

Address correspondence to Dr Alon Y. Avidan, University of California Los Angeles, David Geffen School of Medicine, Reed Neurological Research Center, 710 Westwood Blvd, C153, Los Angeles, CA 90095-1769, avidan@mednet.ucla.edu.

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Unlabeled Use of Products/Investigational Use Disclosure:

Drs Avidan and Neubauer discuss the off-label uses of various central nervous system-acting medications for insomnia, which include sedating antidepressants such as amitriptyline, doxepin, mirtazapine, and trazodone; the antipsychotic quetiapine; antihistamine compounds such as doxylamine; medications available over-the-counter marketed as sleep aids as single compounds or as a combination therapy with analgesics (acetaminophen or ibuprofen); and dietary supplement sleep aids such as chamomile, hops, kava kava, melatonin, passionflower, tart cherry juice, and valerian.

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Chronic Insomnia Disorder

Alon Y. Avidan, MD, MPH, FAAN; David N. Neubauer, MD

ABSTRACT

Purpose of Review: Neurologists, along with all health care providers, commonly encounter patients with insomnia, which is a condition that impacts patients' underlying neurologic conditions in a bidirectional manner. While chronic insomnia is one of the most common sleep disturbances, only a small proportion of individuals with this condition discuss their sleep problems with their providers. When insomnia is described, it is more often in relationship to another medical problem, as opposed to an independent condition. In neurology practice, multiple factors including pain, movement disorders, sleep apnea, and medications that act on the central nervous system often contribute to insomnia. An all-inclusive approach is necessary when evaluating sleep problems in patients with insomnia.

Recent Findings: The US Food and Drug Administration (FDA) has approved several medications for the treatment of insomnia that target specific receptor systems in the brain and incorporate several unique pharmacodynamic and pharmacokinetic profiles that can represent customized therapy for specific insomnia phenotypes. FDA-approved medications for insomnia include γ -aminobutyric acid (GABA)-modulating benzodiazepine receptor agonists, a melatonin receptor agonist, a histamine receptor antagonist, and the newest approved option, a hypocretin (orexin) receptor antagonist.

Summary: This article provides an evidence-based multidisciplinary approach to the treatment of insomnia, highlighting the rationale and utility of cognitive-behavioral therapy and pharmacologic interventions. Neurologists should be proactive in assessing the impact of underlying comorbidities on insomnia, particularly in the setting of psychiatric conditions such as depression, sleep disorders such as circadian rhythm disorders, and medical problems such as nocturia.

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INTRODUCTION

Insomnia is pervasive in neurology practice, but is often undiagnosed and untreated. Specific patient cohorts such as older adults, patients who live in nursing homes, and individuals with underlying chronic comorbid medical, neurologic, and psychiatric disorders are particularly at risk. These patients often present with difficulties falling asleep and maintaining sleep and experience significant daytime consequences such as fatigue, memory problems, and poor psychosocial function.

Chronic insomnia disorder is among the most widely reported clinical con-

ditions in medicine and has a significant impact on populations treated in neurology practices.^{1,2} Sleep difficulties often result from multiple etiologies and may require a multidisciplinary treatment approach based on established evaluation guidelines and evidence-based therapies.³ Recent evidence demonstrates that poor sleep is associated with a wide range of negative health outcomes and that poorer quality of life and medical, neurologic, and psychiatric comorbidities disrupt sleep. Given this bidirectionality, neurologists should take measures to discuss sleep problems and their impact on the

underlying neurologic disease and take specific steps toward enhancing sleep quantity and quality in their patients. By doing so, the clinician may have a broader role in promoting wellness and bringing about improvements in some comorbid conditions as well.

DEFINITION OF INSOMNIA

Insomnia disorder refers to persistent difficulties falling asleep, maintaining sleep, or waking up earlier than habitual rise time and is associated with impairment of daytime functioning despite the opportunity for sufficient sleep duration.⁴ Although patients with insomnia report the chronicity of wakefulness during the night, insomnia disorder is conceptualized to represent a 24-hour condition reflecting a state of hyperarousal leading to both the nighttime and daytime symptomatology.⁵

Several classification systems offer criteria for insomnia nosologies and specific insomnia phenotypes. Insomnia classification schemes are outlined by the *International Classification of Diseases, Tenth Revision (ICD-10)* and the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, which is the American Psychiatric Association's 2013 update to its classification and diagnostic tool.^{6,7} Both the *ICD-10* and *DSM-5* assimilate categorizations of key sleep disorders including various insomnia subtypes. The 2014 American Academy of Sleep Medicine (AASM) *International Classification of Sleep Disorders, Third Edition (ICSD-3)* defines general criteria for chronic insomnia disorder, reviewed in **Table 8-1**, as well as short-term insomnia disorder.⁴ The chronic and short-term insomnia disorder criteria

KEY POINTS

- Recent evidence demonstrates that poor sleep is associated with a wide range of negative health outcomes and that poorer quality of life and medical, neurologic, and psychiatric comorbidities disrupt sleep.
- Insomnia disorder refers to persistent difficulties falling asleep, maintaining sleep, or waking up earlier than habitual rise time and is associated with impairment of daytime functioning despite the opportunity for sufficient sleep duration.

TABLE 8-1 Diagnostic Criteria for Chronic Insomnia Disorder^a

Criteria A through F are required for a diagnosis of chronic insomnia disorder

- A. The patient/family members/caregiver reports or observes one or more of the following
 1. Difficulties with sleep initiation
 2. Difficulties with sleep maintenance
 3. Waking up earlier than desired with difficulties reinitiating sleep
 4. Opposition to going to bed during habitual bedtime schedule
 5. Difficulties sleeping without the intervention of the parent or caregiver
- B. The patient/patient's parent/caregiver report or observe one or more of the following difficulties in relationship to the nighttime sleep difficulty
 1. Malaise/fatigue
 2. Impairment in concentration, attention, or memory
 3. Impairment in domains of social function, fulfillment of family duties, or difficulties with occupational or academic performance
 4. Disturbances in mood and/or irritability
 5. Excessive daytime somnolence
 6. Problems with behavioral function (eg, aggression, hyperactivity, impulsivity)
 7. Impairment in motivation/energy/initiative
 8. Proneness for accidents and/or errors
 9. Concerns about or dissatisfaction with sleep quality

Continued on page 1066

TABLE 8-1 Diagnostic Criteria for Chronic Insomnia Disorder^a*Continued from page 1065*

- C. The reported sleep/wake difficulties cannot be otherwise explained by inadequate opportunity or inadequate circumstances for sleep (ie, the patients should have sufficient allotted time for sleep and environmental conditions are conducive for sleep [safe, dark, quiet, and comfortable]).
- D. Frequency criteria: The sleep difficulties and associated daytime symptoms must occur at a frequency of at least 3 times per week.
- E. Duration criteria: The sleep disturbance and the associated daytime symptoms must be present at least 3 months.
- F. The sleep/wake disturbance is not attributed to or explained by another underlying primary sleep disorder (such as obstructive sleep apnea, circadian rhythm sleep-wake disorder, or a motor disorder of sleep).

Notes

1. Insomnia may be observed across all age groups. Opposition to going to bed on a proper schedule and difficulty sleeping without a parent or in the absence of a caregiver intervention is seen most commonly in children and older adults who require the supervision of a caretaker due to a significant disturbance in cognitive or functional impairment (eg, patients with underlying neurodegenerative diseases such as Alzheimer dementia).
2. A unique circumstance occurs when patients suffer from insomnia and experience recurrent episodes of sleep/wake difficulties lasting several weeks at a time interval persisting for several years, but may not meet the specific duration criteria (listed in E) for any single such episode. These patients should be assigned a diagnosis of chronic insomnia disorder, given the persistence of their intermittent sleep difficulties over time.
3. Patients with chronic insomnia treated with hypnotic medications may improve and thus not meet the criteria for an insomnia disorder while using these agents. In the absence of hypnotics, however, this patient population may meet the diagnostic criteria for insomnia disorder, especially if they express concerns about their dissatisfaction with sleep continuity in the absence of hypnotics.
4. Neurologic, medical, psychiatric, and primary sleep comorbidities such as chronic pain disorders, Parkinson disease, and restless legs syndrome may induce sleep/wake complaints suggestive of insomnia. A distinct diagnosis of insomnia may not apply when these disturbances are suspected to be underlying inducers of the sleep difficulty. In many patients, however, these conditions are chronic and may not be exclusive causes of sleep difficulty. A decision to adjudicate a unique insomnia diagnosis considers: "How much of the time does the sleep difficulty arise specifically as a result of factors directly attributable to the medical/psychiatric/neurologic/sleep comorbidity?" or "Are there specific conditions or settings during which the sleep/wake complaints occur in the absence of these factors?" "Have perpetuating behavioral or cognitive issues (eg, negative expectations, conditioned arousal, and sleep-disruptive habits) arisen, indicative of an autonomous aspect occurring in parallel, but independent of the underlying insomnia?" A distinct diagnosis of chronic insomnia disorder may be established if there is sufficient ground to suspect that the patient's sleep/wake complaints are not distinctly induced by the medical comorbidity. If this is indeed the case, then those sleep/wake complaints could merit the separate need to evaluate the potential for therapeutic interventions.

^a Modified with permission from the American Academy of Sleep Medicine.⁴
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are similar, with key difference being the duration (fewer than 3 months for short-term insomnia disorder and 3 months or more for chronic insomnia disorder).

The *ICSD-3* insomnia classification requires components of both nighttime and daytime elements.⁴ The nighttime sleep symptoms consist of (1) difficulty falling asleep, (2) difficulty maintaining sleep, or (3) early morning awakening despite sufficient sleep opportunity. Subjective problems reported by patients may include a pattern of delayed sleep onset, many brief or protracted awakenings, and a sensation that sleep is fragmented and very light. The most likely motivation prompting patients with insomnia to seek medical attention is related to concerns about daytime consequences. The spectrum of these daytime symptoms varies and may include poor concentration, attention, cognition, and motivation; fatigue; depressed mood; irritability; decreased energy; and a predilection to make errors.

While patients with chronic insomnia tend to worry about their inability to sleep well and the negative impact this has on their lives, they often do not describe excessive daytime sleepiness. In fact, the opposite often is observed; they report abnormal wakefulness during the day and night, which could be the manifestation of their underlying hyperarousal process. A common daytime complaint is feeling “tired and wired.”

EPIDEMIOLOGY

The prevalence of insomnia varies significantly depending on age, gender, comorbidities, and the specific population cohorts being examined.¹ However, women and older adults tend to express a higher risk for insomnia. In the general population, about one-third of adults report inter-

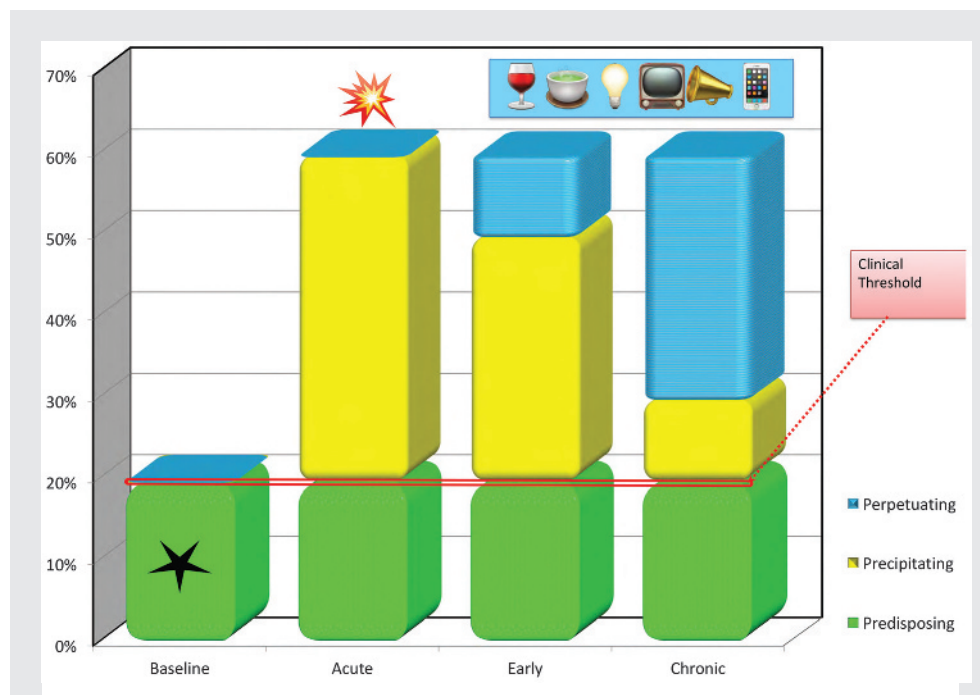
mittent symptoms of insomnia, while about 10% meet the criteria for chronic insomnia disorder associated with daytime sequelae. It is common for brief insomnia episodes to have identifiable precipitants, such as situational crises, a new medication (eg, steroids for multiple sclerosis exacerbation), acute schedule changes (eg, neurology resident on call), or an acute neurologic problem (eg, new stroke requiring intensive care admission).

EVOLUTION OF ACUTE TO CHRONIC INSOMNIA

Several models provide a rationale for the transformation from acute to chronic insomnia. The 3P model describes how chronic insomnia develops as a consequence of underlying *predisposing* features, *precipitating* factors, and *perpetuating* processes. Together these three components elevate a person's insomnia risk above a clinical threshold, as demonstrated in **Figure 8-1**.⁸ The figure provides a representation of Spielman and colleagues⁸ 3P model of chronic insomnia etiology. Everyone has a predetermined risk or a baseline degree of vulnerability for insomnia due to genetics or personality phenotypes. People who do not express sleep disturbance at their baseline would be below the level of clinically significant insomnia (**Figure 8-1**). Acute stressors may raise patients beyond the theoretical clinical insomnia threshold to a point where they develop insomnia symptoms. Over time, perpetuating factors (eg, chronic habitual behaviors such as lying awake in bed, caffeine, alcohol, daytime napping, or nighttime light from television, phone, or other electronic devices) ultimately promote persistent and pervasive insomnia symptoms, which are responsible for propagation of the sleep disturbance. Cognitive-behavioral therapy for insomnia

KEY POINTS

- The insomnia classification by the *International Classification of Sleep Disorders, Third Edition* requires components of both nighttime and daytime elements.
- While patients with chronic insomnia tend to worry about their inability to sleep well and the negative impact this has on their lives, they often do not describe excessive daytime sleepiness.
- In the general population, about one-third of adults report intermittent symptoms of insomnia, while about 10% meet the criteria for chronic insomnia associated with daytime sequelae.
- The 3P model shows how chronic insomnia develops as a consequence of the underlying predisposing features, precipitating factors, and perpetuating processes.

**FIGURE 8-1**

3P model of insomnia etiology.⁸ The 3P (*predisposing*, *precipitating*, and *perpetuating*) model of insomnia etiology explains that all people express a certain vulnerability for insomnia (*predisposing* factors). Insomnia disorder occurs when a *precipitating* event pushes patients above the insomnia threshold. When the precipitating factor diminishes, the insomnia is kept above the threshold when patients develop behaviorally conditioned arousal responses associated with the bedroom environment and maladaptive behaviors that perpetuate the insomnia. These *perpetuating* factors are shown in the figure as use of alcohol too close to bedtime, caffeine too late during the day, and excessive light and use of television and light-emitting electronic devices. People who do not express sleep disturbance at their baseline would be below the level of clinically significant insomnia (as demarcated by the *black star* within the baseline period).

Modified with permission from Spielman AJ, Glovinsky P, Plenum Press.⁸ © 1991 Springer Science and Business Media.

(CBT-I) and pharmacotherapy addresses this third and final *P* as patients move across a continuum from acute to chronic insomnia.

CHRONIC INSOMNIA

For many neurology patients, insomnia is very likely to become a chronic nightly problem that persists for a few weeks, months, and even years, although various temporal patterns are possible. Patients may present with intermittent episodes of insomnia lasting weeks to months interspersed with relatively normal sleep, or they may have recurrent and intermittent sleep problems lasting from several

nights each week or each month. Insomnia may be described as primary insomnia and conceptualized as an independent disorder when no concomitant conditions that seem to be contributing to the sleep disturbance are present. 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. Circadian rhythm disorders can also present with chronic insomnia. Older age is associated with alteration in circadian rhythmicity of sleep with predisposition

for phase advancement of sleep timing, referred to as advanced sleep-wake phase disorder.^{9,10} Patients with Alzheimer disease frequently develop irregular sleep rhythms with difficulty staying asleep for consolidated periods of time, long awakenings at night, and daytime sleepiness requiring frequent naps.

The *ICSD-3* does not differentiate primary from comorbid insomnia given that no apparent biological factors discriminate between possible insomnia subtypes, although previous *ICSD* versions incorporated conceptually useful descriptive subtypes with psychophysiologic, paradoxical, and idiopathic insomnias as examples of primary insomnia.⁴ According to the *ICSD-3* nosology, patients meeting a general insomnia criteria then could be diagnosed with a specific insomnia disorder, including the following subtypes.⁴

Psychophysiologic Insomnia

The underlying mechanism of psychophysiologic insomnia is a behaviorally based phenotype reflecting a conditioned heightened arousal associated with the bed, the environment within the bedroom (ie, clock), and maladaptive bedtime routines. Excessive focus on and worry about sleep, and elevated levels of cognitive and somatic arousal, particularly at bedtime, are common. Learned sleep-preventing associations perpetuate the sleep difficulty and promote this chronic form of insomnia (**Case 8-1**).

Adjustment Insomnia

Adjustment insomnia occurs in temporal association with an identifiable stressor usually spanning a duration of fewer 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. The *ICSD-3*

categorizes this as short-term insomnia as long as the symptoms are present for fewer than 3 months.⁴

Paradoxical Insomnia

Paradoxical insomnia was previously referred to as sleep state misperception and reflects a complaint of severe sleep disturbance in the absence of corroborative and objectively verifiable indicators of the degree of sleep disturbance claimed by the patient. For example, a major mismatch may occur between a patient's misperception of complete sleeplessness during a night of in-laboratory polysomnography that objectively records a total sleep time of 6 hours.

Idiopathic Insomnia

This subtype reflects persistent insomnia unrelated to an identifiable precipitant that begins insidiously in childhood and continues chronically in an unremitting pattern into adulthood. While no consistent genetic biomarkers or neural pathology have been described in these patients, idiopathic insomnia is thought to arise from either genetically based or congenital alterations in the sleep-inducing or wake-promoting systems in the brain.

Inadequate Sleep Hygiene

Patients with this insomnia subtype engage in maladaptive behaviors that interfere with normal sleep promotion or continuity. These detrimental behaviors may include aberrant sleep-wake schedule problems, consumption or use of substances likely to disrupt sleep (eg, caffeine, tobacco, or alcohol), and engaging in evening routines that are not conducive to sleep. Other practices that promote this insomnia subtype include prolonged daytime napping that is too close to bedtime, regularly using the bedroom for activities other than sleep, participating in stimulating or emotionally upsetting

KEY POINT

■ The underlying mechanism of psychophysiologic insomnia is a behaviorally based phenotype reflecting a conditioned heightened arousal associated with the bed, the environment within the bedroom (ie, clock), and maladaptive bedtime routines.

Case 8-1

A 62-year-old man presented to the neurology clinic complaining of insomnia that had begun 2 years ago when he had failed to obtain funding to support his research as a physics professor. He brought his sleep log to the appointment, which revealed prolonged sleep latency and that he had resorted to watching television and using alcohol to help initiate sleep. He noted that stress or sleeping in unfamiliar surroundings exacerbated his sleep problems. He reported working on his laptop until he went to bed at 10:00 PM, when he would start reading the news and doing puzzles on his tablet device in bed, until he eventually felt sleepy around midnight. His sleep diary also revealed that he resorted to drinking two to three shots of vodka to help him relax and induce sleep. He denied snoring or apneic spells and did not feel “restless” or have an urge to move his legs. He denied using caffeine and did not use any medications on a daily or nightly basis. He had no chronic health issues.

His body mass index was 26.5 kg/m². His physical and neurologic examination was normal, and his upper airway examination was completely normal and was not crowded.

The patient was diagnosed with psychophysiologic insomnia. He wished to avoid any pharmacotherapy, but he expressed an interest in conservative behavioral management. He was referred for cognitive-behavioral therapy for insomnia, and he was informed that mentally alerting activities, such as doing puzzles on the tablet device in bed, should be avoided, as well as limiting light sources at night to a minimum level. He was also asked to avoid the use of alcohol before bedtime. After 6 weeks of treatment, he returned to clinic reporting that his symptoms had improved. He was able to sleep for 7 hours per night without interruption and did not need to rely on any agents to induce sleep.

Comment. This patient’s history and physical examination did not point to a primary medical, psychiatric, or sleep disorder and was most consistent with psychophysiologic insomnia, which is characterized by difficulties falling asleep at the desired bedtime, mental hyperarousal in bed, or heightened somatic tension interfering with sleep onset. In addition to cognitive-behavioral therapy for insomnia, appropriate nonpharmacologic suggestions for improving sleep hygiene include avoidance of mentally distracting activities, which can improve anxiety levels and keep hyperarousal from interfering with sleep onset. Another suggestion for improving sleep hygiene is to avoid spending time in bed awake and to read relaxing (or even boring) books. The light source should be limited to a small bedside lamp or book light and set ideally at the minimum level needed to allow undemanding reading. Patients should also avoid the use of alcohol before bedtime because of its adverse impact on sleep architecture.

activities too close to bedtime, or failing to maintain a comfortable environment for sleep.⁴ A significant degree of overlap exists between inadequate sleep hygiene and other forms of insomnia, with most patients with insomnia admitting to at least one of these common maladaptive sleep be-

haviors that are targetable by cognitive-behavioral therapy interventions.

Behavioral Insomnia of Childhood

Behavioral insomnia of childhood is a diagnosis reserved for sleep difficulties in pediatric patients and incorporates

the following three sleep-onset association and limit-setting subtypes:

- The sleep-onset association type reflects the child's dependency on a specific activity/behavior/stimulation, typically objects or settings, for initiating sleep or returning to sleep following an awakening. When these are absent, sleep onset is significantly delayed.
- The limit-setting type is demarcated by behaviors of stalling or refusing going to bed that are attributable to an inadequate limit setting by the parent or caregiver.
- The mixed hybrid type is characterized by features of both sleep-onset association difficulties and bedtime resistance.

Insomnia Due to a Mental Disorder and Insomnia Due to a Medical Condition

Diagnoses of insomnia due to a mental disorder or insomnia due to a medical condition presume the presence of comorbid psychiatric and medical conditions with a clear temporal association with the underlying sleep disturbance and generally are used where the insomnia is severe enough to warrant independent treatment.

Insomnia Due to a Drug or Substance

Insomnia due to a drug or substance represents sleep problems clearly and temporally associated with the drug or substance intoxication or withdrawal from a wide range of medications.

EVALUATION AND ASSESSMENT OF INSOMNIA

A good general rule in the assessment of insomnia is to consider the potential etiology and likely factors that may predispose the patient to develop sleep difficulty, precipitate an insom-

nia episode over the clinical threshold, and perpetuate the insomnia symptoms over time once the precipitant diminishes (**Figure 8-1**).^{3,11}

The clinical guidelines for evaluating insomnia published by the AASM in 2008 highlight the key steps of the historical inventory during the clinical interview, focusing on the specific sleep-related symptoms as well as the potential contributions of psychiatric, medical, and substance use disorders.³ When possible, a bed partner or other family member should be interviewed to provide detailed information about any apneic spells, snoring, abnormal sleep-related movements, leg jerks, dream enactment, or behavioral abnormalities.³

Sleep questionnaires and sleep logs are very important in supplementing the formal evaluation of a patient with insomnia. A sleep diary spanning a period of several weeks can be quite helpful in highlighting patterns of sleep disturbance and uncovering potential circadian rhythm sleep-wake disorders. An example of a sleep diary may be downloaded from the AASM website (yoursleep.aasmnet.org/pdf/sleepdiary.pdf). A recently developed consensus sleep diary provides a standardized patient-informed sleep diary in the assessment of insomnia based on expert consensus.¹²

Neurologists should conduct a general physical and neurologic examination, a dedicated sleep medicine examination, and a baseline mental status examination. Polysomnography may be reserved for patients suspected of having a concomitant sleep disorder (eg, sleep-disordered breathing or periodic limb movement disorder) that is likely contributing to the insomnia symptoms, but it should not be ordered routinely in the absence of these suspected sleep-disturbing symptoms. Home sleep apnea testing is reserved

KEY POINTS

- A good general rule in the assessment of insomnia is to consider the potential etiology and likely factors that may predispose the patient to develop sleep difficulty, precipitate an insomnia episode over the clinical threshold, and perpetuate the insomnia symptoms over time once the precipitant diminishes.
- When possible, a bed partner or other family member should be interviewed to provide detailed information about any apneic spells, snoring, abnormal sleep-related movements, leg jerks, dream enactment, or behavioral abnormalities.
- Sleep questionnaires and sleep logs are very important in supplementing the formal evaluation of a patient with insomnia.

KEY POINT

■ The diversity of influences on sleep and wakefulness, extensive variability in patient expectations, along with the wide spectrum of insomnia phenotypes highlights the view that a unitary treatment pathway is not always possible.

for patients likely to be experiencing sleep apnea. The clinician should be aware of the specific contraindications for home sleep apnea testing, which are likely to contribute to insomnia (ie, movement disorders of sleep).^{13,14} For more information on home sleep apnea testing, refer to the article “Sleep-Disordered Breathing” by Nancy R. Foldvary-Schaefer, DO, MS, and Tina E. Waters, MD,¹⁵ in this issue of *Continuum*.

The core elements of a sleep history should focus on the specific chronicity of insomnia symptoms, impact on daytime activities and functioning, contribution of sleep-wake schedule routines, and other sleep-related symptoms (eg, snoring, movements, behaviors). **Table 8-2** provides an inventory of questions for interviewing patients presenting with insomnia.

MANAGEMENT OF INSOMNIA

Chronic insomnia is complex and often challenging, but can be very

rewarding to patients, bed partners, family members, and providers when successfully managed. Chronic insomnia may result from the interplay of numerous processes frequently occurring simultaneously. Successful intervention requires a multidisciplinary treatment philosophy incorporating several concurrent strategies and, in some cases, a staged approach that may involve further testing.³

General Recommendations

The diversity of influences on sleep and wakefulness, extensive variability in patient expectations, along with the wide spectrum of insomnia phenotypes highlights the view that a unitary treatment pathway is not always possible. The fundamental key to managing patients with insomnia is to creatively customize therapy for individual patients. Clinicians managing insomnia should remember to spend sufficient time collecting the sleep history, appreciate specific patient

TABLE 8-2 Insomnia Inventory Questionnaire

1. How long have you had symptoms of insomnia?
2. Was there a specific trigger?
3. What is the timing of the insomnia symptoms during the night?
4. Please estimate the time of sleep onset and total sleep times and the frequency and character of awakenings.
5. What is the typical rise time?
6. Is the difficulty primarily sleep onset or sleep maintenance, or is it a combination of the two?
7. Describe your evening routines and your bedroom setting.
8. Are there apparent situational or environmental variables?
9. Are you taking medications or using substances specifically for sleep? Are any of these temporally related to worsening of or improvement of sleep?
10. Describe your previous sleep difficulty and the results of any treatment approaches.
11. What specific hypnotics (if any) have you tried? (List name of medication, date of use, dose, instructions given, duration, impact, results, and side effects, if any.)
12. Have you tried cognitive-behavioral therapy? If yes, please describe.

expectations, and collaborate with patients in setting clear treatment goals specific to their nighttime and daytime symptoms. Any patient provided with hypnotics should be monitored prospectively for therapeutic progress and potential. A history of possible treatment-related adverse effects such as complex nocturnal behaviors, amnesic sleep eating, or depressed mood should be sought by the prescribing physician, who should then recalibrate the therapeutic plan as needed.

Insomnia and its Comorbidities

When managing chronic insomnia in the neurology outpatient setting, clinicians must consider the specific underlying neurologic and psychosocial comorbid conditions, as illustrated in **Figure 8-2**. A successful outcome is possible when these conditions (eg, pain syndrome, epilepsy, Parkinson disease, and mental health disorders such as anxiety and depression) are appropriately addressed.

As part of the initial assessment of insomnia, neurologists should attempt

to identify and treat other sleep disorders that may lead to insomnia. Examples of factors that contribute to difficulty initiating sleep include anxiety, excessive caffeine use, and symptoms of restless legs syndrome (RLS). An example of RLS contributing to sleep initiation insomnia is illustrated in **Figure 8-3**.

As shown in **Figure 8-2**, other comorbidities likely to manifest with insomnia include circadian rhythm sleep-wake disorders: advanced sleep-wake phase disorder, manifesting with early bedtime and early morning awakenings, and delayed sleep-wake phase disorder, resulting in difficulties initiating sleep and difficulty awakening before late morning or early afternoon. Sleep apnea may contribute to sleep maintenance insomnia, especially with more advanced stages of Parkinson disease, where nocturia is very common, making the condition difficult to treat. Periodic limb movement disorder may also lead to significant insomnia, especially in patients with pain syndromes, Parkinson disease, narcolepsy,

KEY POINTS

- When managing chronic insomnia in the neurology outpatient setting, clinicians must consider the specific underlying neurologic and psychosocial comorbid conditions.
- As part of the initial assessment of insomnia, neurologists should attempt to identify and treat other sleep disorders that may lead to insomnia.
- Other comorbidities likely to manifest with insomnia include circadian rhythm sleep-wake disorders: advanced sleep-wake phase disorder, manifesting with early bedtime and early morning awakenings, and delayed sleep-wake phase disorder, resulting in difficulties initiating sleep and difficulty awakening before late morning or early afternoon.

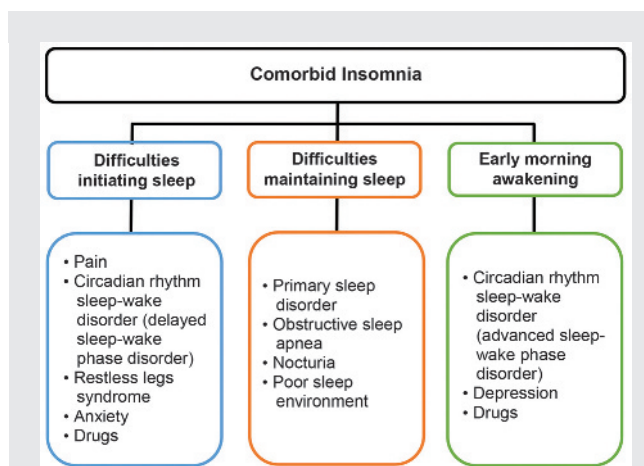
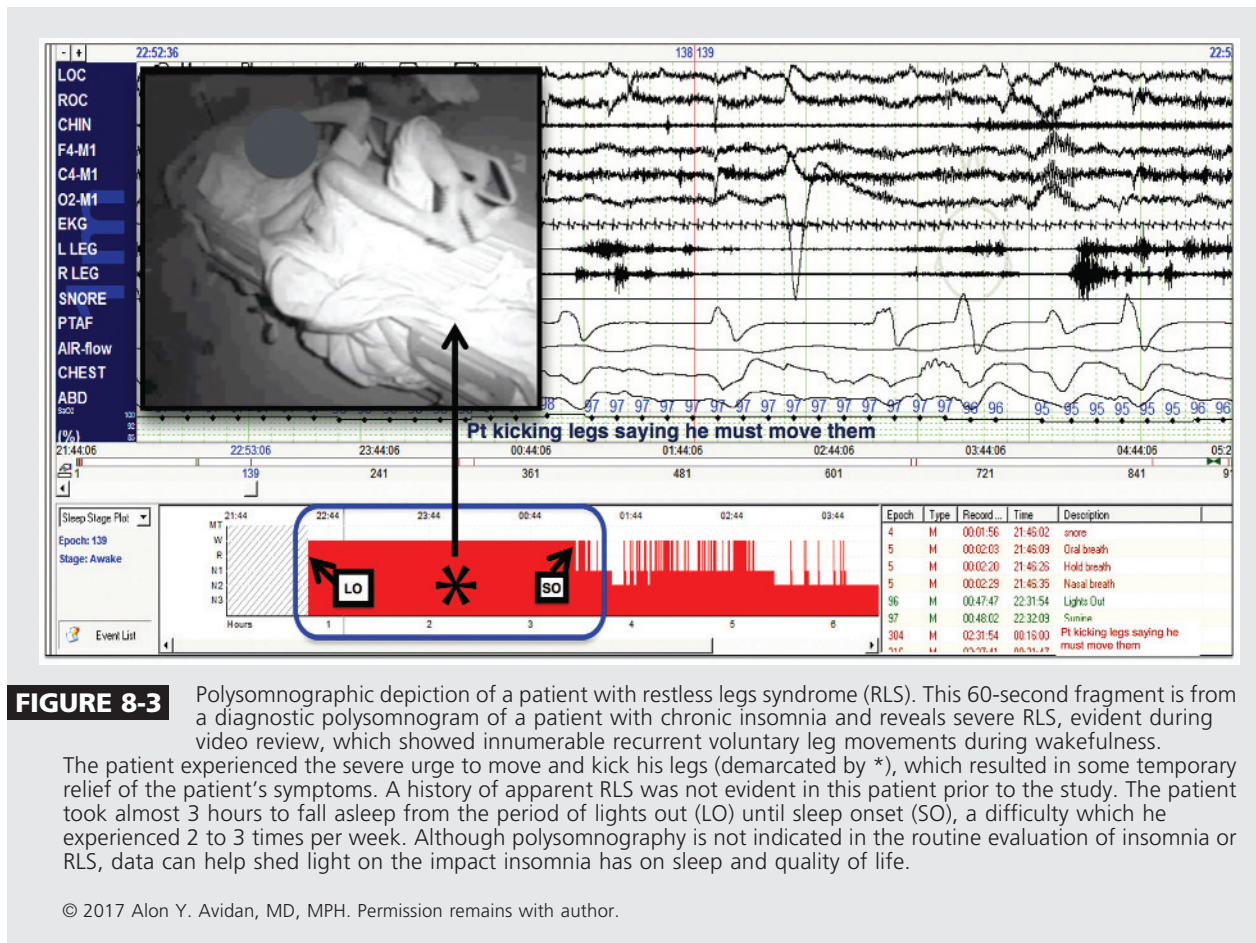


FIGURE 8-2 Differential diagnosis of insomnia according to its manner of occurrence during the night. The flow diagram depicts etiologic considerations in patients presenting with sleep initiation insomnia, sleep maintenance insomnia, and early morning awakenings.

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KEY POINT

■ When managing insomnia, the initial approach should consider the potential influence of intrinsic (patient-related) and extrinsic (environmental) factors, the latter including noise, temperature, light, radio, or television.

and multiple sclerosis. Early morning awakening also may be a sign of a mood disorder. The bidirectional relationship between pain, motor disorders of sleep, as well as psychiatric conditions such as depression and anxiety, as illustrated in **Figure 8-4**, is well established in the literature. Insomnia and poor sleep contribute to worsened pain, anxiety, and depression, which, in turn, worsen the underlying sleep disturbances.¹⁶⁻¹⁸ Interestingly, unhealthy behaviors are also associated with insomnia symptoms in a bidirectional manner; insomnia is associated with heavy drinking and physical inactivity, which are also associated with poorer sleep and insomnia symptoms.¹⁹

When managing insomnia, the initial approach should consider the

potential influence of intrinsic (patient-related) and extrinsic (environmental) factors, the latter including noise, temperature, light, radio, or television, as shown in **Figure 8-4**. These factors should be targeted for patient education and correction during CBT-I. One key item with significant relevance in neurology is the use of medications, particularly antidepressants, stimulants, wake-promoting agents, antiepileptic drugs, and dopamine agonists and antagonists. Neurologists should work closely with primary care physicians and psychiatrists to provide treatment regarding timing and dosages with the lowest potential to impact sleep onset or maintenance. Good general advice for patients with insomnia is to avoid all stimulating drugs and substances (eg,

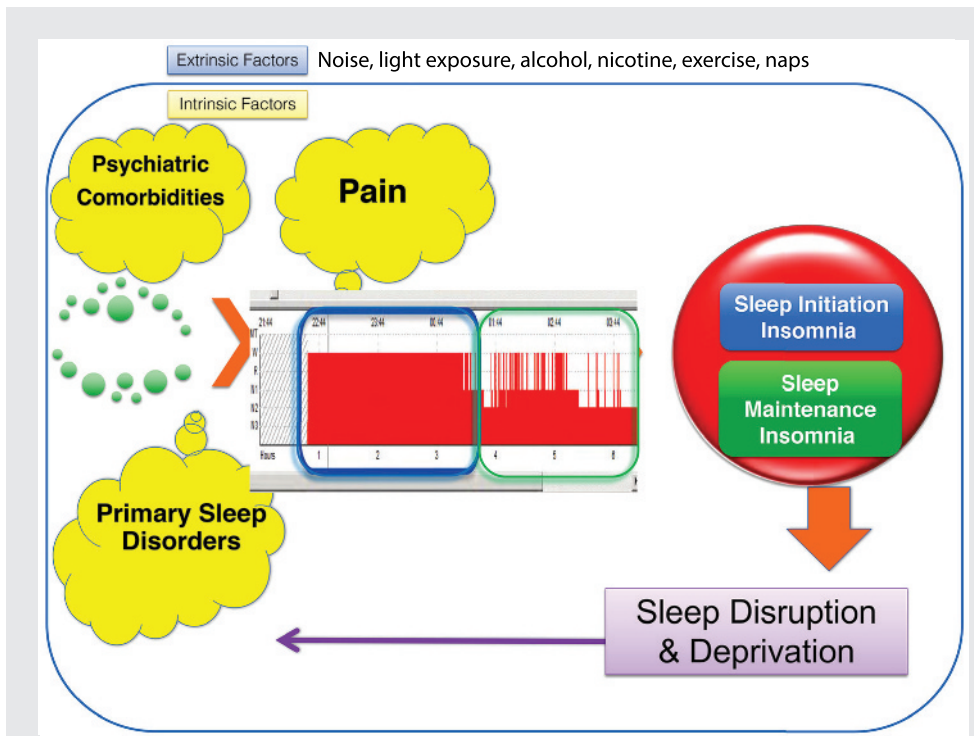


FIGURE 8-4 Mechanism of and contribution of key comorbidities to the perpetuation of chronic insomnia. Specific intrinsic (patient-related) factors are illustrated, depicting how their bidirectional relationship with insomnia worsens insomnia. Insomnia, when poorly treated, often worsens the comorbidities (eg, pain, depression). Extrinsic factors include excessive noise, light exposure, alcohol at bedtime, nicotine, exercise, and long naps too close to bedtime.

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KEY POINT

■ Sleep hygiene education is a good starting point for all patients who present with chronic insomnia because it sets the fundamental ground rules that help eradicate persistent sleep difficulty.

stimulating/alerting antidepressants and antiepileptic drugs, bronchodilators, thyroid hormones, corticosteroids, decongestants, caffeine after lunchtime, nicotine, and evening alcohol) or, when certain activating/alerting prescription drugs are necessary, to time administration earlier in the daytime with avoidance of nighttime dosing whenever possible. When possible, sedating medications (particularly antiepileptic drugs, anxiolytics, and benzodiazepine modulators) should be taken close to bedtime. However, caution should be taken toward possible influences of medications on sleep architecture, alteration, and suppression of upper airway muscle tone, and whether medications may precipitate or exacerbate RLS.

Education and Healthy Sleep Habits

An inventory of healthy sleep behaviors for review with all patients who present with insomnia is provided in **Table 8-3**.²⁰ Sleep hygiene education is a good starting point for all patients who present with chronic insomnia because it sets the fundamental ground rules that help eradicate persistent sleep difficulty. Treatment usually starts with educating patients about the basic processes that impact sleep and mechanisms to optimize the functioning of the existing physiologic mechanisms that regulate the sleep-wake cycle.³

Ensure sleep-wake timing is regular. Patients need to maintain regularity in their sleep and wake times and

TABLE 8-3 Healthy Sleep Habits^a**► Healthy Sleep Habits at Night**

Dedicate at least 30 minutes of wind-down time before bedtime in which you do something relaxing, such as read a book. Dim the lights in the house slightly for an hour or so before bed.

Disconnect electronics: Stay away from light-emitting devices such as television, laptops, phones, and tablets, as the blue light from their screens can alert the brain and make it harder to fall asleep.

Use the bed and bedroom for sleep and sex only.

Establish a regular prebedtime routine and a regular sleep-wake schedule.

Avoid alcohol or heavy meals too 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.

If unable to fall asleep within 20 minutes, get up and return to another space in the house to engage in a relaxing activity, such as reading or listening to music. Lying in bed awake can create an unhealthy conditioned association between your sleeping environment and wakefulness. You want your bed to conjure sleepy thoughts and positive feelings only.

Go to bed and wake up at the same time every day. Even if you have difficulties falling asleep and trouble awakening in the morning because you are tired, try to get up at the same time (weekends included).

This can help adjust your body's clock and aid in falling asleep at night.

► Healthy Sleep Habits During the Day

Avoid caffeine, particularly after noon.

Avoid alcohol and nicotine, especially close to bedtime.

Exercise regularly earlier during the day, but not within 3 hours before bedtime.

Avoid naps, particularly longer than 20 minutes and outside the 1:00 PM to 3:00 PM time window.

Keep a sleep diary to identify sleep habits and patterns that you can share with your doctor.

^a Data from the National Sleep Foundation.²⁰ sleepfoundation.org/insomnia/content/what-do-when-you-cant-sleep.

should allocate sufficient opportunity for adequate sleep duration.

Avoid excessive time awake in bed. Spending habitual time awake in the bed has the potential to perpetuate the behavioral conditioned association of the bedroom environment with insomnia, which reinforces hyperarousal. The patient should be educated to leave the bed after 15 to 20 sleepless minutes, getting up to pursue a quiet

distracting activity (while avoiding work activities, light exposure, or electronic devices) in another room of the home until feeling sleepy enough to return to the bedroom so that the desired association between the bed and sleep is reestablished.

Refrain from inappropriate and excessive napping behavior. For some people, routine regular daytime napping may be appropriate, but for

patients with insomnia, naps should be discouraged, especially in the late afternoon or evening. Prolonged napping too close to the evening could facilitate sleep-onset difficulties. If the patient has difficulty refraining from napping, restricting naps to no longer than a 15- to 20-minute period earlier in the afternoon and, if necessary, setting alarms to limit the nap duration should be suggested.

Encourage environmental conditions conducive to sleep. A relaxing evening and bedtime routine should facilitate sleep onset. Work projects, watching television late in the evening, and computer-related activities should be strictly minimized within 2 hours of bedtime. Inappropriate evening light exposure and device screen time (eg, laptops, video game devices, tablets, and phones) can induce a circadian phase delay that undermines the initiation of sleep at the desired time.

Minimize noise. The sleep environment should be free of disturbing

noises. White noise-generating devices may be beneficial.

Set a cooler room temperature. To optimize sleep, the ideal temperature should be neutral to slightly cool, as sleep onset is typically associated with the body's temperature nadir point in the evening.

Psychological and Behavioral Strategies

A wide variety of well-defined behavioral approaches have been shown to be effective in treating patients with insomnia.²¹ While some patients have an expectation that their insomnia management would include a hypnotic medication, data demonstrate that the ideal strategy is one that specifically incorporates CBT-I.²²

The core elements of CBT-I are outlined in **Table 8-4** and attend to components that regulate the circadian cycle, which include the underlying psychological processes that can impact sleep and the maladaptive cognitive distortions that fuel the perpetuation

KEY POINTS

- While some patients have an expectation that their insomnia management would include a hypnotic medication, data demonstrate that the ideal strategy is one that specifically incorporates cognitive-behavioral therapy for insomnia.
- The core elements of cognitive-behavioral therapy for insomnia attend to components that regulate the circadian cycle, which include the underlying psychological processes that can impact sleep and the maladaptive cognitive distortions that fuel the perpetuation of insomnia.

TABLE 8-4 Techniques and Special Goals Outlined During Cognitive-Behavioral Therapy Sessions

Technique	Goal
Sleep restriction	Restrict actual time spent in bed to enhance and increase the homeostatic drive for sleep, enhance sleep depth and consolidation, improve sleep onset and maintenance
Stimulus control therapy	Associate behaviors conducive to sleep with the activity of falling asleep, imprint bed and bedroom as sleep stimulus
Cognitive therapy	Address dysfunctional beliefs and attitudes about sleep
Relaxation training	Decrease psychological and cognitive hyperarousal and anxiety
Circadian rhythm entrainment	Reinforce or reset biological rhythm using light and/or chronotherapy
Cognitive-behavior therapy	Combination of behavioral and cognitive approaches listed above

of insomnia. CBT-I assimilates specific recommendations that facilitate healthy sleep routines, specifically, bedtime, time in bed, advice on when to attempt to sleep, and individualized cognitive psychotherapy to limit the maladaptive beliefs and assumptions regarding sleep and insomnia from hindering future progress. CBT-I provided as either a short-term or sustained therapy has excellent merit.²³ The basic components of CBT-I consist of a cognitive component and at least one behavioral element, such as stimulus control therapy or sleep restriction therapy. While CBT-I has been investigated primarily as a formalized approach over a series of sessions, studies have reported the benefits of streamlined and more flexible schedules, including online CBT-I for those without access to a provider in their area, limited insurance coverage, or a work/personal schedule that does not allow participation in in-person CBT-I sessions.^{24–27}

Sleep restriction. The goal of sleep restriction therapy is to increase the homeostatic drive for sleep to promote improved sleep onset and maintenance by reducing excessive wakefulness in bed.¹¹ Less wakeful time in bed also should limit the continued reinforcement between being in bed and being awake. This treatment initially curtails patients' time in bed to the amount of sleep they report being able to achieve. Typically, the time in bed is not reduced to fewer than 5 hours. Patients are required to maintain sleep diaries throughout the therapy and work closely with the CBT-I therapist. The morning rise time is kept consistent throughout the therapy to allow the patient to benefit from morning light exposure and to entrain (resynchronize) the existing sleep-wake cycle with the circadian system and photoperiod.

Stimulus control therapy. The aim of stimulus control therapy is to assist

patients in imprinting the activity and behavior of going to bed with falling asleep. It requires them to ensure a regular morning wake-up time and avoid daytime napping.²⁸ The therapy assumes that patients with chronic insomnia have incorrectly assimilated maladaptive bedtime and bedroom routines. These activities promote wakefulness through cognitive conditioning, which is reinforced over time as patients remain awake in bed, become frustrated, and experience mental hyperarousal. Patients participating in stimulus control therapy are instructed to go to bed and attempt sleep when they feel sleepy and able to fall asleep. If sleep fails to occur in 10 minutes, they are instructed to get out of bed and move to another room, repeating the process as needed.

Relaxation therapy. Relaxation therapy attempts to decrease anxiety and tension while awake in bed. Specific relaxation techniques may include progressive relaxation, abdominal breathing, guided imagery, yoga, and meditation.

Pharmacologic Approaches

Medical management of insomnia consists of four main treatment categories: (1) medications approved by the US Food and Drug Administration (FDA) for the treatment of insomnia, (2) sedating prescription medications not specifically approved by the FDA for insomnia treatment, (3) over-the-counter sleep aids that are regulated by the FDA but do not require a prescription, and (4) an extensive list of unregulated dietary supplements that are commercially available, with claims of sleep benefits.

Additionally, people often attempt to treat their insomnia with alcohol, although this strategy is rarely recommended. The sedating effect of alcohol may promote a shorter sleep

onset, but subsequent sleep quality typically is poor, with increased arousals later during the night and ultimately with a net negative effect.

Insomnia medications approved by the US Food and Drug Administration. Pharmacotherapy for insomnia that is approved by the FDA consists of agents with four distinct mechanisms of actions: γ -aminobutyric acid A (GABA-A) receptor modulation, melatonin receptor agonism, histamine 1 (H₁) receptor antagonism, and hypocretin/orexin antagonism. These agents have distinct advantages in that both efficacy and safety have been studied with appropriate doses in unique populations of patients with insomnia.²⁹ **Table 8-5** outlines the commonly used hypnotics based on the mechanism of action, pharmacodynamic profile (sleep onset, sleep maintenance, or difficulties re-initiating sleep following an awakening), available doses, approximate elimination half-lives, specific FDA indication, Drug Enforcement Administration schedule, and pregnancy category for each of these medications. The following sections describe the major pharmacodynamic categories of insomnia medications.

Benzodiazepine receptor modulation. GABA is the principal inhibitory neurotransmitter in the central nervous system, and its receptors are defined structurally and pharmacologically as GABA-A and GABA-B. GABA-A receptors are associated with a central chloride channel ionophore, as illustrated in **Figure 8-5**.³² The benzodiazepine and nonbenzodiazepine receptor agonist hypnotics are allosteric modulators of GABA responses at the GABA-A receptor complex, a pentameric transmembrane protein consisting of five subunits (two alpha, two beta, and one gamma) that form a rosette around the chloride channel, as illustrated in **Figure 8-5**. Activation of GABA-A re-

ceptors by GABA through its binding at the α - β subunit interface opens the chloride channel, leading to an immediate and substantial rise in chloride conductance across the cell membrane, rendering the neuron unable to raise an action potential, which leads to phasic inhibition of the neuron. The result is membrane hyperpolarization, which induces neural inhibition.^{33,34} Traditional benzodiazepine hypnotics (ie, temazepam, triazolam) do not differentiate among GABA-A receptor subtypes. The nonbenzodiazepine receptor agonist hypnotics zolpidem and zaleplon act on the α ₁GABA-A receptor subtypes, which mediate sedation, while eszopiclone preferentially targets the α ₃GABA-A receptor subtype predominantly in the reticular nucleus of the thalamus.

All GABA-A benzodiazepine receptor modulators interact with binding sites with different affinities to the various subunits, which accounts for some of the variation in their pharmacologic responses. The very broad distribution of GABA-A receptors suggests that the benzodiazepine hypnotic action may induce a widespread brain effect depending on the site of action.³⁵ The benzodiazepine hypnotics are generally well tolerated, but because the distribution of GABA-A receptors is widespread, the side effect profile is more extensive, ranging from drowsiness, dizziness, headache, and lightheadedness to ataxia and complex nocturnal behaviors, such as amnesic sleep-related eating and anterograde amnesia.²⁹ Patients using these agents may be more likely to report rebound insomnia on abrupt discontinuation following chronic use. These medications are associated with an abuse potential and therefore are designated by the Drug Enforcement Agency as Schedule IV medications. Benzodiazepine hypnotics are Pregnancy Category X

KEY POINTS

- Pharmacotherapy for insomnia that is approved by the US Food and Drug Administration consists of agents with four distinct mechanisms of actions: γ -aminobutyric acid A receptor modulation, melatonin receptor agonism, histamine 1 receptor antagonism, and hypocretin/orexin antagonism.
- The benzodiazepine hypnotics are generally well tolerated, but because the distribution of γ -aminobutyric acid A receptors is widespread, the side effect profile is more extensive, ranging from drowsiness, dizziness, headache, and lightheadedness to ataxia and complex nocturnal behaviors, such as amnesic sleep-related eating and anterograde amnesia.

TABLE 8-5 Insomnia Medications Approved by the US Food and Drug Administration^a

Medication ^b	Available Formulations	Half-life	Indications
Benzodiazepine immediate release			
Flurazepam	15 mg, 30 mg	48–120 hours	Treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings
Temazepam	7.5 mg, 15 mg, 22.5 mg, 30 mg	8–20 hours	Short-term treatment of insomnia
Triazolam	0.125 mg, 0.25 mg	2–4 hours	Short-term treatment of insomnia
Quazepam	7.5 mg, 15 mg	48–120 hours	Treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings
Estazolam	1 mg, 2 mg	8–24 hours	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
Nonbenzodiazepine immediate release			
Zolpidem	5 mg, 10 mg (recommended maximum dose of 5 mg for women)	1.5–2.4 hours	Short-term treatment of insomnia characterized by difficulties with sleep initiation
Zaleplon	5 mg, 10 mg	1 hour	Short-term treatment of insomnia, shown to decrease the time to sleep onset
Eszopiclone	1 mg, 2 mg, 3 mg	5–7 hours	Treatment of insomnia, administered at bedtime; decreased sleep latency and improved sleep maintenance
Nonbenzodiazepine extended release			
Zolpidem extended release	6.25 mg, 12.5 mg (recommended maximum dose of 6.25 mg for women)	2.8–2.9 hours	Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset)

and nonbenzodiazepines are Pregnancy Category C.

Benzodiazepine and nonbenzodiazepine receptor agonist hypnotics are available in various pharmacologic

formulations: immediate release oral spray, sublingual dissolvable alternative delivery formulations, and an extended-release tablet. All benzodiazepine receptor agonist hypnotics are

Most Common Side Effects	Drug Enforcement Administration Class ^c	Pregnancy Category ^d
Dizziness, drowsiness, lightheadedness, staggering, loss of coordination, falling	IV	X
Drowsiness, dizziness, lightheadedness, difficulty with coordination	IV	X
Drowsiness, headache, dizziness, lightheadedness, pins and needles feelings on the skin, difficulty with coordination	IV	X
Drowsiness, headache	IV	X
Somnolence, hypokinesia, dizziness, abnormal coordination	IV	X
Drowsiness, dizziness, diarrhea, drugged feeling	IV	C
Drowsiness, lightheadedness, dizziness, pins and needles feeling on the skin, difficulty with coordination	IV	C
Unpleasant taste in mouth, dry mouth, drowsiness, dizziness, headache, symptoms of the common cold	IV	C
Headache, sleepiness, dizziness	IV	C

Continued on page 1082

formulated for bedtime use with one exception; the lower-dose dissolvable formulation is indicated for middle-of-the-night insomnia provided that 4 hours of sleep time are available.

With the exception of eszopiclone and zolpidem extended release, for which no limitation on the duration of use is implied, the formal indications for the benzodiazepine receptor agonist

TABLE 8-5 **Insomnia Medications Approved by the US Food and Drug Administration^a**
Continued from page 1081

Medication ^b	Available Formulations	Half-life	Indications
Nonbenzodiazepine alternative delivery			
Zolpidem oral spray	5 mg, 10 mg	Approximately 2.5 hours	Short-term treatment of insomnia characterized by difficulties with sleep initiation
Zolpidem sublingual	5 mg, 10 mg	Approximately 2.5 hours	Short-term treatment of insomnia characterized by difficulties with sleep initiation
	1.75 mg, 3.5 mg	Approximately 2.5 hours	As needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep, provided that 4 hours of sleep time remain
Selective melatonin receptor agonist			
Ramelteon	8 mg	1–2.6 hours	Treatment of insomnia characterized by difficulty with sleep onset
Selective histamine 1 receptor antagonist			
Doxepin	3 mg, 6 mg	15.3 hours	Treatment of insomnia characterized by difficulties with sleep maintenance
Hypocretin (orexin) receptor antagonist			
Suvorexant	5 mg, 10 mg, 15 mg, 20 mg	12 hours	Treatment of insomnia, characterized by difficulties with sleep onset or sleep maintenance

^a Table current as of June 25, 2017.

^b The authors advise readers to review the most current package inserts for each medication listed given that updates are highly dynamic and variable.

^c Drug Enforcement Administration Class IV refers to a lower abuse potential than schedule III drugs and limited physical and/or psychological dependence.³⁰

^d Pregnancy medication Category X refers to studies in animals or human beings that have demonstrated fetal abnormalities or where there is evidence of fetal risk. The drug is contraindicated in women who are or may become pregnant. Pregnancy medication Category C refers to animal studies that have shown risk to the fetus but where there are no controlled studies in women, or where studies in women and animals are not available.³¹ A new US Food and Drug Administration (FDA) pregnancy and lactation labeling rule went into effect on June 30, 2015; however, the timelines for implementing this new labeling information on drug labels and package inserts are variable. All listed pregnancy category information uses past FDA pregnancy labeling practices, as labels and package inserts for some medications have not yet been updated.

hypnotics specify that they are intended for short-term therapy.

Melatonin receptor agonism. A single melatonin receptor agonist, ramelteon, is approved by the FDA for treating insomnia. A second agonist, tasimelteon, is now approved by the FDA for the treatment of non-24-hour sleep-wake disorder. Ramelteon is specifically indicated for the management of insomnia characterized by sleep initiation difficulties. Ramelteon is available at a single dose of 8 mg, which is

indicated for all patient subgroups including women and adults older than age 65. Specific contraindications include the clinical setting of severe hepatic disease or in patients concomitantly taking fluvoxamine, a selective serotonin reuptake inhibitor (SSRI) indicated for obsessive-compulsive disorder that is a potent CYP1A2 inhibitor (a key ramelteon metabolic pathway). Drowsiness, tiredness, and dizziness are the most common side effects. Ramelteon has no abuse

Most Common Side Effects	Drug Enforcement Administration Class ^c	Pregnancy Category ^d
Drowsiness, dizziness, diarrhea, drugged feeling	IV	C
Drowsiness, dizziness, diarrhea, drugged feeling	IV	C
Headache, nausea, fatigue	IV	C
Drowsiness, tiredness, dizziness	None	C
Somnolence/sedation, nausea, upper respiratory tract infection	None	C
Somnolence, depression, rare but possible risk of rapid eye movement (REM) intrusion phenomena	IV	C

potential; hence, it is considered a nonscheduled medication and is classed as Pregnancy Category C.

As a selective agonist of the melatonin types 1 and 2 (MT₁ and MT₂) receptors, ramelteon binds to these receptors with selectivity. These MT receptors are expressed with a high density in the suprachiasmatic nucleus of the anterior hypothalamus.³⁶ Melatonin is produced by the pineal gland in a process regulated by the circadian system. Melatonin exerts its activity by

attenuating the suprachiasmatic nucleus wake-promoting effects as opposed to actively promoting sleep (Figure 8-6). In this model, secretion of melatonin in the evening coincides with the peak of the suprachiasmatic nucleus-driven arousal cycle, ultimately inhibiting the mechanisms that promote evening wakefulness (Figure 8-6B). The presence of melatonin, in turn, reduces the circadian wakeful drive and facilitates activation of the sleep-promoting brain structures.²

KEY POINT

- Melatonin exerts its activity by attenuating the suprachiasmatic nucleus wake-promoting effects as opposed to actively promoting sleep.

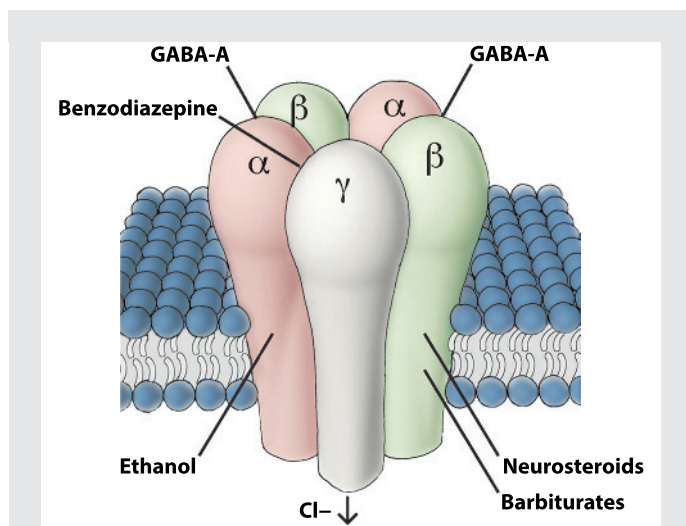


FIGURE 8-5 Schematic illustration of the γ -aminobutyric acid A (GABA-A) receptor and its associated binding sites. The receptor is pentameric, being composed of two alpha, two beta, and one gamma subunit. GABA-A receptors contain recognition sites for a variety of clinically relevant drugs. The binding of GABA in two GABA binding sites at the interface between alpha and beta subunits open the receptor-associated chloride (Cl^-) channel. The benzodiazepine binding site is located at the interface between alpha and gamma 2 subunits. Barbiturates, ethanol, and neurosteroids bind to sites in the membrane-spanning transmembrane regions of the subunit.

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KEY POINT

- Compared with other histaminergic compounds, ultra-low-dose doxepin is unusual for its very high specificity and selectivity for histamine 1 receptor antagonist activity.

The evening melatonin rise and MT_1 agonist action decreases the suprachiasmatic nucleus–driven wake-promoting stimulation that is present during the latter hours of the wake period and thereby facilitates bedtime sleep onset, as illustrated in **Figure 8-6**. The MT_2 action promotes a circadian resynchronizing effect that reinforces the circadian timing and allows for a regular and robust daily rhythm. The circadian system optimizes the ability to sleep during the nighttime and the typical alert waking period from the morning through the evening hours. Melatonin and other melatonin agonists facilitate bedtime sleep onset by reducing the evening circadian arousal, thereby leaving the accumulated homeostatic sleepiness

drive unopposed. Accordingly, melatonin agonists would be expected to enhance sleep onset, as well as stabilize and possibly shift the timing of the circadian system, depending on the timing of the dose. Circadian timing, including the pronounced influence on the timing of sleep, is entrained primarily though light exposure from the photoperiod. The mechanism involves a nonvisual photochemical reaction in retinal ganglion cells with a compound called melanopsin. Light exposure information is transmitted through the relatively short retinohypothalamic tract to the suprachiasmatic nucleus, where the light/dark information is integrated to coordinate the timing of the circadian clock. Note that artificial light, particularly the blue end of the visual spectrum, can alter the rhythm therapeutically (eg, evening bright light exposure to purposely delay the cycle for people with abnormally advanced circadian cycles experiencing early morning awakening) or, much more commonly, can cause an inadvertent delay in the circadian system with later evening sleepiness and bedtime in association with exposure to closely held electronic screens (eg, smartphones, tablets, and laptops).

Histamine 1 receptor antagonism. Currently, the only selective H_1 receptor antagonist approved by the FDA for treatment of insomnia is ultra-low-dose doxepin. The specific FDA-approved indication is for the management of sleep maintenance insomnia. Compared with other histaminergic compounds, ultra-low-dose doxepin is unusual for its very high specificity and selectivity for H_1 receptor antagonist activity. Accordingly, the key pharmacodynamic action is antihistamine-promoted sedation. The available doses are as high as 150 mg/d, and the prescribing guidelines for treating depression are as high as

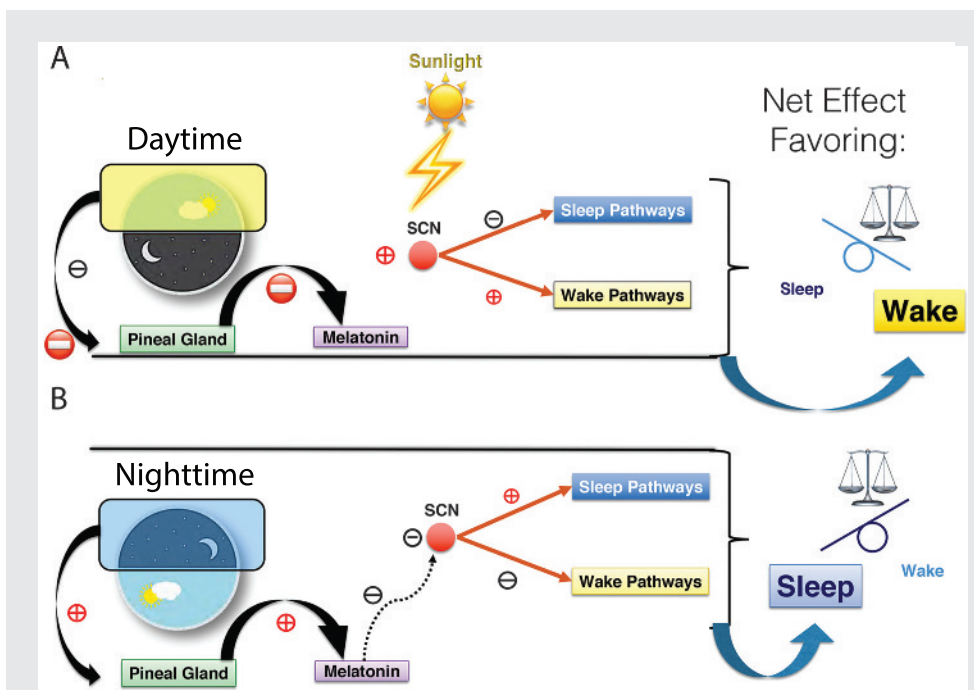


FIGURE 8-6 The suprachiasmatic nucleus (SCN) as modulator of sleep and wakefulness. Modulation of sleep and wakefulness is a product of the interaction between several systems in the central nervous system. *A*, The SCN generates the alerting signals and is responsible for promoting wakefulness during the day. Throughout the daytime, melatonin levels are low, but gradually rise in the evening as a response to darkness. *B*, As bedtime ensues, melatonin levels continue to rise, peaking during the typical nighttime sleep hours and declining by the end of the night. The release of melatonin inhibits the wake signals generated in the SCN. As melatonin release diminishes later during the night, the wake-promoting signal from the SCN predominates and assumes control of the sleep-wake process as the night further progresses toward morning. Sunlight stimulates the SCN, maintaining arousal, while the pineal gland's release of melatonin is suppressed, supporting wakefulness.

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300 mg/d; however, the low-dose formulations approved for insomnia are just 3 mg and 6 mg before bedtime. Adverse events reported include somnolence, sedation, nausea, and upper respiratory tract infection. Ultra-low-dose doxepin should not be prescribed for patients with untreated narrow-angle glaucoma or severe urinary retention or for people also taking monoamine oxidase inhibitors. As with other tricyclic antidepressants, caution should be exercised with use in patients with cardiac disease given the risk for QT-interval prolongation, although with ultra-low-dose doxepin, this is unlikely. With no abuse poten-

tial, ultra-low-dose doxepin is considered a nonscheduled medication and is Pregnancy Category C.

Hypocretin/orexin receptor antagonism. Suvorexant is a novel hypnotic and is the only insomnia medication currently approved by the FDA that works specifically by blocking the wake-promoting effects of orexin/hypocretin. The medication is clinically indicated for insomnia characterized by sleep onset and/or maintenance.^{37,38} Suvorexant is a hypocretin/orexin receptor antagonist that promotes sleep by blocking the arousal promoted by the hypocretin/orexin system, which, during the daytime and evening hours,

KEY POINTS

- Several sedating antidepressant, antipsychotic, antiepileptic, antihypertensive, and other sedating psychotropic medications are occasionally prescribed by neurologists to specifically treat insomnia symptoms.
- All the available over-the-counter sleep aids contain antihistamines, with most containing diphenhydramine or doxylamine, which are first-generation antihistamines with anticholinergic and sedative properties.

helps to stabilize wakefulness. In contrast to other hypnotics, suvorexant blocks the binding of the neuropeptides (orexin-A and orexin-B). Suvorexant is labeled by the FDA as a Schedule IV controlled substance and confers a slight risk of abuse.³⁹ This drug is contraindicated in patients with narcolepsy and is a Pregnancy Category C drug. Suvorexant causes significant somnolence in 7% to 11% of patients, and clinically meaningful sedation can occur at higher doses.³⁹ Current recommendations advocate for a starting dose of 10 mg before bedtime and proceeding with either 15 mg or 20 mg before bedtime, if needed. The maximal FDA-labeled dosage is 20 mg/d, although, in clinical trial development, substantially higher doses of 30 mg/d to 100 mg/d were also used with more carryover sedation and some unfavorable increases in measured reaction time. Suvorexant should be used with caution in patients who are obese and in people taking CYP3A4 inhibitors.⁴⁰ One concern with the hypocretin/orexin antagonist approach to treating insomnia is the theoretical possibility of the intrusion of rapid eye movement (REM) phenomena into wakefulness. These might include sleep paralysis, hypnagogic/hypnopompic hallucinations, and symptoms similar to cataplexy. Suvorexant is contraindicated in patients with narcolepsy.

General considerations when using hypnotic agents. While the FDA-approved insomnia medications have indications for chronic insomnia, therapy should be weighed carefully given the patient phenotype, underlying comorbidities, and unique side effect profiles and warnings. The FDA has required certain warnings for all 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 of which 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 the potential for next-day drowsiness or impairment and ensuring that patients have sufficient time in bed following a medication dose.

Off-label prescription insomnia pharmacotherapy. Several sedating antidepressant, antipsychotic, antiepileptic, antihypertensive, and other sedating psychotropic medications are occasionally prescribed to treat insomnia symptoms. While sometimes helpful, insufficient evidence of the safety and efficacy of these medications exists to support their use to treat these disorders, particularly in neurology patients who are often vulnerable to treatment-related adverse effects, particularly with agents that confer respiratory depression in the setting of neuromuscular disease, amnesia, memory difficulty, and daytime sedation. Prescribers should be mindful of the risk-to-benefit ratio of these agents for insomnia. Specific examples include the sedating antidepressants, such as trazodone, amitriptyline, mirtazapine, and conventional clinical doses of doxepin, which often have been prescribed in this manner. Quetiapine has been prescribed for insomnia; however, it can increase the risk of bleeding when taken concomitantly with warfarin⁴¹ and may place those with concomitant cardiovascular disease at higher risk of mortality because of QT-interval prolongation.⁴²

Over-the-counter sleep aids. All the available over-the-counter sleep aids contain antihistamines, with most

containing diphenhydramine or doxylamine, which are first-generation antihistamines with anticholinergic and sedative properties. The over-the-counter sleep aids are marketed as single compounds or are provided as a combination therapy with analgesics (ibuprofen or acetaminophen), formulated as evening preparations. While the antihistamine sedating effect is the desired activity, these agents may exert adverse and sometimes serious side effects. Most concerning are the anticholinergic effects, which may contribute to delirium, confusion, dry mouth, constipation, and urinary retention. These agents should be used with greater caution in older adults and patients receiving other anticholinergics. Another concern is that these drugs have relatively long durations of action that may lead to next-morning drowsiness following nighttime dosing. Tolerance may develop, with chronic usage leading to inappropriate dose escalation.⁴³

Unregulated compounds. These substances are marketed as dietary supplement sleep aids and often are considered in the realm of complementary and alternative medicine. These unregulated sleep aids are generally promoted as single or multiple compounds containing plant-derived ingredients such as chamomile, passionflower, valerian, hops, and kava kava.

Tart cherry juice was found to be associated with anecdotal subjective reports of sleep enhancement in people with insomnia.⁴⁴ While the effect sizes were moderate and in some cases negligible, the data suggest that a tart cherry juice blend has modest efficacy in the management of insomnia in older adults with insomnia.⁴⁴

At present, with rare exceptions, few convincing data exist regarding efficacy of these dietary supplements. Patients should be warned, however, that while these unregulated dietary

compounds may be marketed as “natural,” they are not necessarily safe. One notable example is kava kava, which may be associated with hepatic toxicity.^{45,46} Because the evidence is not complete, risk-benefit assessments are not reliable, and much knowledge is still lacking.

Melatonin is a unique member of the dietary supplement sleep aid category in the United States, since it is a compound with an established role in sleep physiology and demonstrated efficacy in treating circadian rhythm sleep-wake disorders. It is a neurohormone produced by the pineal gland that can reset sleep onset by synchronization of the internal circadian clock. With advanced age, less melatonin is produced, and is often an underlying cause contributing to advanced sleep-wake phase disorder in older age. Circulating melatonin levels are significantly lower in many elderly patients with insomnia compared to controls, and melatonin onset and peak times are delayed. Melatonin replacement may be beneficial for elderly patients experiencing insomnia. Currently, however, more data are needed to improve our understanding of the appropriate dosage, pharmacologic properties, and indications. Melatonin is not FDA approved, formulations vary, and efficacy and safety data are still needed.

In the European Union, a prolonged-release melatonin formulation is available only by prescription. Prolonged-release melatonin is approved in the European Union for the treatment of primary insomnia characterized by poor sleep quality in patients aged 55 years and older.⁴⁷

Developing an Insomnia Treatment Plan

The evaluation of insomnia should foster a patient-specific customized plan for management that considers

KEY POINT

■ Melatonin is a unique member of the dietary supplement sleep aid category in the United States, since it is a compound with an established role in sleep physiology and demonstrated efficacy in treating circadian rhythm sleep-wake disorders.

KEY POINTS

- The evaluation of insomnia should foster a patient-specific customized plan for management that considers the unique insomnia phenotype, chief complaint specific to the timing and chronicity of the insomnia, underlying comorbidities, sleep-wake pattern symptoms, lifestyle pattern, social habits and routines, previously tried hypnotic therapy (specific agents, dose, duration, and development of adverse effects), and any prior cognitive-behavioral therapy for insomnia.
- The cornerstone of insomnia management for all patients must include education regarding proper sleep hygiene and individualized recommendations about proper sleep-enhancing behaviors.

the unique insomnia phenotype, chief complaint specific to the timing and chronicity of the insomnia, underlying comorbidities, sleep-wake pattern symptoms, lifestyle pattern, social habits and routines, previously tried hypnotic therapy (specific agents, dose, duration, and development of adverse effects), and any prior CBT-I.³ Patients should be asked to share their specific expectations and treatment goals. Over time, clinicians should monitor symptoms regularly with patients to assess the effects of the therapeutic strategies implemented.

The cornerstone of insomnia management for all patients must include education regarding proper sleep hygiene and individualized recommendations about proper sleep-enhancing behaviors. Strategies reviewed by CBT-I specialists should be assimilated into the management plan and should occur in harmony and synchronously with any pharmacotherapy intervention.

FDA-approved hypnotics may be appropriate for initial use in treating patients with insomnia, especially because they are generally better studied in populations where treatment-emergent adverse effects are more

frequent. Prescribers should pay close attention to the pharmacodynamic and pharmacokinetic profiles and undertake therapy to address their patients' symptoms after carefully querying patients about circadian patterns, the nature of the underlying sleep disturbances, and potential impact on health-related quality of life. Careful attention to sleep-wake circadian patterns is especially important as one considers implementation of strategic light exposure in resynchronizing the sleep-wake pattern.

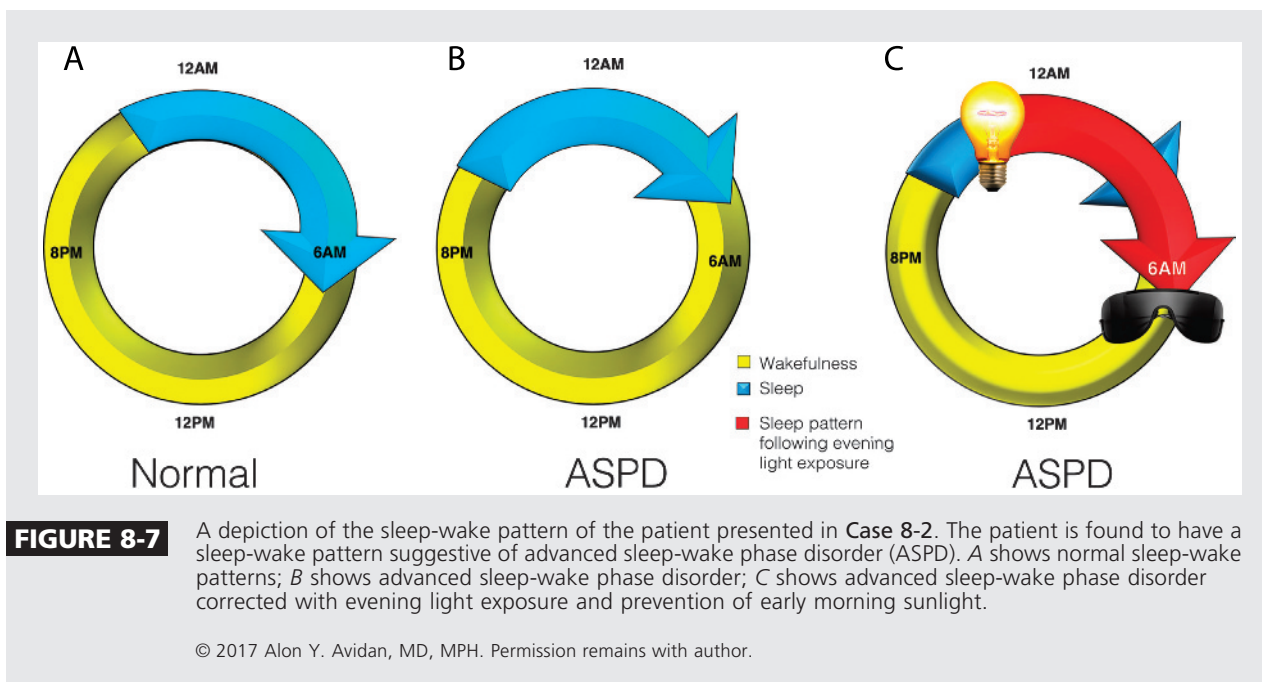
Advanced sleep-wake phase disorder is sometimes encountered among older patients and may be related to depressed melatonin production (**Case 8-2**).

Compared to the normal circadian rhythm demonstrated in **Figure 8-7A**, patients with a phase-advanced cycle generally get sleepy early in the evening and wake up early in the morning, when they are then usually unable to reinitiate sleep (**Figure 8-7B**). Although the older adult may get sleepier in the evening, he or she often still tries to remain awake until a more socially acceptable time (ie, 10:00 PM to 11:00 PM). Then, when the patient awakens early and is

Case 8-2

An 82-year-old man with mild Alzheimer disease presented for evaluation of early morning awakening and the inability to return to sleep. He often became very tired around 6:00 PM and fell asleep around 8:00 PM. He had no difficulty falling asleep. However, when he woke up at around 2:30 AM to 3:00 AM, he was unable to reinitiate sleep. He then stayed awake in bed until about 7:00 AM, when he finally got out of bed and began his day. He denied any symptoms of depression other than his sleep problems.

Comment. This man has insomnia in the setting of advanced sleep-wake phase disorder. The sleep-wake cycle is controlled by the circadian modulator located in the suprachiasmatic nucleus of the anterior hypothalamus. *Zeitgebers*, external cues (predominantly the photoperiod), synchronize the circadian cycle. Disturbances in circadian rhythms are due to a mismatch between the environmental cues and the endogenous circadian rhythms. The hypersomnolence seen in an older person may be due in part to a disintegration of the normal circadian rhythm.



unable to fall back to sleep, time in bed has not been long enough for a sufficient sleep amount, resulting in a state of sleep deprivation. Advanced sleep-wake phase disorder can be treated with bright light therapy during the later afternoon/early evening timeframe, as light is one of the strongest cues for synchronizing circadian rhythms and can delay the sleep cycle when given at this time. Early morning bright light exposure should be avoided since it can further advance the sleep cycle at that time, and the use of sunglasses following dawn may be helpful. One strategy for bright light therapy for this disorder involves exposure to at least 5000 lux for 2 hours in the evening (eg, 7:00 PM to 9:00 PM) at about 1 meter eye level (Figure 8-7C).⁴⁸

CONCLUSION

Chronic insomnia in neurology practice represents a unique opportunity for clinicians to help improve the quality of life across patients with

comorbid neurologic conditions. All patients should be screened to help uncover poor sleep behaviors since insomnia may exacerbate health problems, undermine the quality of sleep, limit the ability to remain awake, and worsen daytime function. As with the approach to other neurologic presentations, the neurologist should conduct a careful sleep history. Insomnia should be considered in every patient, especially those who present with refractory pain, headaches, seizures, and impaired cognition. The treatment approach should incorporate evidence-based therapies, including CBT-I and appropriately selected pharmacotherapies based on the timing of sleep difficulty during the sleep cycle. Even neurologists without specific training in sleep medicine should take opportunities to address the effects of insomnia by integrating proper pharmacologic and behavioral treatment approaches, especially given the pervasive nature of sleep difficulties among neurologic patients.

USEFUL WEBSITES**2017 Insomnia Clinical Guideline from the American Academy of Sleep Medicine**

aasmnet.org/Resources/clinicalguidelines/040515.pdf

Insomnia Practice Parameters from the American Academy of Sleep Medicine

aasmnet.org/practiceparameters.aspx?cid=109

Practice Parameters for the Psychological and Behavioral Treatment of Insomnia: An Update. An American Academy of Sleep Medicine Report

aasmnet.org/Resources/PracticeParameters/PP_BTInsomnia_Update.pdf

Quality Measures for the Care of Patients with Insomnia from the American Academy of Sleep Medicine

aasmnet.org/Resources/QualityMeasures/QualityMeasuresfortheCareofPatientswithInsomnia.pdf

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