Overcoming Barriers to the Diagnosis and Treatment of Insomnia

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Disclosure Note: This CME activity includes discussion about medications not approved by the US Food and Drug Administration and uses of medications outside of their approved labeling.

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

- Apply evidence-based diagnostic guidelines for patients who have clinical features consistent with insomnia
- Use evidence-based guidelines to develop comprehensive treatment plans that include cognitive-behavioral therapy, pharmacologic treatment, and combination therapies to achieve optimal outcomes
- Identify basic elements of cognitive-behavioral therapy for insomnia
- Differentiate among medications FDA-approved for treating insomnia by discussing mechanism of action, safety, efficacy, and use

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of insomnia.

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CASE SCENARIO

A 72-year-old woman describes difficulty staying asleep and daytime fatigue for the past 8 months. Initially, she only had difficulty staying asleep 2 to 3 nights per week, but over the past 5 months, these symptoms have increased in severity and frequency. She notes increased irritability and lack of motivation during the day associated with her disturbed sleep.

EPIDEMIOLOGY

Insomnia, defined as difficulty initiating or maintaining sleep with associated daytime consequence, is 1 of 7 sleep-wake disorders according to the International Classification of Sleep Disorders, 3rd edition (ICSD-3).[1] Insomnia is common, particularly among older adults.[2] The estimated prevalence varies based on the criteria, ranging from 22% using DSM-IV-TR, 15% using Research Diagnostic Criteria/ICSD-2, and 4% using ICD-10 criteria.[3]

TABLE 1. **Assessment of sleep history**[16-18]

Sleep Problem	Sleep Times	Consequences of Disturbed Sleep	Symptom Duration
Number of awakenings Duration of awakenings Duration of the sleep problem	Bedtime Duration until sleep onset Final awakening time Nap time(s) Nap length(s)	Fatigue or malaise Poor attention or concentration Social/vocational/educational dysfunction Motor disturbance or irritability Daytime sleepiness Reduced motivation or energy Increased errors or accidents Behavioral problems Ongoing worry	<3 months or ≥3 months

Insomnia can lead to complications, such as psychiatric disorders,[4-8] falls,[9-12] cardiovascular disorders,[13,14] and metabolic syndrome.[15] Psychiatric complications include depression and anxiety, and cardiovascular disorders include ischemic heart disease, ischemic (but not hemorrhagic) stroke, hypertension, and heart failure.[13,14] Recent evidence indicates severe insomnia is associated with increased risk of metabolic syndrome in women age ≥50, but not men.[15]

DIAGNOSIS

Insomnia is diagnosed clinically based on history and characterizing the nature and severity of the sleep problem (**TABLE 1**).[16-18] Asking the patient to talk through a typical 24-hour day can provide valuable insight. A sleep diary could be helpful for patients with substantial variability in the sleep problem.

Well-rested adults fall asleep within 10 to 20 minutes of attempting to sleep and spend <30 minutes awake during the night. Adults with chronic insomnia, however, usually take ≥30 minutes to fall asleep (for those with sleep initiation difficulty), spend ≥30 minutes awake during the night (for those with sleep maintenance difficulty), and/or terminate sleep ≥30 minutes prior to the desired wake-up time. It is not uncommon for patients to report 1 or more nights of poor sleep followed by a night of better sleep or to have minimal sleep over several consecutive nights. Patients often overestimate the amount of time it takes to fall asleep and underestimate total sleep time.

Asking patients why they are experiencing the sleep problem often identifies contributing factors and comorbid psychiatric or medical disorders, such as depression, anxiety, pain, restless leg syndrome, and obstructive sleep apnea.[16] The Epworth Sleepiness Scale is useful to identify patients with daytime sleepiness. Question patients about the use of prescription and non-prescription medications, such as central nervous system stimulants or depressants, antidepressants, beta-agonists, diuretics, opioids, and glucocorticoids. Ask patients about their consumption of caffeine, alcohol, and complementary and alternative medicines. Actigraphy could be considered to characterize circadian rhythm patterns or sleep disturbances.[16] Other laboratory testing, such as blood, radiography, or polysomnography, is needed only to investigate suspected comorbid disorders.[16]

Because insomnia is a component of many psychiatric and medical conditions, an insomnia diagnosis should be considered only when the symptoms are prominent and require further evaluation and treatment. If an associated comorbidity is identified, consider that it is sometimes difficult to determine whether the insomnia or the comorbidity occurred first. Due to this uncertainty, insomnia is no longer classified as primary or secondary, and treatment targets both insomnia and the comorbid disorder.[1,19]

An insomnia diagnosis requires that the patient experiences difficulty initiating or maintaining sleep despite adequate opportunity and circumstances for sleep that results in daytime consequences.[1] Insomnia differs from sleep deprivation in that insomnia occurs despite adequate opportunity and circumstances for sleep, whereas sleep deprivation does not. Those with chronic insomnia experience symptoms ≥3 times per week for ≥3 months. Daytime consequences include fatigue or malaise, poor attention or concentration, social/vocational/educational dysfunction, increased errors or accidents, motor disturbance or irritability, daytime sleepiness, reduced motivation or energy, or behavioral problems such as hyperactivity, impulsivity, or aggression. Patients with chronic insomnia might have ongoing worry that insufficient sleep could lead to daytime dysfunction, thereby creating a cycle that worsens insomnia.

TREATMENT

Overview of clinical guidelines

Several guidelines for managing patients with insomnia have been developed. Based on growing understanding of the often bi-directional association between insomnia and

comorbid disorders, these guidelines increasingly have emphasized the importance of identifying and treating comorbid condition(s) as well as the insomnia itself.[16,19,20] Discussion regarding the treatment of comorbid disorders associated with insomnia is beyond the scope of this review.

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Treatment options

The goal of therapy is to improve sleep and alleviate distress or dysfunction caused by insomnia.[21] Psychotherapy and pharmacologic therapy, alone or in combination, are recommended most often for insomnia; referral to a sleep specialist, if available, also could be considered.[20,21] Psychotherapies include cognitive-behavioral therapy for insomnia (CBT-I), brief behavioral therapy, stimulus control, relaxation, and sleep restriction.

Cognitive-Behavioral Therapy for Insomnia

Based largely on moderate-quality evidence showing benefit on sleep onset, wake after sleep onset, and sleep efficiency, the American College of Physicians recommends CBT-I as initial therapy for all adults with chronic insomnia.[21] The American College of Physicians panel noted that evidence related to the harms of CBT-I is limited and concluded that CBT-I can be used for long-term treatment of insomnia.

CBT-I consists of a combination of cognitive therapy, behavioral interventions (eg, sleep restriction and stimulus control), and educational interventions (eg, sleep hygiene) to address thoughts and behaviors that interfere with optimal sleep. CBT-I traditionally has been offered one-on-one in the office setting, but is limited by the time required, the need for multiple training sessions, and the availability of trained providers. Telephone- and web-based platforms have shown evidence indicating benefit.[21] Two recent meta-analyses showed that CBT-I delivered via the internet produced clinically significant benefits for 1 year after the end of therapy.[22,23] One of these was restricted to CBT-I delivered in primary care (generally by a non-physician) over 4 to 6 sessions.[23]

Pharmacologic Therapy

Pharmacologic therapy plays a key role in treating chronic insomnia, particularly because not all patients achieve adequate benefits with CBT-I and long-term adherence can be challenging.[20,21] Approved medications include benzodiazepines, nonbenzodiazepine hypnotics, melatonin agonist, doxepin, and orexin receptor antagonists.

Benzodiazepines

Benzodiazepines, such as estazolam, lorazepam, temazepam, and triazolam, bind to several gamma-aminobutyric acid (GABA) type A receptor subtypes.[24] Benzodiazepines reduce the time to sleep onset, prolong stage 2 sleep, prolong total sleep time, and might reduce the length of rapid eye movement sleep.[25] Additionally, benzodiazepines have anxiolytic as well as anticonvulsant properties and produce anterograde amnesia. Although tolerance to the sedative effects could develop, next-day performance can be impaired depending on the elimination half-life of the benzodiazepine.[25] Withdrawal and rebound insomnia could occur with abrupt discontinuation.

Nonbenzodiazepine benzodiazepine receptor agonists

Nonbenzodiazepine benzodiazepine receptor agonists are more selective for a specific GABA type 1 receptor subtype and exert less anxiolytic and anticonvulsant effects than benzodiazepines. This class includes eszopiclone, zaleplon, and zolpidem (immediate- and extended-release). Nonbenzodiazepines decrease sleep latency and number of nighttime awakenings and improve sleep duration and sleep quality.[26-31] Headache and dizziness are common adverse events.[25] Low dosages are recommended to reduce the risk of impaired next-day performance.

Melatonin receptor agonist

Ramelteon binds to melatonin receptors in the suprachiasmatic nucleus with higher affinity than melatonin.[32,33] Short-term use of ramelteon is associated with small improvements in sleep onset and total sleep time.[34] The most common adverse effects are somnolence, fatigue, and abnormal dreams.[35]

Orexin receptor antagonists

Orexin receptor antagonists, suvorexant and lemborexant, which block the neuropeptides orexin A and B from binding in the hypothalamus are the newest class of medications for insomnia. Orexin A and B play a key role in promoting wakefulness and regulating the sleep-wake cycle.[36] Somnolence, fatigue, headache, and abnormal dreams are the most common adverse events.[25] Suvorexant and lemborexant have a reduced addictive potential than other FDA-approved medications for insomnia and are classified as schedule IV controlled substances.

Suvorexant

The safety and efficacy of suvorexant were demonstrated in a pooled analysis of 2 identical randomized, double-blind, placebo-controlled, parallel-group 3-month trials in nongeriatric (age 18 to 64) and geriatric (age ≥65) patients with insomnia.[37,38] At dosages of 15 or 20 mg/d (N = 493) and 30 or 40 mg/d (investigational) (N=770), suvorexant significantly improved most sleep onset and sleep maintenance endpoints compared with placebo (N = 767) beginning with the first treatment.[37] For example, placebo-corrected subjective time to sleep onset was 5.2 to 7.6 minutes and 8.4 to 13.2 minutes shorter with suvorexant 15 or 20 mg/d and 30 or 40 mg/d, respectively, at 3 months in the 2 trials.[37,38] Placebo-corrected subjective total sleep time increased from 10.6 to 19.7 minutes and 22.1 to 25.1 minutes with suvorexant, 15 or 20 mg/d and 30 or 40 mg/d, respectively.[37] Rates of discontinuation because of an adverse event were ≤4.7% for suvorexant and ≤6.0% for placebo.[37]

Lemborexant

Lemborexant has demonstrated safety and efficacy in nongeriatric and geriatric patients with insomnia. In a phase II, dose-ranging study, lemborexant improved both objective and subjective measures of sleep, which were apparent during the first 2 nights of treatment and persisted for the 15 nights of the trial.[39] A phase III trial compared lemborexant, 5 or 10 mg/d, zolpidem extended-release, 6.25 mg/d, and placebo over 1 month in 1008 patients with insomnia.[40] Compared with zolpidem, treatment with both dosages of lemborexant led to significant improvement in latency to persistent sleep, sleep efficiency, and wake-after-sleep onset during the first 2 nights of treatment and continued through the 1 month of the trial. For example, at 1 month patients treated with lemborexant experienced significantly greater reduction in wake-after-sleep onset in the second half of the night with the 5 and 10 mg/d dosages of lemborexant vs zolpidem (–6.7 and –8.0 minutes vs zolpidem, respectively). Similar significant improvements with lemborexant were observed vs placebo. Rates of discontinuation because of an adverse event were 0.4%, 0%, 0.8%, and 0.5% for lemborexant 5 and 10 mg/d, zolpidem, and placebo, respectively.

Guideline recommendations

The most recent guideline on pharmacotherapy for chronic insomnia in adults was developed by the American Academy of Sleep Medicine (AASM) in 2017.[20] The AASM recommendations are based on a systematic review of published literature, including meta-analyses. The AASM panel recognized the critical role of CBT-I because of its favorable benefit-to-risk ratio, but affirmed the need for pharmacotherapy, either alone or in combination with CBT-I, for many patients with chronic insomnia.

TABLE 2. **Recommendations regarding medications for insomnia**[20]

Medication	Recommended Use	
	Sleep Onset	Sleep Maintenance
Benefits outweigh harms		
Ramelteon Zaleplon	✓	
Doxepin Suvorexant		✓
Eszopiclone Temazepam Zolpidem	✓	✓
Benefits approximately equal to harms		
Triazolam	✓	
Diphenhydramine Melatonin	None	None
Harms outweigh benefits		
Tiagabine Trazodone l-Tryptophan Valerian	None	None

Note: Lemborexant is not included because it was approved for use in the United States after publication of the AASM guidelines in 2017.

The AASM panel provided recommendations regarding pharmacotherapy at FDA-approved dosages for sleep onset and/or sleep maintenance (**TABLE 2**).[20] Medications that are relatively short-acting are preferred for patients experiencing difficulty with sleep onset, while longer-acting medications are preferred for those with difficulty maintaining sleep. Lemborexant was not included because it was approved by the FDA after the AASM published their recommendations.

All recommendations were classified as weak, but the AASM panel noted that this reflects the limitations of the evidence as much as the relative benefits and risks of the treatments *per se*. The panel recommended that several agents commonly used for insomnia be avoided, including diphenhydramine, melatonin, tiagabine, trazodone, l-tryptophan, and valerian. Other medications that generally should not be used for chronic insomnia include antidepressants, antipsychotics, and barbiturates. An exception is doxepin at dosages ≤6 mg/d, which is FDA-approved for insomnia. The sedating antidepressants amitriptyline and trazodone should be limited to those with comorbid depression. Recommendations by the AASM panel for the following were not possible because of inadequate data for statistical analysis: estazolam,

flurazepam, gabapentin, oxazepam, paroxetine, quazepam, quetiapine, and trimipramine.

Recommendations regarding the use of medications for insomnia also are included in the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. The Beers Criteria were developed by the American Geriatrics Society to provide guidance regarding the use of medications in older adults based on a systematic review of clinical trials, observational studies, and meta-analyses involving adults age ≥65. According to the 2019 Beers Criteria,[41] several medication classes commonly used to treat insomnia should be avoided in older adults, often because of their anticholinergic properties, prolonged sedation, and/or risk of falls. These include first-generation antihistamines, some antidepressants, barbiturates, short- and long-acting benzodiazepines, benzodiazepine receptor agonists, and first- and second-generation antipsychotics. Lemborexant and suvorexant were not included in the list, and doxepin ≤6 mg/d was deemed acceptable.

Risk of Falls

The risk of falls, and the associated morbidity and mortality, is an important consideration when selecting a hypnotic agent for insomnia, especially in older adults. However, several investigations and meta-analyses provide conflicting conclusions.[42-49] A 2005 retrospective analysis of a database of nursing home residents (N = 34,163) found that hypnotic use did not predict falls (adjusted odds ratio [OR]: 1.13; 95% confidence interval [CI]: 0.98 to 1.30), but that the presence of insomnia did (adjusted OR: 1.52; 95% CI: 1.38 to 1.66). Results were not categorized by type of hypnotic, however.

A recent investigation of 331 nursing home residents found a significantly increased risk of falls with regular use of non-benzodiazepine benzodiazepine receptor agonists, particularly in adults age ≥85, but not with benzodiazepines, antidepressants, or antipsychotics.[50] A systematic review and meta-analysis involving 1.1 million patients found that the risk of fractures in patients treated with zolpidem was nearly twice that of other hypnotics, suggesting a greater risk of falls.[48] A prospective analysis involving 6882 community-dwelling older adults followed for 2 years showed that insomnia symptoms and use of prescription sleep medications independently predicted falls.[51]

CASE SCENARIO (CONTINUED)

Cognitive-behavioral therapy for insomnia is recommended as initial therapy for this woman, as well as all adults with chronic insomnia. If CBT-I does not provide adequate benefit or she is unable to adhere long term, pharmacologic therapy is recommended. Since sleep maintenance is her primary difficulty, medications recommended by the AASM are: doxepin (dose ≤6 mg/d), eszopiclone, suvorexant, temazepam, and zolpidem. Lemborexant, the other orexin receptor antagonist recently approved by the FDA, would also be an option. According to the Beers Criteria, doxepin ≤6mg/d is deemed acceptable, while lemoborexant and suvorexant were not included in the list of medications to avoid.

SUMMARY

Insomnia is common among US adults and, when chronic, increases the risk of other disorders, such as incident and recurring depression and cardiovascular diseases, and diminishes functioning and quality of life. The diagnosis is based primarily on a detailed sleep history and includes assessment of comorbidities. Cognitive-behavioral therapy is first line for patients with insomnia. A variety of medication classes have been used to treat patients with insomnia, but few, mostly newer agents, are recommended in current guidelines because of limited efficacy and/or safety concerns, particularly in older adults. Individualizing treatment is important. ●

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