continuing education for pharmacists

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General Insomnia Disorder in Adults and Treatment Guidelines

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Goal. The goal of this lesson is to provide background information on insomnia, and a summary of recommendations for the non-pharmacologic and pharmacologic treatment based on current guidelines.

Objectives. At the completion of this activity, the participant will be able to:

1. demonstrate an understanding of the scope of insomnia and its effects on both the economy and the healthcare system;
2. recognize common risk factors and clinical presentation associated with insomnia;
3. list non-pharmacologic strategies for treating insomnia; and
4. demonstrate an understanding of pharmacologic agents used in the treatment of insomnia.

Background

Quality of sleep has become increasingly recognized as an important public health topic. Excessive daytime sleepiness may lead to diminished work performance and increased absenteeism from the workplace. Insufficient sleep has also been associated with an increase in motor vehicle accidents, industrial hazards, and occupational errors. Patients who lack sufficient sleep have an increased mortality and reduced quality of life. Several studies have demonstrated an increased risk of psychiatric disorders among individuals with prior insomnia.

Sleep insufficiency takes a toll on the economy with respect to loss of workplace productivity, costing an estimated $63.2 billion in the United States alone. Insufficient sleep may be caused by a broad scale of societal factors, including round-the-clock access to technology and demanding work schedules. However, sleep disorders also play an important role.

Insomnia affects 10 to 30 percent of the U.S. adult population, although as many as 35 to 50 percent of adults report having symptoms associated with the disorder. According to the Centers for Disease Control and Prevention (CDC), an estimated 50 to 70 million U.S. adults have sleep or wakefulness disorder. Insomnia places a large burden on the healthcare system, accounting for a total approximate cost of $30 to $107 billion spent annually.

Insomnia is the most commonly reported sleep disorder in the general population and is characterized by dissatisfaction with sleep quantity or quality. It is associated with difficulty initiating (sleep onset latency) or maintaining sleep and/or early-morning waking with inability to return to sleep.

Insomnia is not defined by a specific amount of sleep, as individuals with other sleep disorders may also report short sleep durations. Insomnia largely differs from minor sleep disturbance conditions in that it affects various aspects of life and has the potential to cause harm due to residual daytime drowsiness. Additionally, diagnostic criteria for insomnia specify adequate opportunity and circumstances for sleep and significant distress or symptoms during wakefulness. The opportunity for adequate sleep further differentiates insomnia from sleep deprivation, which has different causes and consequences. Criteria for the diagnosis of insomnia are listed in Table 1.

While general insomnia is classified as a sleep *disorder*, its pathophysiology suggests *hyperarousal* during sleep and wakefulness. Evidence of hyperarousal includes increased whole-body metabolic rate during sleep and wakefulness, elevated cortisol and adrenocorticotropic hormone during the early sleep period, decreased parasympathetic tone in heart rate variability, and elevated electroencephalographic (EEG) activity during non-REM sleep. Functional imaging studies have demonstrated lesser degrees of differentiation in regional brain metabolism in patients with insomnia, when compared to imaging of patients who are considered "good sleepers."

Two types of insomnia exist. *Sleep onset insomnia* is defined as difficulty initiating sleep; whereas *sleep maintenance insomnia* is defined as difficulty staying asleep and, in particular, waking too early and struggling to return to sleep.

Table 1
Diagnostic Criteria for General Insomnia Disorder

1. Report of difficulty initiating sleep, difficulty maintaining sleep, waking too early, or sleep that is chronically nonrestorative or poor in quality
2. The reported sleep difficulty occurs despite adequate opportunity and circumstances for sleep.
3. At least one of the following forms of daytime impairment related to the nighttime sleep difficulty is reported:
   - Fatigue or malaise
   - Attention, concentration, or memory impairment
   - Social or vocational dysfunction
   - Mood disturbance or irritability
   - Daytime sleepiness
   - Motivation, energy, or initiative reduction
   - Proneness for errors or accidents at work/home or while driving
   - Tension, headaches, or GI symptoms in response to sleep loss
   - Concerns or worries about sleep

Table 2
Comorbid Disease States, Medication Classes, and Conditions Associated with Insomnia

Chronic Disease States	**Psychiatric Conditions**
Breathing disorders (obstructive sleep apnea)	Anxiety
Cancer	Depression
Circadian rhythm disorders	Post-traumatic stress disorder
Dermatologic disorders (pruritus)	**Medication Classes**
Endocrine conditions (diabetes mellitus, menopause, thyroid dysfunction)	Antidepressants
Gastrointestinal conditions (GERD)	Antihypertensives (beta antagonists, calcium channel blockers)
Heart failure	Appetite suppressants
Ischemic heart disease	Central nervous system stimulants (including caffeine)
Neurologic disease (dementia)	Diuretics
Pain	Glucocorticoids
Pulmonary disease	OTC allergy, cough, and cold medications
Restless legs syndrome	Respiratory stimulants (theophylline)
Rheumatic disease (arthritis, fibromyalgia)	Sedatives and hypnotics
Urologic disease (benign prostatic hyperplasia, nocturia)	**Substance Abuse**
	Alcohol
	Illicit drugs
	Tobacco

Primary insomnias may result from a combination of psychological and/or social factors. Conversely, secondary insomnias are iatrogenic in nature and are, therefore, induced by a disease process, underlying medical condition, or external substance (e.g., medication, alcohol). Due to the various causes of clinical insomnia, clinicians must perform a thorough patient evaluation and make the diagnosis based on careful clinical history of the sleep problem and relevant comorbidities. Patient evaluation should include information regarding the individual's sleep characteristics, daytime behaviors, medical and psychiatric history, medications, and symptoms of other sleep disorders.

Pharmacists are often the primary point of contact for patients requiring assistance with health conditions which may potentially be treated with over-the-counter (OTC) agents. Appropriate management of chronic insomnia is critical, as both non-prescription and prescription medications may be used in treating chronic insomnia. Therefore, it is vital for pharmacists to understand chronic insomnia and its effects on patients. Furthermore, pharmacists play a crucial role in patient education with regard to patient expectations and potential adverse effects.

Risk Factors and Clinical Presentation

Insomnia occurs in patients of all ages and races; however, symptoms often vary between younger and older adults. Younger adults have an increased likelihood of reporting issues with sleep onset latency (difficulty falling asleep), whereas older adults generally report difficulty maintaining sleep or waking after sleep onset. Additionally, women are more likely to experience insomnia, especially following menopause and during late pregnancy.

Risk factors for development of chronic insomnia include female sex, increasing age, comorbid medical and/or psychiatric conditions, certain medications, shift work, and possibly unemployment and lower socioeconomic status. Patients with comorbid medical and/or psychiatric conditions are at highest risk, with psychiatric and chronic pain disorders having insomnia rates as high as 50 to 75 percent. Table 2 lists common comorbid disease states, medication classes, and conditions associated with insomnia. Approximately half of patients diagnosed with chronic insomnia report continuing symptoms at one year or more. Chronic insomnia is an independent risk factor for the development of depression anxiety; when these conditions occur concomitantly, a decline in response to treatment has been reported.

Patients with insomnia often complain of difficulty falling asleep, frequently waking, and difficulty returning to sleep or waking too early in the morning. Additionally, patients complain that sleep does not feel restful, refreshing, or restorative. While some patients may complain of one symptom, it is common for patients with chronic insomnia to experience a combination of symptoms. It is also common for the presentation of chronic insomnia to vary over time.

Treatment Goals and Outcomes

Treatment is generally recommended if the insomnia has a significantly negative impact on a patient's sleep quality, health,

comorbid disease states, or daytime function. Treating insomnia is often challenging, as both modes of intervention have limitations. Treatment selection should be individualized with the patient's values and preferences, availability of advanced behavioral therapies, severity and impact of the insomnia, and potential risks versus benefits, costs, and inconveniences taken into account.

Goals of insomnia treatment include improvement in the quality and quantity of sleep, reduction of distress and anxiety associated with insufficient sleep, and improvement in daytime function. Treatment includes two broad categories — non-pharmacologic therapy and pharmacologic therapy. Insomnia may be managed with psychological therapy, medication therapy, or a combination of both. Complementary and alternative approaches such as acupuncture and Chinese herbal medicine have been used to treat insomnia; however, sufficient evidence is lacking in determining the safety and efficacy of these approaches.

Non-Pharmacologic Therapy

Treatment of insomnia should include at least one behavioral intervention. Psychological and behavioral interventions are well-supported by scientific evidence. Behavioral treatments are indicated for both primary and secondary insomnia and include sleep hygiene education, stimulus control, relaxation, and sleep restriction therapy. Psychological intervention includes cognitive behavioral therapy. Such interventions are recommended as an initial approach in treating insomnia and may overlap with one another.

Sleep Hygiene. While the efficacy of sleep hygiene therapy alone has yet to be elucidated, several clinical trials have shown it to be superior to placebo. Achieving sufficient and adequate amounts of sleep is critical to both physical and mental health. Assessment for proper sleep hygiene involves reviewing an individual's bedtime habits and rituals. According to the National Sleep Foundation, frequent sleep disturbances and daytime drowsiness are the most common signs of poor sleep hygiene. Sleep hygiene techniques are recommended as an initial intervention for all adults with insomnia, as the techniques allow personal habits and environmental factors that negatively impact sleep to be identified and corrected.

Patients should be advised to limit daytime napping to 30 minutes or less. Although short naps have been associated with improved alertness and performance, the National Sleep Foundation states that daytime napping cannot replace inadequate nighttime sleep.

Regular exercise promotes good sleep quality. As little as 10 minutes of aerobic exercise may drastically improve nighttime sleep quality. While it is often advised that patients avoid strenuous exercise before bedtime, there is no substantial evidence to support this statement.

Avoiding substances such as caffeine, nicotine, and alcohol within four to six hours before bedtime also helps promote rest. Caffeine and nicotine are stimulants and have the tendency to keep patients overly alert during sleep. While alcohol has the potential to induce sleep initially, its effects are short-lived. Too much alcohol too close to bedtime has been associated with sleep disruption, due to the body processing the alcohol during the sleep cycle. Patients should be advised to avoid heavy or rich foods, fatty or fried foods, and edibles containing spicy, citrus, or carbonated beverages close to bedtime.

For patients who may not venture outdoors regularly, exposure to natural light during the day and darkness at night helps maintain a healthy circadian rhythm. Patients should also ensure they have a pleasant environment for sleep. This often includes eliminating televisions and other electronics at bedtime to associate the bedroom with sleep. Bedroom temperature should be cool and comfortable. The National Sleep Foundation recommends a bedroom temperature between 60 and 67°F as an optimal temperature. Patients should be encouraged to establish a bedtime routine to help the body associate sleep with the routine.

Stimulus Control. Stimulus control involves establishing a regular sleep-wake cycle by associating the bedroom with sleep. Recommendations for stimulus control include lying down to sleep only when feeling sleepy; exclusive use of the bedroom for sleep and sex only; removal of distractions such as electronic devices from the bedroom; leaving the bed if unable to fall asleep within 20 minutes and returning to bed when sleepiness returns; and limiting daytime naps. Additionally, patients should be advised to set an alarm for the same time every morning, regardless of how many hours of sleep occurs during the night, allowing for the establishment of a regular sleep cycle.

Sleep Restriction. Sleep restriction has been beneficial in patients who spend a disproportionately long amount of time in bed attempting to fall asleep. Patients undergoing sleep restriction interventions are advised to limit the amount of time spent in bed to the number of hours they actually spend sleeping. This time should be no less than five hours. As the amount of time of sufficient sleep improves, sleep time is gradually increased so an individual spends the majority of his or her time in bed asleep.

Temporal Control. Temporal control also focuses on re-establishing a consistent sleep-wake cycle. Patients undergoing temporal control intervention are instructed to avoid daytime napping and wake up at the same time every day — regardless of the amount of sleep achieved during the prior night. The most commonly reported limitation of both sleep restriction and temporal control interventions is excessive daytime drowsiness.

Cognitive Behavioral

Therapy. Cognitive behavioral therapy (CBT) is the cornerstone of non-pharmacologic management of insomnia. CBT targets the underlying issues that lead to or exacerbate sleep problems such as maladaptive behaviors, thoughts, and beliefs. Treatment consists of a combination of sleep hygiene education, stimulus control, sleep restriction, relaxation training, journaling, and cognitive restructuring.

CBT is recommended as first-line therapy in older adults and has been shown to increase REM sleep and decrease wakefulness, improving homeostasis. Several randomized controlled trials have demonstrated improved mood and long-term sleep quality with the use of CBT.

Although CBT is considered first-line therapy, its availability is not yet widespread. One-on-one CBT requires the use of local clinicians with specific training. Not only may a patient have a difficult time finding such a clinician, but CBT may also be financially unsustainable for clinicians due to the complicated reimbursement system. Therefore, much interest has been generated in alternatives to face-to-face cognitive behavioral therapy.

One cost-effective and accessible way to provide CBT utilizes online platforms that a patient may log into and go through the basics of CBT via a step-by-step process for six to eight weeks. Another alternative is group cognitive behavioral therapy. Group CBT allows trained clinicians to interact with and treat multiple patients with chronic insomnia. Groups generally consist of five to eight participants and treatment involves five sessions delivered on a weekly or biweekly basis. Lastly, video conferencing offers another low-cost and easily accessible mode of delivering CBT.

Pharmacologic Therapy

The use of sleep aids and self-medication are very common among individuals with chronic insomnia. Therefore, it is imperative to ask about the use of sleep aids in any evaluation of a patient with insomnia symptoms. Several pharmacologic agents have gained FDA approval for the treatment of insomnia, while other agents may be prescribed "off label" for such treatment. Due to the potential adverse effects associated with the use of pharmacotherapy, risks and benefits of all agents must be considered on a case-by-case basis. Table 3 lists indications, dosages, and common adverse effects of medications indicated for the treatment of insomnia. Per the American College of Physicians clinical guideline for management of chronic insomnia, pharmacologic therapy should be supplemented with cognitive behavioral therapy, when possible.

Benzodiazepines. Agents such as triazolam and temazepam have historically been used in treating patients with sleep disturbances. Benzodiazepines (BZDs) bind non-selectively to any of four GABA-A receptor subunits, resulting in several possible outcomes including sedation, anxiolysis, amnesia, and muscle relaxation. The practice of using such agents, however, has fallen largely out of favor due to an increase in observed adverse effects, especially in older adults. Furthermore, several randomized controlled trials have demonstrated insufficient or low levels of evidence to support regular administration of BZDs in the treatment of chronic insomnia.

Benzodiazepines approved by FDA for use in chronic insomnia include estazolam, flurazepam, temazepam (Restoril™), triazolam (Halcion®), and quazepam (Doral®). Of these agents, the American Academy of Sleep Medicine (AASM) only recommends triazolam and temazepam in the treatment of insomnia. Triazolam has a shorter half-life in comparison to the other agents and is, therefore, used in treating issues with sleep onset. Agents with intermediate half-lives, such as temazepam, should generally be reserved for patients with sleep onset or sleep maintenance problems. Longer-acting agents, such as flurazepam, may improve sleep maintenance, but are rarely prescribed due to the higher risk of residual daytime effects. Potential adverse effects of BZDs include drowsiness, dizziness, lightheadedness, impaired motor control, and cognitive impairment. Benzodiazepines carry an FDA Boxed Warning regarding concomitant administration with opioid agonists, as combined use of opioids with BZDs or other drugs that depress the central nervous system (CNS) have resulted in serious adverse reactions, including slowed or difficult breathing and death. Pharmacists should counsel patients and caregivers about the risks of slowed or difficult breathing and/or sedation, and the associated signs and symptoms. Lastly, benzodiazepines are classified as controlled substances and have the potential to become addictive. Pharmacists should exercise caution and clinical judgment in dispensing BZDs.

Non-Benzodiazepine Hypnotics. Non-benzodiazepine hypnotics include zolpidem (Ambien®, Ambien CR®, Intermezzo®), eszopiclone (Lunesta®), and zaleplon (Sonata®). Similar to BZDs, non-BZD hypnotics also target the GABA receptor. However, they have a much higher binding affinity for the alpha-1 subunit, which mediates sedation and amnesia. Non-BZD hypnotics are generally considered to have milder side effect profiles in comparison to BZDs, although administration dose and half-life also play important roles in selecting an appropriate agent. Agents with short half-lives, such as zolpidem and zaleplon, are recommended by current AASM guidelines for treatment of sleep onset insomnia. When administered during middle of the night awakenings, zolpidem has been associated with residual daytime effects at approved doses. Therefore, a patient should be counseled to take zolpidem prior to bedtime and only when he/she has adequate time to sleep. Conversely,

Table 3
Recommended Pharmacologic Therapy for Treatment of Insomnia in Adults vs No Treatment*

Drug Name	Indication	Dose	Common Adverse Effects
Benzodiazepines			
temazepam	sleep onset & sleep maintenance insomnia	7.5–30 mg	**Boxed Warning:** Concomitant use of BZDs with opioids may cause potentially fatal CNS depression •drowsiness, dizziness, lightheadedness, impaired motor control, cognitive impairment
triazolam	sleep onset insomnia	0.125–0.25 mg	
Non-BZD Hypnotics			
eszopiclone	sleep maintenance insomnia	1–3 mg	**Boxed Warning:** Concomitant use of non-BZD hypnotics with opioids may cause potentially fatal CNS depression •sedation, dizziness, impaired motor control, cognitive impairment, headache, amnesia, GI symptoms, unpleasant taste (eszopiclone), parasomnias
zaleplon	sleep onset insomnia	5–20 mg	
zolpidem	sleep onset insomnia	IR: 5–10 mg CR: 6.25–12.5 mg SL: 1.75–3.5 mg	
Orexin Receptor Antagonists			
suvorexant	sleep onset & sleep maintenance insomnia	10–20 mg	Concomitant use with opioids may cause potentially fatal CNS depression •cognitive and/or behavioral changes, complex behaviors, worsening depression, daytime impairment, sleep paralysis, hallucinations
Miscellaneous Agents			
doxepin	sleep maintenance insomnia	≤6 mg	•sedation, dizziness, hypertension, nausea
ramelteon	sleep onset insomnia	8 mg	•dizziness, somnolence, fatigue

**Per the American Academy of Sleep Medicine*

zaleplon has not been found to produce residual daytime effects when taken at middle of the night awakenings. Eszopiclone and the extended-release zolpidem formulations, with long half-lives, may be prescribed for sleep maintenance insomnia or sleep-onset insomnia. Long-term studies of both eszopiclone and extended-release zolpidem have shown continued efficacy without rebound insomnia, which has been observed with shorter-acting agents in the same class.

Potential side effects of non-BZD hypnotics include sedation, dizziness, impaired motor control, cognitive impairment, headache, amnesia, gastrointestinal symptoms, and unpleasant taste (eszopiclone). Parasomnias, such as sleep walking or sleep driving, are potentially dangerous side effects of this class of sleep medications. Parasomnias are often exacerbated when non-BZD hypnotics are concomitantly taken with alcohol or other sedating agents; at times other than the patient's normal bedtime; or in the setting of untreated sleep disorders, such as restless legs syndrome or sleep apnea. Like BZDs, non-BZD hypnotics may be potentially habit-forming and caution should be used when dispensing these agents.

Orexin Receptor Antagonists. Suvorexant (Belsomra®) is a relatively new agent indicated for treatment of sleep onset and/or sleep maintenance insomnia. AASM guidelines, however, recommend suvorexant as a treatment for sleep maintenance insomnia versus no treatment in adults. Suvorexant acts by preventing the binding of wake-promoting neuropeptides orexin A and orexin B to their respective receptors (OX1R and OX2R). Antagonism of OX1R and OX2R is thought to suppress the drive to awaken. Separate clinical trials comparing suvorexant to placebo demonstrated no significant increase in adverse effects in patients taking suvorexant. Additionally, no clinical trials have demonstrated evidence of daytime residual drowsiness or withdrawal symptoms in patients administered suvorexant versus placebo.

Patients taking suvorexant should be counseled to administer the medication approximately 30 minutes prior to anticipated sleep and only if he or she has at least seven hours to devote to sleep. Food may delay the effects of suvorexant; therefore, patients should be counseled against taking suvorexant with or immediately after a meal. Adverse effects of suvorexant include cognitive and behavioral changes such as amnesia, anxiety, hallucinations, and other neuropsychiatric conditions; complex behaviors such as sleep driving or eating; worsening of depression including suicidal ideation in patients with comorbid depression; daytime impairments; sleep paralysis; and hypnagogic/hypopompic hallucinations, which occur during the transition between wakefulness and sleep. Suvorex-

ant is designated as a controlled substance and carries a warning cautioning against its use with opioid agonists, as concomitant administration may further depress the CNS.

Other FDA-Approved Medications. Ramelteon (Rozerem®) is a potent, selective melatonin receptor agonist indicated for the treatment of sleep onset insomnia. Low-dose ramelteon may be effective in treating circadian rhythm disorders. AASM guidelines suggest clinicians use ramelteon for sleep onset insomnia versus no treatment in adults. Long-term studies have shown regular administration of ramelteon consistently improved sleep-onset latency without evidence of residual daytime effects, rebound insomnia, or withdrawal symptoms upon discontinuation of therapy. In contrast to BZDs and non-BZD hypnotics, ramelteon is not a controlled drug and has not been associated with abuse potential. Common adverse effects of ramelteon include dizziness, somnolence, and fatigue. Concurrent administration of ramelteon and fluvoxamine is contraindicated, as fluvoxamine may increase the serum concentration of ramelteon.

Doxepin (Sinequan®, Silenor®), a tricyclic antidepressant, is indicated to treat sleep maintenance insomnia at lower doses. At doses ≤6 mg, doxepin acts less as an antidepressant; rather, it antagonizes the histamine-1 receptor with limited anticholinergic effects. Doxepin can improve sleep efficiency, total sleep time, and wake after sleep onset. Like ramelteon, doxepin is not a controlled substance and does not have a known potential for abuse. Current AASM guidelines recommend clinicians use doxepin as a treatment for sleep maintenance insomnia versus no treatment in adults. Adverse effects of doxepin include sedation, dizziness, hypertension, and nausea. Patients who are prescribed doxepin for treatment of chronic insomnia should be re-evaluated if their symptoms are not remitted within seven to 10 days. Doxepin should be used with caution in patients with diabetes mellitus, as it may alter glucose regulation. Doxepin concentrations may be increased in patients with hepatic impairment; therefore, clinicians should be cautious in prescribing doxepin in such situations.

Non-FDA-Approved Medications. Various medication classes, such as other antidepressants, antiepileptics, atypical antipsychotics, and over-the-counter agents, are commonly prescribed for the treatment of insomnia. Although these medications have not been approved by FDA for use in treating insomnia, they may be administered as an off-label indication in patients with certain comorbid conditions.

Antidepressants such as trazodone (Desyrel®) and mirtazapine (Remeron®) are often prescribed for the treatment of insomnia. Doses of these agents, however, are much lower than doses used in treating depression. Data from limited controlled trials suggest trazodone at doses of 50 to 100 mg administered once nightly may be beneficial as short-term treatment of insomnia symptoms. Due to a lack of supportive evidence, the AASM guidelines for treatment of chronic insomnia recommend against the use of trazodone in treating sleep-onset or sleep-maintenance insomnia. While the package labeling does not specify an indication or dose for treating insomnia, mirtazapine may be prescribed due to its ability to make patients drowsy and may be useful in patients with comorbid depression or anxiety. Antidepressants do not carry the potential for addiction or abuse, providing a potential advantage for patients with insomnia who have histories of substance abuse. Potential adverse effects of antidepressants include dizziness, drowsiness, weight gain, increased suicidal ideation (in young adults), cardiac arrhythmias, orthostatic hypotension, and priapism (with trazodone use). Clinicians should be aware of potential adverse effects and only prescribe these agents for the treatment of insomnia if the benefits outweigh the risks to an individual patient.

Gabapentin (Neurontin®), pregabalin (Lyrica®), and tiagabine (Gabitril®) are *antiepileptic agents* that may be prescribed for insomnia. These agents may be of use for treating insomnia in specific patient populations such as those with generalized anxiety disorder, a history of substance abuse, epilepsy, or chronic pain. The AASM guidelines recommend against the use of antiepileptic agents as treatment for sleep onset or sleep maintenance insomnia, as there has been insufficient evidence to suggest their efficacy for these particular indications. Potential adverse effects of antiepileptic agents include drowsiness, dizziness, cognitive impairment, and mood symptoms.

Although *atypical antipsychotic agents* were not mentioned in the AASM guidelines, agents such as olanzapine (Zyprexa®) and quetiapine (Seroquel®) are commonly prescribed for insomnia in patients with comorbid psychiatric conditions. Some studies have reported improvement in total sleep time and sleep efficiency; however, these studies were small and results evidence was not sufficient to support their use. Possible adverse effects of atypical antipsychotic agents include abnormal lipid regulation, weight gain, new-onset diabetes mellitus, extrapyramidal symptoms, and increased mortality in elderly populations.

Over-the-Counter Agents. Patients often visit the pharmacy counter in search of recommendations regarding over-the-counter (OTC) agents to treat minor sleep disturbances. Agents such as melatonin, valerian root, and diphenhydramine have been long thought to aid in minor sleep issues; however, AASM guidelines recommend against the use of these agents in adult patients with insomnia (vs. no treatment) due to lack of sufficient supportive evidence. Given that many patients will seek out OTC remedies initially, pharma-

cists should be aware of how these agents work and potential adverse effects associated with them.

Melatonin is a naturally-occurring hormone; its release is stimulated by darkness or lack of light. The dietary supplement has not been approved by FDA. Several small clinical trials have demonstrated melatonin's role in reducing sleep onset latency in various sleep-related disorders affecting both adults and children. Although the administration of melatonin has been shown to shift melatonin secretion and circadian rhythm patterns, a direct hypnotic effect has not been clearly established. Therefore, melatonin may be useful in patients with jet lag or in those who work overnight or other shifts that are inconsistent with natural circadian rhythm. Patients experiencing difficulty falling asleep are recommended to take between 3 to 5 mg orally every evening about three to four hours before bedtime for four weeks. Most clinical studies note an absence of adverse reactions associated with melatonin administration. Minor adverse reactions to melatonin have included headache, transient depression, enuresis, dizziness, nausea, insomnia, nightmares, and excessive daytime somnolence.

Products containing valerian root, a perennial herb native to North America, commonly claim to possess sedative and hypnotic qualities. Like most herbal products in the United States, valerian root extracts are not regulated for quality and consistency. Some clinical studies have demonstrated favorable effects of valerian root in treating insomnia — most often by decreasing sleep latency. Administration of commercial preparations resulted in no changes in sleep latency, sleep quality, or night awakenings, and an increase in sleepiness on awakening. Subgroup analyses showed positive effects of valerian root administration were more evident in older male patients, females, smokers, and patients with persistently long sleep latencies. The effective dosage of valerian root for treating insomnia ranges from 300 to 600 mg, administered orally from 30 minutes to two hours prior to bedtime. Studies suggest that valerian root is more effective when utilized continuously rather than as an acute sleeping aid. Valerian root is generally well-tolerated; however, adverse effects such as headache and gastrointestinal upset have been reported.

Diphenhydramine and doxylamine are two first-generation antihistamines which are often sought for their sedative-type qualities. These agents are commonly known to cause drowsiness; therefore, their presumed efficacy in treating insomnia is related more to an adverse effect rather than clinical trial data. Due to their ability to cause drowsiness, first-generation antihistamines may be useful in patients experiencing minor problems with sleep onset. Usual dosing of diphenhydramine for insomnia treatment is 50 mg 30 to 60 minutes prior to bedtime, whereas doxylamine should be administered at a 25 mg dose. Patients should be cautioned against administering these agents habitually, as rebound insomnia has been reported. Pharmacists should be aware that due to anticholinergic properties of first-generation antihistamines, potential side effects may include tachycardia, disorientation, dizziness, drowsiness, dry mouth, urinary retention, constipation, and dry mucous membranes.

Summary

Insomnia is a common complaint among many adults in the U.S. Sleep insufficiency represents a significant burden on both the healthcare system and the economy. Excessive daytime sleepiness has been associated with increased motor vehicle accidents, occupational errors, and workplace hazards. Common characteristics of patients who develop insomnia include female sex, increased age, comorbid medical and/or psychiatric conditions, certain medications, shift work, and possibly unemployment and lower socioeconomic status.

A common approach to treatment of insomnia includes a combination of cognitive behavioral therapy and pharmacologic treatment. Cognitive behavioral therapy relies on addressing a patient's thoughts and behaviors regarding sleep, whereas pharmacologic treatment aims to resolve the overall lack of sleep by utilizing appropriate medication therapy. Several pharmacologic agents have been approved by FDA for the indication of treating insomnia. There are many other pharmacologic agents, however, that while not currently indicated for treating insomnia, may be useful in certain patient populations, according to the American Academy of Sleep Medicine. Pharmacists should be aware of risk factors for development of insomnia, clinical presentation, and potential adverse effects of the various classes of medications commonly prescribed to treat insomnia.

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General Insomnia Disorder in Adults and Treatment Guidelines

1. Excessive daytime sleepiness may cause an increase in all of the following EXCEPT:
   a. motor vehicle accidents.
   b. workplace productivity.
   c. industrial/occupational hazards.

2. Evidence of hyperarousal includes:
   a. decreased whole-body metabolic rate during sleep and wakefulness.
   b. elevated cortisol and adrenocorticotropic hormone during the early sleep period.
   c. increased parasympathetic tone in heart rate variability.

3. Which of the following is a risk factor for developing chronic insomnia?
   a. Female sex
   b. Younger adults
   c. High socioeconomic status

4. All of the following medication classes may be associated with insomnia EXCEPT:
   a. diuretics.
   b. antidepressants.
   c. proton pump inhibitors.

5. All of the following are techniques for adequate sleep hygiene EXCEPT:
   a. drinking a glass of wine within 30 minutes of bedtime.
   b. avoiding rich, fatty foods before bedtime.
   c. regular exposure to natural light.

6. All of the following are recommendations for stimulus control therapy EXCEPT:
   a. lying down to sleep only when feeling sleepy.
   b. maximizing length of daytime naps.
   c. exclusive use of the bedroom for sleep and sex only.

7. Sleep restriction therapy involves which of the following?
   a. Removing all electronic devices and distractions from the bedroom
   b. Waking at the same time every day, regardless of number of hours slept
   c. Limiting amount of time spent in bed to the number of hours spent sleeping

Completely fill in the lettered box corresponding to your answer.

1. [a] [b] [c]	6. [a] [b] [c]	11. [a] [b] [c]
2. [a] [b] [c]	7. [a] [b] [c]	12. [a] [b] [c]
3. [a] [b] [c]	8. [a] [b]	13. [a] [b] [c]
4. [a] [b] [c]	9. [a] [b] [c]	14. [a] [b] [c]
5. [a] [b] [c]	10. [a] [b] [c]	15. [a] [b] [c]

❑ **I am enclosing $5 for this quiz made payable to: Ohio Pharmacists Association.**

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8. CBT is recommended as first-line therapy in older adults and has been shown to increase REM sleep and decrease wakefulness, improving homeostasis.
   a. True b. False

9. Benzodiazepines exert their effects by which mechanism?
   a. Antagonism of melatonin receptors
   b. Selectively binding to and blocking the effects of wake-promoting neuropeptides
   c. Non-selectively binding to any of four GABA-A receptor subunits

10. All of the following are potential adverse effects of benzodiazepines EXCEPT:
   a. unpleasant taste.
   b. cognitive impairment.
   c. lightheadedness.

11. Which of the following agents has not been observed to produce residual daytime effects?
   a. Zolpidem
   b. Zaleplon
   c. Eszopiclone

12. Antagonism of OX1R and OX2R receptors is thought to have which effect in humans?
   a. Enhance the drive to waken
   b. Suppress the drive to sleep
   c. Suppress the drive to awaken

13. All of the following are true for ramelteon EXCEPT:
   a. at high doses it may be effective in treating circadian rhythm disorders.
   b. it is a potent, selective melatonin receptor agonist.
   c. is indicated for the treatment of sleep onset insomnia.

14. Gabapentin may be of use in treating insomnia in patients experiencing all of the following EXCEPT:
   a. epilepsy.
   b. chronic pain.
   c. hypertension.

15. All of the following are potential adverse effects of first-generation antihistamines EXCEPT:
   a. rebound insomnia.
   b. dry mucous membranes.
   c. diarrhea.

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