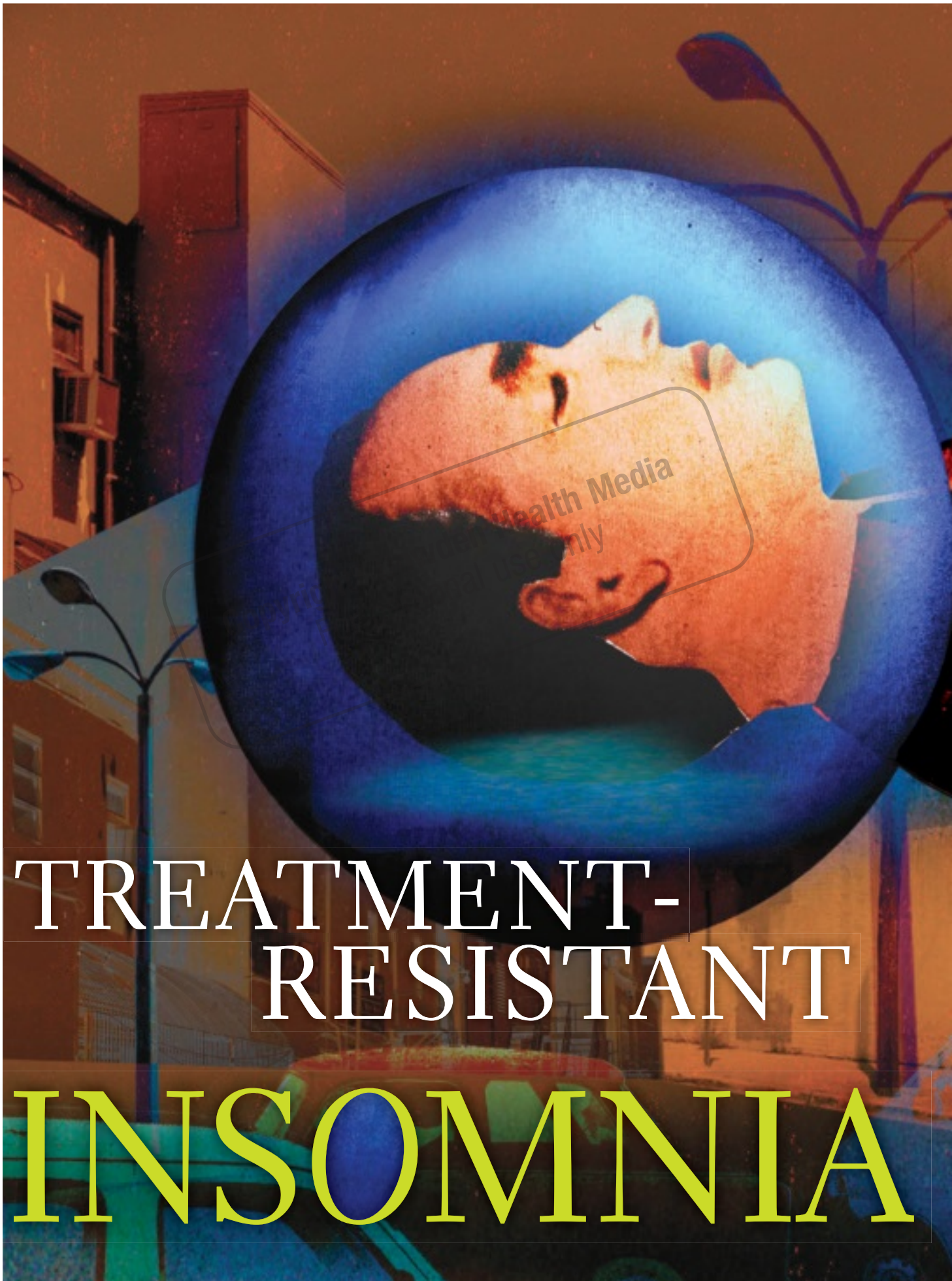

TREATMENT-RESISTANT INSOMNIA

Current PSYCHIATRY

ASK YOURSELF 8 QUESTIONS

When insomnia persists, go back to the basics to discover what you might have missed

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Although many patients with insomnia respond to standard treatments, some continue to experience insufficient sleep. When your patient appears "treatment-resistant," you may be tempted to add another therapy or try an unorthodox medication. But choosing an appropriate next treatment is impossible without first looking back for a rationale:

- Have you overlooked one of insomnia's many causes?
- Have you customized treatment for this patient?
- Is he or she unaware of behaviors that may be undermining attempts to sleep?

Refreshing sleep may elude some thoroughly evaluated and optimally treated patients, but they comprise a small minority. You can help most chronic insomnia sufferers by re-evaluating their behaviors, comorbidities, sleep-wake cycles, and medications (***Table 1, page 48***).

'3 Ps' and 8 questions

Thirty percent of adults experience insomnia at least occasionally, and 10% have persistent insomnia. Women, older persons, and patients with chronic medical conditions such as diabetes mellitus and lung disease have higher insomnia rates than the general population.[1]

continued

Insomnia

Clinical Point

To be diagnosed as a disorder, insomnia must have daytime consequences, such as fatigue, irritability, or poor memory and concentration

Table 1

Recommended approach to treatment-resistant insomnia

Evaluation
Review your patient's 24-hour sleep cycle, sleepiness, and sleeplessness, and note persistent patterns (a sleep log or diary may help)
Re-evaluate stimulating or sedating effects of prescribed and over-the-counter medications, caffeine, and alcohol
Consider: • influences on homeostatic sleep drive, such as napping • influences on circadian rhythm, such as irregular schedules and advanced or delayed phase tendencies • comorbid medical and psychiatric disorders • other sleep disorders, such as restless legs syndrome or sleep apnea
Monitor insomnia-related daytime symptoms as key outcome measure
Treatment
Re-address sleep hygiene (**Table 2, page 52**)
Consider cognitive behavioral therapy for insomnia
Consider an FDA-approved medication for insomnia (**Table 3, page 53**), customized to your patient's symptoms

An enormous variety of psychological and physiologic processes may influence sleep (***Box 1***). Multiple factors may contribute to an individual's inability to achieve sufficient sleep, and the relative significance of these influences can shift over time. Factors that might trigger an insomnia episode are not necessarily those that maintain sleeplessness.

The "3 Ps" model—which includes predisposing, precipitating, and perpetuating factors—is a valuable framework for evaluating patients with treatment-resistant insomnia (***Box 2, page 50***).[2] To help you narrow down the possibilities, consider 8 questions to identify factors that may be perpetuating your patient's insomnia.

1 Does the patient have realistic goals for falling asleep and remaining asleep?

Patients view insomnia as being unable to sleep when they believe they should be sleeping. To be diagnosed as a disorder, insomnia must have daytime consequences associated with:

- difficulty falling asleep
- difficulty maintaining sleep
- awakening excessively early
- or experiencing nonrestorative sleep.

Daytime consequences may include fatigue, irritability, poor concentration and memory, difficulty accomplishing tasks, and worry about sleep.[3,4]

Recommendation. Determine how the patient defines "having insomnia" (there are no absolute thresholds). Ask how he or she is functioning during the day. Those who complain of imperfect nighttime sleep may admit that treatment has helped with the daytime symptoms that prompted them to seek treatment.

If daytime symptoms have diminished, reassure the patient that treatment apparently is helping. Patients are less likely to focus on perceived nighttime impairment when their distress about daytime functioning has eased.

Also determine if the patient has followed recommended treatment. Cognitive-behavioral therapy (CBT) may increase adherence to behavioral changes, sleep hygiene, and medication schedules.

2 Have I identified and optimally managed comorbidities?

Identifying comorbidities that may contribute to chronic insomnia is particularly important because managing these conditions may alleviate the sleep disturbance. Pain or discomfort caused by a medical condition may undermine sleep quality. Certain cardiovascular, pulmonary, endocrine, neurologic, rheumatologic, and orthopedic disorders are associated with insomnia.

Most patients experiencing exacerbations of mood and anxiety disorders suffer insomnia, and many other psychiatric disorders are associated with sleep disruption.

Box 1

Insomnia's clinical features: Subtypes to consider

Diagnostic subtypes recognized by the American Academy of Sleep Medicine may suggest why recommended treatments have not relieved a patient's symptoms. Insomnia may be:

- due to a mental disorder, medical condition, drug or substance
- adjustment-related (acute insomnia), psychophysiologic, paradoxical, or idiopathic
- related to inadequate sleep hygiene
- a behavioral characteristic of childhood
- organic (due to an unspecified physiologic condition)
- nonorganic, NOS (not due to a substance or known physiologic condition).

NOS: not otherwise specified

Insomnia may be the chief complaint of a patient with obstructive sleep apnea or restless legs syndrome.

Insomnia often accompanies substance abuse and may continue after the patient stops abusing drugs or alcohol. Abused stimulants and sedatives can worsen sleep quality, and discontinuation can cause acute and chronic sleep disruption.

Recommendation. Treat mood and anxiety disorders independently of insomnia. Minimize pain and discomfort from medical conditions. Address substance abuse, and dispel patients' notion that alcohol is a sleep aid.

Order sleep laboratory testing for patients at risk for sleep apnea, based on their history, physical exam—including obesity, upper airway anatomy, and neck circumference (collar size ≥17 inches)—and informant reports of snoring and breathing patterns.

3 Is the patient taking medications with stimulating effects?

Because insomnia is highly comorbid with mood and anxiety disorders, patients with insomnia often are prescribed antidepressants. Although some are sedating, antidepressants such as selective serotonin reuptake inhibitors are likely to be stimulating.

Recommendation. When insomnia persists, assess the potential effects of prescribed and over-the-counter (OTC) medications. Consider possible pharmacologic effects of aging that can make patients more sensitive to medications.

Also educate patients about the long-acting effects of caffeine and its varied sources, such as energy drinks and OTC products. Some patients will benefit from

Insomnia

Clinical Point

Have the patient keep a sleep log to reveal possible homeostatic and circadian patterns contributing to insomnia

Box 2

'3 Ps': Framework for evaluating treatment-resistant insomnia

Predisposing factors. Some personalities may be predisposed to insomnia. Persons who tend to be anxious, depressive, or emotionally reactive may be at increased risk for developing insomnia.

Precipitating factors may include situational crises, schedule changes, substance or medication use, and psychiatric, medical, and sleep disorders. A careful history allows you to consider precipitating events.

Perpetuating factors that may reinforce and maintain chronic insomnia include:

- maladaptive behaviors, such as napping or using alcohol as a sleep aid
- conditioned hyperarousal, whereby insomnia sufferers experience anxiety and tension associated with preparing for and getting into bed. Sleepless time in bed may reinforce the conditioning, contribute to anxiety and tension, and undermine sleep on future nights.

Source: Reference 2

completely avoiding caffeine, whereas others may do fine restricting coffee to 1 or 2 cups in the morning. A good general practice is to avoid all caffeine after lunchtime.

4 Does the patient's insomnia have a homeostatic component?

Circadian rhythms and a homeostatic sleep drive are temporally linked in regulating the normal routine of nighttime sleep alternating with day and evening wakefulness.[5,6] The sleep drive promotes a sleep-to-waking ratio of approximately 1:2 (an average of 8 hours sleep per 24 hours). Adequate sleep, from the homeostatic perspective, could be achieved during any hours of the day or night.

Acute sleep deprivation may result from extended wakefulness—such as staying up all night to study for an exam. Chronic sleep deprivation may occur during successive 24-hour periods with insufficient sleep. Both patterns are associated with increasing subjective sleepiness and ultimately with cognitive impairment.

The circadian process optimizes sleep to occur at night through entrainment with the photoperiod (daylight exposure). The master CNS timekeeper is coordinated by the tiny paired suprachiasmatic nuclei (SCN) in the anterior hypothalamus, where neurons maintain approximate 24-hour periodicity through complex transcription-translation feedback loops involving several genes. Circadian rhythm is reinforced by SCN control of pineal gland production and secretion of melatonin, which normally:

- is low throughout the daytime
- rises during the evening as bedtime approaches
- plateaus during nighttime sleep hours
- decreases as the normal morning wake time approaches.

The homeostatic sleep drive accumulates from awakening until sleep occurs again. In the late afternoon and evening, however, homeostatic sleep pressure is opposed by an arousal signal from the circadian system.

Typically, people are more alert in the evening than at any other time in the 24-hour cycle. As bedtime approaches, rising melatonin interacts with SCN melatonin receptors and decreases circadian arousal. Normal sleep onset then can occur rapidly at bedtime, when the homeostatic sleep drive is unopposed.

Nighttime sleep initially is promoted by the homeostatic sleep drive. However, the homeostatic sleep pressure is reversed by sleep and thus decreases as sleep continues during the night. The circadian system promotes minimum stimulation during the latter sleep hours, sustaining total sleep for approximately 8 hours.

Consequences. Individual circadian timing tendencies may affect when people experience alertness and sleepiness and may be associated with persistent complaints of sleep onset difficulty or early

morning awakening.[7] Napping may reduce the homeostatic sleepiness available to aid bedtime sleep onset. Mismatched homeostatic and circadian processes often prevent shift workers from achieving satisfactory sleep.

Recommendation. Have the patient keep a sleep log to identify the time and duration of sleep episodes throughout the 24-hour cycle. Actigraphy may provide useful information about sleep-wake patterns.

5 Are circadian rhythm patterns contributing to insomnia?

Overlooking circadian rhythms' effects on insomnia can lead to apparent treatment failure.[8] Although the circadian system typically promotes sleep from about 10 PM to midnight until about 6 to 8 AM, some individuals have long-standing predispositions for earlier or later sleep episodes.

An advanced circadian phase leads to sleepiness and the ability to fall asleep early in the evening, followed by a tendency to awaken spontaneously relatively early in the morning. In extreme cases, patients with these "lark" tendencies may be diagnosed with advanced sleep phase disorder. Persistent early morning awakening insomnia and sleep maintenance complaints are common.

A delayed circadian phase is associated with inability to fall asleep at a typical late evening bedtime and difficulty awakening at a desired time the following morning. In extreme cases, individuals may sleep from very late at night until the following afternoon. These markedly delayed schedules may be obvious, but the circadian contribution may not be recognized in less severe cases.

People with this predisposition may achieve optimum sleep by following their delayed circadian tendency, but school and work demands often conflict with this approach. They may develop chronic sleep deprivation from late sleep onset coupled with forced morning awakenings. Complaints of chronic difficulty with sleep onset are common.

Recommendation. Have the patient keep a sleep log to demonstrate advanced or delayed circadian phase tendencies. Determine if the patient is a shift worker who is attempting to sleep in the daytime. Consider prescribing ramelteon—a melatonin agonist—and providing strategic bright light exposure:

- in the evening for advanced circadian phase patients
- in the morning for delayed circadian phase patients.[8]

continued

Insomnia

Clinical Point

Medication may provide rapid insomnia relief, but CBT's benefits may be more durable beyond the treatment period

Table 2

Patient education: Sleep hygiene guidelines

Try to maintain a regular sleep–wake schedule
Avoid afternoon or evening napping
Allow yourself enough time in bed for adequate sleep duration (such as 11 PM to 7 AM)
Develop a relaxing evening routine for the hours before bedtime
Spend some idle time reflecting on the day's events before going to bed; make a list of concerns and how some might be resolved
Reserve the bed for sleep and sex; do not do homework, pay bills, watch TV, or engage in serious domestic discussions in bed
Avoid alcohol in the evening
Avoid caffeine in the afternoon and evening
Minimize annoying noise, light, or temperature extremes
Consider a light snack before bedtime
Exercise regularly, but not late in the evening
Do not try harder and harder to fall asleep; if you can't sleep, get out of bed and do something else, in another room if possible
Avoid smoking

6 Is the patient following appropriate sleep hygiene?

Sleep hygiene will not necessarily cure chronic insomnia, but inattention to basic guidelines (***Table 2***) can undermine other treatments. When re-evaluating patients with chronic insomnia, give special attention to their alcohol and caffeine intake, regularity of bedtime and wake-up times, meal times, and the bedroom environment. Advise patients to remove televisions from the bedroom, for example.

CBT that is effective for chronic insomnia typically blends sleep hygiene with education, cognitive psychotherapy, and specific instructions regarding bedtime schedules.[9,10] Relaxation techniques also may be beneficial.

Recommendation. Consider CBT as an option for all patients with persistent insomnia. Combined CBT and pharmacotherapy also may be effective. Medications may provide rapid relief, but CBT's benefits may be more durable beyond the treatment period.

Consider consulting with a sleep specialist if the patient has not been evaluated at a sleep center. Some sleep centers offer CBT.

7 Does the patient regularly experience anxiety and tension as bedtime approaches or spend excessive wakeful time in bed?

Patients who tend to be anxious, depressive, or emotionally reactive are at increased risk for developing an insomnia episode. They then may develop conditioned hyperarousal associated with preparing for and getting into bed, which perpetuates insomnia.

Some patients spend long periods in bed, hoping to achieve any possible sleep that night. Extended time in bed can perpetuate insomnia by increasing frustrating time awake, thereby reinforcing the association between the bed and wakefulness.

Recommendation. CBT often helps ease these conditioned responses.

Stimulus control can help anxious individuals reassociate the bed, bedroom, and bedtime routines with sleep onset, rather than sleep-destructive tension. Advise patients to go to bed in the evening when they feel they can fall asleep. If they do not fall asleep within 10 to 15 minutes or experience their usual worry and frustration about not sleeping, instruct them to leave the bed and try again later. Also tell them to avoid daytime napping.

Sleep restriction therapy may help patients with excessive wakefulness in bed by limiting sleep opportunity to defined hours of the night. For example, a patient who reports getting 5 hours of sleep would be scheduled for 5 hours in bed. If his typical arising time is 7 AM, he would not go to bed until 2 AM. When his sleep log shows he has slept 90% of the time in bed for 5 consecutive nights, he can go to bed 15 to 30 minutes earlier. Over time, as this process is repeated, patients spend greater amounts of time sleeping while in bed.

Sleep restriction creates a degree of sleep deprivation that may enhance sleep onset and maintenance. Caution patients not to drive or perform hazardous activities while sleep-deprived.

8 Has the patient been prescribed appropriate doses of medications with appropriate indications?

Chronic insomnia sufferers often try to get more sleep by using alcohol, food supplement remedies, and OTC antihistamine sleep aids—none of which has demonstrated efficacy for treating insomnia. Although sedating prescription medications may be recommended for comorbid conditions, many also are prescribed off-label to promote sleep.

Examples include sedating antidepressants, antipsychotics, antihistamines, anticonvulsants, and benzodiazepines that are not indicated for insomnia. Little or no evidence supports these medications as safe and efficacious for treating insomnia, and important safety concerns are associated with their use.

FDA-approved medications for treating insomnia include benzodiazepine receptor agonist (BZRA) hypnotics and a selective melatonin receptor agonist (***Table 3***). These allosteric modulators of GABA responses at the GABAA receptor complex promote sleep through sedation.

The BZRA category includes 5 benzodiazepines and 4 nonbenzodiazepine formulations. Half-lives vary from approximately 1 hour to several days. Compared with benzodiazepines, nonbenzodiazepines have greater selectivity for GABAA receptor complexes incorporating the alpha-1 subunit subtype, which may confer some safety and tolerability advantages. One extended-release formulation is available. All may be beneficial for sleep onset, and some have indications for sleep maintenance difficulty.

Ramelteon is a nonsedating selective melatonin receptor agonist approved for treating insomnia characterized by sleep onset difficulty. This agent—which attenuates evening circadian arousal—may help promote sleep onset and enhance sleep during the early part of the night.

Table 3

Insomnia treatment: FDA-approved medications

Medication	Recommended dosage (mg)	Elimination half-life (hr)
Benzodiazepine receptor agonists		
Immediate-release benzodiazepines		
Estazolam	1 to 2	8 to 24
Flurazepam	15 to 30	48 to 120
Quazepam	7.5 to 15	48 to 120
Temazepam	7.5 to 30	8 to 20
Triazolam	0.125 to 0.25	2 to 4
Immediate-release nonbenzodiazepines		
Eszopiclone	1 to 3	5 to 7
Zaleplon	5 to 20	1
Zolpidem	5 to 10	1.5 to 2.4
Extended-release nonbenzodiazepine		
Zolpidem ER	6.25 to 12.5	2.8 to 2.9
Selective melatonin receptor agonist		
Ramelteon	8	1 to 2.6

Administration. Inadequate dosing of insomnia medications may cause treatment to fail, but prescribing beyond approved ranges is rarely necessary. High sedative doses increase the risk of adverse effects, and patients may sleep no better. Adverse effects may include somnolence, headache, dizziness, nausea, diarrhea, and anterograde amnesia. Rarely patients may exhibit sleep walking or confused behaviors within a few hours after taking a hypnotic dose.

The BZRA hypnotics are schedule-IV controlled substances—defined as having a low potential for abuse—and ramelteon is nonscheduled. FDA-approved indications of eszopiclone, ramelteon, and zolpidem extended-release lack the "short-term treatment" wording required in earlier sleep medications' labeling and therefore have no implied limitation on duration of use. The differing indications do not suggest, however, that any of these sleep agents is better or worse for initial insomnia treatment or "treatment-resistant" cases.

continued

Clinical Point

Prescribing beyond approved ranges is rarely necessary; high doses increase the risk of adverse effects, and patients may sleep no better

Insomnia

Clinical Point

When prescribing medication for insomnia, consider whether your patient needs help with sleep onset or maintenance

Recommendation. Customize your selection of FDA-approved insomnia medications. Consider whether your patient needs medication for sleep onset or sleep maintenance. In most cases, prescribe within dosing ranges listed in ***Table 3, page 53***.

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Related Resources

- American Academy of Sleep Medicine. www.aasmnet.org.
- National Sleep Foundation. www.sleepfoundation.org.
- NIH National Center for Sleep Disorders Research. www.nhlbi.nih.gov/about/ncsdr.

Drug Brand Names

Estazolam • ProSom	Temazepam • Restoril
Eszopiclone • Lunesta	Triazolam • Halcion
Flurazepam • Dalmane	Zaleplon • Sonata
Quazepam • Doral	Zolpidem • Ambien
Ramelteon • Rozerem	Zolpidem ER • Ambien CR

Disclosure

Dr. Neubauer is a consultant to Neurocrine Biosciences, sanofi-aventis, and Takeda Pharmaceuticals North America and a speaker for sanofi-aventis and Takeda Pharmaceuticals North America.

Bottom Line

When insomnia persists, re-evaluate the patient's workup and therapeutic strategies. Consider whether the patient has adhered to treatment and if medical or psychiatric comorbidities may be interfering with sleep. Use sleep logs to seek circadian rhythm or homeostatic sleep-wake cycle problems. Review medications for possible stimulating effects, and examine whether appropriate sleep agents have been prescribed at approved dosages.