Current PSYCHIATRY

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

© Christine Allcino / Photonica

Careful investigation can often reveal insomnia's cause[1]—whether 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.[2] Long-term sleeplessness may even increase risk of new psychiatric disorders—most notably major depression.[3]

PRIMARY INSOMNIA

DSM-IV-TR criteria for primary insomnia include:[4]

- 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-

ders.[5] 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 3 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[6] is warranted if:

- sleepiness and fatigue interfere with daytime function
- the patient is significantly distressed
- a pattern of recurring episodes develops.[5]

PSYCHIATRIC DISORDERS AND INSOMNIA

Depression. Up to 80% of depressed persons experience insomnia, although no one sleep pattern seems typical.[7] 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.[8]

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.[9]

WORKUP OF SLEEP COMPLAINTS

The patient history is an important part of the evaluation and treatment of insomnia and other sleep disturbances (*Algorithm*).[12]

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*).[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:

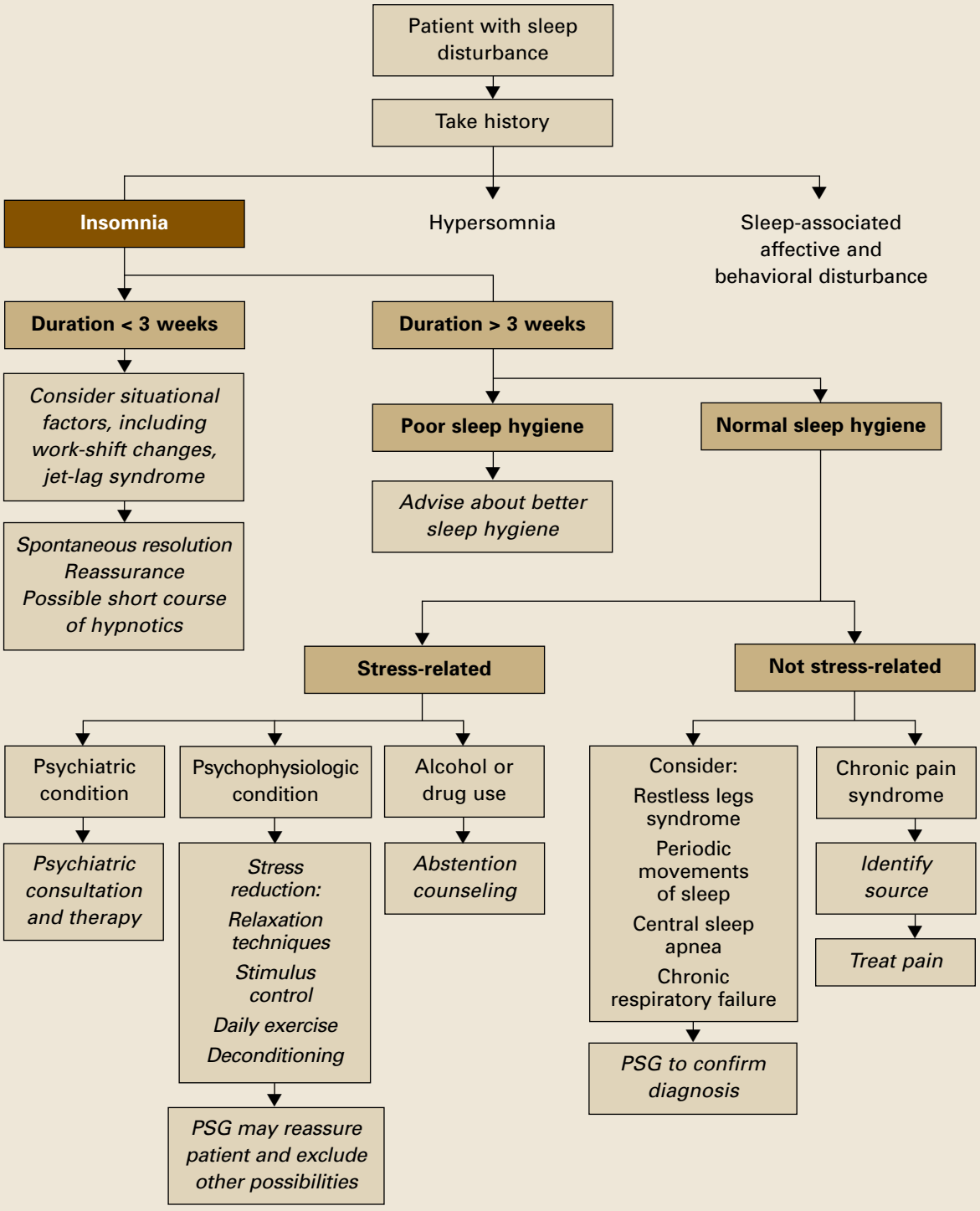
- snoring or breathing pauses during sleep (sleep apnea syndrome)
- restlessness or twitching in the lower extremities (PLMD/RLS).

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.

Algorithm

Evaluation and treatment of insomnia and other sleep disturbances



PSG: polysomnography

Source: Reprinted with permission from Erman M. Clinical update—diagnosis of insomnia in the primary care practice. Available at www.medscape.com/viewprgram/3139_pnt.

continued

Table 1

Possible causes of sleep complaints

Acute, transient	Recent or recurring stress Change in sleeping environment Acute illness or injury New medications Jet lag or shift change	
Chronic	**Difficulty staying asleep** Medications Drug or alcohol use Psychiatric disorder Medical disorder Sleep-disordered breathing Periodic limb movement disorder Restless legs syndrome	**Difficulty falling asleep** Poor sleep hygiene Conditioned insomnia Restless legs syndrome Circadian rhythm disorder Advanced sleep-phase syndrome

Source: Adapted and reprinted with permission from reference 13

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 psychophysiologic 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 later 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*.[14]

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.

continued on page 57

vasodilatation, thinking abnormal, decreased libido, and sweating. ***Commonly Observed Adverse Events in Controlled Clinical Trials for MDD, GAD, SAD, and PD***—Body as a Whole: asthenia, headache, flu syndrome, accidental injury, abdominal pain. Cardiovascular: vasodilatation, hypertension, palpitation. Digestive: nausea, constipation, anorexia, vomiting, flatulence, diarrhea, eructation. Metabolic/Nutritional: weight loss. Nervous System: dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, hypertonia, paresthesia, libido decreased, agitation, anxiety, twitching. Respiratory System: pharyngitis, yawn, sinusitis. Skin: sweating. Special Senses: abnormal vision. Urogenital System: abnormal ejaculation, impotence, orgasmic dysfunction (including anorgasmia) in females. ***Vital Sign Changes***: Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min in depression and GAD trials and a mean increase in pulse rate of 4 beats/min in SAD trials. (See **WARNINGS-Sustained Hypertension**). ***Laboratory Changes***: Clinically relevant increases in serum cholesterol were noted in Effexor XR clinical trials. Increases were duration dependent over the study period and tended to be greater with higher doses. ***Other Events Observed During the Premarketing Evaluation of Effexor and Effexor XR***—N=6,670. "Frequent"=events occurring in at least 1/100 patients; "infrequent"=1/100 to 1/1000 patients; "rare"=fewer than 1/1000 patients. **Body as a whole** - Frequent: chest pain substernal, chills, fever, neck pain; Infrequent: face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; Rare: appendicitis, bacteremia, carcinoma, cellulitis. **Cardiovascular system** - Frequent: migraine, postural hypotension, tachycardia; Infrequent: angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; Rare: aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, hematoma, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor, sinus arrhythmia. **Digestive system** - Frequent: increased appetite; Infrequent: bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; Rare: abdominal distension, biliary pain, cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration. **Endocrine system** - Rare: galactorrhoea, goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. **Hemic and lymphatic system** - Frequent: ecchymosis; Infrequent: anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia; Rare: basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura, thrombocytopenia. **Metabolic and nutritional** - Frequent: edema, weight gain; Infrequent: alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia, SGOT increased, SGPT increased, thirst; Rare: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcinuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia. **Musculoskeletal system** - Frequent: arthralgia; Infrequent: arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; Rare: bone pain, pathological fracture, muscle cramp, muscle spasms, musculoskeletal stiffness, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture. **Nervous system** - Frequent: amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; Infrequent: akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; Rare: abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barré syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, libido increased, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, torticollis. **Respiratory system** - Frequent: cough increased, dyspnea; Infrequent: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; Rare: atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea. **Skin and appendages** - Frequent: pruritus; Infrequent: acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; Rare: brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased. **Special senses** - Frequent: abnormality of accommodation, mydriasis, taste perversion; Infrequent: conjunctivitis, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. **Urogenital system** - Frequent: prostatic disorder (prostatitis, enlarged prostate, and prostate irritability), urination impaired; Infrequent: albuminuria, amenorrhea, breast pain, cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea, menorrhagia, metrorrhagia, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage, vaginitis; Rare: abortion, anuria, balanitis, bladder pain, breast discharge, breast engorgement, breast enlargement, endometriosis, female lactation, fibrocystic breast, calcium crystalluria, cervicitis, orchitis, ovarian cyst, prolonged erection, gynecomastia (male), hypomenorrhea, kidney function abnormal, mastitis, menopause, pyelonephritis, oliguria, salpingitis, urolithiasis, uterine hemorrhage, uterine spasm, vaginal dryness. **Postmarketing Reports**: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; epidermal necrosis/Stevens-Johnson syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, pulmonary eosinophilia, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and SIADH (usually in the elderly). Elevated clozapine levels that were temporally associated with adverse events, including seizures, have been reported following the addition of venlafaxine. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was given to patients on warfarin therapy. **DRUG ABUSE AND DEPENDENCE**: Effexor XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. **OVERDOSAGE**: Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), rhabdomyolysis, seizures, vertigo, liver necrosis, and death have been reported. Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdosage, consider the possibility of multiple drug involvement. Consider contacting a poison control center for additional information on the treatment of overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). **DOSAGE AND ADMINISTRATION**: Consult full prescribing information for dosing instructions. **Switching Patients to or From an MAOI**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. At least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**). This brief summary is based on Effexor XR Prescribing Information W10404C019, revised November 2005.

continued from page 52

Table 2

How to get a good night's sleep

- **Maintain** a regular waking time, regardless of amount of sleep the night before
- **Avoid** excessive time in bed
- **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 something relaxing** before bedtime
- **Don't** watch the clock
- **Eat a light snack** before bedtime if hungry

Although chloral hydrate and barbiturates are effective hypnotics, adverse effects limit their safety and usefulness. Benzodiazepines and more recently introduced agents have milder side-effect profiles (*Table 3, page 54*). Choose agents based on the patient's situation, 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 the 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 the all the

Table 3

Actions and available doses of common hypnotics

Class/drug	Onset of action	Half-life (hrs)	Active metabolites	Doses (mg)
Benzodiazepines				
Flurazepam	Rapid	40 to 250	Yes	15, 30
Quazepam	Rapid	40 to 250	Yes	7.5, 15
Estazolam	Rapid	10 to 24	Yes	0.5, 1, 2
Temazepam	Intermediate	8 to 22	No	7.5, 15
Triazolam	Rapid	<6	No	0.125, 0.25, 0.5
Imidazopyridine				
Zolpidem	Rapid	2.5	No	5, 10
Zolpidem ER	Rapid	2.5	No	6.25, 12.5
Pyrazolopyrimidines				
Zaleplon	Rapid	1	No	5, 10, 20
Cyclopyrrolone				
Eszopiclone	Rapid	6	Minor	2,3
Melatonin receptor agonist				
Ramelteon	Rapid	1 to 2.6	No	8

drugs in class, zalepon—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.[17]

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.[18]

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.[19] 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,[20,21] 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.[22]

Tolerance and rebound. Tolerance can develop after repeated dosing with benzodiazepines—primarily triazolam—and rebound insomnia can follow

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[19], zolpidem[23], and zaleplon.[24] However, periodic re-evaluation is still the prudent clinical standard for hypnotics prescribed over long periods of time.

Table 4

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

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,[25] trazodone,[26] and trimipramine.[27] 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.[28]

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.[29] 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.[30]

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.

References

1. Sateia MJ, Doghramji K, Hauri PJ, Morin CM. Evaluation of chronic insomnia. *Sleep* 2000;23:243-81.
2. Zammit GK, Weiner J, Damato N, et al. Quality of life in people with insomnia. *Sleep* 1999;22(suppl 2):S379-385.

Related resources

- American Academy of Sleep Medicine. Sleep logs, patient education materials. www.aasmnet.org
- American Sleep Apnea Association. National Sleep Foundation. www.sleepapnea.org

DRUG BRAND NAMES

Doxepin • Sinequan
Estazolam • Prosom
Eszopiclone • Lunesta
Flurazepam • Dalmane
Quazepam • Doral
Ramelteon • Rozerem
Temazepam • Restoril
Trazodone • Desyrel
Triazolam • Halcion
Trimipramine • Surmontil
Zaleplon • Sonata
Zolpidem • Ambien

DISCLOSURES

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

3. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. *JAMA* 1989;262:1479-84.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th ed, text rev). Washington DC: American Psychiatric Association, 2000.
5. International Classification of Sleep Disorders: Diagnostic and Coding Manual, 2nd ed. Westchester, IL: The American Academy of Sleep Medicine, 2005.
6. Spielman AJ, Glovinsky P. The varied nature of insomnia. In: Hauri P (ed). Case studies in insomnia. New York: Plenum Press, 1991:1-15.
7. Reynolds CF III, Kupfer DJ. Sleep research in affective illness: state of the art circa 1987. *Sleep* 1987;10:199-215.
8. Labbate LA, Pollack MH, Otto MW, et al. Sleep panic attacks: an association with childhood anxiety and adult psychopathology. *Biol Psychiatry* 1994;43:840-2.
9. Ross RJ, Ball WA, Sullivan KA, et al. Sleep disturbance as the hallmark of posttraumatic stress disorder. *Am J Psychiatry* 1989;146:697-707.
10. Winokur A, Reynolds CF. The effects of antidepressants on sleep physiology. *Primary Psychiatry* 1994;6:22-7.
11. Gillin JC, Rapaport M, Erman MK, et al. A comparison of nefazodone and fluoxetine on mood and on objective, subjective, and clinician-rated measures of sleep in depressed patients: a double blind, 8-week clinical trial. *J Clin Psychiatry* 1997;58(5):185-92.
12. Erman M. Clinical update. Diagnosis of insomnia in the primary care practice. Available at http://www.medscape.com/viewarticle/478849. Accessed Jan. 18, 2005.
13. Rajput V, Bromley SM. Chronic insomnia: A practical review. *Am Fam Physician* 1999;60:1431-8.
14. Doghramji K. The evaluation and management of sleep disorders. In: Stoudemire A (ed). *Clinical psychiatry for medical students (3rd ed)*. Philadelphia: JB Lippincott, 1998:783-818.
15. Gillin JC. The long and short of sleeping pills. *N Engl J Med* 1991; 324:1735-7.
16. Lunesta (eszopiclone). Approved labeling text. Marlborough, MA: Sepracor, Inc., 2005.
17. Corser B, Mayleben D, Doghramji K, et al. No next-day residual sedation four hours after middle-of-the-night treatment with zaleplon. *Sleep* 2000;23(suppl 2):abstract 309.
18. Holm KJ, Goa KL. Zolpidem: an update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. *Drugs* 2000;59:865-89.
19. Scarf MB, Roth T, Vogel GW, Walsh JK. A multicenter, placebo-controlled study evaluating zolpidem in the treatment of chronic insomnia. *J Clin Psychiatry* 1994;55:192-9.
20. Roth T, Stubbs C, Walsh JK. Ramelteon (TAK-375), a selective MT1/MT2-receptor agonist, reduces sleep latency to persistent sleep in a model of transient insomnia related to a novel sleep environment. *Sleep* 2005;28:303-7.
21. Roth T, Seiden D, Sainati S, et al. Phase III outpatient trial of ramelteon for the treatment of chronic insomniain elderly patients (poster presentation). Orlando, FL: American Geriatric Society annual meeting, 2005.
22. Griffiths R, Seuss P. Ramelteonand triazolam in humans: behavioral effectsand abuse potential (poster presentation). Atlanta, GA: American Psychiatric Association annual meeting, 2005.
23. Elie R, Ruther E, Farr I, et al. Sleep latency is shortened during 4 weeks of treatment with zaleplon, a novel nonbenzodiazepine hypnotic. Zaleplon Clinical Study Group. *J Clin Psychiatry* 1999;60:536-44.
24. Krystal A, Walsh J, Laska E, et al. Sustained efficacy of eszopiclone over six months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. *Sleep* 2003;26:793-9.
25. Hajak G, Rodenbeck A, Voderholzer U, et al. Doxepin in the treatment of primary insomnia: a placebo-controlled, double-blind, polysomnographic study. *J Clin Psychiatry* 2001;62:453-63.
26. Walsh JK, Erman M, Erwin CE, et al. Subjective hypnotic efficacy of trazodone and zolpidem in DSM-III-R primary insomnia. *Hum Psychopharmacol* 1998;13(3):191-8.
27. Hohagen F, Monero RF, Weiss E, et al. Treatment of primary insomnia with trimipramine: an alternative to benzodiazepine hypnotics? *Eur Arch Psychiatry Clin Neurosci* 1994;244(2):65-72.
28. Thase ME. Antidepressant treatment of the depressed patient with insomnia. *J Clin Psychiatry* 1999;60(suppl 17):28-31.
29. Johnson EO, Roehrs T, Roth T, Breslau N. Epidemiology of alcohol and medication as aids to sleep in early adulthood. *Sleep* 1998; 21:178-86.
30. Gengo F, Gabos C, Miller JK. The pharmacodynamics of diphenhydramine-induced drowsiness and changes in mental performance. *Clin Pharmacol Ther* 1989;45:15-21.

Bottom Line

Careful investigation often reveals insomnia's cause and its most effective treatment. For acute cases not caused by a psychiatric or medical disorder, sleep hygiene and supportive therapy may be sufficient. For chronic cases, behavioral treatments and short-term hypnotics are useful in combination.