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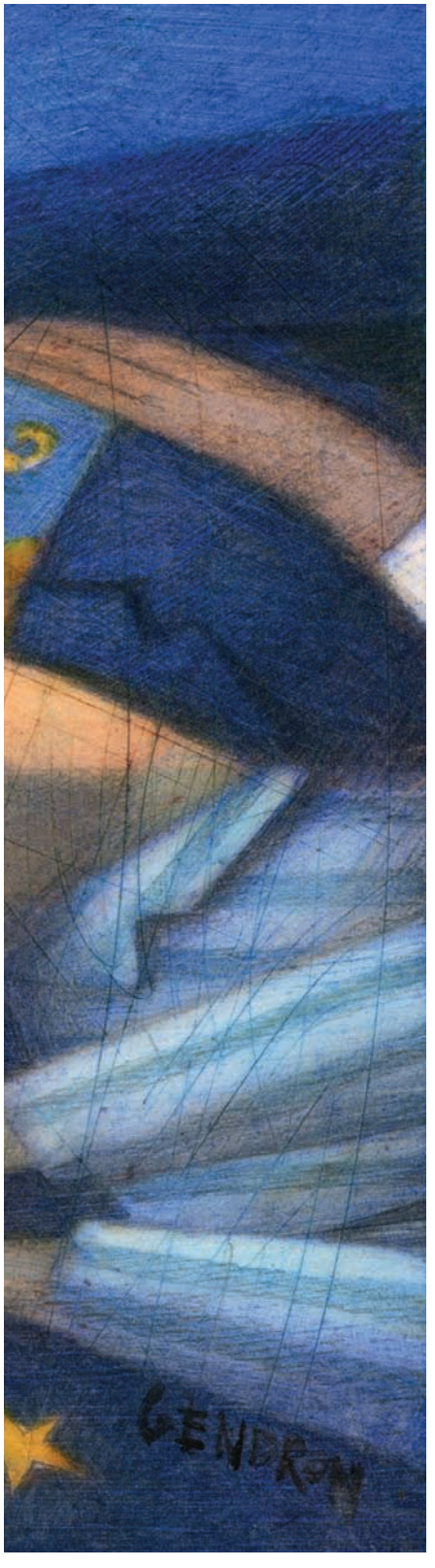


CATHY GENDRON

Pharmacology for insomnia: Consider the options

By Jamie M. Rosini, PharmD, BCPS, and Pooja Dogra, PharmD, BCACP, CDE

INSOMNIA IS POOR SLEEP quality, defined as difficulty initiating and/or maintaining sleep or waking up too early despite adequate sleep opportunity, which then interferes with daytime functioning.[1,2] Considered the most common sleep disorder, insomnia affects approximately 60 million Americans annually.[3]

To care for patients suffering from insomnia, clinicians must first thoroughly assess their sleep habits, identifying and addressing underlying conditions that may contribute to insomnia such as depression, emotional stress, sleep apnea, or substance abuse. Patients should also be counseled about sleep hygiene, stimulus control, and behavioral approaches to improving the quality of sleep. (See *Helping improve a patient's sleep hygiene*.)

If indicated, the healthcare provider may then add a medication to the treatment regimen for a limited period. The choice of medication is based on many factors, including the type of insomnia (difficulty falling asleep, staying asleep, or both).[3,4] (See *Classifying insomnia types*.)

This article provides an overview of agents commonly used to treat insomnia, including prescription drugs, over-the-counter (OTC) medications, and herbal or dietary products. By understanding how and why certain medications help treat insomnia, nurses can help patients use them safely to get a good night's sleep.

Unless otherwise specified, the following information applies to adults, not children. Consult a pharmacist, comprehensive and current drug reference, or the product labeling for more details about potential adverse reactions, drug interactions, and precautions, including information on medication safety during pregnancy and breastfeeding.

PRESCRIPTION SEDATIVE-HYPNOTICS

Medication selection depends on the type of insomnia being treated, the drug's onset of action and duration of action, potential adverse reactions, and patient response. Educate patients about the proper use, risks, and precautions associated with these drugs and review with them the FDA-approved medication guide dispensed with the medications.[5] Emphasize that the medication should be taken exactly as prescribed. Warn them that because sedative-hypnotics can cause daytime drowsiness, they should avoid driving and other activities requiring alertness until they determine how the medication affects them. Instruct them to avoid drinking alcohol or using other substances that may have additive central nervous system (CNS) effects. To avoid potentially dangerous drug interactions, teach patients to inform their healthcare provider and pharmacist about any other medications they're taking.

Benzodiazepine receptor agonists

Benzodiazepine receptor agonist medications enhance the activity of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). This drug class includes both benzodiazepines such as temazepam and the newer nonbenzodiazepines such as zolpidem. The newer agents are preferred in many patients because they have a more selective binding activity and shorter half-lives, resulting in fewer adverse reactions. All of these medications are federally controlled or "scheduled" substances because they can be abused or cause dependence.

Estazolam, flurazepam, temazepam, quazepam, and triazolam are benzodiazepines that are FDA-approved to treat chronic insomnia. (The benzodiazepine lorazepam isn't approved for insomnia but it may be prescribed off-label for this indication.) Although these drugs are widely used for short-term treatment of insomnia, their nonselective binding to the GABA receptor results in many adverse reactions, including alteration of sleep cycles, daytime drowsiness, cognitive and psychomotor impairment, anterograde amnesia, rebound insomnia, and withdrawal symptoms on discontinuation.[4,6] Daytime drowsiness is specifically associated with benzodiazepines with longer durations of action.

Older adults are more sensitive to the effects of benzodiazepines and the slow metabolism of long-acting agents. The Beers criteria list medications that are potentially inappropriate for older adults due to the high risk for adverse reactions. The Beers criteria recommend avoiding all benzodiazepines in older patients due to the increased risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes.[7]

Temazepam is the most commonly prescribed medication in the benzodiazepine class, but its prolonged onset makes it less than ideal for facilitating sleep onset, and its intermediate duration of action often leads to daytime drowsiness.[8] Its quick onset of action and short duration of action make ***triazolam*** a good agent for sleep-onset insomnia with minimal potential for morning hangover. Because ***flurazepam*** and ***quazepam*** have long durations of action, they're the most likely to be associated with daytime drowsiness.

Caution must be used in patients with a history of drug or alcohol use because of the potential of these medications to cause dependency. Caution should also be exercised in patients with respiratory disorders, including chronic obstructive pulmonary disease (COPD) and sleep apnea, because benzodiazepines may cause significant respiratory depression.[9]

Abrupt discontinuation or large dosage decreases may result in rebound insomnia or withdrawal symptoms, such as tremors, abdominal or muscle cramps, diaphoresis, seizures, and vomiting. If a patient has been using any of these drugs for an extended time, the medication

Helping improve a patient's sleep hygiene[4,27]

Many patients with insomnia respond well to changes in lifestyle and behavior that facilitate good sleep habits, known as "sleep hygiene." Helpful habits to cultivate include the following:

- Avoid stimulants such as caffeine and tobacco, which can continue to exert effects for up to 8 hours. Remind patients that many OTC products contain caffeine.
- Avoid alcohol, which interferes with normal sleep patterns.
- Don't eat a heavy meal or exercise vigorously within 5 to 6 hours before bedtime.
- Establish a relaxing bedtime routine. Try to go to bed and get up at about the same time each day.
- Make your bedtime cool, dark, and quiet. Avoid distractions such as watching television or using social media at bedtime.
- Don't nap during the day.

For more lifestyle and behavioral changes that may help, refer patients to the National Institutes of Health/National Heart, Lung, and Blood Institute website: http://www.nhlbi.nih.gov/health/health-topics/topics/inso. The agency offers a free booklet for patients entitled *Your Guide to Healthy Sleep*.

dosage should be slowly tapered to discontinue therapy.

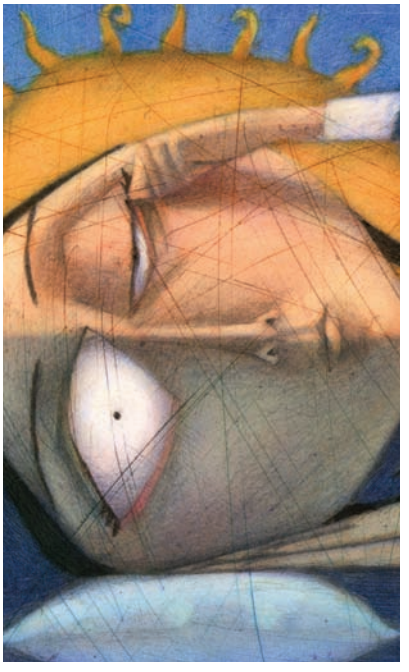
Nonbenzodiazepines

These medications are more specific for sedation with less potential for adverse reactions compared with benzodiazepines due to their selective binding of the GABA receptor. In older adults, however, these drugs cause adverse reactions similar to those of benzodiazepines and, according to the Beers criteria, provide only minimal improvement in sleep latency (the length of time needed to fall asleep) and duration.[7] Chronic use of these medications (more than 90 days) should be avoided in all patients.

Zolpidem has been shown to decrease sleep latency and improve sleep maintenance due to its quick onset of action and intermediate duration of action. It's available in various formulations, including an immediate release (IR) tablet, oral spray, controlled release (CR) tablet, and sublingual (SL) tablet. The CR formulation helps patients fall asleep and stay asleep. The SL formulation is approved for insomnia characterized by problems with sleep initiation.[10]

Zolpidem should be administered immediately before bedtime when the patient can sleep for 7 to 8 hours or more. Advise patients that taking zolpidem with food may delay its onset of action.

In 2013, the FDA notified the public of reports of impaired function in activities that require alertness, including driving, the morning after use of zolpidem.[11] Due to this known risk of next-morning impairment, the FDA called for label changes decreasing the initial dosing of zolpidem, resulting in lower drug blood levels in the morning hours.[12] This risk appears highest with the extended-release formulation, and patients should avoid activities the following day that require alertness. Because women eliminate zolpidem more slowly than men, the recommended starting dose was lowered for women, but the FDA encourages providers to consider prescribing a lower dosage for men as well.[12]



Short-term insomnia generally lasts less than 3 months and may be linked to a specific stressor, such as grief.

Warn patients that after taking zolpidem, they may get out of bed and engage in activities they're not aware of and may not remember the next day. Reported activities include "sleep driving," preparing and eating food, making phone calls, having sex, and sleepwalking.[13] Special care should be taken to prescribe zolpidem at the lowest effective dose for all patients. Instruct patients not to exceed the prescribed dosage, educate them about risks and adverse reactions, and give them the medication guide provided with the medication.

An ultrashort elimination half-life of less than 1 hour distinguishes ***zaleplon*** from zolpidem. Its rapid onset of action and short duration make it ideal for patients who have trouble falling asleep without the concerns for morning drowsiness. It hasn't been shown to increase total sleep time or decrease the number of awakenings.[14] Dosage reductions should be considered in older adults and in patients with mild-to-moderate hepatic impairment. Its use isn't recommended in patients with severe renal or hepatic impairment. Zaleplon is fairly well tolerated, causing adverse reactions similar to placebo.

Similar to zolpidem, ***eszopiclone*** is effective in decreasing sleep latency and improving sleep maintenance.[15] The dosage of eszopiclone can be adjusted based on the

Classifying insomnia types[2,28]

In the International Classification of Sleep Disorders, 3rd ed. (ICSD-3), insomnia is classified into three types:

- **Short-term insomnia.** Generally lasting less than 3 months, this type may be linked to a specific stressor, such as grief or acute pain.
- **Chronic insomnia.** Insomnia is considered chronic when the patient experiences it at least three times per week for 3 months or more, and it's not related to sleep restriction, inappropriate sleep environment, or another sleep disorder. In young adults, criteria include a sleep latency of 20 minutes or more (in older adults, 30 minutes or more) and/or unwelcome wake periods of the same durations. Premature early morning wakening is defined as waking 30 minutes or more before the desired wake time.
- **Other insomnia.** This category covers patients who report difficulty initiating or maintaining sleep but don't meet all the criteria for short-term or chronic insomnia.

patient's primary sleep disorder.[16] The initial dosage should be reduced in patients taking strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, or clarithromycin) and in those with severe hepatic impairment.

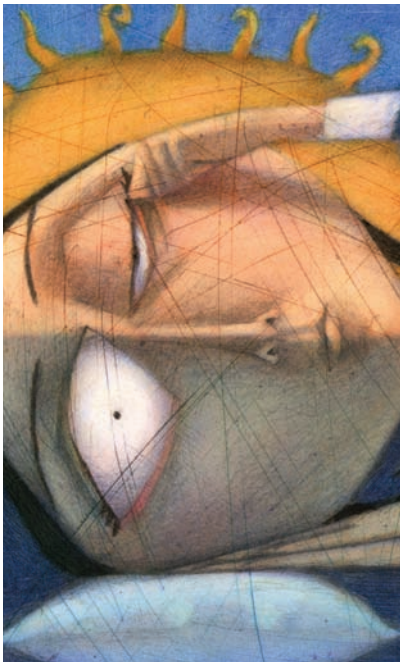
An unpleasant taste was the most frequently reported adverse reaction in clinical trials. Other adverse reactions include headache, somnolence, respiratory infection, anxiety, dry mouth, dizziness, rash, anxiety, and hallucinations.[15,17] Indicated for chronic insomnia, this drug is especially helpful for patients who may need long-term treatment.

MELATONIN RECEPTOR AGONISTS

Ramelteon, a non-scheduled prescription drug approved for insomnia, is less likely to cause dependence than the sedative-hypnotics discussed above. Its effects on the sleep-wake cycle are achieved by binding to the melatonin MT_1 and MT_2 receptors. Stimulating MT_1 receptors induces sleepiness; the drug's effects on MT_2 receptors influence regulation of circadian rhythms.[18]

No dosage adjustments are necessary for older adults or patients with renal impairment. However, caution should be used in patients with mild-to-moderate hepatic impairment or respiratory compromise, including COPD and sleep apnea. This drug isn't recommended for patients with severe hepatic impairment. Adverse reactions to ramelteon are mild; the most commonly reported are somnolence, dizziness, fatigue, nausea, and exacerbated insomnia.[18]

Instruct patients to take the drug within 30 minutes of bedtime, and warn them not to break, chew, or crush the tablet. Also advise them to avoid high-fat meals near the time of administration. Studies have shown that administration with a high-fat meal decreases maximal serum concentrations and delays the time to achieving this.[18]



Advise patients to avoid stimulants such as caffeine and tobacco, which can exert effects for up to 8 hours.

Due to its specificity for MT receptors, ramelteon is unlikely to cause dependence, withdrawal symptoms, rebound insomnia, and motor or cognitive deficits. However, patients should be warned to avoid consuming alcohol in combination with the drug because of additive CNS effects.[18]

Tasimelteon is the only FDA-approved medication for the treatment of non-24-hour sleep-wake disorder, a chronic circadian rhythm disorder that affects completely blind patients. It results from environmental light failing to synchronize their internal clock to the 24-hour light-dark cycle.[19] Tasimelteon is a melatonin receptor agonist at the melatonin MT_1 and MT_2 receptors involved in the control of circadian rhythms.[20] Due to individual differences in circadian rhythms, the effects of this medication may not occur for weeks to months. Tasimelteon shouldn't be taken with food. Avoid concomitant use with strong CYP1A2 inhibitors such as fluvoxamine and strong CYP3A4 inducers such as rifampin and ketoconazole. Smoking induces CYP1A2 and can result in lower tasimelteon levels and reduced efficacy. In clinical trials, the most common adverse reactions were headache, increased alanine aminotransferase, nightmares or unusual dreams, and upper respiratory or urinary tract infection.[20]

OREXIN RECEPTOR ANTAGONIST

Suvorexant is thought to suppress wake drive by blocking the binding of wake-promoting neuropeptides orexin A and orexin B. This antagonism may also trigger adverse reactions such as narcolepsy/cataplexy. Consequently, suvorexant is contraindicated in patients with narcolepsy.[21]

The recommended dose should be taken within 30 minutes of sleep with at least 7 hours remaining before awakening. Exposure is increased in obese persons, more so in women than men, and the potential for adverse reactions should be considered when increasing dosages in this population. Daytime somnolence also increases with increasing doses. When used in combination with other CNS depressant drugs (including alcohol), dose adjustments of either or both medications may be warranted.

A dose-dependent increase in suicidal ideation was observed in clinical trials and patients should be evaluated immediately if suicidal ideation is experienced. Patients should be counseled on possible sleep paralysis (inability to move or speak for up to several minutes during sleep-wake transitions) and

Miscellaneous prescription medications[9]

These medications have hypnotic properties and may be prescribed in patients with certain preexisting conditions. Consult the product labeling for a complete listing of potential adverse reactions.

Drug	Mechanism of action	Adverse reactions
ANTIDEPRESSANTS*		
Doxepin	Inhibits reuptake of norepinephrine and serotonin in the CNS; antagonizes the histamine (H_1) receptor	Higher doses: orthostatic hypotension, anticholinergic effects, cardiac conduction delay
Mirtazapine	Increases release of norepinephrine and serotonin by blocking central presynaptic $alpha_2$ receptors; antagonizes the histamine (H_1) receptor	Increased appetite, weight gain, anticholinergic effects
Trazodone	Inhibits reuptake of serotonin and significantly blocks histamine (H_1) and $alpha_1$-adrenergic receptors	Dizziness, sedation, hypotension, headache, priapism, syncope, dysrhythmias
Amitriptyline	Tricyclic antidepressant: serotonin-norepinephrine reuptake inhibitor with antihistamine and anticholinergic effects	Higher doses: orthostatic hypotension, anticholinergic effects, cardiac conduction delay
ATYPICAL ANTIPSYCHOTICS		
Quetiapine	Serotonin and dopamine antagonist with effects on histamine (H_1) and $alpha_1$ and $alpha_2$ receptors	Dry mouth, constipation, weight gain, asthenia, headache
Olanzapine	Potent antagonist of serotonin, dopamine, histamine (H_1) and $alpha_1$ receptors	Hypotension, weight gain, akathisia, dizziness
ANTIEPILEPTIC DRUGS		
Gabapentin	Structurally related to the neurotransmitter GABA; the exact mechanism of action is unknown	Dizziness, somnolence, ataxia, fatigue
Pregabalin	Binds to voltage-gated calcium channels in the CNS, inhibiting excitatory neurotransmitter release	Peripheral edema, dizziness, somnolence, headache, weight gain, dry mouth

*Caution: Antidepressant medications increase the risk of suicidal thinking and behavior in children, adolescents, and young adults with major depressive disorder and other psychiatric disorders.

hallucinations that may occur while they're taking suvorexant. Advise patients that food may delay onset of the medication's effects. Physical dependence or withdrawal symptoms following prolonged use and discontinuation weren't seen in clinical trials with suvorexant.[21]

MISCELLANEOUS PRESCRIPTION DRUGS

Some antidepressants, antipsychotics, and antiepileptic drugs (AEDs) are prescribed off-label for insomnia. (See *Miscellaneous prescription medications*.) Many of these drugs block the H_1 histamine receptor, resulting in sedation. However, other properties may limit their use; for example, effects on alpha receptors resulting in unwanted orthostatic hypotension or anticholinergic effects such as dry mouth, urinary retention, and constipation. Unlike FDA-approved medications for insomnia with short durations of action, these medications typically have longer half-lives, which can result in residual adverse reactions. This may limit their utility unless the patient has other indications for the medication.[3]

OTC MEDICATIONS

Diphenhydramine and ***doxylamine*** are first-generation central H_1 receptor antagonists that are available in many sleep aid products.[6] Chlorpheniramine, brompheniramine, and pyrilamine are also first-generation antihistamines that can cause drowsiness and induce sleep; however, they haven't been approved by the FDA for insomnia and have a less favorable side effect profile compared with diphenhydramine and doxylamine.[6]

Because of their lipophilic properties, first-generation antihistamines

easily cross the blood-brain barrier, which results in sedation. A hangover-like effect in the morning is caused by a prolonged elimination half-life of 9 hours.[6]

According to the Beers criteria, neither diphenhydramine nor doxylamine is recommended for older adults because both drugs are highly anticholinergic. Clearance is reduced due to age-related declines in renal function, leading to adverse reactions such as dry mouth, urinary retention, constipation, and possible drug interactions.[7]

Many OTC combination products contain diphenhydramine or doxylamine, including combination products. Teach patients to read labels carefully to identify product ingredients correctly. For example, some products with similar trade names contain either diphenhydramine or doxylamine depending on the formulation. If a patient has tried a sleep aid product containing diphenhydramine without success and wants to try a product containing doxylamine instead, make sure the patient understands the difference so diphenhydramine isn't inadvertently restarted.

Because second- and third-generation antihistamines such as loratadine, cetirizine, and fexofenadine don't cross the blood-brain barrier, they don't cause sedation and aren't recommended to treat insomnia.[22]

HERBAL PRODUCTS AND DIETARY SUPPLEMENTS

Many people have the notion that herbal products are safe because they're more natural. Unfortunately, the FDA doesn't regulate the manufacture of herbal products. Limited data are available to support the safety and efficacy of most of these products due to weak studies, short durations of treatment, and varying doses in formulations of products. Herbal options aren't usually recommended based on limited studies and data to support their use.[3,23]

Valerian is derived from the plant species valeriana, also known as *Valeriana officinalis*. It's known to have sedative properties but its value in treating insomnia isn't well established.[23] Its mechanism of action is unclear but it's thought to have GABA-ergic receptor function.[24,25]

Valerian is available in dilute alcohol extracts, and tends to have a more prominent anxiolytic than sleep-inducing effect. Because the extracts degrade quickly, they're usually present in dry formulation.

The FDA considers valerian safe; however, clinical trials have not evaluated tolerance, dependence, or withdrawal and rebound symptoms on discontinuation. It's normally well tolerated for up to 6 weeks. Adverse reactions that have been reported include dizziness, hangover, headache, excitability, insomnia, uneasiness and ataxia. Hepatotoxicity has also been reported.[6,9]

Melatonin is a hormone secreted by the pineal gland. It increases the binding of GABA to its receptors by affecting membrane characteristics, not by increasing the number of receptors. Melatonin regulates the body's circadian rhythm, endocrine secretions, and sleep patterns.[26]

Data to support the use of melatonin for the treatment of insomnia are limited. Some evidence shows short-term benefits in patients with decreased nocturnal melatonin production and circadian disorders, such as shift work and jet lag. It's well tolerated and relatively safe for short term use but may be associated with mood disturbances in older adults.[23] Caution is advised in patients taking warfarin and melatonin together; melatonin may increase the effect of anticoagulant or antiplatelet drugs.[24]

Kava kava is derived from a shrub *piper methysticum,* which originates in the South Pacific. It's considered to have anxiolytic and sedative properties, but no studies have addressed its use for insomnia alone, only insomnia due to anxiety.[24] It's available in the United States as raw plant or material concentrated extracts. The FDA issued a warning that kava kava supplements may be associated with a risk of severe liver damage, especially in patients with a history of liver disease.[23,24]

German chamomile, passionflower, lemon balm, skullcap, hops, lavender, L-tryptophan, St. John's wort, and sour cherries all have sedative properties, but limited data support their use as a treatment for insomnia. Caution is advised with the use of St. John's wort as it is a potent inducer of cytochrome P 450 CYP3A4, which can reduce the effect of many medications. More research is needed before any of these herbal products can be recommended as treatments for insomnia.[27]

Sleep easy

Many pharmacotherapy options are available to treat insomnia. Before prescribing or recommending any medication or sleep aid, however, the clinician must thoroughly assess the patient's condition and review the evidence on the medication's mechanism of action, safety, and effectiveness. By using appropriate caution, starting at minimum dosages, limiting duration of treatment, and monitoring patients for adverse reactions, nurses and other clinicians promote safe and effective pharmacologic treatment for insomnia. ■

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