Counseling Patients on the Use of Pharmacotherapy for Insomnia

by Nicole Van Hoey, PharmD

Supported by an independent education grant from Merck.

Jul. 1, 2016 (expires Jul. 1, 2019)
Activity Type: Application-based
To earn continuing education credit:
ACPE Program 0207-0000-16-007-H01-P;
0207-0000-16-007-H01-T

Pharmacist Objectives
By completion of this program, pharmacists should be able to:

1. Distinguish signs and symptoms of insomnia disorder in the community setting.
2. Assess patient medical history and daily routine for medical/pharmacological or behavioral causes of insomnia.
3. Explain the pathophysiology of the sleep-wake cycle and of hormonal sleep controls as they relate to falling or staying asleep.
4. Select the appropriate OTC option for new-onset insomnia or determine when to refer patients for medical care.
5. Discuss the different practical administration benefits and risks associated with established and new prescription classes for insomnia.

Technician Objectives
By completion of this program, pharmacy technicians should be able to:

1. Distinguish signs and symptoms of insomnia in the community setting.
2. Identify patient behaviors, conditions, or medicines that may cause insomnia.
3. Explain how problems falling or staying asleep develop.
4. Select an appropriate OTC option for new-onset insomnia.
5. Discuss the benefits and risks associated with established and new prescription insomnia treatments.

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INTRODUCTION

Disturbed sleep may be one of the most common yet inadequately treated health conditions shared by people across the globe. Nearly 70 million people across the United States have a diagnosed sleep disorder, and approximately 50 percent of U.S. adults each year report having trouble sleeping. Insomnia can be defined simply as the inability to sleep, but many complexities hide in that definition. Sleeping difficulties affect people of all types and ages; they may be an acute reaction to an identifiable cause or can develop into a chronic concern that contributes to accumulated sleep debt—the difference between how much sleep is recommended and how much actually takes place. Personal and socioeconomic costs of insomnia develop from lost work productivity, accidents, and increased physician and pharmacy visits. Despite the clear adverse effects of poor sleep, the causes and progression of insomnia make it continually difficult to treat successfully.

CASE PRESENTATION

Patient A.H. has filled prescriptions (for diabetes and nasal allergies) at your pharmacy for the past four years. She is a 36-year-old mother of three kids younger than 6, and she is in today for an annual flu shot. She has a bottle of a common over-the-counter (OTC) sleep aid (which contains diphenhydramine and acetaminophen) in her cart.

WHAT IS INSOMNIA?

One of 10 sleep-wake disorders identified in the Diagnostic and Statistical Manual of Mental Disorders, insomnia disorder is defined broadly as a problem falling or staying asleep, and is specifically associated with a feeling of distressed or unrefreshed sleep that affects daytime function. Sometimes, insomnia develops without an identifiable cause, named primary insomnia. In secondary insomnia, a known condition triggers the sleep disturbance. Insomnia can be additionally characterized into acute and chronic subtypes.

Acute insomnia is also known as adjustment insomnia, because it frequently develops when a person is adjusting to a lifestyle change or stressor, such as anxiety about an illness or death, job change, or other type of loss. This common subtype rarely lasts more than 30 days and can resolve without treatment as the body's sleep-wake cycle and neurochemical balance resets itself. The annual U.S. prevalence of brief adjustment insomnia is approximately 30 percent.

When insomnia lasts for more than 30 days, especially if it begins to change daily actions, it becomes a chronic disorder. Chronic insomnia can develop subsequent to acute insomnia or, in more than 75 percent of occurrences, as a result of other physical or mental conditions. Of surveyed adults with insomnia, 10 percent reported chronic problems that occurred more than three times weekly or for more than three months. The chronic subtype warrants evaluation by a health professional to identify the potential conditions that, if treated, will resolve the sleep disorder.

The progression of acute insomnia beyond 30 days is known as psychophysiological chronic insomnia. Here, concern about the original stressors evolves into persistent acute anxiety about the ability to fall asleep. Many of these patients tend to underestimate the amount of sleep they actually receive each night.

Causes

Causes of chronic insomnia, when identifiable, fall into four categories: physical conditions, mental conditions, medications or supplements, and behavioral or lifestyle factors. Pain is a dominant physical contributor, most often as a result of arthritis, back pain, or cancer pain. Physical illnesses that change sleep schedules and increase stress also contribute. Mental disorders frequently coexist with insomnia too: approximately 80 percent of people with depression report insomnia, and approximately 40 percent of people with insomnia are diagnosed with a variety of concomitant mood disorders. Medications and supplements, and the timing of these products, can trigger sleep disturbances and poor sleep habits. For example, thyroid medications mimic endogenous thyroid hormones secreted during the sleep-wake cycle. With high doses, especially if taken later in the day, patients remain stimulated and awake into the evening hours. Caffeine and marketed stimulant products (including energy drinks) induce neuronal arousal over rest, as do illicit products such as amphetamines.

Lifestyle and behavioral choices are closely related to sleep habits but are less likely to be discussed in the pharmacy. However, these highly individualized habits can be key to understanding why insomnia occurs and how to effectively treat it. Evening stimulation, especially when associated with extra light sources such as electronic devices, alter the body's ability to release hormones that trigger sleep and can instead trigger the release of arousal hormones, such as cortisol. Even seemingly minor evening habits, including the timing of meals and exercise, can disrupt sleep.

Manifestations of Chronic Insomnia

As insomnia continues to be left untreated, the body's sleep debt accumulates and leads to symptoms that bring patients to the pharmacy. Common early adverse effects include mood changes like anger and tension; poor focus and attention; and memory difficulties. As insomnia continues, poor motor function, headache, stomach upset, inability to function at work or socially, and increasing accident rates develop. Patients with chronic insomnia lose nearly eight days of work each year, at a cost of $63 billion per year.

According to the Centers for Disease Control and Prevention, insomnia disorder is a public health concern not only because of its broad patient population, but also because of the serious societal risks that result from untreated insomnia—such as greater numbers of motor vehicle collisions and medication errors.

HOW DOES INSOMNIA OCCUR?

Insomnia develops in a variety of people in response to complex, individualized combinations of physical and psychological triggers; these triggers change the balance of neurochemicals and hormones in the sleep-wake cycle differently in every patient. One unifying but perhaps simplified concept is that of hyperarousal—the imbalance tips the patient's nervous system (both central and peripheral) into activation instead of quiet. These changes can be quantitatively measured by, for example, increased heart rate and electroencephalogram (EEG) changes in a sleep lab. Hyperarousal is felt by patients themselves, too, who might admit that they cannot stop their thoughts from racing.

Endogenous molecules with an array of primary functions can be grouped into wake-promoting or sleep-promoting classes. Sleep suppressors (wake promoters) include histamine and orexin. Sleep promoters include molecules commonly used to exogenously change sleep patterns: serotonin, melatonin, prostaglandins, and gamma-aminobutyric acid (GABA). GABA broadly inhibits neuronal activity, so it remains the main target of most prescription treatments. New research into the role of other molecules that may offer more specificity and fewer side effects is ongoing.

Along with neuronal molecules, hormones (such as cortisol, thyroid-stimulating hormone) from systems such as the adrenal and endocrine systems interact with the nervous system to affect the body's ability to be alert or at rest. In particular, the cortisol's role in insomnia is well studied. Cortisol's role in the hypothalamic-pituitary-adrenal (HPA) axis is integral to sleep routine, so any disruption to the regularity of cortisol levels can lead to insomnia. Cortisol levels are at their highest in the morning (around 9 a.m.), as melatonin is at its lowest. After about 2-3 hours of sleep, cortisol levels begin to increase slowly until their morning peak. Disruption of cortisol patterns can be a cause of insomnia or a response to anxiety about ongoing insomnia, because cortisol activates alertness and is released in stress responses. Exercise, caffeine, meals, medication timing, and combinations of these factors also can increase cortisol and reset its normal decline in the evening to delay sleep.

One sleep aspect pathophysiology that overlaps between insomnia and other sleep disorders is the circadian rhythm or cycle. This rhythm uses melatonin to guide the body into restfulness on a regular path. Melatonin is made in the pineal gland and is released every evening as a result of a hypothalamic trigger. Its release, which correlates directly with the absence of light, occurs around 9 p.m. naturally. Melatonin remains high for 12 full hours before it falls to a low of nearly zero by 9 a.m. Thus, melatonin naturally follows the cycle of light and dark in a 24-hour day. Melatonin release is diminished by excessive direct sunlight or bright artificial light. In patients with circadian rhythm disorder, a separate diagnosis from insomnia disorder, the patient's melatonin release and light-dark exposure are misaligned, and insomnia or other sleep disruptions result as a symptom. Exogenous melatonin products (both OTC and prescription) are available to treat circadian rhythm disorder and its associated sleep problems. Melatonin does not work as well in patients whose melatonin release is already aligned, though, and should be reserved specifically for patients whose sleep patterns do not follow usual daylight patterns (such as shift workers, cross-time-zone travelers).

Sleep disruption that patients may report as insomnia (the inability to fall or stay asleep) should be assessed not only for circadian rhythm disorder but also for other known sleep conditions. For example, sleep deprivation—the lack of enough sleep—also accumulates sleep debt like insomnia and may lead to poor sleep habits that later promote insomnia. However, sleep deprivation is distinct from insomnia disorder, because the lack of sleep results from the patient's choice to sleep too few hours.

What Are Appropriate Sleep Goals?

According to the National Institutes of Health and the National Sleep Foundation, most adults 18 and older should aim for 7-9 hours of sleep each night (7-8 hours for elderly). Actual sleep needs exist on a spectrum that is affected by genes (which determine not only how much sleep a person needs to feel rested but also at what times of the day they best fall and stay asleep), but this complex sleep system is not clearly understood. Many people claim to be alert on fewer than seven hours of sleep, but whether some individuals really do need less sleep is still up for debate.

Unfortunately, at least one third of adults (overall and in the elderly population age 60 or older) in the United States consistently report six or fewer hours of sleep on CDC surveys, and National Health and Nutrition Examination Surveys from 2005 through 2009. In the 40- to 59-year-old age range, 40 percent of surveyed adults slept less than the recommended hours.

Without adequate sleep on a regular basis, sleep deficits accumulate and compound existing health problems.

Despite the clear adverse effects of these sleep deficits and a better understanding of the complex interplay of hormones and the environment on the sleep cycle, treatment and self-care for insomnia remain notoriously unsuccessful.

CASE UPDATE

Your patient, A.H., received her flu shot and was amenable to your request to discuss the sleep aid (she is without kids for this visit). She tells you that she recently (two weeks ago) started working part-time in the afternoons and falls asleep quickly when she comes home at 8:30 p.m. However, since work began, she wakes at 1 a.m. every night and struggles to go back to sleep until her alarm goes off at 5 a.m. Thus, she is regularly missing out on the suggested minimum of seven hours nightly, so daytime insomnia symptoms are likely. What are your next counseling and assessment questions?

CAN PHARMACISTS ASSESS THE INSOMNIAC IN THE PHARMACY?

Unlike other mental health conditions, insomnia disorder is diagnosed and treated in large part according to patient-provided history that is guided by professional assessment questionnaires about health and behavioral habits. Informally, community pharmacists can play a crucial role in referring patients with symptoms of chronic insomnia to behavioral therapy or physician care and potential prescription therapy.

Asking a few simple questions during a short counseling session can identify triggers to insomnia and determine appropriate treatment options and referral needs.

Sleep problems can be as difficult to treat as they are to diagnose, in part because self-care is so prevalent. In one month, only 4 percent of U.S. adults reported use of prescription sleep aids. However, in 2013, OTC sleep aid sales were greater than $300 million dollars in the United States. Without health professional advice, adults skip important behavioral changes and potentially miss out on supervised, long-term prescription treatments. Early pharmacist efforts here can focus first on documenting habits and encouraging behavior change, then on selection of OTCs and referrals as needed for additional assessment and care (see table 1 and 2).

CASE UPDATE

A look at A.H.'s medications shows nothing new, but her meal, exercise, and sleep routines have become altered. She denies alcohol use or smoking and denies changes in her diabetes regimen. She used to sleep from 10:30 p.m. to 5:30 a.m. after an evening meal around 6 p.m. A.H. appears to be experiencing acute adjustment insomnia as a result of her changed work-life routine, but—because this new schedule is not a temporary lifestyle circumstance—the situation warrants assessment for behavioral treatment or medication to reset A.H. into a healthy sleep routine.

BEHAVIORAL TREATMENT OPTIONS FOR INSOMNIA

Patients who cannot fall or stay asleep should evaluate, with the pharmacist's help, their daytime and evening behaviors to adjust them and prepare a new sleep hygiene routine. Sleep hygiene refers to the choices and habits people observe to guide their bodies smoothly from wake to sleep states.

The body's sleep-wake cycle is extremely complex and involves hormonal controls, from melatonin to cortisol, serotonin, and gamma-amino-butyric-acid (GABA), from

Table 1. Identifying Potential Insomnia Triggers

Counseling Question	Reason for Sleep Disturbance
Purpose	Identify patients who might drink a night cap, smoke, exercise, or use tablets/computers in the evenings.
What medications do you take at night?	Determine stimulant use, medicines with short-term sedation only, and OTC factors.
What times do you last eat and drink before bed?	Identify patients who may be going to bed hungry, using alcohol to fall asleep, or trying to sleep too soon after a meal.
Do you have trouble falling asleep, staying asleep, or both?	Although prescription and OTC medicines are indicated for all types of insomnia disorder, the timing and selection of treatment are formed by the clinical experience and pharmacology of the choices.
How long has this problem lasted?	If acute, especially if fewer than 30 days, anxiety causes should be explored, and short-term hygiene recommendations and OTC treatment can be considered. If the problem is longer lasting, the patient should be referred to medical care regardless of recommendations for behavior change or OTC treatments.

Table 2. Insomnia Contributors and How They Disturb Sleep	
Contributor	**Reason for Sleep Disturbance**
Smoking	Stimulant effect when cravings start/nicotine wears off
Alcohol use	Short-term sedation only + abuse potential
Eating patterns	Too close to bed for body to relax or too early and hunger wakens patient
Exercise patterns	Within five hours of bed, acts as a stimulant
Work-life stressors	Increasing anxiety can delay or interrupt sleep
Medication timing	Sedatives that are short-acting can interrupt sleep later
TV/tablet use	Lights disrupt circadian rhythm and delay sleep

numerous body systems that continually send messages to the brain to be alert or at rest. Usually, an imbalance in at least one of these, if not multiple, triggers the onset of sleep problems like insomnia. The CDC and the NSF recognize the importance of personal actions to the release of these hormonal triggers and recommend ways to overcome sleep problems with good sleep hygiene choices.

To avoid triggering arousal signals before bedtime, patients with insomnia should reset their sleep habits with the following sleep hygiene adjustments:

- Avoid large night-time meals and caffeine but do not go to sleep hungry.
- Avoid alcohol, because it is an abuse risk but also because it induces sleep initially but may not prevent mid-cycle awakenings.
- Set one start time and end time for sleep and wake every day—regardless of the amount of actual sleep achieved at night—to adjust the body to a routine that encourages regular melatonin cycling along with light-dark triggers, too. Similarly, avoid midday naps even when tired, because they make it more difficult to fall and stay asleep at night. This type of sleep restriction can increase the body's likelihood of sleep when the new sleep schedule is observed regardless of fatigue.
- Avoid activities that stimulate arousal hormones or melatonin: any projects, even reading, performed in bright light should be tapered off in the evening before bedtime to encourage melatonin release. Watch exciting movies or television shows earlier in the evening, not right before bed, to avoid bright light and stimulation of arousal hormones, too.
- Avoid exercise, which stimulates cortisol and other arousal hormones, directly before bedtime. A better recommendation is up to 20 minutes of exercise around five hours before bedtime, to allow the body time to return to a resting state.
- For patients who experience awakenings, remove stimuli that release light and trigger anxiety, like such as LCD clocks, or at least move the stimuli away from a distraction-free zone near the bed. Sleep masks, sound machines, and other tools to counter the stimuli may help, too.

If insomnia has become a chronic problem, the missing restful hours from the accumulated sleep debt also should be replenished as much as possible. Pharmacists can help patients break down debt into smaller quantities that can be added to the recommended minimum of seven sleep hours. Alternately, using weekend or vacation time to refresh with extra sleep hours may be more appropriate with high deficits.

Establishing good sleep habits is the first step to insomnia treatment, before formal cognitive behavioral therapy (CBT) is tried. In the pharmacy, products that promote good sleep hygiene can be placed strategically near OTC sleep aids. For example, sleep masks and ear plugs can help patients who are distracted by external stimulation and can supplement better sleep habits, such as reducing external light before going to bed. Similarly, lavender oil, sound machines, or caffeine-free teas may encourage patients looking for medication to transition more gently from wakefulness to sleep.

When these efforts are not enough, professionally guided CBT and relaxation therapy may be needed, too. CBT is a disciplined approach of psychological care. When applied to insomnia, CBT provides a structured set of steps to help a patient reset sleep-related habits. Rates of successful treatment of insomnia with CBT are as high as 80 percent, and CBT appears equally effective to treatment with prescriptions like benzodiazepines. Relaxation therapy combined with changes to sleep habits is also supported by research evidence as an insomnia treatment. This type of CBT is particularly helpful to guide patients who have anxiety as a cause or result of acute or psychophysiological insomnia. Experts in CBT techniques often work in sleep centers accredited by the American Academy of Sleep Medicine. Pharmacists can suggest that interested patients ask their general practitioner to help them find such a facility.

SELF-TREATMENT OPTIONS FOR INSOMNIA

Although many people experience insomnia at least once in their lives, not many people consider visiting their prescriber right away. Pharmacists have the responsibility as the accessible health care provider at the site of OTC purchases to identify patients who need counseling for causes, treatments, and referrals of insomnia.

OTC Antihistamines

OTC antihistamines have an important role in overcoming the barriers to sleep, but they should not be used indiscriminately. These easily accessible sleep aids are recommended for short-term use only, in part because of their side effect profiles and in case a more complicated health condition is causing the sleep interruption. For example, if a patient with cancer pain comes to the pharmacy seeking a recommendation for a sleep aid, it may be more appropriate to assess and adjust their pain medications than to suggest an additional OTC product.

The antihistamine (H1 receptor blocker) drug class is the most common type of OTC medicine approved for insomnia treatment. Although second-generation antihistamines are used to treat seasonal allergy symptoms, all antihistamines have sedation or drowsiness as a main side effect. Older antihistamine products have higher rates of this adverse effect, so these drugs are selected for sleep aid formulations. Diphenydramine hydrochloride (25 or 50 mg) or citrate (38 mg) and doxylamine succinate (25 mg) are the most frequently used OTC antihistamines for sleep, found in a wide array of marketed products.

Antihistamines have a long history of safe use in adults, but some caution is suggested with these drugs:

- Because the drowsiness can be unpredictable and individualized, patients should avoid alcohol or other antihistamine use and should avoid driving or doing anything that requires alertness (such as slicing foods, cooking, operating appliances) when they use these sleep aids.
- Many marketed products contain acetaminophen or ibuprofen as well, which is unnecessary for patients without pain as a cause of their sleep disruption. These patients should try a different, single-drug formulation if possible, and any patient who takes a combination product should avoid taking additional acetaminophen or ibuprofen to avoid excessive dosing.
- Antihistamines should be used with caution in patients with asthma and in patients 65 or older, and they should not be used in patients with benign prostatic hyperplasia or angina because of the drugs' anticholinergic effects, such as increased heart rate and blood pressure and decreased urination.

Antihistamine sleep aids should be used only for 7-10 days, in part because tolerance to the sedative effect develops with continued use. More importantly, patients with continued symptoms after approximately two weeks of treatment should be referred to a physician for assessment of chronic insomnia.

Supplements

Supplements are touted as natural sleep aids; however, many of these marketed options are newer than—and have less research support than—diphenhydramine or prescription drug products. Also, herbal supplements remain unregulated in the United States and may not contain the ingredients that are claimed on the label. The United States Pharmacopeia independently verifies some brand names to provide ingredient quality control. If you, as the pharmacy owner/manager, have a preferred reputable USP-designated supplement line, melatonin, lavender, and valerian are treatment options with historical or documented efficacy for sleep disorders.

Melatonin products offer a synthetic version of the natural sleep-wake cycle regulator. Exogenous melatonin shortens the time to fall asleep and reduces the number of awakenings if taken at appropriate doses and times. Because its mechanism of action is so specifically related to the circadian rhythm, melatonin is best used in patients whose insomnia develops only as a result of a light-dark imbalance. An example beyond the traditional populations of shift workers or travelers is the patient with extended computer use at or past bedtime that has repeatedly delayed natural melatonin release.

OTC melatonin products claim to contain a variety of doses, from 0.2 mg to 5 mg. A dose of 1-3 mg increases blood levels from 1-20 times normal concentrations. Adults should use the lowest dose needed to induce sleep. Too much melatonin can cause headaches, nausea, dizziness, and irritability that further disrupt sleep. Pharmacists should recommend that any adult patient start with 0.2-mg doses and increase from there only as needed. Melatonin should be taken one hour before bedtime to simulate natural melatonin release.

A prescription receptor agonist of melatonin, ramelteon (Rozerem), was approved in 2005 to help patients who have trouble falling asleep. It is not used for nighttime wakenings. The 8 mg tablet should be taken 30 minutes before bedtime and works best when taken without food. Although ramelteon reduces the time it takes to fall asleep better than placebo, it is most appropriate in patients whose insomnia results from circadian rhythm disruption.

Melatonin supplements interact with diabetes medicines, warfarin, oral contraceptives, and more, so these products, although available to any patient, should not be considered safer than prescription medicines and should be used with health professional supervision. Melatonin has been used for up to three months for insomnia caused by circadian rhythm problems.

Many herbal products appear to induce relaxation and sleep although the mechanisms of action for the effects

are unclear. Products such as lemon balm or lavender may alter neurochemical regulators of arousal and relaxation or may simply contribute to soothing sleep habits. Lavender, a Mediterranean shrub, was used underneath pillows in folklore to prevent restlessness. Now, the flowers may be boiled for tea or its essential oil can be diluted for inhalation or massage. Lavender appears to increase sleep quality and reduce agitation by slowing the nervous system. Adding 1-2 drops to a tablespoon of a massage oil may be most effective for patients with insomnia secondary to back pain or tension. Up to four drops can be added to three cups of boiling water for inhalation, although this technique should be avoided in patients with lung problems, such as asthma.

Approved by the German Commission E, a regulator of herbal products in Europe, valerian has been used since the second century as a mild sedative. In the United States, valerian is generally regarded as safe, and it is believed to increase GABA and reduce anxiety much like benzodiazepines. Valerian can be used alone or in combination with other sedating herbs, but it does not appear to have an immediate relaxing effect. After a step-up period of almost two weeks, the full sleep benefits begin. Patients can try dissolving two to three grams of valerian root products (often preformulated into liquids with this dose in a single teaspoon) in one cup of boiling water for a calming tea. Valerian should be continued for 2-6 weeks. Side effects include headache and dizziness. A few patients may experience paradoxical anxiety and should not continue valerian use.

CASE UPDATE

You believe that the new sleep and meal pattern for A.H. are contributing to her insomnia, so behavioral changes should be enough to improve her sleep. Specifically, you recommend eating a small meal at or just after work and waiting until around 9 p.m. to go to bed. You also suggest that A.H. review her tablet and TV use and exercise routine and try to exercise before her part-time job (around five hours before she comes home for the night). A.H. plans to take a vacation next month without kids to catch up on sleep, so she is not very concerned about long-term sleep disturbance. However, she agrees to try the recommended behavioral options but would still like to use her OTC selection for two weeks before returning for another consultation. You ensure that she is not taking additional acetaminophen and agree to follow up with her then.

WHEN BEHAVIOR CHANGE AND OTCS AREN'T ENOUGH

Historically, insomnia that did not respond to behavioral or OTC treatment attempts had been treated with neuroactive drugs that caused side effects of sleepiness or drowsiness. Examples of first-line indications for these treatments ranged from depression and anxiety, to alcohol withdrawal and seizure disorders. When a side effect is used as the main reason for treatment, though, the other pathophysiological changes it causes are usually not required or desired.

The benzodiazepine class, which includes alprazolam, midazolam, diazepam, and more, offers short- and long-acting treatment of depression, anxiety, panic, and other mental health conditions. These drugs work by increasing the GABA effects at receptors in the brain to quiet excitation and induce sedation. The range of their effects depend on how broad or localized their GABA receptor actions are, but common side effects include dizziness, confusion, blurred vision, and poor coordination.

Low benzodiazepines doses such as alprazolam, with a half-life of 6-26 hours, are often used as sleep aids. Short-acting agents are preferred, because next-day drowsiness is less likely than with longer agents. Although benzodiazepines both hasten and maintain sleep, they are C-IV controlled substances that, with long-term use (more than one month), have a dependence risk. In older patients, benzodiazepines can also accumulate and cause daytime confusion and increased falls. Benzodiazepines are most appropriate for fast relief in adults with acute anxiety-related insomnia. Their mechanism of action is unlikely to address the cause of longstanding insomnia from physical or behavioral contributors, and chronic use increases the likelihood of withdrawal symptoms, such as irritability, panic and anxiety, nausea, heart palpitations, and cognitive difficulties.

Along with the benzodiazepines, a handful of other antidepressants or anti-anxiety agents, such as trazodone, may be used off label to treat insomnia. Like the benzodiazepines, lower doses are recommended (25-50 mg trazodone at bed time). Also like the benzodiazepines, these other neurologic classes work best for patients with existing anxiety or depressive disorders.

Newer Hypnotics

In 1992, a new type of prescription hypnotic was approved with an indication for insomnia treatment. Zolpidem (Ambien) is a GABA agonist in the central nervous system and was the first of a new class of neurologic drugs that selectively bind GABA-A receptors implicated in the sleep-wake cycle. Zolpidem is absorbed quickly, with peak concentrations after a mean of 1.6 hours with 5-10 mg doses, and an elimination half-life ranging from 1.4-4.5 hours. Zolpidem has been studied in acute and chronic insomnia and reduced the time it takes to get to sleep significantly better than placebo.

Zolpidem is available as a 5 mg or 10 mg tablet, and a cost-effective generic formulation was approved in 2007. An extended-release product (Ambien CR) is available to help reduce the number of night-time awakenings, but this product should only be taken if 7-8 hours of sleep time is available after the dose. Ambien CR should not be crushed or cut. An oral spray formulation of zolpidem, Zolpimist,

was approved in 2008 for patients to use like the regular-release tablet, right before getting into bed.

Along with zolpidem, eszopiclone (Lunesta) and zaleplon (Sonata) are hypnotics approved to treat transient or chronic insomnia. Like zolpidem, they should be taken directly before bed to avoid a risk of falls or accidents from drowsiness. Eszopiclone absorption peaks in just one hour, but the drug has a half-life of six hours. Like zolpidem, this medicine helps people fall asleep more quickly, but it also is recommended for patients who have trouble staying asleep. The starting dose of eszopiclone tablets is 1 mg immediately before bed, which can be increased to a maximum of 3 mg. However, elderly patients experience more than 40 percent greater exposure than other adult age ranges and should receive a maximum 2-mg dose. Next-day grogginess is more common with the highest dose and in elderly patients. Patients who take 3 mg should not drive or operate machinery the next day, even if they feel alert.

Zaleplon offers the shortest onset and duration of action in the non-benzodiazepine hypnotics class, with peak absorption within one hour and an elimination half-life of approximately one hour as well. When capsules are taken with a fatty meal, absorption is lower and is delayed by almost two hours. Age does not appear to affect zaleplon absorption or effects. Capsules are available in 5 mg, 10 mg, and 20 mg strengths and should be taken at the lowest effective dose, to reduce adverse effects, directly before bed. Zaleplon shortens the time to fall asleep in patients with acute or chronic insomnia, but it does not appear to improve sleep duration or the number of sleep disruptions.

Although the newer hypnotics have documented efficacy, they share some of the same safety concerns with benzodiazepines. Like benzodiazepines, these drugs are C-IV controlled substances. Dependence or addiction is possible, especially when used at high doses or for long durations. Withdrawal irritability or temporary rebound insomnia (perceived or documented) are possible after these medications are used for more than a few weeks. Like benzodiazepines, these drugs should not be used with alcohol or while driving, and daytime grogginess is possible particularly when a full 7-8 hours of sleep is not achieved. At higher doses, the hypnotic drugs can induce sleep activities, including eating, that occur without patient awareness. After any of these agents are prescribed, patients whose insomnia continues must be reassessed for potential physical or mental health causes of insomnia. These hypnotic agents opened the door to prescription therapies for insomnia but have not fully met patients' needs by focusing only on the role of GABA in sleep.

THE ROLE OF OREXINS IN THE SLEEP-WAKE CYCLE AND IN INSOMNIA TREATMENT

Orexins, also known as hypocretins, are small proteins that play a role in sleep and appetite sensations. First identified in the late 1990s, orexins are produced in the hypothalamus, and early research identified a link between abnormal endogenous orexin levels and narcolepsy, another sleep disorder. The presence of orexins activates brainstem and hypothalamic responses that maintain alertness or arousal (in part via norepinephrine, cholinergic, and histamine responses), so orexins are wake-promoting molecules. Orexins appear to interact with glucose and energy/metabolic cycles as well as with neurochemicals like acetylcholine and norepinephrine in sleep-wake cycles, so they might play a role in obesity, addiction, and stress in relation to and separate from their sleep disturbance role. Orexin release appears to be activated by metabolic changes such as low blood sugar, and higher levels of orexins stimulate physiologic changes, such as increases in heart rate and blood pressure, and higher levels of insulin and cortisol.

Suvorexant (Belsomra) is the first orexin inhibitor on the U.S. prescription drug market. Approved by the Food and Drug Administration in 2014, suvorexant is an orexin receptor antagonist indicated for adults who have trouble falling and staying asleep. The drug prevents the orexin alertness response to enhance the transition from wake to sleep and to minimize nighttime arousals.

In clinical trials, suvorexant appeared well tolerated. The drug peaks in the blood after approximately two hours and has a 12-hour half-life; it reaches steady state in three days. Doses should be taken within 30 minutes of bedtime and only if at least seven hours of sleep are possible after administration.

Suvorexant is metabolized by the CYP450 liver enzyme system and is a mild CYP3A inhibitor. Most drug interactions identified through this system have not required dose alterations; patients who take oral contraceptives, digoxin, or warfarin may be monitored to assess any possible changes in drug levels during suvorexant use, but dose adjustment is unlikely. Fluconazole, a CYP3A inhibitor, can increase suvorexant levels, though, so concomitant use should be avoided, or the lowest available suvorexant dose (5 mg) should be used, and the dose should not exceed 10 mg. Conversely, CYP3A inducers such as phenytoin or carbamazepine may lower suvorexant efficacy and require dose titration to effect.

Doses of 5 mg, 10 mg, 15 mg, and 20 mg of suvorexant are available in tablet form. Meals may delay the onset of action but are not contraindicated. The recommended starting and maintenance dose is 10 mg, and 20 mg is the maximum recommended dose for patients who tolerate the 10-mg dose but do not see improvement. Patients should use the lowest effective dose and should be reassessed after 7-10 days. If insomnia does not improve after use of the maximum dose, evaluation for other external causes is recommended.

Side effects associated with suvorexant are similar to placebo, except for increased rates of next-day sleepiness, confusion, or sleep activities (such as sleep walking or

talking). Tested doses of 30 mg and 40 mg were associated with more balance and next-day impaired driving problems than placebo, and were not approved. The approved 20-mg formulation also causes excessive daytime drowsiness and worsens next-day driving ability. Patients should not perform activities that require clear thinking within eight hours after a suvorexant dose—or during the day after taking suvorexant until they feel fully awake, especially if they did not meet the recommended minimum of seven hours set aside for sleep after taking a dose.

Although suvorexant works more specifically in the nervous system than broad GABA-active classes such as the benzodiazepines or hypnotics, and thus has potentially more localized actions, it was still approved as a C-IV controlled substance. The classification was based on the potential for human abuse of suvorexant as a marketed drug with similar effects, if not mechanisms, as established insomnia treatments, such as zolpidem. Clinical trials did not identify evidence of physical dependence, but overuse or abuse of suvorexant can lead to dangerous impairment of abilities (driving, concentration). The drug is prescribed with a patient medication guide that explains the risks of high or prolonged dose regimens.

CASE RESOLUTION

A.H. returns after two weeks and states that she has successfully adjusted her diet and exercise to earlier in the day and has started going to bed and getting up at the same times regardless of actual sleep hours. She sees a benefit in the routine but is still having trouble staying asleep and quieting her anxiety upon awakening. She does not like the OTC treatment, which makes her feel too groggy in the mornings when she is with her kids. She wonders if she should try melatonin or a prescription option. Because of her work shift, melatonin may be appropriate but should not be used indiscriminately or for long durations. You recommend that she visit a sleep center or her general practitioner to discuss combined CBT and prescription therapy and to look for causes in addition to the work schedule that may be contributing to the ongoing insomnia disorder. ■

Nicole Van Hoey, PharmD, is a freelance medical writer and editor in Arlington, Va.

Editor's Note: For the list of references used in this article, please contact *America's Pharmacist* Managing Editor Chris Linville at 703-838-2680, or at chris.linville@ncpanet.org.

Continuing Education Quiz

Select the correct answer.

1. How does insomnia disorder differ from other mental health conditions?
a. It develops in a highly specific patient population.
b. It always resolves on its own, given at least three months.
c. Its diagnosis and sometimes treatment rely heavily on patient-reported history instead of testing.
d. Its treatments have low abuse potential and are effective within 7-10 days.

2. Which of the following statements is false?
a. Insomnia is one of at least 10 sleep-wake disorders described by the Diagnostic and Statistical Manual of Mental Health Disorders.
b. Insomnia can be defined as a sleep debt that results when a person chooses not to set aside adequate time for sleep.
c. Insomnia sometimes, but not always, leads to long-term sleep problems.
d. Insomnia often develops secondary to physical, mental, or lifestyle conditions.

3. Physical (not mental health) conditions that may contribute to insomnia development are:
a. High cholesterol
b. Major depressive disorder
c. Osteoarthritis
d. Family heart attack history
e. Two of the above

4. Which of the following medications can lead to sleep disruption and why?
a. Cetirizine at bedtime because of its drowsiness side effect interrupting the ability to stay asleep
b. Dextromethorphan at bedtime because of its drowsiness side effect interrupting mid-cycle sleep
c. Alcohol because of its stimulant effect when used right before bedtime
d. Nitroglycerin because of its extremely short duration of action to treat cardiovascular morbidity

5. Which of the following statements is true?
a. GABA is the only neurochemical known to affect the sleep-wake cycle as a sleep promoter.
b. GABA is one of many sleep-promoting chemicals and is the focus of prescription classes to treat insomnia.
c. Cortisol is a sleep-promoting hormone that closely follows the cycle of melatonin.
d. Cortisol awakens people mid-sleep because of the fight-or-flight response.

6. Which of the following activities may disrupt sleep by increasing cortisol release too late in the day?
a. Exercise just after lunchtime
b. Exercise just after dinner
c. An evening stress experience (such as a late work deadline, or illness onset)
d. Both B and C

7. Insomnia pathophysiology can be characterized in a simplified way as which of the following?
a. A state of excessive melatonin that induces sleep despite the wake-promoting activity of other hormones or molecules
b. An abnormal state of arousal that is triggered by the same neurochemical changes in everyone with chronic insomnia
c. A state of hyperarousal, when normal sleep promoting and wake promoting molecules are not balanced
d. A state of arousal triggered by GABA-inhibiting prescription drugs

8. Which questions are valid during pharmacy counseling sessions to assess the extent of insomnia?
a. What time do you go to work in the morning?
b. How often do you go out to eat in restaurants?
c. What time do you last eat or drink before bedtime?
d. How long has your sleep problem been happening?
e. Both C and D

9. Concerns about over-the-counter sleep aids include:
a. Lack of Food and Drug Administration oversight of products with two medications in one formulation.
b. Long-term use can lead to blackouts.
c. Only short-term use is recommended because driving becomes erratic after 7-10 days.
d. Only short-term use is recommended because longer-lasting insomnia warrants assessment by a health professional to identify secondary causes that can be treated instead.

10. Doses of lavender used today or in folklore include:
a. Taking 1-2 drops per tablespoon of oil as a massage treatment
b. Three drops in three cups of boiling water as an inhalant in patients without asthma
c. Dried flower sachets placed under pillows to enhance restfulness at bedtime
d. All of the above

11. Melatonin is considered:
a. A dietary supplement that is not regulated by the FDA.
b. A dietary supplement that also receives special FDA regulation.
c. A prescription drug used to reset circadian rhythms safely in adults and children.
d. A natural hormone that is not available as an external product.

12. Which of the following statements is true?
a. Taking more melatonin before bedtime increases the likelihood of staying asleep all night.
b. Melatonin release increases arousal and wakefulness.
c. Melatonin can be used for years without adverse effects in people whose light-dark cycle is upset.
d. Melatonin release is fairly consistent among adults, with a 9 p.m. release, and morning taper after 12 hours.

13. Benzodiazepines are the preferred first-line prescription treatment for insomnia because:
a. They are short-acting enough to prevent daytime grogginess.
b. They are not associated with withdrawal symptoms.
c. They are safe to use in all adult age ranges without contraindications.
d. None of the above.

14. The first non-benzodiazepine hypnotic to treat insomnia, _____, should be taken _____.
a. Zolpidem, at dinner time because of its longer time to peak absorption
b. Zalpelon, at bedtime because it is the only hypnotic with a risk of falls or accidents when taken earlier
c. Zolpidem, at bedtime because it is used to decrease the time to sleep onset
d. Zalpelon, at midnight awakenings, because there is still enough time to get a full night's sleep afterward

15. Because melatonin is a natural supplement, doses of 1 to 3 mg:
a. Are safe in any age population, because they increase blood concentrations only 1-3 times normal.
b. Can be taken regularly for up to one year without supervision, as melatonin is already found in the body.
c. Can be taken when people naturally go to bed, because it works immediately to induce sleep.
d. None of the above

16. A molecule identified in the 1990s, ____, plays a key role in the sleep-wake cycle by ____.
a. Orexin, reducing the levels of melatonin released by the pineal gland
b. Orexin, stimulating neurochemical systems of arousal and alertness
c. Melatonin, increasing the release of histamine, insulin, and cortisol in the brain
d. Glucose, by increasing appetite and reducing restfulness

17. Which of the following are appropriate doses of suvorexant in the given patient population?
a. A 5 mg starting dose in adults age 18 years or older with step-up to 10 mg dose after 7-10 days
b. A 10 mg starting dose in adults age 18 years or older with step-up to 20 mg maintenance dose after 7-10 days
c. A 10 mg starting and maintenance dose in adults age 18 years or older, with 20 mg reserved for well-tolerated but ineffective 10-mg trial (usually for 7-10 days)
d. A 20 mg dose for all ages with a warning about the risk of next-day drowsiness and driving impairment
e. Two of the above

18. Wake-promoting hormones:
a. Include GABA and cortisol, the two most studied molecules in insomnia pathophysiology.
b. Counteract the body's natural sleep-wake cycle by inducing a state of arousal instead of rest.
c. Block receptors in the central nervous system on a regular schedule to disrupt sleep at the same time each night.
d. Two of the above.

19. New hypnotic agents offer which advantages over benzodiazepines?
a. They are not controlled substances.
b. They do not cause daytime grogginess to the same extent.
c. There is at least one extended-release option that helps patients sleep sooner and longer.
d. They can be effective only at maintaining sleep.

20. Suvorexant is the first orexin-modulating prescription drug approved by the FDA, and it works by
a. Reducing orexin production in the brain.
b. Reducing orexin release at bedtime.
c. Blocking orexin release only in the presence of a fatty meal.
d. Blocking orexin activity at brain receptors that stimulate arousal.