

When patients can't sleep

Practical guide to using

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Tips to effective workup
and treatment of insomnia—
whether acute or chronic
and associated with almost any
psychiatric or medical disorder.

Careful investigation can often reveal insomnia's cause¹—whether a psychiatric or medical condition or poor sleep habits. Understanding why patients can't sleep is key to effective therapy.

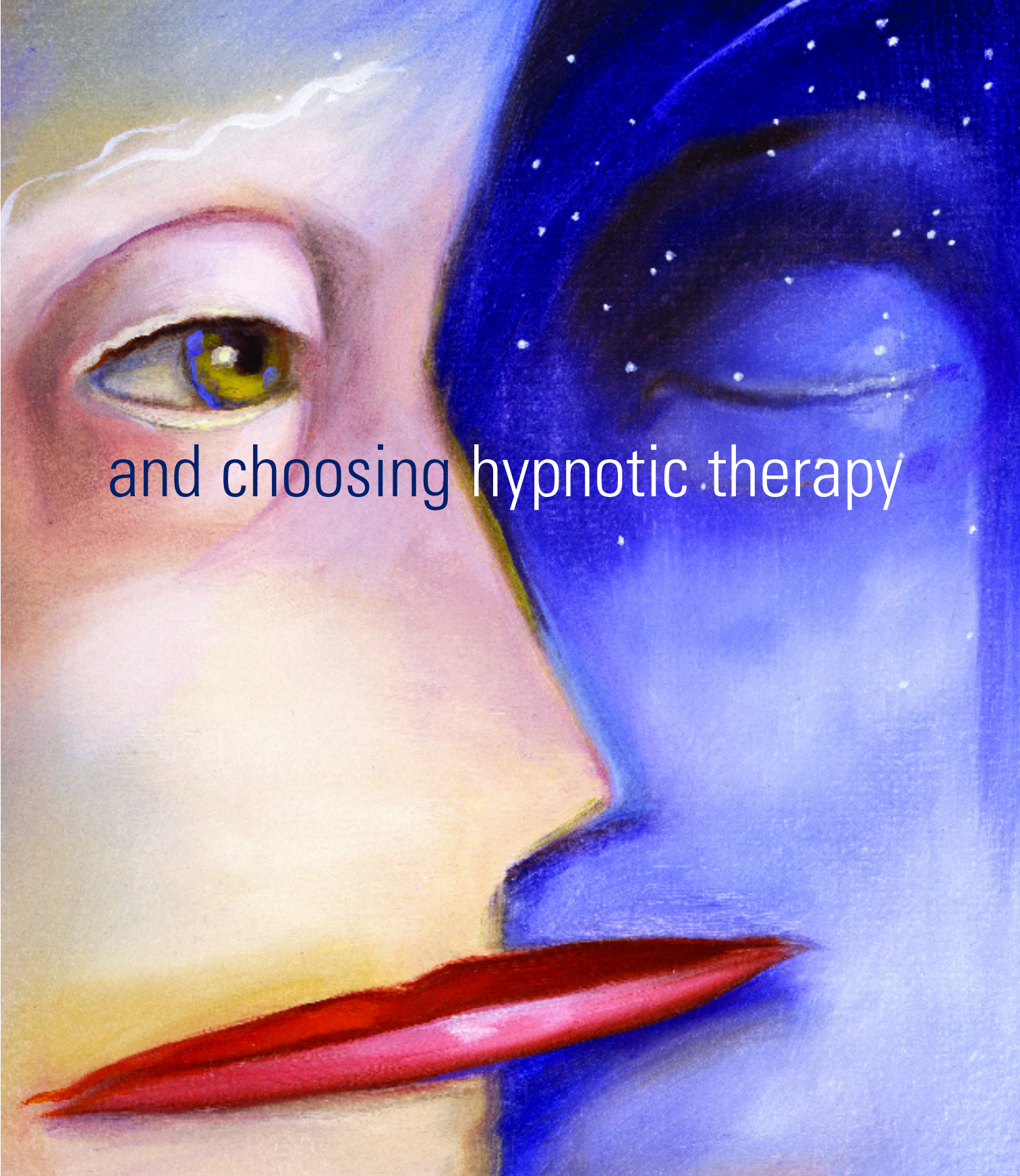
Acute and chronic sleep deprivation is associated with measurable declines in daytime performance (*Box*). Some data even suggest that long-term sleeplessness increases the risk of new psychiatric disorders—most notably major depression.³

PSYCHIATRIC DISORDERS AND INSOMNIA

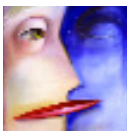
Depression. Many depressed persons—up to 80%—experience insomnia, although no one sleep pattern seems typical.² Depression may be associated with:

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

Anxiety disorders. Generalized anxiety disorder (GAD), social phobia, panic attacks, and post-traumatic stress disorder (PTSD) are all associated with disrupted sleep. Patients with GAD



and choosing hypnotic therapy



Box

The sleepless society: Chronic insomnia's impact

One-half of adult Americans experience insomnia during their lives, and 10% report persistent sleep difficulties (longer than 2 weeks). Individuals who complain of insomnia report:

- **daytime** drowsiness
- **diminished** memory and concentration
- **depression**
- **strained** relationships
- **increased risk** of accidents
- **impaired** job performance.

Despite these complaints, a surprising 70% of those with insomnia never seek medical help. Only 6% visit their physicians specifically for insomnia, and 24% address sleep difficulty as a secondary complaint. Many (40%) self-medicate with over-the-counter sleep aids or alcohol.²

Insomnia becomes more frequent with aging, associated with increased rates of medical and psychiatric illness and an age-related deterioration in the brain's sleep-generating processes.³

experience prolonged sleep latency (time needed to fall asleep after lights out) and fragmented sleep, similar to those with primary insomnia.

Subjective sleep quality may be impaired in patients with social phobia. Some patients experience panic symptoms while sleeping, possibly in association with mild hypercapnia. Patients with sleep panic attacks tend to have earlier onset of panic disorder and a higher likelihood of comorbid mood and other anxiety disorders.⁴

In patients with PTSD, disturbed sleep continuity and increased REM phasic activity—such as eye movements—are directly correlated with severity of PTSD symptoms. Nightmares and disturbed REM sleep are hypothesized hallmarks of PTSD.⁵

Schizophrenia. Patients with schizophrenia often

have disrupted sleep patterns. These include prolonged sleep latency, fragmented sleep with frequent arousals, decreased slow-wave sleep, variable REM latency, and decreased REM rebound after sleep deprivation. Despite investigations going back to the 1950s, no specific link between REM sleep and psychosis has been found.⁶ Interestingly, increases in REM sleep time and REM activity have been associated with an increased risk of suicide in patients with schizophrenia.⁷

Adjustment sleep disorder. Acute emotional stressors—such as bereavement, job loss, or hospitalization—often cause adjustment sleep disorder. Symptoms typically remit soon after the stressors abate, so this transient insomnia usually lasts a few days to a few weeks. Treatment with behavioral therapies and hypnotics⁸ is warranted if:

- sleepiness and fatigue interfere with daytime functioning
- a pattern of recurring episodes develops.⁹

Psychophysiologic insomnia. Once initiated—regardless of cause—insomnia may persist well after its precipitating factors resolve. Thus, short-term insomnia may develop into long-term, chronic difficulty with recurring episodes or a constant, daily pattern of insomnia. Sufferers often spend hours in bed awake focused upon—and brooding over—their sleeplessness, which in turn further aggravates their insomnia.

Adjustment sleep disorder and psychophysiologic insomnia are included within DSM-IV's term "primary insomnia."

OTHER CAUSES OF INSOMNIA

Medications that may affect sleep quality include antidepressants (*Table 1*),^{10,11} antihypertensives, antineoplastic agents, bronchodilators, stimulants, corticosteroids, decongestants, diuretics, histamine-2 receptor blockers, and smoking cessation aids.

Recreational drugs, such as cocaine, often cause insomnia. Hypnotics and anxiolytics can cause insomnia following long-term use and during withdrawal.

Other disorders known to disturb sleep include periodic limb movement disorder (PLMD), restless legs syndrome (RLS), sleep apnea syndrome, disrupted circadian rhythms (as with travel or shift work), cardiopulmonary disorders, chronic pain, diabetes, hyperthyroidism, hot flashes associated with menopause, seizures, dementia, and Parkinson's disease, to name a few.

WORKUP OF SLEEP COMPLAINTS

Acute. Most short-term insomnias—lasting a few weeks or less—are caused by situational stressors, circadian rhythm alterations, and sleep hygiene violations. A logical initial approach, therefore, is to combine sleep hygiene measures with supportive psychotherapy. Hypnotic agents may be considered for apparent daytime consequences—such as sleepiness and occupational impairment—or if the insomnia seems to be escalating.

Chronic. For longer-term insomnias—lasting more than a few weeks—consider a more thorough evaluation, including medical and psychiatric history, physical examination, and mental status examination. Inquire 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 (PLMS/RLS).

Question the bed partner, who may be more aware of such symptoms than the patient.

Table 1

Antidepressants' effects on sleep and wakefulness

| | |
|--------------------------|---|
| Activating agents | Bupropion, protriptyline, most selective serotonin reuptake inhibitors, venlafaxine, monoamine oxidase inhibitors |
| Sedating agents | Amitriptyline, doxepin, trimipramine, nefazodone, trazodone, mirtazapine |
| Neutral agents | Citalopram, escitalopram |

Carefully review sleep patterns on weekdays and weekends, bedtime habits, sleep hygiene habits, and substance and medication use.

Sleep clinic referrals. Consider an evaluation by a sleep disorders center when:

- the diagnosis remains unclear
- or treatment of the presumed conditions fails after a reasonable time

BEHAVIORAL TREATMENTS

Behavioral treatments—with or without hypnotics—are appropriate for a wide variety of insomnia complaints, including adjustment sleep disorder, psychophysiological insomnia, and depression. Behavioral measures may take longer to implement than drug therapy, but their effects have been shown to last longer in patients with primary insomnia. In many cases, 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 habitual behaviors 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

Behavioral measures take longer to implement but last longer than drug therapy

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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*.¹²

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 electromyography (EMG) biofeedback, abdominal breathing exercises, or progressive muscle relaxation techniques, among others. Relaxation training is usually effective within a few weeks.

Psychotherapy. Cognitive-behavioral therapy can help identify and dispel tension-producing thoughts that are disrupting sleep, such as preoccupation with unpleasant work experiences or school examinations. Reassurance may help patients overcome fears about sleeplessness; suggest that patients deal with anxiety-producing thoughts during therapy sessions and at times other than bedtime.

Insight-oriented psychotherapy may enhance patients' awareness of psychological conflicts from their past that may be producing anxiety and contributing to sleeplessness.

PRESCRIBING HYPNOTICS

Sedative-hypnotics are indicated primarily for short-term management of insomnia. Most are used prophylactically 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 not recommended by stan-

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



Prolonged hypnotic treatment given in short bouts is often best for recurrent insomnias

dard textbooks but is clearly needed by a small number of patients with chronic insomnia. In these cases, carefully monitor for tolerance, as manifested by dosage escalation. Long-term hypnotic treatment is not suitable for patients with drug abuse or dependence histories.

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*). 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*).

Elimination half-life is the primary pharmacokinetic property that differentiates the hypnotics from each other:¹³

- longer half-life: flurazepam, quazepam
- intermediate half-life: estazolam, temazepam

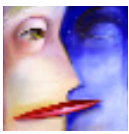


Table 3

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 |
| Pyrazolopyrimidine | | | | |
| Zaleplon | Rapid | 1 | No | 5, 10, 20 |

- short half-life: triazolam, zolpidem, zaleplon (*Table 3*).

Whereas benzodiazepines bind to benzodiazepine receptor types 1 and 2, zolpidem and zaleplon (and possibly quazepam) bind selectively to type 1. This selectivity may explain why zolpidem and zaleplon are more easily tolerated.

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.

Nonbenzodiazepines. Because of its ultra-short half-life, zaleplon 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 following administration. Zaleplon can be safely taken after nocturnal awakenings if

the patient remains in bed 4 hours or longer after taking it.¹⁴

Some patients feel that taking zaleplon only when needed allows them to use hypnotics more sparingly. On the other hand, zaleplon's ultra-short half-life makes it less useful for patients who have frequent episodes of sleep-interruption insomnia every night. For them, a longer elimination half-life agent such as zolpidem may be more predictably effective for the entire night.¹⁵ Short half-life hypnotics have many advantages, but they do not offer anxiolysis for patients with daytime anxiety, as the longer half-life agents do.

Drinking alcohol at bedtime can impair sleep quality, resulting in daytime drowsiness

Tolerance and rebound. Tolerance can develop following repeated dosing with benzodiazepines—primarily triazolam—and rebound insomnia can follow abrupt discontinuation. Despite widespread concerns, neither tolerance nor rebound insomnia has been well documented. Nevertheless, 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. In preliminary uncontrolled trials, zolpidem and zaleplon did not show evidence of these problems in 1 year of continued use.

NONHYPNOTIC SLEEP AIDS

Sedating antidepressants. Physicians often prescribe low doses of sedating antidepressants to control insomnia, a practice supported by some controlled clinical trials. For example, polysomnography showed that patients who took doxepin, 25 to 50 mg at bedtime, had enhanced sleep efficiency (ratio of time slept to time spent in bed) yet no change in sleep latency. Liver abnormalities, leukopenia, and thrombopenia developed in a few patients.¹⁶ Controlled studies have also shown subjective efficacy of trazodone¹⁷ and trimipramine¹⁸ in treating insomnia.

Some physicians advocate using the 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.¹⁹

Although possibly helpful as sleep aids, antidepressants are also associated with side effects. Trazodone, for example, may cause daytime sedation, orthostatic hypotension, and priapism. As a class, the tricyclics are associated with anticholinergic effects such as dry mouth, urinary flow difficulties, and cardiac dysrhythmias.

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

Alcohol. Patients with insomnia often self-medicate with agents that are not specifically indicated to induce sleep. Alcohol is widely used at bedtime because it enhances sleepiness and induces a more rapid sleep onset.²⁰ Drinking a “nightcap” is a poor choice, however, because alcohol—especially after prolonged use—can impair sleep quality, resulting in daytime somnolence. Alcohol is also associated with rapid development of tolerance.

Patients who use alcohol report unrefreshing and disturbed sleep, with frequent nocturnal awakenings even after prolonged abstinence. Alcohol also can further impair sleep-related respiration in patients with obstructive sleep apnea syndrome.

Antihistamines and over-the-counter products whose main active ingredients are antihistamines—such as doxylamine and diphenhydramine—can cause unpredictable efficacy and side effects such as daytime sedation, confusion, and systemic anticholinergic effects.²¹

Melatonin is a 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, jetlag, blindness, delayed sleep phase syndrome—and in the elderly. However, melatonin’s efficacy has not been established conclusively and is in doubt. Concerns have been expressed regarding the purity of available preparations and possible coronary artery tissue stimulation, as observed in animal studies of melatonin.

Related resources

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

DRUG BRAND NAMES

- | | |
|------------------------|--------------------------|
| Amitriptyline • Elavil | Protriptyline • Vivactil |
| Bupropion • Wellbutrin | Quazepam • Doral |
| Citalopram • Celexa | Temazepam • Restoril |
| Doxepin • Sinequan | Trazodone • Desyrel |
| Escitalopram • Lexapro | Triazolam • Halcion |
| Estazolam • Prosom | Trimipramine • Surmontil |
| Flurazepam • Dalmane | Venlafaxine • Effexor |
| Mirtazapine • Remeron | Zaleplon • Sonata |
| Nefazodone • Serzone | Zolpidem • Ambien |

DISCLOSURE

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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 psychotherapy may be sufficient. For chronic cases, behavioral treatments and short-term hypnotics are useful in combination.

BottomLine