Chronic Insomnia

David N. Neubauer, MD

Address correspondence to Dr David N. Neubauer, Johns Hopkins Bayview Medical Center, 4940 Eastern Ave, Box 151, Baltimore, MD 21224, *neubauer@jhmi.edu*.

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ABSTRACT

Purpose of Review: This article provides an overview of current strategies for evaluating and treating patients who experience chronic insomnia.

Recent Findings: The US Food and Drug Administration (FDA) has approved several medications for the treatment of insomnia that incorporate a variety of pharmacodynamic and pharmacokinetic properties, thus allowing the development of a customized therapeutic approach. FDA-approved medications include γ-aminobutyric acid–modulating benzodiazepine receptor agonists, a melatonin receptor agonist, and a histamine receptor agonist. Psychological and behavioral techniques combined as cognitive-behavioral therapy also have been shown to be effective in the treatment of chronic insomnia.

Summary: Insomnia is the most common sleep disturbance and represents a chronic condition for many people. Difficulty falling asleep and maintaining sleep are highly prevalent problems in patients with neurologic disorders. Multiple factors typically contribute to insomnia. Accordingly, a rather broad approach to evaluating patients is warranted. Evidence-based guidelines support the use of cognitive and behavioral strategies and selected medications in the treatment of patients with chronic insomnia.

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INTRODUCTION

Insomnia is among the most commonly reported clinical complaints in general medicine and is highly prevalent in patients treated in neurology practices.[1,2] Sleep disturbances often result from multiple causes and may necessitate multimodal management for eventual success, and by employing established evaluation guidelines and evidence-based therapies, it should be possible to help most patients with insomnia achieve significant improvements in their sleep.[3] Addressing the sleep concerns of these patients can have a considerable effect on improving their sense of well-being and the quality of their lives. Emerging evidence documents that poor sleep is associated with a wide range of negative health outcomes; therefore, enhancement of sleep quantity and quality may have broader roles in promoting wellness and bringing about improvements in some comorbid conditions. In fact, neurologists should educate all patients about the importance of getting adequate sleep and address their sleep problems, just as patients are encouraged to improve other aspects of a healthy lifestyle, such as diet and exercise.

WHAT IS INSOMNIA?

Most basically, an insomnia disorder is persistent difficulty falling asleep or remaining asleep, with some element of daytime impairment that is presumably related to the sleep problem. Contemporary views conceptualize chronic insomnia as a 24-hour condition that may involve hyperarousal, leading to both the nighttime and daytime symptomatology.[4] Several nosologies offer criteria for insomnia and specific

insomnia diagnoses. While the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*) (and evolving *DSM-V*) and the *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *ICD-10* incorporate useful categorizations of sleep disorders, including various types of insomnia, the most comprehensive organization of insomnia is outlined in the *International Classification of Sleep Disorders: Diagnostic and Coding Manual, Second Edition: Diagnostic and Coding Manual* (*ICSD-2*), although a third edition currently is in development. The *ICSD-2* defines general criteria for insomnia (**Table 3-1**) and specific criteria for 11 individual insomnia disorders (**Table 3-2**).

The general *ICSD-2* insomnia criteria include required nighttime and daytime elements.[5] The nighttime sleep complaint may involve difficulty falling asleep, problems remaining asleep, awakening excessively early, or a sense of sleep that is not refreshing. This inadequate sleep must be in the context of the patient having had the opportunity to be sleeping. Patients may describe various patterns of delayed sleep onset, multiple brief or extended awakenings, and a feeling that their sleep is very light and easily interrupted. Often, concern about the daytime consequences motivates people to seek help for their inadequate sleep. These daytime complaints very often are fatigue and poor concentration but also may include low mood and irritability, poor motivation, low energy, various physical symptoms, and an increased tendency to make mistakes. Patients with chronic insomnia typically worry greatly about their inability to sleep well and the negative impact it has on their lives. The criteria

KEY POINTS

- Poor sleep, whether due to inadequate quality or quantity, increases the risk for multiple chronic comorbid health conditions.
- Wellness promotion should include good quality sleep along with a healthy diet and exercise plan.
- The diagnosis of insomnia requires some degree of daytime impairment in addition to persistent difficulty falling asleep or remaining asleep.
- Insomnia currently is conceptualized as a disorder of the wake system resulting in round-the-clock hyperarousal.

TABLE 3-1 ***International Classification of Sleep Disorders, Second Edition: Diagnostic and Coding Manual*** **Diagnostic Criteria for General Insomnia**[a]

A. A complaint of difficulty initiating sleep, difficulty maintaining sleep, or waking up too early, or sleep that is chronically nonrestorative or poor in quality. In children, the sleep difficulty is often reported by the caretaker and may consist of observed bedtime resistance or inability to sleep independently.

B. The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep.

C. At least one of the following forms of daytime impairment related to the nighttime sleep difficulty is reported by the patient:

1. Fatigue or malaise
2. Attention, concentration, or memory impairment
3. Social or vocational dysfunction or poor school performance
4. Mood disturbance or irritability
5. Daytime sleepiness
6. Motivation, energy, or initiative reduction
7. Proneness for errors or accidents at work or while driving
8. Tension, headaches, or gastrointestinal symptoms in response to sleep loss
9. Concerns or worries about sleep

[a] Reprinted from American Academy of Sleep Medicine.[5] Used with permission of the American Academy of Sleep Medicine, Darien, IL, 2012.

KEY POINTS

- During the daytime most patients with chronic insomnia feel fatigued but not sleepy.
- Chronic insomnia associated with daytime consequences affects about one in 10 adults.

TABLE 3-2 ***International Classification of Sleep Disorders, Second Edition: Diagnostic and Coding Manual*** **Diagnostic Criteria for Specific Insomnia Disorders**[a]

1. Adjustment insomnia
2. Psychophysiological insomnia
3. Paradoxical insomnia
4. Idiopathic insomnia
5. Insomnia due to mental disorder
6. Inadequate sleep hygiene
7. Behavioral insomnia of childhood
8. Insomnia due to drug or substance
9. Insomnia due to medical condition
10. Insomnia not due to substance or known physiologic condition, unspecified
11. Physiologic insomnia, unspecified

[a] Reprinted from American Academy of Sleep Medicine.[5] Used with permission of the American Academy of Sleep Medicine, Darien, IL, 2012.

options for daytime consequences are listed in **Table 3-1**. It is interesting that patients with chronic insomnia rarely describe excessive daytime sleepiness. Often it is just the opposite: they describe a pleasant past when they were able to nap but now find that it is frustratingly impossible to catch up on sleep during the daytime. Perhaps this is a manifestation of a hypothesized round-the-clock hyperarousal process.

The prevalence of insomnia varies with the population.[1] Women and older adults are at somewhat greater risk for insomnia. In the general population about one of three adults reports at least occasional symptoms of insomnia, while roughly one of 10 has chronic symptoms with reports of daytime consequences. It is common for brief insomnia episodes to have identifiable precipitants, such as situational crises, schedule changes, acute health problems, and medication changes. Chronic insomnia, persisting for at least 1 month, often has a more complex etiology with multiple predisposing and precipitating factors and processes that perpetuate the insomnia over time. As poor sleep and accompanying distress continue, people may develop maladaptive behaviors (eg, increased daytime caffeine intake, bedtime alcohol, and excessive time in bed) that contribute to continued sleep difficulty, and they may develop a psychologically conditioned arousal associated with the bedroom and bedtime routines that perpetuates the insomnia.

For many patients, insomnia is a nightly problem that persists from months to years, although any temporal patterns are possible: people may have recurrent insomnia episodes lasting weeks to months interspersed with relatively good sleep, or they may have intermittent sleep difficulty several nights each week or month. In some cases the sleep disturbance is seemingly random in occurrence and duration, and for others it is highly predictable in association with work or social schedules or in relation to physiologic changes, as with the menstrual cycle. Insomnia may be described as primary insomnia and conceptualized as an independent disorder when no concomitant disorders seem to contribute

to the sleep disturbance. In contrast, a patient with sleep difficulty presumably influenced by the presence of another disorder, such as major depression, fibromyalgia, substance abuse, or obstructive sleep apnea, may be viewed as having a comorbid type of insomnia. The *ICSD-2* psychophysiological, paradoxical, and idiopathic insomnias are examples of primary insomnia.

According to the *ICSD-2* nosology, patients meeting the general insomnia criteria (**Table 3-1**) can be diagnosed with one of the specific insomnia disorders (**Table 3-2**). Each of the insomnia disorders has associated criteria. *Adjustment insomnia* occurs in temporal relationship with an identifiable stressor and lasts less than 3 months. Sleep should improve with the resolution of the stressor. In some cases, adjustment insomnia may evolve into a chronic form and warrant a new insomnia diagnosis. People with *psychophysiological insomnia* experience conditioned heightened arousal associated with the bed, bedroom, and bedtime routines. Learned sleep-preventing associations perpetuate the sleep difficulty in this chronic form of insomnia. The diagnosis of *paradoxical insomnia* may be applied in situations where a clear mismatch occurs between the patient's description of severe sleep difficulty compared with objective evidence of apparently adequate sleep. *Idiopathic insomnia* refers to persistent insomnia without identifiable precipitants that begins insidiously in childhood and continues chronically into adulthood. The *inadequate sleep hygiene* diagnosis may be applied when patients engage in behaviors that would be expected to interfere with normal sleep. These detrimental behaviors may include sleep-wake schedule problems, use of sleep-disrupting substances, and evening routines or a bedroom environment that is not conducive to sleep. *Behavioral insomnia of childhood* is reserved for sleep difficulties in children and incorporates sleep-onset association and limit-setting subtypes. Examples include persistent problems when children are unable to fall asleep independently or routinely stall attempts to fall asleep. The *insomnia due to a mental disorder* and *insomnia due to a medical condition* diagnoses assume the presence of the associated condition and a clear temporal association with the sleep disturbance, and generally are used when the insomnia is severe enough to warrant independent treatment. *Insomnia due to a drug or substance* represents sleep problems clearly temporally associated with the intoxication or withdrawal from a wide range of medications or abuse substances.

KEY POINTS

- Patients with chronic insomnia frequently have comorbid conditions associated with their sleep disturbance.
- Use a comprehensive approach in evaluating chronic insomnia; the etiology is multifactorial for most patients.

EVALUATION

The best general advice for considering the causes of a patient's insomnia is to think very broadly about the etiology and expect multiple factors that may predispose the person to sleep difficulty, precipitate an insomnia episode, and perpetuate the sleep disturbance over time.[3,6] Whatever triggered the sleep difficulty is not necessarily what currently contributes to persistent symptoms. The clinical guidelines for evaluating insomnia published by the American Academy of Sleep Medicine emphasize the essential role of the patient history, focusing not just on the specific sleep-related symptoms but also on possible psychiatric, medical, and substance use disorders. Whenever possible, a bed partner or other family member should be interviewed to provide information regarding the patient's snoring, breathing irregularities, or any sleep-related movement or behavioral abnormalities. Patient-completed questionnaires and sleep logs or diaries can supplement the

KEY POINTS

- Sleep logs and questionnaires completed by patients are very helpful in the insomnia evaluation process.
- Sleep laboratory studies are not routinely performed in the insomnia evaluation, but they are invaluable for selected patients with risk factors for comorbid sleep disorders.
- It is useful to establish clear goals with patients when treating their insomnia symptoms.
- Always consider the potential influences of sleep-disordered breathing and circadian rhythm sleep disorders when evaluating insomnia symptoms.

insomnia patient evaluation. A log or diary covering several weeks can be quite helpful in highlighting patterns of sleep disturbance and are especially useful to show where school or work schedules affect the timing of sleep or where circadian rhythm sleep-phase disorders influence the timing of insomnia symptoms. The comprehensive insomnia evaluation also should include physical and mental status examinations. Sleep laboratory testing, while not a routine element in the insomnia workup, can be quite useful when there is suspicion that a concomitant sleep disorder (eg, sleep-disordered breathing) may be contributing to the insomnia symptoms.

Essential elements of the sleep history include the specific insomnia complaints, daytime activities and functioning, sleep-wake schedule routines, and other sleep-related symptoms (eg, snoring, movements, and behaviors). Questions should focus on the timing of the insomnia symptoms, estimates of sleep onset and total sleep times, and the frequency and character of awakenings. Is the difficulty primarily sleep onset or sleep maintenance, or is it a combination of the two? Further inquiries should target the evening routines and bedroom setting. Are situational or environmental variables apparent? Is the patient taking medications or using substances that may affect sleep? Patients also should be asked about previous sleep difficulty and the results of any treatment approaches.

TREATMENT

General Considerations

The treatment of chronic insomnia is often challenging. While a solution to a patient's inability to sleep soundly is sometimes a simple matter, more commonly multimodal approaches and clinical creativity are necessary. Since insomnia may result from various processes, often simultaneously, effective management may require several concurrent strategies and in some cases a staged approach that may involve further testing.[3] The diversity of influences on sleep and wakefulness makes a universal treatment algorithm impossible. The management of insomnia must be customized for individual patients. It is possible, however, to offer several general principles in the attempt to help patients achieve refreshing sleep and alertness at appropriate times throughout their sleep-wake cycles. Overall, it is important to collaborate with patients in developing clear treatment goals regarding their nighttime and daytime symptoms, monitor patients for therapeutic progress and possible adverse effects, and revise the therapeutic plan as necessary.

The chronic insomnia treatment plan should address any comorbid conditions revealed in the comprehensive evaluation that are recognized as potential factors undermining satisfactory sleep. Of course, it may not be possible to eliminate comorbid medical and psychiatric disorders, but attempts should be made to optimize their management. For example, improved treatment of a pain syndrome, seizure disorder, Parkinson disease, asthma, and major depression may allow more consolidated sleep. It is especially important to identify and address other sleep disorders that may cause insomnia symptoms (**Case 3-1**). Common sleep disorders resulting in difficulty falling asleep or remaining asleep include obstructive sleep apnea and circadian phase disturbances (advanced or delayed), although some other sleep disorders (eg, parasomnias) may present primarily with insomnia complaints. It is not unusual for patients to seek help for severe insomnia symptoms and experience a complete resolution of their sleep difficulty as a result of being diagnosed with obstructive sleep apnea

Case 3-1

A 63-year-old widow presented at the sleep clinic seeking a solution to the insomnia she experienced for at least 5 years. She described occasional difficulty falling asleep but light and frequently interrupted sleep later during the night. She never felt refreshed when she got out of bed in the morning. She estimated getting between 4 and 6 hours of sleep most nights. During the daytime she usually felt fatigued, although she did not experience inadvertent sleep episodes. She napped about once each week. Her history was notable for depression 6 years before, at the time of her husband's death. She took a selective serotonin reuptake inhibitor antidepressant at that time but stopped a few years later. She denied feeling depressed currently but admitted that she felt miserable because of her sleep difficulty. Her medical history was notable for hypertension that was well controlled with medication. She denied snoring. Her physical examination was unremarkable, except for mildly elevated blood pressure and a body mass index of 27 kg/m^2. Because of her risk factors for obstructive sleep apnea, a polysomnographic study was recommended.

The patient was seen for follow-up soon after the sleep study to review the results, which demonstrated an apnea-hypopnea index of 45 events/h associated with modest oxygen desaturations. (Apnea-hypopnea index severity: four or fewer events per hour is considered normal; five to 15, mild; 15 to 30, moderate; and more than 30, severe.) The sleep stage distribution showed excess non-REM stage N1 sleep, representing 30% of the 320 minutes that she slept. Frequent arousals and several brief awakenings occurred during the study night. When shown the sleep study results, she initially argued that the files had been mixed up because she could not possibly have sleep apnea. She said that she was familiar with sleep apnea because her obese brother slept with one of those masks and ''you're not putting one on me.'' With further education and encouragement she agreed to try nasal continuous positive airway pressure treatment. The sleep center staff spent considerable time reassuring her and helping her become familiar with the equipment. With continuous positive airway pressure treatment, her sleep was much improved.

Comment. Sleep apnea should be on the treating physician's mental radar in all patients presenting with insomnia, especially sleep maintenance difficulty, but even with patients experiencing sleep-onset difficulty. No treatment for insomnia will help until the apnea is treated.

KEY POINT

- Be sure to review the complete list of a patient's medications to identify possible sleep-disturbing effects.

and subsequently receiving continuous positive airway pressure (CPAP) or related treatments.

An initial approach to treating insomnia also must consider the potential influence of any medications patients are taking and other substances they may be using regularly. It may be possible to recommend an alternate medication or dosage timing that is less likely to interfere with sleep. Greater attention now must be given to caffeine intake because of the growing diversity and marketing of caffeinated products. Good general advice for patients with insomnia is to avoid all caffeine past lunchtime, although some may need to discontinue using it completely. Reduction or elimination of evening alcohol additionally may be necessary to improve sleep quality and duration.

Education and Healthy Sleep Habits

The treatment of chronic insomnia begins with patient education regarding

KEY POINT

- Strongly encourage healthy sleep habits for all patients. Primary treatment modalities may fail if patients have irregular bedtime hours or drink excessive caffeinated beverages.

basic processes that influence sleep and ways to maximize the functioning of the natural mechanisms regulating the sleep-wake cycle.[3] Ensuring that patients follow sleep hygiene recommendations may not represent a cure for chronic insomnia, but attention to relevant behavioral and sleep environment guidelines can help enhance sleep and provide an important foundation for other therapeutic strategies. A typical list of healthy sleep behaviors is provided in **Table 3-3**.[7] The patient history will determine the initial focus for suggested sleep hygiene changes. Generally, patients should attempt to maintain regularity in their bedtime and wake-up times, and they certainly should allocate sufficient time in bed for adequate sleep. On the other hand, excessive wakeful time in bed may reinforce frustrating arousal and perpetuate a conditioned association of the sleep environment with sleeplessness. Although routine napping may not be problematic for some individuals, avoiding afternoon or evening naps may be important for patients with insomnia. A relaxing evening routine should enhance sleep onset, in contrast to a flurry of evening activities leading up to turning off the bedroom light with the expectation of a rapid sleep onset. Although many people fall asleep while watching television, patients with insomnia may find that the stimulation of viewing television has an immediate and sustained effect that undermines sleep onset. Exciting drama and disturbing evening news may not be soporific. Moreover, viewing televisions and other screens (eg, laptops, video game devices, and smart phones) may have the biological effect of promoting a phase delay that could further undermine the ability to fall asleep at a desired time. The bedroom environment should be relatively dark and free of disturbing noises. White noise from a bedside fan or a device marketed to generate background noise may be comforting and help block out potentially arousing extraneous sounds. For most individuals, the

TABLE 3-3 Healthy Sleep Habits[a]

▶ **At Night**
Use the bed and bedroom for sleep and sex only.
Establish a regular bedtime routine and a regular sleep/wake schedule.
Do not eat or drink too much close to bedtime.
Create a sleep-promoting environment that is dark, cool, and comfortable.
Avoid disturbing noises; consider a bedside fan or white-noise machine to block out disturbing sounds.
▶ **During the Day**
Consume less or no caffeine, particularly late in the day.
Avoid alcohol and nicotine, especially close to bedtime.
Exercise, but not within 3 hours before bedtime.
Avoid naps, particularly in the late afternoon or evening.
Keep a sleep diary to identify your sleep habits and patterns that you can share with your doctor.

[a] Reprinted with permission from National Sleep Foundation.[7] *www.sleepfoundation.org/article/sleep-related-problems/insomnia-and-sleep*.

ideal bedroom temperature for sustained sleep is neutral to slightly cool. Warm rooms tend to promote more awakenings. Certainly a comfortable sleep surface may facilitate sound sleep, but an expensive new mattress rarely represents a cure for chronic insomnia.

Psychological and Behavioral Strategies

A variety of well-defined psychological and behavioral approaches have been effective in treating patients with insomnia.[8] In a therapeutic setting, these strategies typically are combined as cognitive-behavioral therapy for insomnia (CBT-I).[9] The elements of CBT-I address factors that regulate the sleep-wake cycle, psychological processes that can affect sleep, and cognitive distortions that can contribute to the predisposition and perpetuation of insomnia. CBT-I generally blends advice regarding healthy sleep habits, close attention to the scheduled time in bed, guidelines on when to attempt to sleep, and cognitive psychotherapy to reframe maladaptive beliefs and assumptions regarding sleep and insomnia (**Case 3-2**). Abundant evidence has demonstrated both the short-term and sustained benefits of CBT-I.[10] At a minimum, CBT-I involves a cognitive component and at least one behavioral element, such as sleep restriction therapy or stimulus control therapy. Additional options include relaxation therapy, biofeedback, and paradoxical intention. CBT-I may be performed in a structured format with weekly to biweekly group or individual sessions,

KEY POINT

- Psychological and behavioral strategies combined as cognitive-behavioral therapy for insomnia have been shown to be effective in numerous well-controlled studies.

Case 3-2

A 32-year-old single woman came to the sleep center for help with the insomnia that had been worsening in recent months. She said that sleep had been a problem for her since she started college. She now worked as an accountant in a large corporation and found this very stressful. She had difficulty falling asleep and then experienced repeated awakenings. Her sleep was never refreshing. She described feeling exhausted throughout the daytime but being unable to fall asleep if she tried to nap. She worried all day about whether she would be able to sleep that night, and that concern intensified as bedtime approached. Occasionally she would fall asleep on the sofa while watching television, but then would get into bed only to have a sense of her mind racing. Her primary care physician recommended a commonly prescribed hypnotic, which helped a little, but she took it only once or twice a week because she feared becoming dependent on it. She had recently started seeing a therapist to discuss the stress in her life regarding her work, family issues, and relationship with her boyfriend. Her examination was unremarkable except for 2+ tonsillar enlargement and a body mass index of 27 kg/m^2. She said no one had told her that she snored. She drank one cup of coffee in the morning and avoided caffeine sources later in the day. She rarely drank alcoholic beverages.

Comment. This patient is an excellent candidate for cognitive-behavioral therapy for insomia, which will target her thoughts about sleep and insomnia and provide specific behavioral guidelines. Her psychotherapy probably would help with her assorted life stressors, but it does not directly address her immediate sleep problems. The hypnotic may continue to be helpful on an as-needed basis. She does have mild risk factors for obstructive sleep apnea, so a future sleep study should be considered as her evaluation and treatment continue.

and it may be provided by a certified behavioral sleep medicine specialist or less formally in any treatment setting. While CBT-I has been best studied with a formalized approach over a series of sessions, studies have reported the benefits of streamlined and more flexible schedules.[11]

Sleep restriction therapy addresses the common problem of patients with insomnia spending excessive wakeful time in bed, while also generating increased homeostatic pressure for sleep in order to promote improved sleep onset and maintenance.[6] Generally, sleep restriction therapy involves limiting patients' time in bed to the amount of sleep they report achieving on an average night, although the time in bed typically would not be restricted to less than 5 hours. They maintain nightly sleep logs throughout the therapy. The morning rise time usually is planned as an individual's desired wake-up time and is kept the same throughout the therapy to allow morning light exposure to reinforce the circadian system and its influence on the sleep-wake cycle. Therefore, the bedtime is delayed and adjusted earlier or later according to the updated average sleep duration. Specific sleep restriction therapy guidelines are listed in **Table 3-4**.

The goal of *stimulus control therapy* is to help patients associate going to bed with falling asleep.[12] It is assumed that with chronic insomnia the bedroom and bedtime routines have become stimuli associated with wakefulness through a process of psychological conditioning reinforced over time as people remain in bed while awake, frustrated, and mentally aroused. With stimulus control therapy, patients are advised to go to bed and attempt sleep only when they feel sleepy and able to fall asleep. They are instructed to get out of bed and go to another room if they are unable to fall asleep within about 10 minutes. The processes of attempting sleep when sleepy should be repeated as necessary. The routine is followed with extended middle-of-the-night awakenings. The stimulus control therapy guidelines also require that patients maintain a regular morning

TABLE 3-4 Sleep Restriction Therapy Guidelines[a]

▶ **Initial Instructions**
Allow yourself to be in bed only the amount of time determined by your average nightly sleep from a 2-week sleep log. (Do not limit your time in bed to less than 5 hours.)
Delay your bedtime to restrict your time in bed.
Awaken by alarm the same time every day of the week at your typical workday wake-up time.
Do not nap.
Expect some daytime fatigue and sleepiness with shorter time in bed schedules.
▶ **Time in Bed Adjustments**
Reassess the sleep log weekly and change bedtime to adhere to guidelines according to your average sleep efficiency (sleep time divided by time in bed).
If sleep efficiency is ≥90%, bedtime is adjusted 15 to 30 minutes earlier.
If sleep efficiency is ≤85%, bedtime is adjusted 15 minutes later.

[a] Reprinted with permission from Ebben MR, Spielman AJ, J Behav Med.[6] © 2009, Springer Science and Business Media. *link.springer.com/article/10.1007%2Fs10865-008-9198-8.*

TABLE 3-5 Stimulus Control Therapy Guidelines[a]

1. Lie down intending to sleep only when you are sleepy.
2. Do not use your bed for anything except sleep. Do not read, watch television, eat, or worry in bed. Sexual activity is the only exception to this rule. On such occasions, the instructions are to be followed afterward when you intend to go to sleep.
3. If you find yourself unable to fall asleep, get up and go to another room. Stay up as long as you wish and then return to the bedroom to sleep. Do not watch the clock, but get out of bed if you do not fall asleep immediately. The goal is to associate your bed with falling asleep quickly. If you are in bed for more than 10 minutes without falling asleep and have not gotten up, you are not following this instruction.
4. If you still cannot fall asleep, repeat rule 3. Do this as often as is necessary throughout the night.
5. Set your alarm and get up at the same time every morning irrespective of how much sleep you got during the night. This will help your body acquire a consistent sleep rhythm.
6. Do not nap during the day.

[a] Data from Bootzin RR, Perlis ML, J Clin Psychiatry.[12]

wake-up time and avoid daytime napping. Finally, the bed should be used for no activities other than sleep and sexual relations. Stimulus control therapy guidelines are shown in **Table 3-5**.

With *paradoxical intention*, patients are advised to go to bed at their normal bedtimes but attempt to remain awake instead of expecting to fall asleep. The underlying idea is that patients may be able to reduce the worry and anxiety they experience when trying to fall asleep. *Relaxation therapy* also may help reduce the tension and anxiety patients with insomnia feel while awake in bed. Relaxation techniques may include progressive relaxation, abdominal breathing, guided imagery, and types of yoga and meditation. Practicing these approaches to relaxation at times when patients are not attempting to sleep should make them more valuable when patients eventually employ them to aid with sleep onset. Similarly, biofeedback strategies may help people develop relaxation skills that can facilitate sleep.

Pharmacologic Approaches

People with insomnia often try many different remedies, some prescribed and evidence-based and some that are neither. Similarly, prescribers treating patients with insomnia utilize a wide range of medications, some indicated for treating sleep disorders and others because they just might work and not be too risky. It is useful to categorize these assorted substances into four broad groups based in part on regulatory issues, but also to a limited extent on pharmacodynamics: (1) medications approved by the US Food and Drug Administration (FDA) for the treatment of insomnia; (2) prescription medications, generally sedating agents, not formally indicated for the treatment of insomnia; (3) over-the-counter products marketed as sleep aids, which by definition are regulated by the FDA but do not require a prescription; (4) the huge collection of unregulated compounds that are commercially available or perhaps grown or collected from natural sources. One other pharmacologic

TABLE 3-6 US Food and Drug Administration–Approved Insomnia Medications

Medication[a,b]	Doses (mg)[c]	Half-Life (hours)	US Food and Drug Administration–Approved Indications	Most Common Side Effects
Benzodiazepine Immediate Release[b]				
Flurazepam	15, 30	48–120	Treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakening	Dizziness, drowsiness, lightheadedness, staggering, loss of coordination, falling
Temazepam	7.5, 15, 22.5, 30	8–20	Short-term treatment of insomnia	Drowsiness, dizziness, lightheadedness, difficulty with coordination
Triazolam	0.125, 0.25	2–4	Short-term treatment of insomnia	Drowsiness, headache, dizziness, lightheadedness, ''pins and needles'' feelings on skin, difficulty with coordination
Quazepam	7.5, 15	48–120	Treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings	Drowsiness, headache
Estazolam	1, 2	8–24	Short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings; administered at bedtime improved sleep induction and sleep maintenance	Somnolence, hypokinesia, dizziness, abnormal coordination
Nonbenzodiazepine Immediate Release				
Zolpidem	5, 10	1.5–2.4	Short-term treatment of insomnia characterized by difficulties with sleep initiation	Drowsiness, dizziness, diarrhea, drugged feelings
Zaleplon[c]	5, 10	1	Short-term treatment of insomnia….shown to decrease the time to sleep onset	Drowsiness, lightheadedness, dizziness, ''pins and needles'' feeling on skin, difficulty with coordination
Eszopiclone	1, 2, 3	5–7	Treatment of insomnia…. administered at bedtime decreased sleep latency and improved sleep maintenance	Unpleasant gustatory and metallic taste in mouth, dry mouth, drowsiness, dizziness, headache, symptoms of the common cold
Nonbenzodiazepine Extended Release (ER)				
Zolpidem ER	6.25, 12.5	2.8–2.9	Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset)	Headache, sleepiness, dizziness

Continued on next page

TABLE 3-6 *Continued*

Medication[a,b]	Doses (mg)[c]	Half-Life (hours)	US Food and Drug Administration–Approved Indications	Most Common Side Effects
Nonbenzodiazepine Alternate Delivery				
Zolpidem oral spray	5, 10	~2.5	Short-term treatment of insomnia characterized by difficulties with sleep initiation	Drowsiness, dizziness, diarrhea, drugged feelings
Zolpidem sublingual	5, 10	~2.5	Short-term treatment of insomnia characterized by difficulties with sleep initiation	Drowsiness, dizziness, diarrhea, drugged feelings
Zolpidem sublingual	1.75, 3.5	~2.5	As needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep[d]	Headache, nausea, fatigue
Selective Melatonin Receptor Agonist				
Ramelteon	8	1.0–2.6	Treatment of insomnia characterized by difficulty with sleep onset	Drowsiness, tiredness, dizziness
Selective Histamine H_1 Receptor Antagonist				
Doxepin	3, 6	15.3	Treatment of insomnia characterized by difficulties with sleep maintenance	Somnolence/sedation, nausea, upper respiratory tract infection

[a] All medications listed have a Drug Enforcement Administration (DEA) class of IV with the exceptions of ramelteon and doxepin, which have no DEA class.
[b] All medications have a pregnancy category of C with the exception of those listed under the heading of ''Benzodiazepine Immediate Release,'' which are categorized as X.
[c] Initial dose depends on the patient's age and comorbid conditions. Maximum doses are the highest pill strength with the exception of zaleplon, which may be prescribed for 20 mg at bedtime.
[d] Patient must have 4 hours of sleep remaining before using this medication.

approach to the sleep problem that is highly regulated, rarely recommended, but commonly consumed is alcohol. The sedating effect of alcohol may facilitate sleep onset, but the subsequent sleep is more likely to be disrupted, with a negative net effect.

FDA-approved insomnia medications. The medications specifically approved by the FDA for the treatment of insomnia comprise three major pharmacodynamic actions: (1) γ-aminobutyric acid (GABA) response modulator, (2) melatonin receptor agonist, and (3) histamine receptor antagonist. All have been evaluated for efficacy and safety at specific recommended doses in populations of insomnia subjects.[13] The indications all specify use for insomnia, and in some cases further suggest use for sleep onset, sleep maintenance, or returning to sleep following an awakening. **Table 3-6** shows the generic names, available doses, approximate elimination half-life, indication, Drug Enforcement Administration (DEA) schedule, and pregnancy category for each of these medications.

The *benzodiazepine receptor agonists* (BZRAs) include the two broad categories of benzodiazepine and nonbenzodiazepine BZRA hypnotics, all of which are allosteric modulators of GABA responses at the $GABA_A$ receptor complex. The $GABA_A$ receptor complex is a pentameric transmembrane structure with a central chloride ion

KEY POINT

- Insomnia medications approved by the US Food and Drug Administration include γ-aminobutyric acid response modulators, a melatonin receptor agonist, and a histamine H_1 receptor antagonist.

KEY POINTS

- Benzodiazepine receptor agonist hypnotics all are allosteric modulators of γ-aminobutyric acid responses at the $GABA_A$ receptor complex.
- In addition to immediate-release and extended-release pill and tablet formulations, benzodiazepine receptor agonist hypnotics are available in oral spray and sublingual dissolvable formulations.

channel surrounded by five subunits, most typically two alpha, two beta, and one gamma. A GABA attachment site between alpha and beta subunits allows the net inhibitory GABA agonist action of an inward flow of chloride ions that increases the polarity across the membrane and decreases the likelihood of an action potential. The allosteric benzodiazepine receptor site on the alpha-gamma subunit interface permits BZRA compounds to attach in a manner that positively modulates the GABA action by allowing an enhanced inward chloride ion flow and thereby a greater inhibitory effect.[14] The very broad distribution of $GABA_A$ receptors suggests that the BZRA hypnotic action may be a widespread brain effect; however, there likely also is a targeted effect at key sleep-wake cycle regulatory nuclei within the hypothalamus (eg, ventrolateral preoptic nuclei).[15]

The BZRA hypnotics, benzodiazepines and nonbenzodiazepines, share the same fundamental pharmacodynamic action, although it has been argued that the latter category may be differentiated based on varying selectivity for different $GABA_A$ alpha subunit subtypes. In general, benzodiazepines appear to be less discriminative among alpha subtypes compared with the nonbenzodiazepine BZRA hypnotics, while certain nonbenzodiazepines have increased selectivity for alpha-1 or alpha-3 subtypes. The clinical implications of these pharmacologic properties remain an area of research interest. In contrast, the BZRA hypnotic compounds vary considerably in their pharmacokinetic profiles, especially in the elimination half-lives ranging from about 1 hour to a few days. With the exception of triazolam, the benzodiazepines are moderate to long acting, while the nonbenzodiazepines range from very short to intermediate durations of action. All are relatively rapidly absorbed and thus may aid sleep onset. The degree to which the medications continue to exert a sedating effect that is desired (continued sleep) or undesired (morning grogginess) depends on the elimination half-life, as well as the initial dose.

BZRA hypnotics typically are well tolerated. The list of potential rare adverse effects is long; however, those reported most commonly in clinical trials include drowsiness, dizziness, headache, and lightheadedness.[13] Ataxia and anterograde amnesia may occur within a few hours after taking the medication. Patients may experience rebound insomnia on abrupt discontinuation following nightly use for several weeks or longer. These medications are associated with a low abuse potential and therefore are designated by the DEA as schedule IV medications. Benzodiazepine hypnotics are Pregnancy Category X, and nonbenzodiazepines are Pregnancy Category C.

Benzodiazepine and nonbenzodiazepine BZRA hypnotics are available in immediate-release formulations. Zolpidem is the one compound now produced in an extended-release tablet as well as in an oral spray and sublingual dissolvable alternate delivery formulations. All BZRA hypnotic formulations are intended for bedtime use with the exception of the lower-dose dissolvable formulation indicated for returning to sleep following nighttime awakenings. The formal indications for the BZRA hypnotics note that they are intended for short-term treatment, although no limitation on the duration of use is implied for eszopiclone and zolpidem extended-release.

A single *melatonin receptor agonist* is approved by the FDA for treating insomnia. Ramelteon is a selective agonist of the melatonin type $(MT)_1$ and MT_2 receptors, which are present in high concentrations in the hypothalamic suprachiasmatic nuclei (SCN).[16] Melatonin is

produced by the pineal gland in a process regulated by the SCN circadian system. Normally melatonin levels are low throughout daytime, gradually rise in the evening as nighttime approaches, peak during the typical nighttime sleep hours, and decline by the end of the night. The evening melatonin rise and MT_1 agonist action decrease the SCN-driven wake-promoting stimulation that is present during the latter hours of the wake period and thereby facilitate bedtime sleep onset. The MT_2 effect relates to reinforcement of the circadian timing and helps maintain the regular daily rhythm.

The ramelteon indication is for the treatment of insomnia characterized by difficulty with sleep onset. While it may benefit sleep maintenance early during the night, it is not likely to be helpful for early morning awakenings. Ramelteon is produced in a single 8-mg dose that the prescribing instructions recommend for all patient groups, although it should not be prescribed for patients with severe liver disease or people concomitantly taking fluvoxamine, a potent cytochrome P450 enzyme 1A2 isozyme inhibitor. The prescribing guidelines suggest that ramelteon be taken about 30 minutes before bedtime. Drowsiness, tiredness, and dizziness are the most common side effects. Studies with ramelteon have demonstrated safety in patients with mild hepatic disease, moderate to severe chronic obstructive pulmonary disease, and mild to moderate obstructive sleep apnea. Ramelteon has no abuse potential and is considered a nonscheduled medication. It is classed as Pregnancy Category C.

The single selective *histamine receptor antagonist* approved by the FDA for insomnia treatment is low-dose doxepin. This tricyclic was approved for depression over 40 years ago, but clinical experience and eventually clinical trials demonstrated that very low doses were safe and effective in treating insomnia. The specific indication is for the treatment of insomnia characterized by difficulty with sleep maintenance. Among the tricyclic antidepressants, doxepin is unusual for its very high selectivity for H_1 histamine receptor antagonist activity. Accordingly, the key pharmacodynamic action is antihistamine-promoted sedation. The available doses are as high as 150 mg, and the depression prescribing guidelines are as high as 300 mg daily; however, the low-dose formulations approved for insomnia are just 3 mg and 6 mg. In clinical trials, commonly reported adverse events were somnolence/sedation, nausea, and upper respiratory tract infection. Doxepin should not be prescribed for patients with untreated narrow-angle glaucoma or severe urinary retention, or for people also taking monoamine oxidase inhibitors. With no abuse potential, doxepin is considered a nonscheduled medication. It is classified as Pregnancy Category C.

While each of the FDA-approved insomnia medications may have unique side-effect profiles and warnings, the FDA has required certain warnings for all of the insomnia medications. One warning relates to rare severe anaphylactic and anaphylactoid reactions. The other broad warning targets possible abnormal thinking and behavior following hypnotic doses, and it notes the potential for complex behaviors associated with amnesia. Examples include driving, preparing and eating foods, talking on the telephone, and engaging in sexual behaviors when not fully awake. Patients are advised to discontinue the medication if these symptoms occur. Other general warnings relate to ensuring that patients have sufficient time in bed following a medication dose, and the potential for next-day drowsiness or impairment.

Off-label prescription insomnia pharmacotherapy. Many antidepressant,

KEY POINT

- Low-dose doxepin is approved for the treatment of insomnia characterized by difficulty with sleep maintenance.

KEY POINT

- Beware of the anticholinergic effects associated with over-the-counter antihistamines people often use as sleep aids.

antipsychotic, antiepileptic, and other sedating psychotropic medications at times are prescribed specifically to treat insomnia symptoms. While this approach occasionally may be effective, very little evidence is available to guide health care providers regarding the safety and efficacy of these medications for populations of patients with insomnia. The practice is less problematic when patients have comorbid conditions for which the medications are indicated and where the choice of a more sedating option is beneficial for the individual. However, these medications are also often prescribed (sometimes as a first-line treatment) for people with chronic insomnia and no relevant comorbidities. The risk-benefit ratio of these medications for insomnia may be very different than that associated with the indicated condition. Among the antidepressants, trazodone, amitriptyline, mirtazapine, and doxepin often have been prescribed in this manner; historically, doxepin has been prescribed for insomnia at a higher dose than the new low-dose, FDA-approved formulation. Quetiapine is the antipsychotic most commonly utilized for insomnia. Some antiepileptic examples include gabapentin, pregabalin, and tiagabine.

Over-the-counter sleep aids. All over-the-counter sleep aids are antihistamines. While most of these products contain diphenhydramine as the active ingredient, some contain doxylamine. The over-the-counter sleep aids are marketed as single compounds or combined with analgesics as "PM" formulations. The antihistamine sedating effect is the desired pharmacodynamic action, although these drugs can interact with other receptors and lead to common and sometimes serious side effects. Most problematic is the anticholinergic action that may contribute to dry mouth, constipation, urinary retention, confusion, and delirium. Therefore, these medications should be used with greater caution in older adults and in people taking other medications incorporating anticholinergic effects. The elimination half-lives are relatively long and may lead to morning grogginess following bedtime use. Patients may become tolerant to the sedating effect with continued use.[17] This leads some people to escalate their nightly dose to several hundred milligrams.

Unregulated compounds. This final category is defined not so much by what it is, but rather by what it is not. These are nonprescription and non–over-the-counter products that typically are marketed as dietary supplement sleep aids, although people sometimes use fresh herbs and other plant products. Generally this pharmacologic approach falls within the realm of complementary and alternative medicine. Hundreds of unregulated sleep aid products are available. They may be promoted as single compounds or as combinations of ingredients, while some of the plant-derived products contain innumerable different molecules. Common ingredients include valerian, hops, chamomile, passionflower, and kava kava. Convincing evidence is minimal regarding efficacy, but fortunately these compounds typically are regarded as safe. The one major safety exception is kava kava, for which the FDA has issued a warning regarding possible hepatic toxicity.[18] Oddly, melatonin also falls into this unregulated group and is one of the most common ingredients. Abundant evidence supports the use of melatonin, particularly with circadian rhythm sleep disorders (**Case 3-3**).[19]

The insomnia pipeline. The development of new pharmacologic approaches to treating insomnia has been actively investigated for decades. The most recent FDA approvals for insomnia have been for new formulations and refinements of previously approved

compounds. Several novel pharmacodynamic directions have been explored in recent years, although most have been abandoned because of safety problems or insufficient efficacy. One unique strategy that continues to be investigated is the use of orexin receptor antagonists.[20] Alternate GABA modulators and melatonin receptor agonists also are being studied as possible insomnia treatments.

Developing an Insomnia Treatment Plan

A comprehensive insomnia evaluation should provide the basis for developing a customized plan for therapy considering the patient's chief complaint, sleep-wake cycle symptoms, lifestyle pattern, habits and routines, and comorbid conditions.[3] As noted above, it is especially useful to elaborate specific treatment goals with the patient and to monitor symptoms and the results of therapeutic strategies over time. Education regarding sleep and individualized recommendations about sleep-enhancing behaviors should be the foundation of treatment for all patients. Cognitive and behavioral strategies always should be incorporated into the treatment plan, and in some cases that will involve referral to a CBT-I specialist. Pharmacotherapy is an additional option. Fortunately, numerous FDA-approved medications with various pharmacodynamic and pharmacokinetic properties are

KEY POINTS

- Melatonin, which is unregulated in the United States, may be beneficial in the treatment of certain circadian rhythm sleep disorders, especially in people with a phase-delay pattern.
- Currently the most promising novel pipeline compounds are orexin receptor antagonists.

Case 3-3

A 20-year-old man presented for evaluation at the insistence of the dean of students at his college because he had missed many classes, performed poorly on examinations, and been placed on academic probation. He was a sophomore majoring in business administration and was threatened with not being able to return for his junior year. During the evaluation, he stated that he was very motivated to do well in college and complete his degree but had tremendous difficulty getting up for any morning classes. He slept through multiple loud alarms or turned them off and immediately returned to deep sleep. Usually he did not fall asleep until some point between 2:00 AM and 4:00 AM. When in high school, he would stay up late and then sleep late the next day on weekends and vacations, but the problem became much more severe during his freshman year of college. That next summer he had worked at a restaurant most nights until midnight and did not go to bed until about 5:00 AM. He would then sleep until the next afternoon. His sleep problems during his sophomore year had been significantly worse. He became very frustrated about his inability to get to sleep earlier and wake up for required classes. He had briefly tried taking a prescribed hypnotic at about midnight, but it seemed to have no effect.

Comment. Difficulty falling asleep or staying asleep is often a symptom of a circadian rhythm phase disorder that is not necessarily apparent to patients or their health care providers. Phase-delayed patients have great difficulty falling asleep at a desired earlier bedtime, and phase-advanced patients report habitually waking up too early. These disorders should be apparent when the evaluation considers the sleep propensity throughout the 24-hour cycle and the person's longstanding sleep patterns. That this man did not benefit from the hypnotic taken hours before his typical sleep-onset time is not surprising since he was within the temporal zone of maximum circadian arousal usually experienced by people earlier in the evening. Strategically timed evening melatonin and morning bright-light exposure may be helpful for phase-delayed patients such as this one.

available, allowing choices to best manage patients' symptoms considering their patterns of sleep disturbance, life circumstances, and related health issues. Attention to circadian factors will be important for some patients, and strategic exposure to light or darkness may be valuable therapeutically. Many possible insomnia treatment approaches can be explored over time with patients who do not initially respond to therapy.

CONCLUSIONS

Insomnia is a widespread health concern that may result from multiple diverse processes. A comprehensive insomnia evaluation may reveal factors that undermine the experience of satisfying sleep and daytime alertness, although in some cases specific causes may not be readily discernible. Most often the evaluation will lead to a rational treatment plan that incorporates evidence-based therapies, such as CBT-I and pharmacotherapeutic approaches. Sleep difficulties can contribute to other health problems and to a worsening quality of life for patients. All patients should be screened for sleep disorders, and appropriate treatments should be pursued. Satisfying sleep should be viewed as an essential component of wellness.

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