

*Current Concepts***MANAGEMENT OF INSOMNIA**

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INSOMNIA is a common symptom, and clinicians need a diagnostic approach that allows them to choose from among many different types of therapy. This review focuses on the practical management of insomnia in adults¹ and on the scientific basis of current treatments.^{2,3} Reports of insomnia tend to increase with age⁴ and are more prevalent among women,⁵ even though laboratory studies show that older men have more disrupted sleep.^{6,7} People who are divorced, widowed, or separated report having insomnia more often than married people; lower socioeconomic status is also a correlate of insomnia.⁸ The course of insomnia can vary over time,^{9,10} but insomnia tends to be persistent or recurrent in both clinical and community samples.^{8,11,12} Persistent insomnia is both a risk factor for⁸ and a precursor of¹³ mood disorders. Thus, effective treatment of insomnia may represent an opportunity to prevent major depression.^{8,13} Chronic insomnia is also associated with an increased risk of automobile accidents, increased alcohol consumption, and daytime sleepiness.¹⁴ Thus, patients with insomnia merit serious attention.

INSOMNIA: SYMPTOM VERSUS SYNDROME

Patients who report having insomnia often have several problems, including sleep that is unrefreshing or nonrestorative as well as the inability to fall asleep or to remain asleep. The duration of a patient's insomnia has important diagnostic implications. Transient insomnia, lasting only a few days, is often a result of acute stress, acute medical illness, jet lag, or self-medication. Insomnia lasting longer than three weeks is considered chronic and usually has different causes.¹⁵ The duration of the symptom is important

both in determining the differential diagnosis and in evaluating secondary problems, including the use and misuse of alcohol and drugs — which can be both a cause and an effect of chronic insomnia — and obsessive concern about an inability to sleep (which often becomes a self-fulfilling prophecy). The diagnostic and pharmacotherapeutic considerations depend on whether symptoms are short term or chronic.

The diagnosis of chronic primary insomnia requires difficulty in initiating or maintaining sleep or the presence for at least one month of nonrestorative sleep that causes marked distress or impairment in social, occupational, or other important areas of functioning.^{16,17} The sleep disturbance of primary or psychophysiological insomnia is not due to another sleep disorder, a mental disorder, or the effects of a drug or medical condition. Thus, it is typically a diagnosis of exclusion, reached after more specific medical and psychiatric diagnoses have been ruled out. Often, patients are intensely worried about not sleeping and engage in self-defeating behavior, such as following irregular or unpredictable sleep-wake schedules or spending excessive amounts of time in bed.

EVALUATION: PRINCIPLES AND PITFALLS

Physicians should try to determine the cause of insomnia, remembering that it may have more than one cause.¹⁸ There are effective treatments for specific conditions, and physicians need to understand the cause of chronic insomnia to establish a long-term approach to its management.

The first step is to define the chief sleep symptom — for example, insomnia, excessive sleepiness, or disturbed behavior during sleep. Physicians must then consider the possible causes, which include: concurrent medical conditions or their treatment; the use of substances such as caffeine, nicotine, or alcohol; psychiatric disorders, such as mood or anxiety disorders; acute or chronic stress, such as that resulting from bereavement; disordered circadian rhythms (occasioned by jet lag, shift work, or advanced- or delayed-sleep-phase syndrome); sleep-disordered breathing (heralded by snoring or obesity); nocturnal myoclonus, sometimes associated with restlessness of the legs at the beginning of sleep; events such as panic attacks or recurrent nightmares during sleep; behavioral conditioning, including excessive worrying about not sleeping; and behavior that is destructive to sleep, including an irregular schedule or the habit of lying in bed ruminating.

It is often useful to have the patient complete a two-week log or diary indicating the patient's usual

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bedtime and time of arising, the timing and quantity of meals, use of alcohol, exercise, medications (prescribed and over-the-counter), and descriptions of the duration and quality of sleep each day. Such information may reveal aspects of the patient's lifestyle that can be destructive to sleep. If the patient has a bed partner, it is also important to ask that person whether the patient snores loudly, behaves abnormally during sleep (e.g., has episodes of confusion or combativeness), or is excessively sleepy during the day. Such collateral information can provide important clues to a differential diagnosis. Physicians should refer patients suspected of having sleep-disordered breathing for an evaluation that includes electroencephalographic sleep staging and simultaneous electrocardiography and monitoring of respiration and limb movements. (For more on sleep apnea and its management, see Strollo and Rogers.¹⁹) A task force of the American Sleep Disorders Association²⁰ also recommends referring a patient if chronic insomnia persists after behavioral and pharmacological intervention (as described below) or if the sleep symptom is not adequately explained by the type or degree of the patient's medical illness or medications.

The most common pitfall in diagnostic evaluation is the failure to understand that chronic insomnia has many causes. Despite the complexity of the condition, a systematic, long-term approach to management and to working through sleep disorders can lead to success in therapy.²¹

MANAGEMENT

After evaluating any medical and psychiatric problems, physicians' primary goals are to remove or mitigate these underlying problems, to prevent progression from transient to chronic insomnia, and to improve the patient's quality of life. Achieving these goals involves educational, behavioral, and often pharmacologic intervention.

Educational and Behavioral Intervention

It is essential to educate patients about the kinds of behavior that disrupt sleep (stimulus control) and to stabilize sleep-wake schedules (temporal control). A behavioral intervention called stimulus-control therapy is useful, simple, and effective.²² Patients should be instructed to go to bed only when sleepy and to use the bedroom only for sleep and sex and not for reading, watching television, eating, or working. If patients are unable to sleep after 15 to 20 minutes in bed, they should get out of bed and go into another room. They should read with a dim light and avoid watching television, which radiates full-spectrum bright light and therefore has an arousing effect, and they should return to bed only when sleepy. The aim is to reestablish the psychological connection between the bedroom and sleeping,

rather than the bedroom and insomnia. Patients should get out of bed at the same time each morning regardless of how much they slept during the previous night. This stabilizes the sleep-wake schedule (temporal control) and enhances sleep efficiency (the percentage of time in bed actually spent sleeping). Finally, daytime napping should be minimized or avoided in order to increase the drive to sleep at night. If the patient needs it, a 30-minute nap early in the afternoon probably will not disrupt sleep at night.

Another helpful behavioral intervention with demonstrated efficacy consists of curtailing the amount of time spent in bed to the actual amount of time spent sleeping. The efficacy of this approach, known as sleep-restriction therapy,²³ has been demonstrated in a randomized clinical trial with elderly subjects.²⁴ This method allows a slight sleep debt to accrue, which increases patients' ability to fall asleep and to stay asleep. The time allowed in bed is increased incrementally, as long as a desired sleep efficiency is maintained. For example, if a patient with chronic insomnia is sleeping 5.5 hours nightly, the time in bed is limited to 5.5 to 6.0 hours. The patient then adds approximately 15 minutes per week to the start of each night's time in bed, rising at the same time every morning, as long as at least 85 percent of the time in bed is spent sleeping.

Physicians should supplement stimulus control, temporal control, and sleep restriction with education about health practices, such as diet, exercise, and substance use, and environmental factors, such as light, noise, and temperature, that may be detrimental or beneficial to sleep. More specialized approaches involve relaxation therapies, such as progressive muscular relaxation and biofeedback, to reduce arousal.²⁵ Cognitive-behavioral treatment for insomnia targets maladaptive patterns that perpetuate insomnia. This approach has been shown to be of value in producing long-term benefit.²⁶

Pharmacotherapeutic Management

Five basic principles characterize rational pharmacotherapy for insomnia, especially chronic insomnia, in both adult and geriatric patients: use the lowest effective dose; use intermittent dosing (two to four times weekly); prescribe medication for short-term use (i.e., regular use for no more than three to four weeks); discontinue the medication gradually; and be alert for rebound insomnia following discontinuation. In addition, agents with shorter elimination half-lives are generally to be preferred in order to minimize daytime sedation. Alcohol and over-the-counter agents (such as antihistamines) are only minimally effective in inducing sleep, further impair the quality of sleep, and adversely affect performance the next day. Table 1 lists commonly prescribed sedative hypnotic agents, with information about the dose (adult

TABLE 1. AGENTS COMMONLY PRESCRIBED TO TREAT INSOMNIA.*

MEDICATION (TRADE NAME)	USUAL THERAPEUTIC DOSE		TIME UNTIL ONSET OF ACTION	T _{1/2β} †	ACTIVE METABOLITE
	ADULT	GERIATRIC			
	mg/day				
Clonazepam (Klonopin)‡	0.5–2	0.25–1	20–60	19–60	No
Clorazepate (Tranxene)	3.75–15	3.75–7.5	30–60	6–8§ 48–96¶	Yes
Estazolam (ProSom)	1–2	0.5–1	15–30	8–24	No
Lorazepam (Ativan)‡	1–4	0.25–1	30–60	8–24	No
Oxazepam (Serax)	15–30	10–15	30–60	2.8–5.7	No
Quazepam (Doral)	7.5–15	7.5	20–45	15–40§ 39–120¶	Yes
Temazepam (Restoril)	15–30	7.5–15	45–60	3–25	No
Triazolam (Halcion)	0.125–0.25	0.125	15–30	1.5–5	No
Chloral hydrate (Noctec)	500–2000	500–2000	30–60	4–8	Yes
Haloperidol (Haldol)‡	0.5–5	0.25–2	60	20	No
Trazodone (Desyrel)‡	50–150	25–100	30–60	5–9	No
Zolpidem (Ambien)	5–10	5	30	1.5–4.5	No

*Data are from the American Hospital Formulary Service,²⁷ Garzone and Kroboth,²⁸ Greenblatt,^{29,30} Farney and Walker,³¹ and Bezchlibnuk-Butler and Jeffries.³²

†T_{1/2β} denotes terminal elimination half-life.

‡Use of this drug as a hypnotic agent is not an indication approved by the Food and Drug Administration.

§The value applies to the parent compound.

¶The value applies to the active metabolite.

||These drugs are not benzodiazepines.

and geriatric), onset of activity, elimination half-life, and presence or absence of active metabolites.^{27–32} Table 2 lists several widely used over-the-counter sleeping medications and their ingredients.^{33–38} Table 3^{39,40} lists the most common medications that interfere with sleep.

With respect to clinical-efficacy trials in adult patients with chronic insomnia,² we reviewed 123 controlled medication studies (with a total of 9114 patients) and 33 controlled behavioral-intervention studies (1324 patients). We concluded that subjective symptoms and objective signs of chronic insomnia respond to short-term behavioral and pharmacologic intervention. Both types of intervention typically reduce the amount of time it takes to fall asleep by 15 to 30 minutes as compared with pretreatment times and the number of awakenings by one to three per night. Although pharmacologic agents appear to act more reliably in the short run and behavioral interventions appear to produce more sustained effects, no direct comparisons with respect to long-term efficacy are available. On the basis of the data from controlled trials, benzodiazepines, zolpidem, antidepressants, and melatonin (only one controlled trial) are effective pharmacologic agents. Stimulus control, sleep restriction, relaxation strategies, and cognitive–

behavioral therapy are effective behavioral interventions for short-term management.

We have examined the randomized, double-blind trials in elderly patients with chronic insomnia of various causes.³ In 23 trials with 1082 patients, including 516 psychogeriatric inpatients or residents of nursing homes, we found scientific support for the short-term (up to three weeks) efficacy of zolpidem and triazolam in the elderly, as well as temazepam, flurazepam, and quazepam, but not chloral hydrate.

Since the introduction of chlordiazepoxide 30 years ago, all pharmacologic clinical trials in adult patients and geriatric patients have addressed only short-term interventions (lasting several days to several weeks) and their immediate responses; there are no data from randomized clinical trials about the ability of interventions to produce sustained effects for more than 35 days. Questions remain unanswered about the long-term efficacy of medications in a disorder that is typically chronic and relapsing. This deficiency, along with the risk of physical dependence, led the Food and Drug Administration to establish guidelines that discourage the use of benzodiazepine hypnotic agents for more than four weeks.¹⁵

The elimination half-lives of sedative hypnotic agents vary widely. Adverse events such as memory

TABLE 2. COMMONLY USED OVER-THE-COUNTER SLEEP AIDS.*

MEDICATION (TRADE NAME)	DOSE OF ACTIVE INGREDIENT mg/day	TIME UNTIL ONSET OF ACTION min	T _{1/2β} † hr	OTHER INGREDIENTS
Diphenhydramine (Nytol, Sleep-Eze, Sominex)	25–50	60–180	2.4–9.3	None
Doxylamine (Unisom Nighttime)	25	60–120	10	None
Diphenhydramine in combination (Anacin P.M., Doan's P.M. Extra Strength, Excedrin P.M., Tylenol P.M., Unisom with Pain Relief)	25–50	60–180	2.4–9.3	Acetaminophen, 250–650 mg
Tryptophan‡	1000–2000	Not available	Not available	Various
Melatonin§	1–2	60–120	0.5–1	Vitamins B ₆ , B ₁₂ , calcium, magnesium, amino acids (L-glutamine, L-tyrosine, L-glutamic acid), herbs, zinc

*Data are from Crismon and Jermain,³³ Aldhous et al.,³⁴ Dollins et al.,³⁵ MacFarlane et al.,³⁶ Zhdanova et al.,³⁷ and Hagan and Oakly.³⁸

†T_{1/2β} denotes terminal elimination half-life.

‡In 1990, the Food and Drug Administration recalled all products containing tryptophan except protein supplements, infant formulas, and parenteral and enteral nutritional products.

§Melatonin is available in the United States from a variety of manufacturers, although it is not regulated as a drug by the Food and Drug Administration. Therefore, there is considerable variation in content from one tablet to another.

TABLE 3. COMMON PRESCRIPTION DRUGS KNOWN TO CAUSE INSOMNIA.*

Antihypertensives	Central nervous system stimulants	Antineoplastics
Clonidine	Methylphenidate	Medroxyprogesterone
Beta-blockers		Leuprolide acetate
Propranolol	Hormones	Goserelin acetate
Atenolol	Oral contraceptives	Pentostatin
Pindolol	Thyroid preparations	Daunorubicin
Methyldopa	Cortisone	Interferon alfa
Reserpine	Progesterone	Miscellaneous
Anticholinergics	Sympathomimetic amines	Phenytoin
Ipratropium bromide	Bronchodilators	Nicotine
	Terbutaline	Levodopa
	Albuterol	Quinidine
	Salmeterol	Caffeine (over-the-counter products)
	Metaproterenol	Anacin
	Xanthine derivatives	Excedrin
	Theophylline	Empirin
	Decongestants	Cough/cold preparations
	Phenylpropanolamine	
	Pseudoephedrine	

*Data are from Lacy et al.³⁹ and Crismon.⁴⁰

impairment, falls, excessive sleepiness, and accidents occur more often at higher doses and when active metabolites accumulate. Flurazepam and quazepam have the longest elimination half-lives (36 to 120 hours) and therefore have the advantages of providing next-day anxiolytic action and lowering the likelihood of rebound insomnia. However, prolonged

use of these agents can lead to daytime sleepiness, cognitive impairment, incoordination, and worsening of depression. Agents with intermediate elimination half-lives (10 to 24 hours) and no active metabolites include temazepam and estazolam. They are less likely to be associated with excessive daytime sleepiness. Agents with very short elimination half-lives (2 to 5 hours) include triazolam and zolpidem.

The efficacy of zolpidem, an imidazopyridine, has been found to be similar to that of benzodiazepines in studies of acute and chronic insomnia.⁴¹⁻⁴³ Although both zolpidem and benzodiazepines exert their effect through modulation of the γ -aminobutyric acid (GABA)-receptor complex,²⁹ zolpidem may be less likely than benzodiazepines to disturb the architecture of sleep and to cause cognitive and psychomotor side effects (and may have fewer withdrawal effects).⁴⁴⁻⁴⁶ Although these potential advantages suggest that zolpidem may prove useful in the treatment of acute and chronic insomnia, because it acts through the GABA-receptor complex it theoretically carries the same risks, including dependence, as the benzodiazepines, and as a result its use for more than four weeks is discouraged.

Before prescribing any sleep medication, physicians need to consider general issues of safety. For example, pregnant women, as well as patients with possible sleep apnea — which may be exacerbated by sleep medications — and patients with renal and hepatic insufficiency, may be at greater risk for sedative side effects.

Clinicians' concern about the possibility of dependence on and the side effects of benzodiazepines and zolpidem, together with regulatory requirements such as that for triplicate prescription, have contributed in recent years to a 30 percent decrease in benzodiazepine prescriptions and a 100 percent increase in the use of antidepressants as hypnotic agents.⁴⁷ There is, however, little controlled evidence bearing on the effects of antidepressants on chronic insomnia in the absence of a mood disorder. The single reported study used trimipramine, which produced subjective improvements in the quality and quantity of sleep and objective improvements as measured by polysomnography.⁴⁸ Trimipramine and other sedating tertiary tricyclic agents (e.g., amitriptyline and doxepin) have troublesome anticholinergic side effects and pose a risk of more serious conditions, such as orthostasis and cardiac dysrhythmias. An additional risk posed by tricyclic antidepressants as compared with benzodiazepines and zolpidem is the danger of overdose. However, the risk associated with ingesting alcohol with a benzodiazepine or zolpidem and the risk of dependence on either drug also remain dangers. Patients and their families must be educated about the appropriate use of sleep medications.

Serotonin-specific antidepressants, such as trazodone, nefazodone, and paroxetine, alleviate the sleep disturbance that accompanies depression⁴⁹ and have fewer side effects than tertiary amine antidepressants. The potential benefit of serotonin-specific antidepressants in chronic insomnia has not been systematically evaluated. However, given the side effects of benzodiazepines and zolpidem (and the additional risks of dependence, withdrawal, and rebound insomnia) and the danger of overdose with traditional tricyclic agents, controlled evaluation of serotonin-specific antidepressants in the treatment of chronic primary insomnia should become a priority in insomnia research, particularly since chronic insomnia is an established risk factor for major depression.^{8,13} It is possible that the use of a safe antidepressant medication could diminish the burden of chronic insomnia and prevent major depression. Antidepressants are now used widely and are prescribed at much lower doses for the treatment of insomnia than for depression. This practice has developed without data from controlled clinical trials. It is possible that the use of a medication for which the antidepressant dose is lower (e.g., 20 mg of paroxetine per day) would both improve sleep and help prevent depression in chronic insomnia.

Melatonin has received considerable attention in the lay press in the context of sleep and circadian rhythms. A single double-blind, placebo-controlled study of the effects of melatonin on chronic insomnia unrelated to circadian disturbances found melatonin (2 mg per day) superior to placebo in improving sleep efficiency in the elderly.⁵⁰

CONCLUSIONS

Although chronic primary insomnia defies easy diagnosis and treatment, clinicians should recognize the importance of determining the cause of insomnia while bearing in mind that it may have multiple causes in the same patient. Taking a long-term approach to the management of chronic insomnia and working through insomnia complaints systematically help to achieve success in therapy, even in patients with complex cases — especially since chronic insomnia is often a relapsing disorder. More data are needed about preventive strategies and the long-term efficacy of both behavioral and pharmacologic approaches. We view sleep-restriction therapy and selected antidepressant medications (especially serotonin-specific antidepressants) as promising candidates for studies of long-term efficacy.

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