In the Clinic

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The content of In the Clinic is drawn from the clinical information and education resources of the American College of Physicians (ACP), including ACP Smart Medicine and MKSAP (Medical Knowledge and Self-Assessment Program). Annals of Internal Medicine editors develop In the Clinic from these primary sources in collaboration with the ACP’s Medical Education and Publishing divisions and with the assistance of science writers and physician writers. Editorial consultants from ACP Smart Medicine and MKSAP provide expert review of the content. Readers who are interested in these primary resources for more detail can consult http://smartmedicine.acponline.org, http://www.acponline.org/products_services/mksap/15/?pr31, and other resources referenced in each issue of In the Clinic.

CME Objective: To review current evidence for the screening, diagnosis, treatment, and practice improvement of insomnia.

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People with insomnia have trouble falling asleep, staying asleep, and/or waking up too early. The result may be poor-quality sleep or sleep of insufficient duration that can cause excessive daytime sleepiness, irritability, and lack of energy. Long-term insomnia is associated with depression and anxiety (1), cognitive difficulties (memory, attention, concentration) (2), and workplace underperformance (3, 4). Increasing evidence also suggests that patients with insomnia may have an increased risk for cardiovascular disease (including hypertension [5] and myocardial infarction [6]), and diabetes (7-9).

Insomnia symptoms are common—35% to 50% of adults report sleep difficulties annually (10, 11). Although different criteria exist for defining insomnia as a specific sleep-related condition, up to 20% of adults with symptoms may meet diagnostic criteria for insomnia disorder (12, 13). Given its prevalence and substantial health consequences, clinicians should be skilled in detecting and managing insomnia.

**Screening**

Which patient populations have the highest prevalence of insomnia?

Women are more likely than men to experience insomnia symptoms and are twice as likely to be diagnosed with insomnia disorder (14). Additionally, the prevalence of insomnia symptoms in women is increased in the third trimester of pregnancy and following menopause (14).

Insomnia can occur at any age but is particularly prevalent in the elderly, with insomnia symptoms present in as many as 65% of individuals 65 years of age or older, with a high level of persistence of symptoms over time (14-16).

Individuals with coexisting medical disorders (particularly pulmonary disease; heart failure; and conditions associated with pain, such as cancer) are at increased risk for insomnia, as are patients with neurologic diseases (such as Alzheimer dementia and Parkinson disease) (17). An increased prevalence of insomnia is also associated with a variety of rheumatologic, endocrine, urologic, and dermatologic disorders (18). Psychiatric disorders, including depression, anxiety, substance abuse, and posttraumatic stress disorder, are also strongly associated with insomnia (19, 20).

Population studies also suggest that individuals who are unemployed, divorced, widowed, separated, or of lower socioeconomic status have a higher prevalence of insomnia (21, 22).

Patients taking a wide range of pharmacologic agents are at increased risk for insomnia, including stimulants (e.g., caffeine, nicotine), antidepressants, β-antagonists, calcium-channel blockers, and glucocorticoids. Additionally, individuals withdrawing from certain medications, such as alcohol or hypnotic medications, may have resulting insomnia.

Should clinicians screen for insomnia, and if so, how?

Although there is no evidence that screening for insomnia improves patient outcomes and there are no formal recommendations for or against screening in the general patient population, clinicians should consider screening for insomnia as part of regular patient care given its high prevalence and potential effect on well-being.

Screening may be accomplished simply by asking patients whether
they have difficulty with initiating sleep, have early morning waking, and/or experience nonrestorative sleep. This may be done using the Sleep Condition Index questionnaire: “Thinking about a typical night in the last month, how many nights do you have a problem with sleep?” (with ≥3 representing a positive response), and “Thinking about the past month, to what extent has poor sleep troubled you in general?” (with “somewhat” to “very much” being a positive response). Positive responses to these 2 questions correlate with other, more extensive assessments and may be effective for clinicians as a screening tool to detect insomnia (23). Other, more extensive validated screening instruments for insomnia are available and include the Pittsburgh Sleep Quality Index and the Insomnia Severity Index.

What are the components of a comprehensive sleep history?

In patients with insomnia, a comprehensive sleep assessment enables clinicians to diagnose the condition, establish factors that may be disrupting sleep, and plan effective treatment (24). Sleep and wakefulness should be assessed across the entire day to characterize sleep issues and their effect on daytime function (see the Box).

The temporal aspects of sleep should be elicited, including when the patient goes to bed, attempts to go to sleep (“lights out time”), wakes up, and gets out of bed. Evaluating quantitative sleep is important, including how long it takes to fall asleep (sleep latency), how often the person awakens and stays awake before falling back to sleep, and the total time the person sleeps. The quality of a patient’s sleep should be determined, including the perceived causes of sleep difficulty and how well rested they feel on awakening. Careful documentation of environmental factors affecting sleep is important, including the sleep environment (light, sound, temperature) and other stimuli (television, telephone, computer). Behaviors potentially affecting sleep are also important, such as sleep habits, the amount of time allotted for sleep, daytime napping, exercise, stimulant use, and psychosocial stressors.

A sleep diary may be more accurate than general questioning alone in characterizing sleep issues by formally documenting these factors and minimizing recall bias. Several instruments are available for patient use and should be used daily for at least 1 to 2 weeks (25, 26).

Which conditions should clinicians consider in the diagnosis and treatment of insomnia?

Insomnia disorder has traditionally been classified as primary (occurring without a clear cause) or secondary (associated with and possibly caused by another medical, psychiatric, or neurologic condition). However, it is often difficult to determine the actual cause of insomnia, and treating the presumed cause may not always resolve the sleep disturbance. Additionally, the apparent bidirectional

**Screening...** Clinicians should consider asking patients about insomnia as a regular part of patient care. It can be done in a relatively straightforward way that does not take much time by asking patients if they have difficulty with initiating or maintaining sleep, early morning waking, and/or nonrestorative sleep.

**CLINICAL BOTTOM LINE**

**Things to Ask When Taking a Comprehensive Sleep History**

- Problems of sleep initiation, sleep maintenance, early morning waking, or nonrestorative sleep
- Whether the patient has acute, short-term, or chronic insomnia
- Whether the insomnia is stable, worsening, or improving
- Precipitating causes of insomnia
- Bedtime, wake time, length of sleep time
- Caffeine and alcohol use
- Any current or previous behavioral therapies used to treat insomnia
- Previous over-the-counter or prescription sedative-hypnotic use
- Shifting work and irregular sleep schedule
- Potential acute stressors, such as:
  - Medical or psychiatric illness
  - Medication use, both prescribed and illicit
  - Acute stress at home or work
  - Circadian rhythm stressors, such as jet lag
nature of insomnia with other medical, psychiatric, and neurologic disorders makes it unclear that insomnia is a direct result of these specific conditions. Because of this, insomnia is currently preferably classified as insomnia disorder and insomnia disorder with comorbidity. Once an insomnia disorder has been identified, it warrants treatment with careful evaluation for and treatment of concurrent factors (comorbid conditions) that may affect sleep.

The third edition of the International Classification of Sleep Disorders (ICSD-3) (27) was published in 2014 and includes 7 major categories of sleep disorders, one of which is insomnia. Three major forms of insomnia are recognized: short term (present for less than 3 months), chronic (symptoms occur at least 3 times per week for 3 months or more and are not related to an inadequate opportunity for sleep or another sleep disorder), and other (for conditions not meeting the criteria for acute or chronic insomnia). Unlike previous editions, ICSD-3 does not contain subclassifications of chronic insomnia, such as idiopathic insomnia, psychophysiological insomnia, or paradoxical insomnia, because they were not able to be reliably identified in clinical practice.

Table 1 indicates the sleep disorder-related differential diagnosis for insomnia, and Table 2 reviews other medical conditions frequently associated with disrupted sleep. Coupled with the sleep history, the clinical evaluation should focus on the possible presence of these sleep-related conditions and comorbid conditions requiring consideration in treating insomnia.

What is the role of the physical examination?

The physical examination is helpful in identifying signs that suggest a specific disorder potentially contributing to sleep disruption. Examples include clinical findings consistent with thyroid dysfunction, cardiopulmonary or neurologic disease, or supportive of a possible diagnosis of the obstructive sleep apnea syndrome (OSAS).

When should clinicians consider laboratory testing?

Insomnia is a clinical diagnosis; therefore, the sleep and medical history, in conjunction with the physical examination, are the primary diagnostic tools. Additional testing is not routinely required, but may be appropriate in patients when a possible underlying sleep disorder is suspected or there is clinical evidence of concomitant disease that may be associated with insomnia.

Polysonmography
An overnight sleep study, or polysomnography, is not routinely used to evaluate insomnia but may be indicated in patients with suspected sleep-related breathing issues (such as OSAS or central sleep apnea), other sleep disorders (including narcolepsy and periodic limb movement disorder), or for characterizing poorly defined sleep disturbances.

Multiple Sleep Latency Test
The Multiple Sleep Latency Test objectively measures an individual’s tendency to fall asleep. It involves a series of monitored naps in a sleep laboratory that measure the time to onset of rapid eye movement sleep. This test is not a routine study for evaluation of insomnia and is primarily used to diagnose narcolepsy.

Sleep Actigraphy
Actigraphy uses a small, watch-like electronic device worn around the wrist of the nondominant arm that detects motion, with periods of inactivity suggesting periods of sleep. This test also is not used routinely to evaluate insomnia but may be useful in assessing or confirming
sleep patterns and circadian rhythms in selected patients and in those with difficulty in recalling their sleep patterns.

**Other Tests to Evaluate for Comorbid Conditions**
Other studies may be needed to evaluate for underlying cardiac, pulmonary, gastrointestinal, or neurologic disorders contributing to insomnia.

The restless legs syndrome (RLS) is associated with diabetes mellitus, kidney disease, and iron deficiency; exclusion of these disorders and measurement of iron stores is indicated when this disorder is suspected.

Both hyper- and hypothyroidism are associated with sleep disturbances and should be evaluated through thyroid function testing. Urine drug screening may also be useful in some patients because of the association of stimulants and other substances with altered sleep.

Directed testing is indicated for other conditions possibly underlying reports of insomnia as suggested by the clinical history and physical examination. Examples include evaluation for congestive heart failure, chronic obstructive pulmonary disease, and gastroesophageal reflux disease in patients considered at risk for these conditions (Table 2).

### Table 1. Sleep Disorder Differential Diagnosis of Insomnia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristics</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep-related breathing disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The obstructive sleep apnea syndrome</td>
<td>Upper airway obstruction during inspiration in sleep.</td>
<td>History of snoring, witnessed pauses in respiration, and daytime sleepiness. Patients may report non-restful sleep or insomnia. Polysomnography is necessary for diagnosis.</td>
</tr>
<tr>
<td>The central sleep apnea syndrome</td>
<td>Repetitive pauses in breathing during sleep without upper airway occlusion.</td>
<td>History of congestive heart failure or central nervous system disease. Polysomnography is necessary for diagnosis.</td>
</tr>
<tr>
<td><strong>Sleep-related movement disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The restless legs syndrome</td>
<td>Uncomfortable or restless feeling in legs most prominent at night and at rest; alleviated by movement.</td>
<td>Occurs in up to 10% of the general population. Approximately 80% of patients with this syndrome also have periodic leg movement disorder on polysomnography, although polysomnography is not necessary for diagnosis.</td>
</tr>
<tr>
<td>Periodic limb movement disorder</td>
<td>Repetitive stereotypic leg movement in sleep and during quiet wakefulness.</td>
<td>Strongly associated with the restless legs syndrome. Polysomnography is necessary for diagnosis.</td>
</tr>
<tr>
<td>Nocturnal leg cramps</td>
<td>Pain in calf or foot resulting in awakening from sleep.</td>
<td>Painful cramp awaken the patient from sleep. Predisposing factors include diabetes, exercise, pregnancy, and metabolic and endocrine abnormalities.</td>
</tr>
<tr>
<td><strong>Circadian rhythm sleep–wake disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time zone change syndrome (jet lag)</td>
<td>Travel leads to reports of poor sleep, daytime sleepiness, or both.</td>
<td>History of recent travel across multiple time zones.</td>
</tr>
<tr>
<td>Shiftwork sleep disorder</td>
<td>Insomnia as a consequence of shiftwork. Sleep occurs at times counter to normal circadian rhythm and social and environmental factors.</td>
<td>History of insomnia associated with shiftwork; this disorder also affects persons who permanently work the night shift.</td>
</tr>
<tr>
<td>The delayed sleep-phase syndrome</td>
<td>Delay of the major sleep phase relative to clock time.</td>
<td>History of sleep-onset insomnia and difficulty awakening at the desired time. Patients have no difficulty maintaining sleep once asleep. Sleep log and actigraphy can aid diagnosis.</td>
</tr>
<tr>
<td>The advanced sleep-phase syndrome</td>
<td>The major sleep phase is advanced relative to clock time.</td>
<td>Inability to stay awake until desired bedtime and early-morning awakening. Occurs most commonly in elderly. Sleep log and actigraphy can aid diagnosis. Disorders of arousal that may be a cause of disrupted sleep. Sleep history and input from bed partner or family may aid in identification.</td>
</tr>
<tr>
<td>Parasomnias related to non–rapid eye movement</td>
<td>Include confusional arousals, sleepwalking, sleep terrors, and sleep-related eating disorders.</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Other Disorders That May Be Associated With Insomnia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristics</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma/chronic obstructive pulmonary</td>
<td>Nighttime attacks of lower airway obstruction may occur in asthma. Cough,</td>
<td>History of nocturnal awakenings due to cough, wheezing, or shortness of</td>
</tr>
<tr>
<td>pulmonary disease</td>
<td>sputum production, wheezing, or dyspnea/hypoxia may interrupt sleep in</td>
<td>breath. Asthma may present with symptoms at night as an initial</td>
</tr>
<tr>
<td></td>
<td>chronic obstructive pulmonary disorder.</td>
<td>manifestation of suboptimal control.</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>Disrupted sleep due to reflux of gastric contents into the esophagus during</td>
<td>History of sleep-related heartburn, nocturnal cough, and water brash.</td>
</tr>
<tr>
<td></td>
<td>sleep.</td>
<td></td>
</tr>
<tr>
<td>Substance use</td>
<td>Sleep disruption may result from use of alcohol to promote sleep, stimulant</td>
<td>A comprehensive medical and sleep history will facilitate identification</td>
</tr>
<tr>
<td></td>
<td>medication intake, or withdrawal from sleep-promoting medications.</td>
<td>of these potential contributing factors.</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>Chronic generalized fatigue and musculoskeletal symptoms associated with non-</td>
<td>Patients frequently report lack of deep sleep, early morning awakening</td>
</tr>
<tr>
<td></td>
<td>refreshing sleep.</td>
<td>with difficulty returning to sleep, and no improvement in tiredness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>symptoms regardless of length of sleep.</td>
</tr>
<tr>
<td>Dementia</td>
<td>Insomnia associated with dementing illnesses.</td>
<td>Sleep disorders may affect 25% to 35% of patients with dementia and are</td>
</tr>
<tr>
<td></td>
<td></td>
<td>probably multifactorial, including side effects from cholinesterase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>inhibitor therapy.</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>Insomnia is commonly associated with Parkinson disease.</td>
<td>May affect up to 60% of patients with Parkinson disease and is often</td>
</tr>
<tr>
<td></td>
<td></td>
<td>characterized by problems with sleep initiation, sleep maintenance,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and early awakening.</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Anxiety, depression, and posttraumatic stress disorder have a strong</td>
<td>Insomnia and psychiatric conditions frequently coexist, although there</td>
</tr>
<tr>
<td></td>
<td>association with sleep disturbances and insomnia.</td>
<td>seems to be a bidirectional cause-and-effect relationship.</td>
</tr>
<tr>
<td>Headache</td>
<td>Several subtypes of headache are closely tied to sleep, including migraine,</td>
<td>Headache and its effects on sleep should be documented as part of the</td>
</tr>
<tr>
<td></td>
<td>cluster headache, paroxysmal nocturnal hemigrania, and hypnic headache.</td>
<td>medical and sleep history.</td>
</tr>
<tr>
<td>Epilepsy syndromes</td>
<td>Epilepsy may disrupt sleep directly through seizures and epileptiform activity.</td>
<td>A reciprocal relationship exists between sleep and epilepsy as sleep</td>
</tr>
<tr>
<td></td>
<td></td>
<td>state affects seizure activity and epilepsy may disrupt sleep.</td>
</tr>
<tr>
<td>Altitude-associated sleep disturbance</td>
<td>Disturbed sleep associated with movement to higher altitudes.</td>
<td>Associated with ascent to high altitudes and exposure to lower oxygen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>concentrations. Can begin at as low as 2000 m (6560 feet) for persons</td>
</tr>
<tr>
<td></td>
<td></td>
<td>from sea level and is common above 4000 m (13 100 feet). Characterized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>by periodic breathing and central apnea events.</td>
</tr>
<tr>
<td>Fatal familial insomnia</td>
<td>Prion-related thalamic degeneration resulting in progressive insomnia.</td>
<td>Very rare cause of insomnia associated with dysautonomia and endocrine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>disturbances. Mean time to death is 13 months.</td>
</tr>
</tbody>
</table>

Diagnosis... Insomnia is often associated with an underlying medical or psychological condition, medications or other substances that interfere with sleep, or a poor sleep environment. A detailed sleep and medical history and physical evaluation are necessary in evaluating insomnia. The use of sleep questionnaires, sleep diaries, and laboratory testing to evaluate for underlying conditions may be helpful.

**CLINICAL BOTTOM LINE**

**Treatment**

What is sleep hygiene and what is its role in the treatment of patients with insomnia?  
Sleep hygiene refers to the optimization of the environmental and behavioral factors associated with sleep (28). Poor sleep hygiene can contribute to sleep fragmentation, disturbance of normal circadian rhythms, and overstimulation.
Clinicians should review and advise correction of poor sleep hygiene in all patients who report insomnia (see the Box) to promote sound sleep and daytime wakefulness.

Are behavioral therapies useful? Behavioral treatments are highly effective and considered a standard treatment for insomnia (29, 30). They are preferred as primary therapy, particularly in patients with chronic insomnia. However, they are frequently used in conjunction with pharmacologic therapy and may reduce the need for medication in some patients.

Cognitive Behavioral Therapy
Cognitive behavioral therapy for insomnia (CBT) is a brief, multi-component therapy that includes both cognitive components (sleep education and addressing maladaptive beliefs and expectations about sleep) and behavioral components (sleep-restriction therapy, stimulus-control therapy, and relaxation techniques). Many studies show the efficacy of CBT for insomnia in both the long-term, for which it is more effective than sleep medication, and the short-term (31–33). There is also considerable evidence CBT is effective in persons with medical and/or psychiatric comorbid conditions who experience insomnia.

Unfortunately, not all clinicians are skilled at providing CBT, and the availability of this treatment method may be limited in some areas. Providing CBT by telephone or the Internet are promising options (34–36) that might make this treatment more widely available.

Sleep Restriction. Sleep restriction is a behavioral intervention that attempts to increase the drive to sleep by limiting, and then slowly increasing, the time for sleep. Patients keep a sleep diary for 1 to 2 weeks, and their time in bed is then reduced to their average total sleep time calculated from the sleep diary (but not to less than 5 hours a night). The sleep efficiency (the reported time asleep relative to the amount of time spent in bed) is used to increase the amount of sleep time allotted; 15 to 30 minutes is added when sleep efficiency exceeds 85%. This process continues until the patient feels optimal during the day and/or sleep efficiency begins to drop due to reaching the patient’s sleep need. It has been shown to effectively improve measured sleep diary variables, although its impact on objectively measured sleep parameters and daytime function has not been established (37).

Stimulus-Control Therapy. Stimulus-control therapy is particularly important in helping patients associate the bed and bedroom with sleepiness. Because the bedroom is often used for purposes other than sleep (such as watching television or exercising), individuals may lose the association of the bedroom with sleep when going to bed. To reinforce this connection, patients should be advised to keep set bedtimes and rising times (including on weekends), remove sleep-incompatible stimuli (such as electronic devices), and use the bedroom only for sleep. Patients should spend no more than 20 minutes awake in bed. If they are unable to fall asleep within that period, then they should leave the bedroom to engage in nonstimulating activity until becoming tired before returning to bed.

Relaxation Techniques. Relaxation techniques, such as diaphragmatic breathing, visualization, and progressive muscle relaxation, are based on evidence that physiologic, muscular, and cognitive arousal can interfere with sleep (38) and that conscious relaxation can alleviate this hyperarousal and help in treating insomnia. In these interventions, patients practice ways to reduce high levels of arousal by using specific techniques of progressively

**Good Sleep Hygiene Behaviors**

- Maintain stable bed times and rising times
- Allow adequate time for sleep, usually 7 to 8 hours for adults
- Try not to force sleep and avoid clock watching
- Maintain a quiet, dark bedroom
- Remove potential disruptors of sleep (such as television, telephone, or computer)
- Avoid sleep-fragmenting substances before bedtime, such as caffeine, nicotine, and alcohol
- Maintain regular exercise but avoid heavy exercise within several hours of bedtime
- Attempt to resolve stressful situations and maintain a 30-minute relaxation period before bedtime
- Avoid daytime naps

such natural pharmacotherapies as valerian, L-tryptophan, and kava. The quality of data regarding the effectiveness of these agents for treating insomnia is low, and results of available studies are inconclusive (42); as a result, their use is generally discouraged.

Melatonin is a hormone secreted by the pineal gland and influences sleep phasing and other circadian rhythms, with levels being highest during times of sleep. Exogenous melatonin affects multiple aspects of sleep architecture, and there is evidence that it is effective for treatment of circadian rhythm disorders, such as jet lag (43). There is also evidence that it may be helpful in treating insomnia by improving sleep onset and maintenance. In the United States, it is available as an over-the-counter dietary supplement and a prescription melatonin-specific–receptor agonist that has been approved for treatment of insomnia (see below). The over-the-counter form is generally well-tolerated, but which patients will likely benefit from treatment, the timing of dosing, and the optimal dosing range are not known (44).

Other potentially useful techniques for treating insomnia that have some evidence of effectiveness include structured exercise training (moderate-intensity aerobic exercise or high-intensity resistance exercise) (45), acupuncture, acupressure, tai-chi, and yoga (42).

When should clinicians consider prescription drug therapy?

When other approaches prove inadequate, prescription drug therapy may be warranted (see the Box). Pharmacologic therapy seems to be similar to CBT with regard to short-term effectiveness for insomnia, but there is limited evidence that initial combination therapy with medication and CBT is superior to CBT alone for insomnia.
The choice of medication for insomnia is typically individualized based on a number of factors. A primary consideration is the nature of the sleep disturbance. For example, for individuals with problems of sleep onset (difficulty falling asleep), use of a rapid-onset, short-acting agent may be appropriate, whereas patients with issues of sleep maintenance (staying asleep), a drug with slower-onset but longer half-life may be preferable. Additional considerations include whether the patient has acute or chronic symptoms, the presence of other medical or psychiatric conditions, potential side effects, or cost issues that might influence medication choice.

Several classes of drugs are used for insomnia, including those with a specific indication for treatment of sleep disturbances and those approved for another indication but used for this purpose. Medications approved by the U.S. Food and Drug Administration (FDA) to treat insomnia are listed in Table 3.

**Benzodiazepines**

Benzodiazepines exert their effects primarily through nonspecific

### Table 3. U.S. Food and Drug Administration–Approved Prescription Drug Treatments for Insomnia

<table>
<thead>
<tr>
<th>Agent*</th>
<th>Usual Dose</th>
<th>Onset†</th>
<th>Duration‡</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines (oral)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estazolam</td>
<td>1–2 mg</td>
<td>Slow</td>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>Flurazepam</td>
<td>15–30 mg</td>
<td>Rapid</td>
<td>Long</td>
<td></td>
</tr>
<tr>
<td>Quazepam</td>
<td>7.5–15 mg</td>
<td>Slow</td>
<td>Long</td>
<td></td>
</tr>
<tr>
<td>Temazepam</td>
<td>7.5–30 mg</td>
<td>Slow</td>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.125–0.5 mg</td>
<td>Rapid</td>
<td>Short</td>
<td></td>
</tr>
<tr>
<td>Nonbenzodiazepines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolpidem</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral tablet</td>
<td>5–10 mg</td>
<td>Rapid</td>
<td>Short</td>
<td></td>
</tr>
<tr>
<td>Extended-release oral tablet</td>
<td>6.25–12.5 mg</td>
<td>Rapid</td>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>Sublingual</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermezzo (Transcept Pharmaceuticals)</td>
<td>1.75–3.5 mg</td>
<td>Rapid</td>
<td>Short</td>
<td></td>
</tr>
<tr>
<td>Edluar (Meda Pharmaceuticals)</td>
<td>10 mg</td>
<td>Rapid</td>
<td>Short</td>
<td></td>
</tr>
<tr>
<td>Oral spray</td>
<td>10 mg</td>
<td>Rapid</td>
<td>Short</td>
<td></td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>1–3 mg</td>
<td>Rapid</td>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>Zaleplon</td>
<td>10–20 mg</td>
<td>Rapid</td>
<td>Short</td>
<td></td>
</tr>
<tr>
<td>Orexin-receptor antagonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suvorexant</td>
<td>5–20 mg</td>
<td>Slow</td>
<td>Long</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxepin</td>
<td>3–6 mg</td>
<td>Rapid</td>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>Melatonin agonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramelteon</td>
<td>8 mg</td>
<td>Rapid</td>
<td>Short</td>
<td></td>
</tr>
</tbody>
</table>


*All agents classified as schedule C-IV by the Drug Enforcement Agency except doxepin and ramelteon, which are not scheduled.

†Onset of action: rapid = 15 to 30 min; slow = 30 to 60 min.

‡Based on elimination half-life and preparation: short = 1 to 5 h; intermediate = 5 to 12 h; long = > 12 h.
enhancement of the γ-aminobutyric acid (GABA) type A-receptor complex. GABA is an inhibitory neurotransmitter that reduces neuronal firing, thereby decreasing arousal and facilitating sleep. Benzodiazepines decrease sleep latency and prolong total sleep time. Although specific benzodiazepines differ somewhat in their receptor affinity and may carry different indications, all have a hypnotic (sleep-promoting) effect, and a major consideration in prescribing them for insomnia is their time of onset, elimination half-life, and route of metabolism.

Because of the nonspecific activation of GABA receptors, benzodiazepines have additional effects beyond promoting sleep. In addition to possible daytime sedation, benzodiazepines may also cause cognitive impairment, dizziness, lightheadedness, motor incoordination, and anterograde amnesia. Respiratory depression is a concern in patients with ventilatory issues, such as OSAS or the obesity-hypoventilation syndrome. Benzodiazepines also have potential for dependence and abuse.

Nonbenzodiazepine GABA Agonists
Nonbenzodiazepines GABA agonists are chemically unrelated to the benzodiazepines but bind more specifically to certain subunits of the GABA type A-receptor complex; this tends to result in fewer side effects than benzodiazepines and other sedative-hypnotics. Their effect on sleep seems to be similar to that of benzodiazepines, with decreased sleep latency and extended total sleep time. Nonbenzodiazepines tend to have a more rapid onset and shorter half-lives than most benzodiazepines.

Adverse reactions associated with nonbenzodiazepine agents may include residual sedation, disorientation, nightmares, amnesia, mood changes, nausea, vertigo, headache, and visual distortion.

Nonbenzodiazepine abuse can occur, especially among patients with comorbid substance abuse and psychiatric illness. However, these agents are generally preferred over other hypnotic agents because of their effectiveness and safety profile.

Orexin-Receptor Antagonists
Orexins are excitatory neurotransmitters secreted by the hypothalamus that act on various brain nuclei to stimulate arousal. These drugs work by inactivating the stimulation of wakefulness instead of actively promoting sleep, as occurs with benzodiazepines and nonbenzodiazepine GABA stimulants. It is believed that this mechanism of action may cause fewer side effects than those commonly associated with GABA-stimulants, although next-day drowsiness impairing activities requiring alertness may occur. Data that directly compare these drugs with other insomnia medications are limited. Suvorexant is the first orexin antagonist approved for insomnia.

Melatonin-Receptor Agonists
The prescription form of melatonin, ramelteon, has increased agonist affinity for the MT1 melatonin receptor with a primary effect of decreasing sleep latency. It is indicated only for treatment of sleep-onset insomnia.

The most common side effects are nausea, headache, dizziness, and fatigue, but it is not associated with daytime somnolence or other cognitive changes. It is also not considered to be habit-forming and is not classified as a controlled substance. Although it may elevate prolactin levels, routine monitoring is not indicated.

Antidepressants
Antidepressants, particularly other antidepressants, may have a sedating effect and are sometimes used as therapy for insomnia, often in lower doses than...
those used for treating depression. Only one antidepressant, doxepin, has an FDA-approved indication for treatment of insomnia. Although doxepin is a tricyclic, the approved dose for insomnia is much lower than that used for treatment of depression, and the pharmacologic effect at that level is primarily antihistaminic. This tends to avoid the antiserotonergic and antiadrenergic effects and the potential complications seen with tricyclic antidepressants at higher dosing levels. Other tricyclic antidepressants are also frequently used off-label to treat insomnia, although evidence of effectiveness for treating sleep disorders not associated with depression is limited.

Trazodone, a novel antidepressant, is also commonly prescribed for insomnia despite limited evidence of effectiveness. Other later-generation antidepressants, such as mirtazapine, are also sometimes prescribed for insomnia. However, there have been no studies of this agent used for treatment of non–depression-related sleep disturbances.

Because of the lack of demonstrated effectiveness and the potential for significant adverse effects, in the absence of depression treating insomnia with antidepressants other than doxepin is not recommended (46).

Other Drugs

Barbiturates were historically used to treat insomnia, but their use has been supplanted by newer agents with decreased adverse effects and dependency issues, and they are not currently recommended. Antipsychotic agents (such as quetiapine and olanzapine) are helpful in treating sleep disturbances in patients with associated psychiatric disorders; however, their effectiveness in treating insomnia in patients with only insomnia disorder has not been established. Anticonvulsants (such as gabapentin and pregabalin) may be useful in treating underlying conditions associated with disturbed sleep (such as chronic pain or fibromyalgia) but do not seem to be effective for treating insomnia.

Drug Therapy for Insomnia Secondary to the Restless Legs Syndrome or Periodic Limb Movement Disorder

In addition to exclusion of iron deficiency and the avoidance of caffeine, nicotine, and alcohol, patients with RLS that is disruptive of sleep may also benefit from pharmacologic therapy. A low dose of a dopaminergic agonist agent, such as pramipexole or ropinirole, at bedtime is the usual first-line therapy. If dopaminergic agents are ineffective, poorly tolerated, or contraindicated, other treatment options include levodopa, benzodiazepines, or opioids (such as tramadol, codeine, hydrocodone, or oxycodone). The pharmacologic treatment for periodic limb movement disorder is similar.

What is the appropriate duration of prescription drug therapy?

Data on long-term use of prescription drug therapy for insomnia are limited, with most studies evaluating the effectiveness of treatment for less than 12 weeks (47). Therefore, it has been generally recommended to limit continuous drug therapy to 1 month to avoid the risk for tolerance (defined as the loss of effectiveness over time), dependence, or withdrawal on discontinuation. This recommendation has been tempered by more recent evidence from longer-term studies using nonbenzodiazepine medications that did not show evidence of tolerance or withdrawal when used continuously for up to 1 year (48, 49). In addition, many individuals take medication for insomnia on an as-needed basis instead of continuously, and studies of this dosing pattern extending to 6 months have shown symptomatic benefit without apparent adverse effects (50, 51).
Without available evidence to guide the optimal use of medications for insomnia, a prudent approach is to establish an effective medication regimen for a specific patient, and then tailor the dosing pattern and duration of treatment to that person’s needs while attempting to avoid prolonged or excessive therapy. This should include a discussion of the risks and benefits of drug therapy with patients and an individual determination of whether they would benefit from as-needed or continuous dosing. Candidates for as-needed use may be those with only intermittent insomnia who are able to assess when drug treatment would be helpful. In those initially treated with continuous therapy, periodic tapering and discontinuation trials are useful in determining whether longer-term therapy is needed.

What are the contraindications to drug therapy?

Patients with insomnia considering over-the-counter medications should be cautioned regarding side effects and potential interactions with other drugs. Because of the anticholinergic effects associated with sedating antihistamines, they are generally not recommended for patients with cardiopulmonary disease, glaucoma, or problems with urination. Patients considering use of complementary and alternative medications should be advised to discuss starting these therapies with their physicians before doing so to assess for possible interactions with other medications.

Caution should be exercised and possible harms weighed against potential benefits when considering pharmacologic treatment in older patients as most of these centrally acting agents have been shown to significantly increase the risk for adverse cognitive and psychomotor events in this population. Some sedative-hypnotic medications have been associated with anterograde amnesia, complex sleep-related behaviors (such as somnambulation and performing other activities, such as driving) while not fully awake, and aggression. There is also some risk for rebound insomnia, particularly when short-acting agents are used or treatment continues for longer periods.

All patients receiving sedating antihistamines or any sedative-hypnotic agents should restrict alcohol intake or avoid it all together. These agents should also be avoided or used with caution in patients taking other sedating medications. Additionally, all patients taking these drugs should be advised to use particular care when driving or using hazardous equipment.

Patients who are pregnant or breastfeeding should avoid sedative-hypnotics. These medications should also not be used in patients with specific underlying medical disorders (such as OSAS) in which sedation might be detrimental.

Benzodiazepines, and probably to a lesser extent nonbenzodiazepine medications, have abuse potential and should not be used by patients with a current alcohol or drug abuse problem or by patients in recovery. Although intentional or accidental overdose of benzodiazepines or nonbenzodiazepine agents alone rarely results in death or serious illness, they are frequently taken with either alcohol or other medications, which can be dangerous.

When should clinicians consider specialty referral?

Clinicians should consider referring patients with insomnia to a sleep specialist if there is suspicion of an underlying sleep disorder, such as OSAS, RLS, periodic limb movement disorder, narcolepsy, or circadian rhythm disturbance. Referral is also appropriate for patients with insomnia who do not respond to
The most common causes of acute insomnia in hospitalized patients? The most common causes of acute insomnia in hospitalized patients are the effects of the illness leading to admission, pain, drugs affecting sleep, and the hospital environment (52). Older patients with underlying cognitive deficits or delirium may be particularly susceptible to insomnia in hospital settings.

Nonpharmacologic treatment alone can often be effective in treating insomnia in hospitalized patients. Interventions include addressing sleep hygiene and hospital environmental issues, identifying medications that may be disrupting sleep, and treating medical conditions that impair sleep. If necessary, drug treatment requires careful consideration of its effects on any underlying medical conditions and potential interactions with other drugs (53).

What type of follow-up care should clinicians provide?

Optimal management of insomnia involves close clinical follow-up beyond initial evaluation. Subsequent visits may involve ongoing assessment of comorbid conditions, education about sleep hygiene and behavioral techniques, and monitoring the response and adjusting the dose if medications are used.

How should clinicians manage insomnia in hospitalized patients? The most common causes of acute insomnia in hospitalized patients are available behavioral interventions or drug therapy. Referral to a sleep specialist offers an opportunity for reassessment of insomnia symptoms, possible additional testing to better characterize the sleep disturbance, and implementation of more comprehensive CBT interventions. Referral to a psychiatrist for diagnostic evaluation can be helpful when it is unclear whether a concurrent psychiatric disorder, such as depression, is present.

Referral to other specialists may be helpful depending on the nature of associated comorbid conditions. A pulmonologist consultation is appropriate for patients with suspected sleep-disordered breathing who may need polysomnography or other testing. An otolaryngologist, an oral surgeon, or a dentist may help in evaluating patients with excessive snoring or other oropharyngeal or airway issues that might disturb sleep. A neurologist may be considered for management of sleep disorders associated with such neurologic diseases as Parkinson disease, cerebrovascular disease, or dementia.

Treatment... Initial therapy for insomnia should address sleep hygiene factors and include CBT, which involves a combination of cognitive training, sleep restriction, stimulus control guidelines, and relaxation techniques; referral to clinicians specifically trained in these techniques may be helpful. When CBT is unsuccessful, pharmacologic therapy may be warranted. Use of nonprescription treatments, such as antihistamines, should be discussed with patients, including potential adverse effects. GABA agonists (nonbenzodiazepine drugs preferred) may be useful in some patients, although side effects are common. Most antidepressants should be reserved for patients with underlying depression, and other classes of medication used off-label for insomnia lack evidence of effectiveness. Some evidence, consensus, and the U.S. Food and Drug Administration recommend limiting the use of sedative-hypnotics to 1 month, although longer periods of treatment and intermittent use may be appropriate in selected patients.

Are there professional organization guidelines for insomnia?

The American Academy of Sleep Medicine has published guidelines and practice parameters for insomnia, including guidelines for managing chronic insomnia (24) and practice parameters for treating psychological and behavioral insomnia (54). The British Association for Psychopharmacology has also issued a consensus statement on evidence-based treatment of insomnia, parasomnias, and circadian rhythm disorders (55).

What is the role of patient education?

Patient education plays an important role in insomnia management (see the Box), and clinicians should provide patients with information about insomnia and its treatment.

**Important Components of Patient Education About Insomnia**

Insomnia has multiple causes. It may precede or be a cause of depression or other mood disorders. It is necessary to address all contributing factors to insomnia. Patients should actively engage in behavioral treatments, including making changes in sleep hygiene, if applicable. Behavioral treatments have longer-lasting benefit than drug therapy alone. Progress often takes at least 1 to 2 months.

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**ACP Smart Medicine Module**

http://smartmedicine.acponline.org/content.aspx?gbosId=118

Access the American College of Physicians Smart Medicine module on insomnia.

**Patient Information**

www.sleep.pitt.edu/content.asp?id=1484&subid=2316

Pittsburgh Sleep Quality Index.


Insomnia Severity Index.

www.acponline.org/atpro/timssnet/catalog/books/restful_sleep.htm

Order copies of the ACP’s Guide to a Restful Sleep, a 30-minute patient education DVD and accompanying guidebook.

www.uptodate.com/contents/insomnia-beyond-the-basics

Patient information on insomnia from UpToDate.

**Clinical Guidelines**

www.aasmnet.org/Resources/PracticeParameters/PP_BTInsomnia_Update.pdf

Practice parameters for the psychological and behavioral treatment of insomnia from the American Academy of Sleep Medicine in 2006.

www.aasmnet.org/Resources/clinicalguidelines/040515.pdf


www.ncbi.nlm.nih.gov/pubmed/20813762

Consensus statement on evidence-based treatment of insomnia, parasomnias, and circadian rhythm disorders from the British Association for Psychopharmacology in 2010.

**Sleep Diaries**


http://smartmedicine.acponline.org/data/gbos/Module/118/d166-f1.png

www.journalsleep.org/ViewAbstract.aspx?pid=28419

**Evaluating Patients for a Sleep Disorder**

www.nlm.nih.gov/health/health-topics/topics/slpst/types.html
WHAT YOU SHOULD KNOW ABOUT INSOMNIA

What is insomnia?
Insomnia is a medical condition in which a person can have trouble falling asleep, trouble staying asleep, waking up too early, or having poor quality of sleep. Not getting enough sleep can affect a person’s coordination, memory, and thinking skills. People do not always know why they have insomnia, but the following are some common causes:

- Stress
- Caffeine
- Alcohol
- Distractions or disruptive sleep environment
- Changes in work schedules
- Pain or other symptoms from health conditions

What are the symptoms?
- Problems with falling asleep
- Trouble staying asleep or trouble returning to sleep after waking throughout the night
- Waking up too early
- Not feeling refreshed or rested after sleep
- Feeling sleepy throughout the day
- Having trouble concentrating or paying attention
- Falling asleep at unusual times

How is it diagnosed?
Your doctor will ask about your sleep and medical history. He or she may order blood tests to see if there is an underlying condition causing insomnia and ask you to keep a sleep diary. A sleep diary helps keep track of your sleep and other factors that could be causing insomnia.

How is it treated?
Treatment depends on many factors and can be as easy as changing your sleep habits. Your doctor may ask you to try to follow good sleep habits to see if there is an improvement in sleep. Good sleep habits include:

- Keeping a consistent bed time and waking time
- Spending no more than 8 hours in bed
- Trying not to force sleep and avoid watching the clock
- Keeping your bedroom quiet and dark
- Removing anything that may disrupt sleep (such as a television, telephone, or computer)
- Avoiding caffeine, nicotine, and alcohol before bedtime

Bottom Line
- Insomnia can have multiple causes. Talk with your doctor to better understand what causes your sleep problems.
- Keeping a sleep diary can help you and your doctor to understand your sleep patterns and habits.
- Insomnia can be treated and resolved. Treatment for insomnia depends on the cause.
- Many people improve simply by changing sleep habits.

For More Information

www.acponline.org/patients_families/products/brochures/sleepguide.pdf
American College of Physicians

www.sleepeducation.com
American Academy of Sleep Medicine

www.behavioralsleep.org/Default.aspx
Society of Behavioral Sleep Medicine

www.nhlbi.nih.gov/health/dci/Diseases/inso/
National Heart Lung and Blood Institute

National Library of Medicine
1. A 45-year-old man is evaluated for difficulty sleeping the past several months. He reports trouble both falling asleep and staying asleep. He has not tried any over-the-counter medications. He drinks two or three beers on the weekends only and this has not changed; he also drinks two cups of coffee in the mornings. His wife, who is present, has not heard any snoring, gasping, or other breathing problems at night. He reports no leg symptoms. They have recently moved to a new apartment; he reports that the bedroom may be hotter than the previous one, although his wife reports feeling comfortable.

Results of the physical examination are unremarkable. Vital signs are normal, BMI is 26, and mood and mental status are normal.

Which of the following is the best initial management for this patient?
A. Advise alcohol abstinence  
B. Benzodiazepine  
C. Counseling regarding sleep hygiene  
D. Over-the-counter antihistamine

2. A 76-year-old-woman is evaluated in the emergency department after she fell at home last night. She has long-standing sleeping difficulties and last night got out of bed and fell in her hallway. She had no loss of consciousness and notes left hip pain. She has hypertension, hyperlipidemia, and gastroesophageal reflux disease. Her current medications are lisinopril, simvastatin, and omeprazole.

On physical examination, she is afebrile. Blood pressure is 142/82 mm Hg supine and 138/76 mm Hg standing, and pulse rate is 76/min supine and 78/min standing. She appears frail, with no leg symptoms. There are no ecchymoses in the left lateral hip and femur reveals no fracture. Acetaminophen is prescribed for pain. Arrangements are made for home physical therapy and for a visiting nurse to perform a home safety evaluation.

Which of the following is the most appropriate additional management of this patient?
A. Discontinue lisinopril  
B. Prescribe vitamin D  
C. Prescribe zolpidem at bedtime  
D. Refer for prescription glasses with bifocal lenses

3. A 30-year-old man is evaluated for daytime fatigue of 9 months' duration. He has never fallen asleep at the wheel, but falls asleep at other times during the day. He does not think he snores, but his wife is unavailable to confirm this. He reports no leg symptoms. He has no significant medical history and takes no medications. He does not smoke. He drinks two or three beers on Friday and Saturday nights. He does not exercise regularly, and has gained 9.1 kg (20 lb) since getting married 18 months ago.

On physical examination, temperature is normal, blood pressure is 128/76 mm Hg, and pulse rate is 82/min. BMI is 32. Neck circumference is 43 cm (17 in). Pharynx is normal. The thyroid is difficult to palpate owing to the patient's large neck size. The lungs are clear, and cardiovascular and neurologic examinations are normal.

In addition to counseling regarding sleep hygiene and weight loss, which of the following is the most appropriate management for this patient?
A. Advise alcohol abstinence  
B. Initiate therapy with zolpidem  
C. Begin mirtazapine at bedtime  
D. Refer for polysomnography

4. A 74-year-old woman is evaluated for a 4-month history of insomnia, with difficulty falling asleep. The patient was the major caretaker for her husband, who had advanced heart failure and died suddenly 4 months ago. She has lost 3.6 kg (8 lb) and does not have much of an appetite. The patient used to volunteer at the hospital, but she does not enjoy going there any longer. She also does not have much energy. The patient is tearful and says that nearly everything reminds her of her husband.

Medical history is otherwise unremarkable. The physical examination is unremarkable.

Which of the following is the most appropriate management option for this patient?
A. Begin dextroamphetamine  
B. Begin mirtazapine at bedtime  
C. Begin zolpidem at bedtime  
D. Reassure the patient and schedule a follow-up appointment in 3 months

Disclosures: Dr. Masters, ACP Contributing Author, has disclosed the following conflict of interest: Employment: American College of Physicians. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M14-1830.