CONTINUING EDUCATION

Insomnia across the lifespan

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Intended audience: This continuing education (CE) activity has been designed to meet the educational needs of women's health nurse practitioners (NPs), adult NPs, family NPs, certified nurse midwives (CNMs), and other healthcare providers (HCPs) who care for women.

CE approval period: Now through June 30, 2021

Estimated time to complete this activity: 1 hour

CE approval hours: 1.0 contact hour of CE credit, including 1.0 contact hour of pharmacology content

Goal statement: HCPs will increase their clinical skills in the evaluation and nonpharmacologic and pharmacologic management of patients presenting with sleep problems.

Needs assessment: Among adults in the United States, about 30% have symptoms of insomnia on occasion and 6%-10% have chronic insomnia meeting *DSM-V* criteria, including the all-important element of dissatisfaction with one's sleep. HCPs who provide primary care to women need to inquire about sleep problems and understand the many treatment options available to women with impaired sleep.

Educational objectives: At the conclusion of this educational activity, participants should be able to:

1. discuss the incidence and prevalence of insomnia across the lifespan;
2. identify the appropriate work-up of the individual with insomnia; and
3. describe nonpharmacologic and pharmacologic treatment options for the patient with insomnia.

Accreditation statement: This activity has been evaluated and approved by the Continuing Education Approval Program of the National Association of Nurse Practitioners in Women's Health (NPWH), and has been approved for 1.0 contact hour of CE credit, including 1.0 contact hour of pharmacology content.

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Healthcare providers (HCPs) caring for women of any age will find that a substantial proportion of them have difficulty falling and/or staying asleep. When insomnia interferes with their daily life and causes distress, they may seek professional help. This article provides background information about sleep, and offers HCPs useful and up-to-date information regarding the evaluation of patients presenting with sleep problems and the wide variety of treatments that are available.

KEY WORDS: **insomnia, sleep hygiene, benzodiazepine hypnotics, non-benzodiazepine hypnotics, ramelteon, suvorexant**

The American Academy of Sleep Medicine (AASM) defines insomnia as a complaint of trouble initiating/maintaining sleep that is associated with daytime consequences and that is not attributable to environmental circumstances or an inadequate opportunity to sleep.[1] According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V)*, insomnia is characterized by difficulty initiating and/or maintaining sleep and/or waking earlier than desired, occurring at least 3 nights per week for at least 3 months, and causing dissatisfaction with sleep.[2] Unlike in days past, when insomnia was classified as a condition secondary to another diagnosis, it is now considered an entity of its own.

The *DSM-V* lists insomnia among 10 other sleep–wake disorders.[2] Healthcare providers (HCPs) may need to rule out other sleep–wake disorders (e.g., obstructive sleep apnea, circadian rhythm sleep–wake disorder, restless leg syndrome [RLS]) before making a definitive diagnosis of insomnia in a given patient.

Prevalence and adverse consequences

Among adults in the United States, about 30% have symptoms of insomnia on occasion and 6%-10% have chronic insomnia meeting *DSM-V* criteria, including the all-important element of dissatisfaction with one's sleep.[3,4] Insomnia is more common in women than in men, in older adults than in younger adults, and in persons affected by co-morbid physical or mental health conditions than in persons in the general population.[1,4]

Chronic insomnia, defined as insomnia lasting longer than 3 months, has many adverse effects on daily functioning, health, and quality of life.[1] It is linked to increased rates of work absenteeism and occupational and motor vehicle accidents, and it has been identified as a major risk factor for developing psychiatric disorders, especially mood disorders; for relapse among persons with depression or alcoholism; for adverse effects in persons with chronic health conditions; and for development of hypertension and cardiovascular disease.[1]

Background information about sleep

The typical adult falls asleep within 30 minutes of going to bed. If she awakens in the middle of the night, it generally takes 30 minutes or less for her to fall back to sleep. A full night's sleep lasts 7-8 hours. Her *sleep efficiency*—the amount of time asleep relative to the amount of time spent in bed—is about 85%.

The sleep-wake cycle

Wakefulness and sleep are under the control of highly complex neural circuitry consisting of neuronal populations, neurotransmitters, and pathways that form orchestrated wake- or sleep-promoting networks.[5] Neurotransmitters involved in wakefulness include dopamine, norepinephrine, serotonin, acetylcholine, histamine, and orexin,[6] the lattermost of which was identified in 1998 and has been found to play a critical role in maintaining wakefulness.[7] Neurotransmitters involved in sleep promotion include adenosine, GABA, melatonin, and galanin.[6] *The role of these neurotransmitters is particularly relevant in that the medications used to treat insomnia either*

activate sleep-promoting neurotransmitters or suppress wakefulness-promoting neurotransmitters.

Effect of life stage on sleep

Life stages in women, including pregnancy, menopause, and older age, can have major effects on sleep quality, duration, and efficiency.

Pregnancy

Increased rhinorrhea, low back discomfort, need for an altered sleep position, fetal movements, heartburn, RLS-type symptoms, and shortness of breath can disturb sleep during pregnancy.[8,9]

Menopause

According to The North American Menopause Society, sleep disturbances occur mainly in women bothered by nighttime hot flashes, although a firm cause-and-effect relationship has not been established.[10] Other contributors to insomnia during this life stage include general aging effects, stress, negative mood, and hormonal changes.[10]

Aging

Alterations in sleep architecture that occur as a part of normal aging, including a decrease in total sleep time and increases in arousals and awakenings secondary to lighter and more fragmented sleep, contribute to sleep problems such as insomnia in older persons.[11] Other factors contributing to insomnia in older adults include co-morbid physical and mental health conditions and the medications used to treat them, changes in lifestyle and schedule, and altered circadian rhythm. Insomnia in older adults is typically characterized by difficulty sleeping through the night or waking up too early, as opposed to difficulty falling asleep.[4]

Screening

Unless HCPs specifically ask a patient about her sleep habits during a well-woman visit or a patient broaches the topic herself—perhaps as she is about to leave the exam room—they may not learn about any sleep problems she is having. But a sleep problem such as insomnia, especially if chronic and distressful, merits a workup and treatment in many cases.

Even in a busy office setting, HCPs can start with a two-question screen: *Do you experience difficulty sleeping? If so, do you have difficulty falling or staying asleep?* To elicit more information, HCPs can then ask: *Are you dissatisfied with your sleep? Do you suffer daytime fatigue?* Affirmative answers to any or all of these questions suggest a diagnosis of insomnia, and may determine the type of treatment needed.

Another screening option is the **BEARS** Sleep Assessment Tool.[12] Initial letters of the acronym stand for **B**edtime problems (e.g., Does the patient have difficulty falling asleep?); **E**xcessive daytime drowsiness; **A**wakenings during the night (e.g., Is the patient making frequent trips to the bathroom? Is she being interrupted by a crying baby or a sick child?); **R**egularity and duration of sleep; and **S**leep-disordered breathing (e.g., Does the patient have obstructive sleep apnea?).

Workup: Taking a targeted history

For a patient whose screening responses suggest she may have a sleep disorder, HCPs should ask these questions (if not posed during initial screening): *Do you suffer from daytime fatigue? Do you snore or have episodes where you stop breathing when you sleep (based on the report of someone sharing your bedroom or your bed)? How many hours are you in bed each night? How many hours do you sleep each night? Do you feel refreshed upon awakening and throughout the next day? Do you have restless leg symptoms? Do you ever sleepwalk or have vivid dreams?*

In addition, HCPs should ask the patient about alcohol or illicit drug use, which can have profound effects on sleep. HCPs should also consider aspects of her current health that may be affecting her sleep; common offenders include overactive bladder, chronic pain, mental health disorders, fibromyalgia, hyperthyroidism, perimenopause, and RLS. In patients complaining of RLS-type symptoms, HCPs should consider checking a ferritin level. RLS can be associated with iron-deficiency anemia and ferritin levels below 50 ng/mL.[13]

If a patient does have ongoing health problems, HCPs should inquire about the over-the-counter (OTC) and prescription medications she is using to treat them. Commonly used medications that can disturb sleep include selective serotonin reuptake inhibitors, dopamine agonists, amphetamines, anticonvulsants, decongestants, corticosteroids, beta agonists, theophylline, antihypertensives, diuretics, and appetite suppressants.[14] In addition, HCPs should ask the patient which treatments, including alcohol, marijuana, OTC preparations, and prescription drugs, she has tried to help her sleep.

Some patients may have sleep-state misperception; they believe that they are awake much of the night but are actually asleep for a normal period of time. They think that it takes them an abnormally long time to fall asleep (even though it does not) and/or they underestimate how long they remain asleep. To identify this misperception, or to better understand the nature of any patient's sleep problem, HCPs can recommend a home sleep study.

Home sleep study

This study, conducted primarily to check for obstructive sleep apnea (OSA) with a small, portable monitor, measures oxygen saturation, heart rate, airflow, and movement in the chest and abdomen, and records time spent snoring and sleep position. The AASM recommends its use for the diagnosis of OSA in uncomplicated adult patients presenting with signs and symptoms indicating an increased risk of OSA.[15] HCPs can incorporate the use of home sleep studies into their own practices.[16]

Sleep apnea affects 6%-17% of the general population—and not just men, obese persons, or older persons, although these are the strongest risk factors.[17] One sign of OSA with which HCPs may not be aware is recurrent uvulitis. A patient who presents with frequent sore throats not ascribed to other causes and a beefy-looking uvula may in fact have OSA.[18] Of note, a home sleep study does not replace polysomnography performed in a sleep laboratory. The latter is preferred if HCPs suspect that a patient has severe OSA or another type of sleep abnormality or disorder that needs to be identified.

Non-medication approaches to therapy

For a patient who meets criteria for insomnia and who wants to improve her sleep, the first step is to treat any co-morbid condition(s) that may be causing or contributing to her insomnia. At the same time, HCPs should consider the medications that the patient is already taking, including OTC/prescription medications and alcohol, to determine whether any of them may be causing or exacerbating her problem.

The next step is to evaluate the patient's sleep hygiene and, if less than optimal, advise her to make changes. Good sleep hygiene entails[19]:

- being consistent—that is, going to bed at the same time each night and getting up at the same time each morning, including on weekends;
- making sure one's bedroom environment is quiet, dark, cool, and relaxing;
- removing electronic devices from the bedroom;
- avoiding large meals, caffeine, and alcohol before bedtime;
- getting some exercise on most days; and
- receiving daily exposure to sunlight (if possible) and keeping lights on until bedtime.

If making improvements in sleep hygiene proves inadequate, a patient can try a course of psychotherapy such as cognitive-behavioral therapy for insomnia (CBT-I). CBT-I addresses sleep-disruptive beliefs, maladaptive habits, and physiologic factors and incorporates elements of cognitive therapy, stimulus control, sleep restriction, sleep hygiene, and relaxation.[4,20] A systematic review and meta-analysis demonstrated that CBT-I is effective for adults with chronic insomnia.[20] Two possible downsides of CBT-I, as delivered by an HCP, are that it may be difficult to access and it may be expensive. As an alternative, online CBT-I options are available and have been reported to be effective.[21,22]

Non-medication approaches may be particularly useful for pregnant women with insomnia because many, if not most, medications used to treat insomnia can have a potentially adverse impact on the developing fetus. A recent study of pregnant women with insomnia showed that CBT-I was preferred over drug therapy or acupuncture.[8] CBT-I is also recommended as first-line treatment in healthy midlife women with insomnia and moderately bothersome vasomotor symptoms.[23]

Nonprescription medication options

For patients still experiencing troublesome insomnia after non-medication interventions have been tried, several OTC medications are available. Although not included in the *Table*, the most common nonprescription "medication" used to treat insomnia is alcohol.[24] An alcoholic drink may facilitate sleep onset, but it can also cause insomnia, manifested by multiple nighttime awakenings, increased urination, and difficulty falling back to sleep.

Melatonin, valerian root, and diphenhydramine are three nonprescription medications commonly used to treat insomnia. The *Table* provides information about their mechanisms of action, indication(s), dosing (*in most cases, women and older patients should receive only the lowest dose*), appropriateness of use in pregnancy/lactation, and precautions. The Table also includes recommendations from the AASM and from the American Geriatrics Society (AGS), specifically with regard to the AGS Beers Criteria, which lists medications that can cause side effects in older adults related to the physiologic changes of aging.[25]

Prescription medication options

Three general categories of prescription medication options for treatment of insomnia are the benzodiazepine (BZ) hypnotics, non-BZ hypnotics, and miscellaneous hypnotics. The *Table* provides the same categories of information for these prescription medications as for the nonprescription medications. *Again, in most cases, women and older adults should receive only the lowest dose of a given medication.*

Benzodiazepine hypnotics

Five BZ receptor agonists, all Sched-

Table. Medications used to treat insomnia

Medication	Mechanism of action	FDA approved for insomnia?	Dose (mg)	Use in pregnancy and lactation	Precautions	Recommended by AASM?	Beers Criteria	Comments
Nonprescription medications								
Melatonin, a hormone produced endogenously by the pineal glands[a-e]	Regulation of the sleep–wake cycle through its actions on melatonin receptors in the suprachiasmatic nucleus	Not categorized as a drug Used for sleep onset and sleep maintenance, but only weak evidence to support efficacy	0.2-5.0*	Should not be used during pregnancy or lactation without further studies	Because it inhibits CYP1A2 substrates, it may increase concentrations of drugs such as fluvoxamine, an SSRI, and warfarin, an anticoagulant.	No for sleep onset, no for sleep maintenance	—	Can cause tachycardia, flushing, itching, headaches, and vivid dreams. Should not be administered with a high-fat meal, which reduces absorption.
Valerian root, an herbal product[a,e-h]	Modulation of GABA-ergic transmission	Not categorized as a drug Used for sleep onset and sleep maintenance, but no evidence to support efficacy	300-600*	Should not be used during pregnancy or lactation without further studies	Interacts adversely with general anesthetics; must be stopped ≥1 week before surgery. Long-time users can experience BZ-like withdrawal symptoms. Should not be used in persons with liver or pancreatic disease.	No for sleep onset, no for sleep maintenance	—	Used to treat anxiety as well as insomnia. Can cause headache, stomach upset, mental dullness, excitability, heart disturbances, and even insomnia.
Diphenhydramine, used primarily as an antihistamine[a,e,i-k]	Histamine H1 antagonist	Yes Used for sleep onset and sleep maintenance; no strong evidence to support efficacy	12.5-50*	May be used in pregnancy, but not by lactating mothers; can lead to CNS depression in infant and may decrease breast milk production	Should be avoided by persons older than 65 years, primarily because of its sedative and anticholinergic effects	No for sleep onset, no for sleep maintenance	Avoid	Can cause constipation, dry mouth, difficulty urinating, upset stomach, blurred vision, tremor, loss of appetite, headache
Benzodiazepine hypnotics (Schedule IV drugs)								
Temazepam (Restoril)[e,k-m]	See article text on class description	Yes Indicated for sleep onset and sleep maintenance	7.5-30	Pregnancy Category X; should be used with caution by nursing mothers	Should be used with caution in persons with respiratory depression or chronic obstructive pulmonary disease, in those with impaired renal or hepatic function, and in older adults.	Yes for both sleep onset and sleep maintenance	Avoid	Because the drug has no active metabolite, cognitive impairment and grogginess the following day are reduced.
Triazolam (Halcion)[e,k,l,n]	See article text on class description	Yes Indicated for sleep onset	0.125-0.5	Pregnancy Category X; should not be used by nursing mothers	Should not be used with drugs that significantly impair the oxidative metabolism mediated by CYP3A (e.g., ketoconazole, itraconazole, nefazodone, several HIV protease inhibitors). Dosing should be adjusted in patients with hepatic impairment.	Yes for sleep onset	Avoid	
Nonbenzodiazepine hypnotics (Schedule IV drugs)								
Eszopiclone (Lunesta)[e,k,o]	See article text on class description	Yes Indicated for sleep onset and sleep maintenance	1-3	Data are insufficient to make definitive recommendations	In patients with severe hepatic impairment or in those taking other potent CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir), the dose should not exceed 2 mg.	Yes for both sleep onset and sleep maintenance	Avoid	
Zaleplon (Sonata)[e,k,p]	See article text on class description	Yes Indicated for sleep onset	5-20†	Pregnancy Category C; can be used with caution by nursing mothers	See article text on class description	Yes for sleep onset	Avoid	
Zolpidem (Ambien, Ambien CR)[e,k,q,r]	See article text on class description	Yes Indicated for sleep onset (Ambien) or sleep onset and sleep maintenance (Ambien CR)	5-10; 6.25-12.5	Pregnancy Category C; can be used with caution by nursing mothers	See article text on class description	Yes for both sleep onset and sleep maintenance	Avoid	

Miscellaneous hypnotics								
Ramelteon (Rozerem), a melatonin agonist[e,k,s]	Melatonin receptor agonist with both high affinity for melatonin MT1 and MT2 receptors and relative selectivity over the MT3 receptor	Yes Indicated for sleep onset	8	Pregnancy Category C; can be used with caution by nursing mothers	Should not be used in patients with severe hepatic impairment or with the SSRI fluvoxamine, and should be used with caution in patients with moderate hepatic impairment and in those taking other CYP1A2-inhibiting drugs. Avoid in patients with severe sleep apnea.	Yes for sleep onset	Can be used in older adults	Should not be administered with a high-fat meal, which reduces absorption
Trazodone (Desyrel), an antidepressant[e,k,t,u]	Not fully understood; thought to enhance serotonergic activity in the CNS	No, but used off label, often as an adjunct to SSRI treatment	25-150*	Pregnancy Category C; can be used with caution in nursing mothers	Can cause excessive sedation and anticholinergic effects, prolong QT interval, cause OH and syncope, increase risk of bleeding when used with anticoagulants or antiplatelet drugs, and aggravate glaucoma	No for sleep onset, no for sleep maintenance	Can be used with caution in older adults	As with all antidepressants, PI has boxed warning regarding risk for suicidality in pediatric and young adult patients
Doxepin (Silenor), a TCA prescribed in a very low dose[e,k,v]	Central histamine H1 receptor antagonist	Yes Indicated for sleep maintenance	3-6	Pregnancy Category C; may be harmful to infants of lactating mothers	Contraindicated in patients with glaucoma or severe urinary retention. Users should avoid eating within 3 hours of taking the medication.	Yes for sleep maintenance	Can be used with caution in older adults	See above about boxed warning
Mirtazapine (Remeron), a tetracyclic antidepressant[e,k,w]	Serotonin receptor and histamine receptor antagonist	No, but used off label to treat insomnia	15-45*	Pregnancy Category C drug; can be used with caution by nursing mothers	For patients wishing to stop long-term treatment, the drug should be tapered gradually, not stopped abruptly, to avoid withdrawal symptoms. See PI for multiple precautions.	Not mentioned	Can be used with caution in older adults	See above about boxed warning; may be helpful for patients who need to gain weight
Suvorexant (Belsomra), an orexin inhibitor agonist[e,k,x]	Highly selective antagonist of orexin receptors (turns off wakefulness centers)	Yes Indicated for sleep onset and sleep maintenance	5-20	Pregnancy Category C; can be used with caution in nursing mothers	Schedule IV drug. Can cause complex sleep behaviors. Should be taken only if patient can get a full night's sleep. Dose should be 5 mg when used with moderate CYP3A inhibitors. Can be raised to 10 mg if 5 mg not effective. Avoid in patients using strong CYP3A inhibitors.	Yes for sleep maintenance	Can be used in older adults	Time to effect may be delayed if taken with or soon after a meal

*Suggested dose or dose range. These agents are not FDA approved to treat insomnia. †Maximum dose in older adults, 10 mg. AASM, American Academy of Sleep Medicine; BZ, benzodiazepine; CNS, central nervous system; OH, orthostatic hypotension; PI, prescribing information; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant..

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ule IV drugs, have been approved by the FDA for short-term treatment of insomnia.[26] Two drugs in this class—temazepam and triazolam—are listed in the *Table*; the others, which are similar to temazepam and triazolam, are estazolam, quazepam, and flurazepam. Their mechanism of action entails binding to a modulatory site on the $GABA_A$ receptor and enhancing GABA activity.[27]

The prescribing information for drugs in this class includes a boxed warning about administering them concurrently with an opioid, which could result in profound sedation, respiratory depression, coma, and even death. BZ hypnotics can cause *complex sleep behaviors* (e.g., sleep-driving, having sex or eating while asleep and having no memory of it afterward).[28,29] Based on the Beers Criteria, these agents should be avoided in older adults.[25] Patients who take BZ hypnotics for a prolonged period (despite the fact that they are indicated only for short-term use) and who wish to discontinue them should taper them gradually, as opposed to stopping them abruptly, to avoid withdrawal symptoms.

Nonbenzodiazepine hypnotics

These Schedule IV drugs, eszopiclone, zaleplon, and zolpidem (*Table*), are known as the "Z" drugs because their generic name or their predecessor's generic name starts with "Z" (eszopiclone is the active stereoisomer of zopiclone, which is available in Japan, Brazil, and some European countries). Or perhaps these drugs are so nicknamed because they help people get their zzz's.

Non-BZ hypnotics act through the BZ binding sites associated with $GABA_A$ receptors.[30] Their effects may be slowed if they are ingested with or shortly after a meal.[31-34] They should be taken only if patients can be assured of getting a full night's sleep.[31-34] Based on the Beers Criteria, these drugs should be avoided in older adults.[25] Doses should be as low as possible in patients with mild to moderate hepatic impairment; in those with severe hepatic impairment, these drugs should be used at the lowest possible dose, with great caution, or avoided.[31-34]

Other concerns regarding the "Z" drugs include short-term effects such as complex sleep behaviors, next-day sedation, and long-term effects such as amnesia, dementia, and rebound insomnia after the drug is stopped.[31-34] If these drugs are to be halted after prolonged use, they should be slowly tapered to avoid withdrawal symptoms.[31-34]

Miscellaneous hypnotics

These agents include ramelteon, a prescription-strength melatonin agonist; three antidepressants; and suvorexant, which inhibits the action of orexin, a neurotransmitter involved in wakefulness (*Table*).[35-40]

Follow-up care

Patients and HCPs should not expect to find an effective solution for insomnia in one visit. Patients receiving any type of medication for insomnia should return for follow-up after 4-8 weeks for evaluation of efficacy, safety, and the need for ongoing treatment. The American College of Physicians guidelines suggest that patients who require medication for longer than 4-5 weeks be assessed regularly for the need to continue it.[4]

Conclusion

Insomnia affects millions of individuals in the U.S. Because many patients with insomnia do not mention their sleep problem at HCP visits, they should be screened for insomnia on a regular basis. Numerous treatment options, both nonpharmacologic and pharmacologic, exist. In most cases, HCPs should proceed in step-wise fashion, starting with behavioral approaches and advancing to OTC or prescription medication; the choice of medication depends on a patient's age, health status, particular form of insomnia (problem with sleep onset, sleep maintenance, or both), and other considerations (e.g., a need to avoid drugs with addictive potential). Regardless of therapeutic choice, HCPs should follow patients with insomnia on a regular basis to ensure that treatment is effective, well tolerated, and still needed.

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