, Mavandadi S, Perlis ML, Sturgis EB, Oslin DW. Suicidal ideation in veterans misusing alcohol: relationships with insomnia symptoms and sleep duration. Addict Behav. 2014;39(2):399–405.
25. Bernert RA, Kim JS, Iwata NG, Perlis ML. Sleep disturbances as an evidence-based suicide risk factor. Curr Psychiatry Rep. 2015;17(3):554.
26. Nadorff MR, Salem T, Winer ES, Lamis DA, Nazem S, Berman ME. Explaining alcohol use and suicide risk: a moderated mediation model involving insomnia symptoms and gender. J Clin Sleep Med. 2014;10(12):1317–23.
27. Currie SR, Clark S, Rimac S, Malhotra S. Comprehensive assessment of insomnia in recovering alcoholics using daily sleep diaries and ambulatory monitoring. Alcohol Clin Exp Res. 2003;27(8):1262–9.
28. Zhabenko N, Wojnar M, Brower KJ. Prevalence and correlates of insomnia in a Polish sample of alcohol-dependent patients. Alcohol Clin Exp Res. 2012;36(9):1600–7.
29. Gildner TE, Liebert MA, Kowal P, Chatterji S, Snodgrass JJ. Associations between sleep duration, sleep quality, and cognitive test performance among older adults from six middle income countries: results from the Study on Global Ageing and Adult Health (SAGE). J Clin Sleep Med. 2014;10(6):613–21.
30. Lo JC, Loh KK, Zheng H, Sim SK, Chee MW. Sleep duration and age-related changes in brain structure and cognitive performance. Sleep. 2014;37(7):1171–8.
31. Kurina LM, McClintock MK, Chen JH, Waite LJ, Thisted RA, Lauderdale DS. Sleep duration and all-cause mortality: a critical review of measurement and associations. Ann Epidemiol. 2013;23(6):361–70.
32. Xiao Q, Keadle SK, Hollenbeck AR, Matthews CE. Sleep duration and total and cause-specific mortality in a large US cohort: interrelationships with physical activity, sedentary behavior, and body mass index. Am J Epidemiol. 2014;180(10):997–1006.
33. Brower KJ, Aldrich M, Robinson EAR, Zucker RA, Greden JF. Insomnia, self-medication, and relapse to alcoholism. Am J Psychiatry. 2001;158:399–404.
34. Crum RM, Storr CL, Chan YF, Ford DE. Sleep disturbance and risk for alcohol-related problems. Am J Psychiatry. 2004;161(7):1197–203.
35. Wong MM, Brower KJ, Nigg JT, Zucker RA. Childhood sleep problems, response inhibition, and alcohol and drug outcomes in adolescence and young adulthood. Alcohol Clin Exp Res. 2010.
36.• Hasler BP, Martin CS, Wood DS, Rosario B, Clark DB. A longitudinal study of insomnia and other sleep complaints in adolescents with and without alcohol use disorders. Alcohol Clin Exp Res. 2014;38(8):2225–33. **A large (N = 696) longitudinal study (5 years) showing increased insomnia in adolescents (ages 12–19) with AUDs and how baseline sleep characteristics prospectively predicted an increase in symptomatic alcohol use.**
37. Reite M, Weissberg M, Ruddy J. Clinical manual for evaluation and management of sleep disorders. Washington, DC: American Psychiatric Publishing; 2009.
38. Gann H, Feige B, Fasihi S, van Calker D, Voderholzer U, Riemann D. Periodic limb movements during sleep in alcohol dependent patients. Eur Arch Psychiatry Clin Neurosci. 2002;252(3):124–9.
39. Aldrich MS, Brower KJ, Hall JM. Sleep-disordered breathing in alcoholics. Alcoholism Clin Exp Res. 1999;23(1):134–40.
40. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540–5.
41. Ohayon MM, Mahowald MW, Dauvilliers Y, Krystal AD, Leger D. Prevalence and comorbidity of nocturnal wandering in the U.S. adult general population. Neurology. 2012;78(20):1583–9.
42. Carney CE, Buysse DJ, Ancoli-Israel S, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep. 2012;35(2):287–302.

43. Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol. 1976;4(2):97–110.
44. Conroy D, Arnedt JT. Sleep and substance use disorders: an update. Curr Psychiatry Rep. 2014;16(10):1–9.
45. Garcia AN, Salloum IM. Polysomnographic sleep disturbances in nicotine, caffeine, alcohol, cocaine, opioid, and cannabis use: a focused review. Am J Addict. 2015.
46. Conroy DA, Brower KJ. Alcohol, toxins, and medications as a cause of sleep dysfunction. Handb Clin Neurol. 2011;98:587–612.
47. Yang C, White DP, Winkelman JW. Antidepressants and periodic leg movements of sleep. Biol Psychiatry. 2005;58(6):510–4.
48. Armitage R. The effects of antidepressants on sleep in patients with depression. Can J Psychiatry. 2000;45(9):803–9.
49. Chaudhary NS, Kampman KM, Kranzler HR, Grandner MA, Debbarma S, Chakravorty S. Insomnia in alcohol dependent subjects is associated with greater psychosocial problem severity. Addict Behav. 2015;50:165–72.
50. Levenson JC, Kay DB, Buysse DJ. The pathophysiology of insomnia. Chest. 2015;147(4):1179–92.
51. Buysse DJ, Reynolds III CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28:193–213.
52. Bastien CH, Vallieres, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2001;2:297–307.
53. Soldatos CR, Dikeos DG, Paparrigopoulos TJ. The diagnostic validity of the Athens Insomnia Scale. J Psychosom Res. 2003;55(3):263–7.
54. Roth T. Does effective management of sleep disorders reduce substance dependence? Drugs. 2009;69 Suppl 2:65–75.
55. Stepanski EJ, Wyatt JK. Use of sleep hygiene in the treatment of insomnia. Sleep Med Rev. 2003;7(3):215–25.
56.•• Brooks AT, Wallen GR. Sleep disturbances in individuals with alcohol-related disorders: a review of cognitive-behavioral therapy for insomnia (CBT-I) and associated non-pharmacological therapies. Subst Abuse Res Treat. 2014;8:55–62. **Comprehensive review and rating of behavioral therapy studies for insomnia in AUD patients, including CBT-I and progressive relaxation training**.
57. Kaplan KA, McQuaid J, Batki SL, Rosenlicht N. Behavioral treatment of insomnia in early recovery. J Addict Med. 2014;8(6):395–8.
58. Trauer JM, Qian MY, Doyle JS, Rajaratnam SM, Cunnington D. Cognitive behavioral therapy for chronic insomnia: a systematic review and meta-analysis. Ann Intern Med. 2015;163(3):191–204.
59. Morin CM, Beaulieu-Bonneau S, Ivers H, et al. Speed and trajectory of changes of insomnia symptoms during acute treatment with cognitive-behavioral therapy, singly and combined with medication. Sleep Med. 2014;15(6):701–7.
60. Friedmann PD, Rose JS, Swift R, Stout RL, Millman RP, Stein MD. Trazodone for sleep disturbance after alcohol detoxification: a double-blind, placebo-controlled trial. Alcohol Clin Exp Res. 2008;32(9):1652–60.
61. Currie SR, Clark S, Hodgins DC, El-Guebaly N. Randomized controlled trial of brief cognitive–behavioural interventions for insomnia in recovering alcoholics. Addiction. 2004;99(9):1121–32.
62. Arnedt JT, Conroy DA, Armitage R, Brower KJ. Cognitive-behavioral therapy for insomnia in alcohol dependent patients: a randomized controlled pilot trial. Behav Res Ther. 2011;49(4):227–33.
63. Yang CM, Spielman AJ, Glovinsky P. Nonpharmacologic strategies in the management of insomnia. Psychiatr Clin North Am 2006. 29(4):895–919. abstract viii.
64. Smith N, Hill R, Marshall J, Keaney F, Wanigaratne S. Sleep related beliefs and their association with alcohol relapse following residential alcohol detoxification treatment. Behav Cogn Psychother. 2013:1–12.
65. Greeff AP, Conradie WS. Use of progressive relaxation training for chronic alcoholics with insomnia. Psychol Rep. 1998;82:407–12.
66.• Kolla BP, Mansukhani MP, Schneekloth T. Pharmacological treatment of insomnia in alcohol recovery: a systematic review. Alcohol Alcohol. 2011;46(5):578–85. **Includes several studies not reviewed here**.
67. Kaplan KA, McQuaid J, Primich C, Rosenlicht N. An evidence-based review of insomnia treatment in early recovery. J Addict Med. 2014;8(6):389–94.
68. Brower KJ, Myra Kim H, Strobbe S, Karam-Hage MA, Consens F, Zucker RA. A randomized double-blind pilot trial of gabapentin versus placebo to treat alcohol dependence and comorbid insomnia. Alcohol Clin Exp Res. 2008;32:1429–38.
69. Trevisan LA, Ralevski E, Keegan K, et al. Alcohol detoxification and relapse prevention using valproic acid versus gabapentin in alcohol-dependent patients. Addict Disord Their Treat. 2008;7(3):119–28.
70. Anton RF, Myrick H, Baros AM, et al. Efficacy of a combination of flumazenil and gabapentin in the treatment of alcohol dependence: relationship to alcohol withdrawal symptoms. J Clin Psychopharmacol. 2009;29(4):334–42.
71. Anton RF, Myrick H, Wright TM, et al. Gabapentin combined with naltrexone for the treatment of alcohol dependence. Am J Psychiatry. 2011;168(7):709–17.
72. Mason BJ, Quello S, Goodell V, Shadan F, Kyle M, Begovic A. Gabapentin treatment for alcohol dependence: a randomized clinical trial. JAMA Intern Med. 2014;174(1):70–7.
73. Le Bon O, Murphy JR, Staner L, et al. Double-blind, placebo-controlled study of the efficacy of trazodone in alcohol post-withdrawal syndrome: polysomnographic and clinical evaluations. J Clin Psychopharmacol. 2003;23(4):377–83.
74. Litten RZ, Fertig JB, Falk DE, et al. A double-blind, placebo-controlled trial to assess the efficacy of quetiapine fumarate XR in very heavy-drinking alcohol-dependent patients. Alcohol Clin Exp Res. 2012;36(3):406–16.
75. Chakravorty S, Hanlon AL, Kuna ST, et al. The effects of quetiapine on sleep in recovering alcohol-dependent subjects: a pilot study. J Clin Psychopharmacol. 2014;34(3):350–4.
76. Staner L, Boeijinga P, Danel T, et al. Effects of acamprosate on sleep during alcohol withdrawal: a double-blind placebo-controlled polysomnographic study in alcohol-dependent subjects. Alcohol Clin Exp Res. 2006;30(9):1492–9.
77. Perney P, Lehert P, Mason BJ. Sleep disturbance in alcoholism: proposal of a simple measurement, and results from a 24-week randomized controlled study of alcohol-dependent patients assessing acamprosate efficacy. Alcohol Alcohol. 2012;47(2):133–9.
78. Johnson BA, Rosenthal N, Capece JA, et al. Improvement of physical health and quality of life of alcohol-dependent individuals with topiramate treatment: US multisite randomized controlled trial. Arch Intern Med. 2008;168(11):1188–99.
79. Simpson TL, Malte CA, Dietel B, et al. A pilot trial of prazosin, an alpha-1 adrenergic antagonist, for comorbid alcohol dependence and posttraumatic stress disorder. Alcohol Clin Exp Res. 2015;39(5):808–17.
80. Kuriyama A, Honda M, Hayashino Y. Ramelteon for the treatment of insomnia in adults: a systematic review and meta-analysis. Sleep Med. 2014;15(4):385–92.
81. Kishi T, Matsunaga S, Iwata N. Suvorexant for primary insomnia: a systematic review and meta-analysis of randomized placebo-controlled trials. PLoS One. 2015;10(8):e0136910.
82. McCall C, McCall WV. What is the role of sedating antidepressants, antipsychotics, and anticonvulsants in the management of insomnia? Curr Psychiatry Rep. 2012;14(5):494–502.
83. Leach MJ, Page AT. Herbal medicine for insomnia: a systematic review and meta-analysis. Sleep Med Rev. 2014;24C:1–12.

84. Griffiths RR, Johnson MW. Relative abuse liability of hypnotic drugs: a conceptual framework and algorithm for differentiating among compounds. J Clin Psychiatry. 2005;66 Suppl 9:31–41.
85. Roehrs T, Roth T. Insomnia pharmacotherapy. Neurother J Am Soc Exp Neurother. 2012;9(4):728–38.
86. Mueller TI, Pagano ME, Rodriguez BF, Bruce SE, Stout RL, Keller MB. Long-term use of benzodiazepines in participants with comorbid anxiety and alcohol use disorders. Alcohol Clin Exp Res. 2005;29(8):1411–8.
87. Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. PLoS One. 2013;8(5):e63773.
88.•• Hasler BP, Smith LJ, Cousins JC, Bootzin RR. Circadian rhythms, sleep, and substance abuse. Sleep Med Rev. 2012;16(1):67–81. **Reviews the bidirectional relationship between circadian rhythms and sleep in substance users, including the role of circadian rhythms in reward regulation**.
89. Brower KJ, Conroy DA, Kurth ME, Anderson BJ, Stein MD. Ramelteon and improved insomnia in alcohol-dependent patients: a case series. J Clin Sleep Med. 2011;7(3):274–5.
90. Grosshans M, Mutschler J, Luderer M, Mann K, Kiefer F. Agomelatine is effective in reducing insomnia in abstinent alcohol-dependent patients. Clin Neuropharmacol. 2014;37(1):6–8.
91. Freiesleben SD, Furczyk K. A systematic review of agomelatine-induced liver injury. J Mol Psychiatry. 2015;3(1):4.
92. Yeung WF, Chung KF, Yung KP, Ng TH. Doxepin for insomnia: a systematic review of randomized placebo-controlled trials. Sleep Med Rev. 2015;19:75–83.
93. de Bejczy A, Soderpalm B. The effects of mirtazapine versus placebo on alcohol consumption in male high consumers of alcohol: a randomized, controlled trial. J Clin Psychopharmacol. 2015;35(1):43–50.
94. Yoon SJ, Pae CU, Kim DJ, et al. Mirtazapine for patients with alcohol dependence and comorbid depressive disorders: a multicentre, open label study. Prog Neuropsychopharmacol Biol Psychiatry. 2006;30(7):1196–201.
95. Friedmann PD, Herman DS, Freedman S, Lemon SC, Ramsey S, Stein MD. Treatment of sleep disturbance in alcohol recovery: a national survey of addiction medicine physicians. J Addict Dis. 2003;22(2):91–103.
96. Umhau JC, Schwandt ML, Usala J, et al. Pharmacologically induced alcohol craving in treatment seeking alcoholics correlates with alcoholism severity, but is insensitive to acamprosate. Neuropsychopharmacology. 2011;36(6):1178–86.
97. Monnelly EP, Locastro JS, Gagnon D, Young M, Fiore LD. Quetiapine versus trazodone in reducing rehospitalization for alcohol dependence: a large data-base study. J Addict Med. 2008;2(3):128–34.
98. Kolla BP, Schneekloth TD, Biernacka JM, et al. Trazodone and alcohol relapse: a retrospective study following residential treatment. Am J Addict. 2011;20(6):525–9.
99. Khoo SY, Brown RM. Orexin/hypocretin based pharmacotherapies for the treatment of addiction: DORA or SORA? CNS Drugs. 2014;28(8):713–30.
100. Coe HV, Hong IS. Safety of low doses of quetiapine when used for insomnia. Ann Pharmacother. 2012;46(5):718–22.
101. Kalk NJ, Lingford-Hughes AR. The clinical pharmacology of acamprosate. Br J Clin Pharmacol. 2014;77(2):315–23.
102. Seda G, Sanchez-Ortuno MM, Welsh CH, Halbower AC, Edinger JD. Comparative meta-analysis of prazosin and imagery rehearsal therapy for nightmare frequency, sleep quality, and posttraumatic stress. J Clin Sleep Med. 2015;11(1):11–22.
103. Fox HC, Anderson GM, Tuit K, et al. Prazosin effects on stress- and cue-induced craving and stress response in alcohol-dependent individuals: preliminary findings. Alcohol Clin Exp Res. 2012;36(2):351–60.
104. Simpson TL, Saxon AJ, Meredith CW, et al. A pilot trial of the alpha-1 adrenergic antagonist, prazosin, for alcohol dependence. Alcohol Clin Exp Res. 2009;33(2):255–63.