When patients can’t sleep
Updated guide to workup and hypnotic therapy

Karl Doghramji, MD
Professor of psychiatry and human behavior
Director, Sleep Disorders Center
Thomas Jefferson University
Philadelphia, PA

Careful investigation can often reveal insomnia’s cause—a medical or psychiatric condition or poor sleep habits. Understanding why patients can’t sleep is key to effective therapy.

Insomnia is associated with increased risk of accidents, work-related difficulties, and relationship problems. Long-term sleeplessness may even increase risk of new psychiatric disorders—most notably major depression.

PRIMARY INSOMNIA
DSM-IV-TR criteria for primary insomnia include:
• For at least 1 month, the patient’s main complaint has been trouble going to sleep, staying asleep, or feeling unrested.
• The insomnia or resulting daytime fatigue causes clinically important distress or impairs work, social, or personal functioning.
• The insomnia does not occur solely in the course of a breathing-related or circadian rhythm sleep disorder, a parasomnia, or as part of another mental disorder such as delirium, generalized anxiety disorder, or major depressive disorder.

The International Classification of Sleep Disorders outlines discrete insomnia types that are unrelated to other medical, mental, or sleep disor-
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...ders. These include, among others, adjustment sleep disorder and psychophysiologic insomnia. **Adjustment sleep disorder.** Acute emotional stressors—such as bereavement, job loss, or hospitalization—can cause insomnia or daytime sleepiness. Symptoms typically remit soon after the stressors abate, so this insomnia usually lasts a few days (acute) to a few months (short-term). It can also become chronic, lasting 1 months or longer. **Psychophysiologic insomnia.** Once insomnia begins—regardless of its cause—sleep problems may persist well after precipitating factors resolve. The mechanism may be related to somatized tension and learned sleep-preventing associations (trying too hard to sleep and conditioned arousal to the bedroom). Thus, short-term insomnia may develop into long-term, chronic difficulty with recurring episodes or a constant, daily pattern of insomnia.

Treatment for both adjustment sleep disorder and psychophysiologic insomnia with behavioral therapies and hypnotics is warranted if:

- sleepiness and fatigue interfere with daytime function
- the patient is significantly distressed
- a pattern of recurring episodes develops.  

**PSYCHIATRIC DISORDERS AND INSOMNIA**

**Depression.** Up to 80% of depressed persons experience insomnia, although no one sleep pattern seems typical. Depression may be associated with:

- difficulties in falling asleep
- interrupted nocturnal sleep
- early morning awakening.

**Anxiety disorders.** Generalized anxiety disorder (GAD), panic attacks, and posttraumatic stress disorder (PTSD) are associated with disrupted sleep. Patients with GAD experience prolonged sleep latency and fragmented sleep, similar to those with primary insomnia.

Some patients experience panic symptoms while sleeping, possibly in association with mild hypercapnia. Those patients tend to have earlier onset of panic disorder and a higher likelihood of comorbid mood and other anxiety disorders.

In patients with PTSD, disturbed sleep continuity and increased REM phasic activity—such as eye movements—are directly correlated with PTSD symptom severity. Nightmares and disturbed REM sleep are hallmarks of PTSD.

**WORKUP OF SLEEP COMPLAINTS**

The patient history is an important part of the evaluation and treatment of insomnia and other sleep disturbances (Algorithm).  

**Acute.** Many short-term insomnias—lasting a few weeks or less—are caused by situational stressors, circadian rhythm changes, or poor sleep hygiene (Table 1). A logical approach is to begin sleep hygiene measures and explore the patient’s life situation to uncover what might be causing the insomnia. Hypnotic agents may be considered if insomnia is associated with daytime sleepiness or occupational impairment or if it seems to be escalating and your assessment indicates that it is a primary condition.

**Chronic.** For longer-term insomnias—lasting more than a few months—consider a more thorough evaluation, including medical and psychiatric history, physical examination, and mental status examination. A differential assessment can be made on the basis of whether a patient has difficulty falling or staying asleep (Table 1). Ask about cardinal symptoms of disorders associated with insomnia, including:

- snoring or breathing pauses during sleep (sleep apnea syndrome)
- restlessness or twitching in the lower extremities (PLMD/RLS).

If possible, question the patient’s bed partner, who may be more aware of such symptoms than the patient.

Carefully review the patient’s weekday and weekend sleep patterns, bedtime habits, sleep hygiene habits, and substance and medication use.
Evaluation and treatment of insomnia and other sleep disturbances

Patient with sleep disturbance

Take history

Insomnia

Hypersomnia

Sleep-associated affective and behavioral disturbance

Duration < 3 weeks

Consider situational factors, including work-shift changes, jet-lag syndrome

Spontaneous resolution
Reassurance
Possible short course of hypnotics

Duration > 3 weeks

Poor sleep hygiene

Advise about better sleep hygiene

Normal sleep hygiene

Stress-related

Not stress-related

Psychiatric condition

Psychophysiologic condition

Alcohol or drug use

Consider:
Restless legs syndrome
Periodic movements of sleep
Central sleep apnea
Chronic respiratory failure

Chronic pain syndrome

Identify source

Treat pain

PSG to confirm diagnosis

Psychiatric consultation and therapy

Stress reduction: Relaxation techniques
Stimulus control
Daily exercise
Deconditioning

Abstention counseling

PSG may reassure patient and exclude other possibilities

PSG: polysomnography

Sleep clinic referrals. Consider an evaluation by a sleep disorders center when the diagnosis remains unclear or treatment of the presumed condition fails after a reasonable time.

**BEHAVIORAL TREATMENTS**

Behavioral treatments—with or without hypnotics—are appropriate for many insomnia complaints, including adjustment sleep disorder and psychophysiological insomnia. Behavioral measures may work more slowly than drug therapy, but their effects have been shown to last longer in patients with primary insomnia. It may be useful to start with both hypnotic and behavioral treatments and withdraw the hypnotic after behavioral measures take effect.

Sleep hygiene. Many individuals unknowingly engage in habits that impair sleep. Those with insomnia, for example, often try to compensate for lost sleep by staying in bed longer in the morning or by napping, which further fragment nocturnal sleep. Advise these patients to adhere to a regular awakening time—regardless of how long they slept the night before—and to avoid naps. Other tips for getting a good night’s sleep are outlined in Table 2, page 57.

Caffeine has a plasma half-life of 3 to 7 hours, although individual sensitivity varies widely and caffeine’s erratic absorption can prolong its effects. Advise patients with insomnia to avoid caffeine-containing beverages—including coffee, tea, and soft drinks—after noon.

**Relaxation training.** Muscle tension can be reduced through techniques such as electromyography (EMG) biofeedback, abdominal breathing exercises, or progressive muscle relaxation. Relaxation training is usually effective within a few weeks.

**Psychological counseling.** Counseling can help identify and dispel tension-producing thoughts that may be disrupting sleep, such as preoccupation with unpleasant work experiences or school examinations. Reassurance may help patients overcome fears about sleeplessness; suggest that they deal with anxiety-producing thoughts during counseling sessions and at times other than bedtime.

**PRESCRIBING HYPNOTICS**

Sedative-hypnotics are indicated primarily for short-term insomnia management. Most are used at bedtime until insomnia dissipates or the physician advises the patient to take a break.

**Treatment principles.** Because many insomnias are recurrent, prolonged hypnotic treatment given in short bouts is often optimal. Longer treatment—months to years—is clearly needed by a few patients with chronic insomnia. In these cases, carefully monitor for tolerance, as manifested by dosage escalation. Hypnotic treatment is generally not suitable for patients with drug abuse or dependence histories.
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Table 2

How to get a good night’s sleep

- **Maintain a regular sleep/wake rhythm**, regardless of the time of day.
- **Avoid excessive time in bed**, even if awake.
- **Avoid naps**, except if a shift worker or elderly.
- **Spend time in bright light while awake**. Use the bed only for sleeping and sex.
- **Avoid nicotine, caffeine, and alcohol**.
- **Exercise regularly early in the day**.
- **Do not watch the clock**.
- **Eat a light snack before bedtime if hungry**.

Although chloral hydrate and barbiturates are effective hypnotics, adverse effects limit their use. Benzodiazepines and more recently introduced agents have milder side-effect profiles (Table 3, page 54). Choose agents carefully, considering preferences, and effects of prior trials with similar agents. Guidelines for hypnotics discourage chronic use to minimize abuse, misuse, and habituation (Table 4, page 59).

Elimination half-life is one of the most important pharmacological properties that differentiates hypnotics from each other.15

- **longer half-life**: flurazepam, quazepam
- **intermediate half-life**: estazolam, temazepam, eszopiclone
- **short half-life**: triazolam, zolpidem, zolpidem ER, zaleplon, ramelteon

Hypnotic agents with relatively longer half-lives tend to be associated with greater potential for residual daytime effects such as sedation, motor incoordination, amnesia, and slowed reflexes. These effects may impair performance and increase the risk of auto accidents and injuries, especially hip fractures in the elderly.

Benzodiazepine receptor agonists. Of all the
drugs in class, zaleplon—because of its ultra-short half-life—is least likely to cause residual daytime effects when administered at bedtime. At 10-mg doses, its side effects seem to last no more than 4 hours after administration. Zaleplon can be safely taken after nocturnal awakenings if the patient remains in bed 4 hours or longer after taking it. An ultra-short half life is less desirable for patients with difficulty with sleep initiation and discontinuous sleep throughout the night. For them, longer elimination half-life agents—such as zolpidem, zolpidem extended release (ER), and eszopiclone—may be more predictably effective for the entire night. Short half-life hypnotics do not offer anxiolysis for patients with daytime anxiety, as the longer half-life agents do.

Zolpidem ER and eszopiclone do not have a limitation imposed on duration of use. Although zolpidem ER has not been investigated in controlled trials greater than 3 weeks, eszopiclone was evaluated during a 6-month study that demonstrated lack of tolerance during the entire period, and lack of rebound after rapid discontinuation. Eszopiclone is the only hypnotic indicated for long-term (lasting > 3 weeks) insomnia.

Melatonin receptor agonists. Ramelteon’s activity at MT1 and MT2 receptors is believed to contribute to its sleep-promoting properties. This agent has been found to reduce sleep latency, and it is indicated to treat insomnia characterized by sleep-onset delays. Although controlled, long-term studies are lacking, ramelteon does not have a limit on duration of use. It demonstrated a lack of abuse liability when compared with triazolam and placebo in subjects with a history of sedative/hypnotic or anxiolytic drug abuse. Tolerance and rebound. Tolerance can develop after repeated dosing with benzodiazepines—primarily triazolam—and rebound insomnia can follow.

### Table 3

<table>
<thead>
<tr>
<th>Class/drug</th>
<th>Onset of action</th>
<th>Half-life (hrs)</th>
<th>Active metabolites</th>
<th>Doses (mg)</th>
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<tbody>
<tr>
<td><strong>Benzodiazepines</strong></td>
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</tr>
<tr>
<td>Flurazepam</td>
<td>Rapid</td>
<td>40 to 250</td>
<td>Yes</td>
<td>15, 30</td>
</tr>
<tr>
<td>Quazepam</td>
<td>Rapid</td>
<td>40 to 250</td>
<td>Yes</td>
<td>7.5, 15</td>
</tr>
<tr>
<td>Estazolam</td>
<td>Rapid</td>
<td>10 to 24</td>
<td>Yes</td>
<td>0.5, 1, 2</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Intermediate</td>
<td>8 to 22</td>
<td>No</td>
<td>7.5, 15</td>
</tr>
<tr>
<td>Triazolam</td>
<td>Rapid</td>
<td>&lt;6</td>
<td>No</td>
<td>0.125, 0.25, 0.5</td>
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<tr>
<td><strong>Imidazopyridine</strong></td>
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<td>Zolpidem</td>
<td>Rapid</td>
<td>2.5</td>
<td>No</td>
<td>5, 10</td>
</tr>
<tr>
<td>Zolpidem ER</td>
<td>Rapid</td>
<td>2.5</td>
<td>No</td>
<td>6.25, 12.5</td>
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<td><strong>Pyrazolopyrimidines</strong></td>
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<tr>
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<td>1</td>
<td>No</td>
<td>5, 10, 20</td>
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<tr>
<td><strong>Cyclopyrrolone</strong></td>
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<tr>
<td>Eszopiclone</td>
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<td>Minor</td>
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<tr>
<td><strong>Melatonin receptor agonist</strong></td>
<td></td>
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<tr>
<td>Ramelteon</td>
<td>Rapid</td>
<td>1 to 2.6</td>
<td>No</td>
<td>8</td>
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</table>
abrupt discontinuation. Both can be minimized by using benzodiazepines at the lowest effective dosages and for brief periods. Gradual tapering when discontinuing the drug can help control rebound.

Tolerance and rebound seem to be less of a concern with the newer hypnotics than with benzodiazepines, as shown by controlled studies of eszopiclone, zolpidem, and zaleplon. However, periodic re-evaluation is still the prudent clinical standard for hypnotics prescribed over long periods of time.

**NONHYPNOTIC SLEEP AIDS**

**Sedating antidepressants.** Some physicians prescribe low doses of sedating antidepressants to control insomnia, a practice supported by controlled clinical trials of some tricyclic antidepressants (TCAs) such as doxepin, trazodone, and trimipramine. Some physicians also advocate using more-sedating antidepressants—at dosages needed to treat depression—to control insomnia in depressed patients.

Evening dosing can minimize daytime sedation. If you choose an activating antidepressant, the potential side effect of insomnia can be managed by judicious use of hypnotic agents. Little is known about antidepressants’ effects on sleep quality after the first 6 to 8 weeks of treatment.

Although possibly helpful as sleep aids, TCAs are associated with anticholinergic effects such as dry mouth, urinary flow difficulties, and cardiac dysrhythmias.

**Alcohol.** Patients with insomnia sometimes self-medicate with alcohol at bedtime because it enhances sleepiness and induces a more rapid sleep onset. Drinking a “nightcap” is a poor choice, however, because alcohol can impair sleep quality, resulting in daytime somnolence. Alcohol is also associated with rapid development of tolerance.

**Antihistamines** and over-the-counter products whose main active ingredients are antihistamines—such as doxylamine and diphenhydramine—are used for insomnia and may help individuals fall asleep and stay asleep. However, antihistamine use is complicated by unpredictable efficacy and side effects such as daytime sedation, confusion, and systemic anticholinergic effects.

**Melatonin** is a nonprescription dietary supplement used in dosages of 0.5 to 3,000 mg. Anecdotal reports indicate it may be efficacious in certain subtypes of insomnia—such as shift work, jet lag, blindness, delayed sleep phase syndrome—and in older patients with sleep complaints.

Melatonin’s efficacy has not been established conclusively, however, and concerns have been expressed regarding the purity of over-the-counter preparations and possible coronary artery tissue stimulation, as observed in animal studies.

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**Guidelines for safe use of hypnotics**

- Define a clear indication and treatment goal
- Prescribe the lowest effective dose
- Individualize the dose for each patient
- Use lower doses with a CNS depressant or alcohol
- Consider dose adjustment in the elderly and in patients with hepatic or renal disease
- Avoid in patients with sleep apnea syndrome, pregnancy, and history of abuse
- Limit duration of use
- Consider intermittent therapy for patients who need longer-term treatment
- Taper doses to avoid abrupt discontinuation
- Re-evaluate drug treatment regularly; assess both efficacy and adverse effects

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**References**

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1 Related resources

2 DISCLOSURES
Dr. Doghramji receives research grant support from Cephalon Inc., GlaxoSmithKline, Merck & Co., and Sanofi-Synthelabo.
