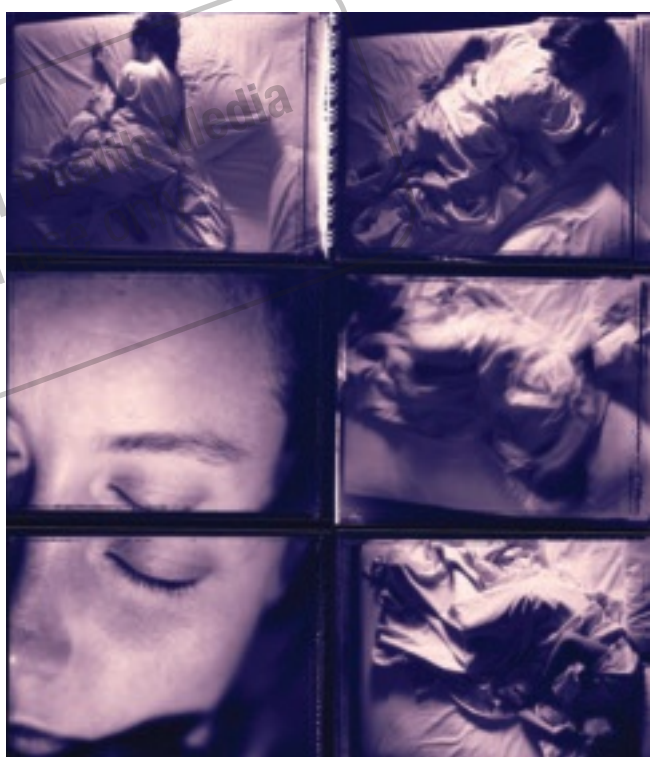
Current PSYCHIATRY

Insomnia in patients with addictions: A safer way to break the cycle

Fight relapse by improving sleep with nonaddictive agents and behavior therapy



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From alcohol to opioids, most addictive substances can induce sleep disturbances that persist despite abstinence and may increase the risk for relapse. Nearly all FDA-approved hypnotics are Schedule IV controlled substances that—although safe and effective for most populations—are prone to abuse by patients with substance use disorders.

You're not alone if you hesitate to prescribe hypnotics to these patients; a study of 311 addiction medicine physicians found that they prescribed sleep-promoting medication to only 30% of their alcohol-dependent patients with insomnia.[1]

This article presents evidence on how alcohol and other substances disturb sleep in patients with addictions. We discuss the usefulness of hypnotics, off-label sedatives, and cognitive-behavioral therapy (CBT). Our goal is to help you reduce your patients' risk of relapse by addressing their sleep complaints.

Workup: 3 principles

Insomnia is multifactorial. Don't assume that substance abuse is the only cause of prominent insomnia complaints. Insomnia in patients with substance use disorders may be a manifestation of protracted withdrawal or a primary sleep disorder. Evaluate your patient's:

- other illnesses (psychiatric, medical, and other sleep disorders)
- sleep-impairing medications (such as activating antidepressants and theophylline)

continued

Clinical Point

Insomnia is a clinical diagnosis that does not require overnight sleep laboratory studies

Table 1

Sleep disruptions caused by substances of abuse

Substance	Effect on sleep
Nicotine	Difficulty falling asleep, sleep fragmentation, less restful sleep compared with nonsmokers, increased risk for OSA and SDB[a-e]
Marijuana	Short-term difficulty falling asleep and decreased slow-wave sleep percentage during withdrawal[f-j]
Cocaine	Prolonged sleep latency, decreased sleep efficiency, and decreased REM sleep with intranasal self-administration; hypersomnia during withdrawal[k-m]
Other stimulants (amphetamine, methamphetamine, methylphenidate)	Sleep complaints similar to those reported with cocaine use disorders[n]
Opioids	Decreased slow-wave sleep, increased stage-2 sleep, but minimal impact on sleep continuity; dreams and nightmares; central sleep apnea[o-t]

OSA: obstructive sleep apnea; SDB: sleep-disordered breathing; REM: rapid eye movement
Source: For reference citations, see this article at CurrentPsychiatry.com

- inadequate sleep hygiene
- dysfunctional beliefs about sleep.

Nevertheless, assume that substances are part of the problem, even if not necessarily the only cause of insomnia. Substance-induced sleep problems usually improve with abstinence but may persist because of enduring effects of chronic drug exposure on the brain's sleep centers.

Insomnia is a clinical diagnosis that does not require an overnight sleep laboratory study (polysomnography [PSG]). Diagnose insomnia when a patient meets DSM-IV-TR criteria (has difficulty falling asleep or staying asleep or feels that sleep is not refreshing for at least 1 month; and the sleep problem impairs daytime functioning and/or causes clinically significant distress). In addition, consider:

- PSG if you suspect other sleep disorders, particularly obstructive sleep apnea (OSA) and periodic limb movement disorder (PLMD)
- an overnight sleep study for treatment-resistant insomnia, when you have adequately treated other causes.

A primary sleep disorder—such as OSA, restless legs syndrome (RLS), or PLMD—typically requires referral to a sleep specialist. For more information about sleep disorders—including OSA or RLS—see ***Related Resources, page 109***.

Sleep logs are useful. Ask patients to keep a sleep log for 2 weeks during early recovery, after acute withdrawal subsides. These diaries help assess sleep patterns over time, document improvement with abstinence, and engage the patient in treatment. The National Sleep Foundation can provide examples (see ***Related Resources, page 109***).

Alcohol and sleep disturbances

Insomnia is extremely common in active drinkers and in those who are in treatment after having stopped drinking. Across 7 studies of 1,577 alcohol-dependent patients undergoing treatment, more than one-half reported insomnia symptoms (mean 58%, range 36% to 91%),[2,3] substantially higher than the rate in the general population (33%). Nicotine, marijuana, cocaine and other stimulants, and opioids also can disrupt sleep (***Table 1***).

Which came first? Sleep problems may be a pathway by which problematic substance use develops. In 1 study, sleep problems reported by mothers in boys ages 3 to 5 predicted onset of alcohol and drug use by ages 12 to 14.[4] This relationship was not mediated by attention problems, anxiety/depression, or aggression. Thus, insomnia may increase the risk for early substance use.

In an epidemiologic study of >10,000 adults, the incidence of new alcohol use disorders after 1 year in those without psychiatric disorders at baseline was twice as high in persons with persistent insomnia as in those without insomnia.[5]

Patients with sleep disturbances may use alcohol to self-medicate,[6] and tolerance to alcohol's sedating effects develops quickly. As patients consume larger quantities with greater frequency to produce sleep, the risk for dependence may increase.

Comorbid sleep disorders. Alcohol-dependent patients with difficulty falling asleep may have abnormal circadian rhythms, as suggested by delayed onset of nocturnal melatonin secretion.[7] They also may have low homeostatic sleep drive, another factor required to promote sleep.[8]

Habitual alcohol consumption before bedtime (1 to 3 standard drinks) is associated with mild sleep-disordered breathing (SDB) in men but not in women.[9] SDB also may be more prevalent in alcohol-dependent men age >60.[10]

Consuming >2 drinks/day has been associated with restless legs and increased periodic limb movements during sleep. Twice as many women reporting high alcohol use were diagnosed with PLMD, compared with women reporting normal alcohol consumption.[10-11] Recovering alcohol-dependent patients have significantly more periodic limb movements associated with arousals (PLMA) from sleep than controls. Moreover, PLMA can predict 80% of abstainers and 44% of relapsers after 6 months of abstinence.[12]

Multifaceted treatment

A thorough history is essential to evaluate sleep and guide treatment decisions. Refer patients to an accredited sleep disorders center if their history shows:

- loud snoring
- cessation of breathing
- frequent kicking during sleep
- excessive daytime sleepiness.

Short-term insomnia. Judicious use of medications with appropriate follow-up can be effective for short-term insomnia. Keep in mind, however, that treating insomnia without addiction treatment may improve sleep but worsen addiction. Tailor medications' pharmacokinetic characteristics to patients' sleep complaints. For

Box 1

Stimulus control: 7 steps to a better night's sleep

Step 1. Get into bed to go to sleep only when you are sleepy

↓

Step 2. Avoid using the bed for activities other than sleep; for example, do not read, watch TV, eat, or worry in bed. Sexual activity is the only exception; on these occasions, follow the next steps when you intend to go to sleep

↓

Step 3. If you are unable to fall asleep within 15 to 20 minutes, get out of bed and go into another room. Remember, the goal is to associate your bed with falling asleep quickly. Return to bed intending to go to sleep only when you are very sleepy

↓

Step 4. While out of bed during the night, engage in activities that are quiet but of interest to you. Do not exercise, eat, smoke, or take warm showers or baths. Do not lie down or fall asleep when not in bed

↓

Step 5. If you return to bed and still cannot fall asleep within 15 to 20 minutes, repeat Step 3. Do this as often as necessary throughout the night

↓

Step 6. Set your alarm and get up at the same time every morning, regardless of how much sleep you got during the night. This will help your body acquire a sleep-wake rhythm

↓

Step 7. Do not nap during the day

Source. Adapted from Bootzin R, Nicassio P. Behavioral treatments for insomnia. In: Hersen M, Eissler R, Miller P, eds. *Progress in behavior modification*, vol. 6. New York, NY: Academic Press; 1978:30

Clinical Point

Treating insomnia without treating addiction may improve sleep but worsen addiction

Clinical Point

Cognitive-behavioral therapy for insomnia has improved sleep, anxiety, depression, fatigue, and quality of life in patients with addictions

Box 2

Cognitive-behavioral therapy for insomnia (CBT-I): 4 components

Stimulus control (SC). Patients with chronic insomnia may watch television, talk on the telephone, or worry about not sleeping while lying in bed. The goal of SC is to alter this association by reestablishing the bed and bedroom with the pleasant experience of falling asleep and staying asleep.[13] Instructions for SC (***Box 1, page 99***) are commonly provided with sleep restriction.

Sleep restriction (SR) addresses the excessive time that patients with insomnia spend in bed not sleeping. SR temporarily restricts time spent in bed and prohibits sleep at other times. The resulting mild sleep deprivation may promote consolidated sleep, leading to improved patient-reported sleep quality.[14]

Sleep hygiene (SH) addresses behaviors that may help or hinder sleep. Patients with addiction may benefit from learning how drug use and withdrawal affects sleep or how substance use for sleep may exacerbate sleep problems. Other SH recommendations include avoiding caffeine, nicotine, and exercise in close proximity to bedtime.

Cognitive therapy. Goals are to:

- identify and explore dysfunctional beliefs that cause patients anxiety about sleep problems
- replace these beliefs with more appropriate self-statements that promote sleep-healthy behaviors.

Common themes address patients' unrealistic sleep expectations, inability to control or predict sleep, and faulty beliefs about sleep-promoting practices.

example, a medication with rapid onset may be indicated for sleep-onset insomnia but not for sleep-maintenance insomnia.

Chronic insomnia. Patients who report chronic insomnia and behaviors incompatible with sleep may be good candidates for cognitive-behavioral therapy for insomnia (CBT-I). Patient education can change maladaptive behaviors, such as staying in bed for long periods of time to compensate for sleep loss, using the bed for activities other than sleep, or worrying excessively about sleep (***Box 1, page 99***).[13]

Pharmacotherapy may be preferred:

- for patients with unstable physical or mental illness
- when CBT-I could exacerbate a comorbid condition (such as restricting sleep in a patient with bipolar disorder)
- for patients with low motivation for behavior change
- when trained CBT-I providers or resources to pay for CBT-I are limited.

Patient preferences are critical to successful insomnia treatment. Some cannot or will not make the commitment required for CBT-I, and some do not wish to use medications. Combining medication and CBT-I to capitalize on medications' immediate relief and CBT-I's durability may be effective for patients who do not respond to either approach alone.

CBT-I is effective for primary insomnia and insomnia associated with medical conditions. Using sleep restriction, stimulus control, sleep hygiene, and cognitive therapy, it addresses maladaptive sleep behaviors and counters dysfunctional beliefs about sleep (***Box 2***).[13,14]

In older adults with insomnia but no history of addiction, CBT-I was more effective than placebo and as effective as a hypnotic alone (temazepam, 7.5 and 30 mg qhs) and a hypnotic/CBT-I combination in reducing nighttime wakefulness, increasing total sleep time, and increasing sleep efficiency. After 2 years, patients treated with CBT-I alone were most likely to maintain these initial treatment gains.[15]

Limited data exist on CBT-I's effectiveness in patients with addiction. In 2 studies, alcohol-dependent patients reported improved sleep.[16,17] CBT-I also improved measures of anxiety and depression, fatigue, and some quality-of-life items.[16]

Precautions about hypnotics. The newer alpha-1-selective benzodiazepine receptor

continued on page 106

trials: ***Body as a Whole***—asthenia, back pain, accidental injury, chest pain; ***Cardiovascular***—hypertension; **Digestive**—dry mouth, increased appetite, thirst, constipation, increased salivation; ***Metabolic and Nutritional***—weight gain, peripheral edema, edema; ***Nervous System***—somnolence, tremor, depression, dizziness, speech disorder, amnesia, paresthesia, apathy, confusion, euphoria, incoordination; ***Respiratory***—pharyngitis, dyspnea; ***Skin and Appendages***—sweating, acne, dry skin; ***Special Senses***—amblyopia, abnormal vision; ***Urogenital***—dysmenorrhea, vaginitis.

Adverse Events with an Incidence ≥1% in Intramuscular Trials—The following treatment-emergent adverse events were reported at an incidence of ≥1% with intramuscular olanzapine for injection (2.5-10 mg/injection) and at incidence greater than placebo in short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar mania: ***Body as a Whole***—asthenia; ***Cardiovascular***—hypotension, postural hypotension; ***Nervous System***—somnolence, dizziness, tremor.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials—Extrapyramidal Symptoms—In an acute-phase controlled clinical trial in schizophrenia, there was no significant difference in ratings scales incidence between any dose of oral olanzapine (5±2.5, 10±2.5, or 15±2.5 mg/d) and placebo for parkinsonism (Simpson-Angus Scale total score >3) or akathisia (Barnes Akathisia global score ≥2). In the same trial, only akathisia events (spontaneously reported COSTART terms akathisia and hyperkinesia) showed a statistically significantly greater adverse events incidence with the 2 higher doses of olanzapine than with placebo. The incidence of patients reporting any extrapyramidal event was significantly greater than placebo only with the highest dose of oral olanzapine (15±2.5 mg/d). In controlled clinical trials of intramuscular olanzapine for injection, there were no statistically significant differences from placebo in occurrence of any treatment-emergent extrapyramidal symptoms, assessed by either rating scales incidence or spontaneously reported adverse events.

Other Adverse Events—Dose-relatedness of adverse events was assessed using data from this same clinical trial involving 3 fixed oral dosage ranges (5±2.5, 10±2.5, or 15±2.5 mg/d) compared with placebo. The following treatment-emergent events showed a statistically significant trend: asthenia, dry mouth, nausea, somnolence, tremor.

In an 8-week, randomized, double-blind study in patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder comparing fixed doses of 10, 20, and 40 mg/d, statistically significant differences were seen between doses for the following: baseline to endpoint weight gain, 10 vs 40 mg/d; incidence of treatment-emergent prolactin elevations >24.2 ng/mL (female) or >18.77 ng/mL (male), 10 vs 40 mg/d and 20 vs 40 mg/d; fatigue, 10 vs 40 mg/d and 20 vs 40 mg/d; and dizziness, 20 vs 40 mg/d.

Vital Sign Changes—Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials (*see* PRECAUTIONS).

Laboratory Changes—Olanzapine is associated with asymptomatic increases in SGPT, SGOT, and GGT and with increases in serum prolactin and CPK (*see* PRECAUTIONS). Asymptomatic elevation of eosinophils was reported in 0.3% of olanzapine patients in premarketing trials. There was no indication of a risk of clinically significant neutropenia associated with olanzapine in the premarketing database.

ECG Changes—Analyses of pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in incidence of potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine was associated with a mean increase in heart rate of 2.4 BPM compared to no change among placebo patients.

Other Adverse Events Observed During Clinical Trials—The following treatment-emergent events were reported with oral olanzapine at multiple doses ≥1 mg/d in clinical trials (8661 patients, 4165 patient-years of exposure). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. *Frequent* events occurred in ≥1/100 patients; *infrequent* events occurred in 1/100 to 1/1000 patients; *rare* events occurred in <1/1000 patients. ***Body as a Whole***—*Frequent:* dental pain, flu syndrome; *Infrequent:* abdomen enlarged, chills, face edema, intentional injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt; *Rare:* chills and fever, hangover effect, sudden death. ***Cardiovascular***—*Frequent:* hypotension; *Infrequent:* atrial fibrillation, bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation, vasodilatation, ventricular extrasystoles; *Rare:* arteritis, heart failure, pulmonary embolus. ***Digestive***—*Frequent:* flatulence, increased salivation, thirst; *Infrequent:* dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, tooth caries; *Rare:* aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, liver fatty deposit, tongue discoloration. ***Endocrine***—*Infrequent:* diabetes mellitus; *Rare:* diabetic acidosis, goiter. ***Hemic and Lymphatic***—*Infrequent:* anemia, cyanosis, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; *Rare:* normocytic anemia, thrombocythemia. ***Metabolic and Nutritional***—*Infrequent:* acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, upper extremity edema; *Rare:* gout, hyperkalemia, hypernatremia, hypoproteinemia, ketosis, water intoxication. ***Musculoskeletal***—*Frequent:* joint stiffness, twitching; *Infrequent:* arthritis, arthrosis, leg cramps, myasthenia; *Rare:* bone pain, bursitis, myopathy, osteoporosis, rheumatoid arthritis. ***Nervous System***—*Frequent:* abnormal dreams, amnesia, delusions, emotional lability, euphoria, manic reaction, paresthesia, schizophrenic reaction; *Infrequent:* akinesia, alcohol misuse, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, delirium, dementia, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido decreased, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, vertigo, withdrawal syndrome; *Rare:* circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage, tobacco misuse. ***Respiratory***—*Frequent:* dyspnea; *Infrequent:* apnea, asthma, epistaxis, hemoptysis, hyperventilation, hypoxia, laryngitis, voice alteration; *Rare:* atelectasis, hiccup, hypoventilation, lung edema, stridor. ***Skin and Appendages***—*Frequent:* sweating; *Infrequent:* alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin discoloration, skin ulcer, urticaria, vesiculobullous rash; *Rare:* hirsutism, pustular rash. ***Special Senses***—*Frequent:* conjunctivitis; *Infrequent:* abnormality of accommodation, blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, tinnitus; *Rare:* corneal lesion, glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, pigment deposits lens. ***Urogenital***—*Frequent:* vaginitis*; *Infrequent:* abnormal ejaculation*, amenorrhea*, breast pain, cystitis, decreased menstruation*, dysuria, female lactation*, glycosuria, gynecomastia, hematuria, impotence*, increased menstruation*, menorrhagia*, metrorrhagia*, polyuria, premenstrual syndrome*, pyuria, urinary frequency, urinary retention, urinary urgency, urination impaired, uterine fibroids enlarged*, vaginal hemorrhage*; *Rare:* albuminuria, breast enlargement, mastitis, oliguria. (*Adjusted for gender.)

The following treatment-emergent events were reported with intramuscular olanzapine for injection at one or more doses ≥2.5 mg/injection in clinical trials (722 patients). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. ***Body as a Whole***—*Frequent:* injection site pain; *Infrequent:* abdominal pain, fever. ***Cardiovascular***—*Infrequent:* AV block, heart block, syncope. ***Digestive***—*Infrequent:* diarrhea, nausea. ***Hemic and Lymphatic***—*Infrequent:* anemia. ***Metabolic and Nutritional***—*Infrequent:* creatine phosphokinase increased, dehydration, hyperkalemia. ***Musculoskeletal***—*Infrequent:* twitching. ***Nervous System***—*Infrequent:* abnormal gait, akathisia, articulation impairment, confusion, emotional lability. ***Skin and Appendages***—*Infrequent:* sweating.

Postintroduction Reports—Reported since market introduction and temporally (not necessarily causally) related to olanzapine therapy: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, jaundice, neutropenia, pancreatitis, priapism, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

DRUG ABUSE AND DEPENDENCE: Olanzapine is not a controlled substance.

Literature revised October 1, 2007

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continued from page 100

agonists (zolpidem, zaleplon, and eszopiclone) and the older nonselective benzodiazepines (such as flurazepam, temazepam, and triazolam) share an equivalent range of abuse liability.[18] Consequently, all benzodiazepine receptor agonists are classified as Schedule IV controlled substances and should be used with caution, if at all, in substance-abusing or substance-dependent patients (***Table 2***).

In general, most physicians who specialize in treating addictions would not recommend these drug classes as first choice in postwithdrawal, substance-dependent patients complaining of chronic insomnia. Nevertheless, you are likely to encounter patients with a history of substance abuse/dependence who are taking legally prescribed benzodiazepine receptor agonists for insomnia, and they may be very reluctant to discontinue these medications.

Weigh and discuss with the patient the risks and benefits of taking vs discontinuing the hypnotic, as well as alternatives. Because chronic hypnotic use may interfere with addiction recovery, it is important to discuss the patient's recovery plan.

If you decide to prescribe a hypnotic with abuse liability, the newer alpha-1-selective benzodiazepine receptor agonists are preferable—as they would be for nonaddicted patients—because they are less likely to disrupt sleep architecture. They are also less likely than the long-acting benzodiazepines (such as flurazepam) to accumulate over time and result in daytime impairment.

Patient contracts. A written agreement can be useful whenever you prescribe a controlled substance for a patient with an addiction history. Include these issues:

- frequency of clinic visits for monitoring response and refills, requests for early refills, and telephone refills
- obtaining prescriptions from only one prescriber and one pharmacy
- abstinence from other abused substances
- urine drug screens and pill counts
- authorization for you to share information with other care providers or significant others

Table 2

FDA-approved benzodiazepine receptor agonists for insomnia*

Agent	Dose range (mg)	T_{MAX} (hr)	$T_{1/2}$ (hr)
Benzodiazepine receptor agonists (benzodiazepine structures)			
Estazolam	1 to 2	0.5 to 1.6	10 to 24
Flurazepam	15 to 30	3 to 6	50 to 100†
Quazepam	7.5 to 15	2	25 to 100†
Temazepam	15 to 30	2 to 3	10 to 17
Triazolam	0.125 to 0.5	1 to 2	1.5 to 5.5
Selective benzodiazepine receptor agonists (nonbenzodiazepine structures)‡			
Eszopiclone	1 to 3	1	~6
Zaleplon	5 to 20	1	~1
Zolpidem	5 to 10	1.6	2.5 (1.5 to 3.8)
Zolpidem CR	6.25 to 12.5	1.5	2.8 (1.6 to 4)

T_{MAX}: time to reach maximal plasma concentrations; $T_{1/2}$: elimination half-life (all values are approximate for any given individual)

* All benzodiazepine receptor agonists are Schedule IV controlled substances. Use with caution, if at all, in alcohol-dependent patients
† Including active metabolites
‡ Selective $GABA_A$ receptor agonists bind the alpha-1 protein subunit of $GABA_A$ receptors. Alpha-1 containing $GABA_A$ receptors are thought to mediate sedative and amnesic effects but not antianxiety or muscle relaxant effects of the GABA system

- an addiction recovery plan for other abused substances
- consequences of nonadherence.

Ramelteon, a melatonin receptor agonist, is the only noncontrolled substance FDA-approved for treating insomnia. It may be preferred in alcohol-dependent patients, given its lack of abuse liability[19] and preliminary evidence of decreased melatonin levels in alcoholic patients.[7] Nevertheless, no studies have examined ramelteon in patients with substance use disorders.

Off-label sedatives for insomnia

Like ramelteon, sedating agents that do not have abuse liability are first-choice medications for patients with addiction and co-occurring insomnia (***Table 3, page 108***):

- The most studied are gabapentin and trazodone.
- Quetiapine and mirtazapine may be considered as second-choice options.

Gabapentin. The sedative properties of selected anticonvulsants can be useful in alcohol-dependent patients, in part because these agents do not lower the seizure threshold—an important issue given the risk of seizures in this population. Gabapentin can help to improve sleep in some alcohol-dependent patients. It has little known abuse potential (although it may have some), is not metabolized by the liver, does not interfere with metabolism of other medications, and does not require blood monitoring for toxicity.

In 2 open-label pilot studies of alcohol-dependent patients with insomnia:

- gabapentin (mean dose 953 mg) significantly improved sleep quality over 4 to 6 weeks[20]
- both gabapentin (mean 888 mg qhs) and trazodone (mean 105 mg qhs) significantly improved Sleep Problems Questionnaire scores, but patients receiving gabapentin were less likely than those taking trazodone to feel tired upon awakening.[21]

In a controlled study, however, 6 weeks of gabapentin treatment did not improve insomnia more than placebo in recovering alcohol-dependent patients.[22]

Although gabapentin and the anticonvulsant pregabalin increase slow-wave sleep in healthy control subjects, evidence of a similar effect is lacking in alcohol-dependent patients.

continued

Clinical Point

A written agreement can be useful when you prescribe a controlled substance for a patient with an addiction history

Clinical Point

Alcohol-dependent veterans given quetiapine for sleep complaints remained abstinent more days and had fewer hospitalizations

Table 3

Noncontrolled sedating agents for treating insomnia in patients with a history of substance abuse

Agent	Dose range (mg)	T_{MAX} (hr)	$T_{1/2}$ (hr)
Melatonin receptor agonist			
Ramelteon	8	0.5 to 1.5	1 to 2.6
Sedating anticonvulsant			
Gabapentin	300 to 1,500	2 to 3	6 to 7
Sedating antidepressants			
Amitriptyline†	25 to 150	2 to 8	5 to 45
Doxepin†	25 to 150	2 to 8	10 to 30
Mirtazapine	7.5 to 45‡	1 to 3	20 to 40
Nefazodone	50 to 150	1	6 to 18*
Nortriptyline†	10 to 75§	2 to 8	20 to 55
Trazodone	25 to 300	1 to 2	3 to 9¶
Sedating second-generation antipsychotic			
Quetiapine	25 to 100	1.5	6

T_{MAX}: time to reach maximal plasma concentrations; $T_{1/2}$: elimination half-life (all values are approximate for any given individual)

* Including active metabolites
† Tricyclic antidepressants
‡ Antihistaminergic effects predominate at low doses (7.5 to 15 mg)
§ Can be titrated to morning serum level (50 to 150 mcg/mL) 12 hr after bedtime dose if no effect at lower doses
¶ Major metabolite, mCPP, has 14-hour half-life

Trazodone is the most commonly prescribed antidepressant for insomnia because of its sedating effect and low abuse potential. Trazodone was associated with greater sleep improvements vs placebo as measured via PSG in a randomized, double-blind trial of alcohol-dependent patients with insomnia.[23] In a second study, sleep outcomes were better with trazodone vs placebo over 12 weeks in alcohol-dependent patients, although patients in the trazodone group drank more heavily.[24]

Other sedating antidepressants such as mirtazapine and doxepin have not been studied in patients with substance use disorders.

Quetiapine is a second-generation antipsychotic with sedating properties. When quetiapine, 25 to 200 mg/d, was given to alcohol-dependent veterans with sleep complaints, they remained abstinent more days and had fewer hospitalizations than veterans not receiving quetiapine.[25] Both groups had high rates of psychiatric comorbidity, and 90% had posttraumatic stress disorder. Improved abstinence was thought to result from improved sleep, but no sleep measures were included to test this hypothesis.

A recently published, randomized controlled pilot study reported significantly reduced drinking and craving in severely alcohol-dependent patients receiving quetiapine vs placebo, although sleep data were not included.[26]

Other options. Tricyclic antidepressants carry risks of cardiotoxicity and other side effects but can be useful when other options have not worked or patients have comorbidities such as neuropathic pain or migraine headaches. Combinations of agents also may be considered for treatment-resistant insomnia.

Nonprescription remedies such as antihistamines, valerian root extract (from the herb *Valeriana officinalis*), and melatonin are commonly used for sleep, although data are limited in substance-abusing patients.

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Related Resources

- American Academy of Sleep Medicine. www.sleepeducation.com.
- National Sleep Foundation. Sleep logs for downloading. www.sleepfoundation.org.
- Restless Legs Syndrome Foundation. www.rls.org.
- Brower KJ. Insomnia, alcoholism and relapse. *Sleep Med Rev* 2003;7:523-39.

Drug Brand Names

Amitriptyline • Elavil, Endep	Nortriptyline • Pamelor
Doxepin • Sinequan	Pregabalin • Lyrica
Estazolam • ProSom	Quazepam • Doral
Eszopiclone • Lunesta	Quetiapine • Seroquel
Flurazepam • Dalmane	Ramelteon • Rozerem
Gabapentin • Neurontin	Temazepam • Restoril
Methamphetamine • Desoxyn	Theophylline • Theo-24, others
Methylphenidate • Concerta, Ritalin, others	Trazodone • Desyrel
Mirtazapine • Remeron	Triazolam • Halcion
Nefazodone • Serzone	Zaleplon • Sonata
	Zolpidem • Ambien, Ambien CR

Disclosures

Dr. Conroy and Dr. Arnedt report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products. Dr. Brower is a consultant to Pfizer.

Acknowledgment

This work was supported by an NIH grant to Dr. Brower (2K24 AA00304).

Clinical Point

The sedative properties of gabapentin may improve sleep in some alcohol-dependent patients

Bottom Line

Addictive substances can disrupt sleep, and sleep disruption can increase risk of relapse to addiction. Thus, treat insomnia as an adjunct to addiction treatment in patients with both disorders. Cognitive-behavioral therapy for insomnia—alone or with medication—is well-validated for chronic insomnia. Ramelteon, gabapentin, trazodone, quetiapine, and other sedating, noncontrolled agents are preferred sleep aids for this population, with some caveats.