REVIEW

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Advances in treating insomnia

ABSTRACT

Too often, insomnia is treated as a symptom without investigation of the cause. Insomnia may be a condition unto itself (primary insomnia), or it may be associated with a medical or psychiatric condition (comorbid insomnia), and it may be acute or chronic. Inadequate treatment often leads to significant frustration and lost productivity. We review the classification, pathophysiology, and treatment of insomnia and discuss how we can minimize its adverse consequences.

KEY POINTS

Cognitive behavioral therapy, in some cases coupled with drug therapy, is the most effective treatment of chronic insomnia once underlying disorders affecting sleep are addressed.

Comorbid insomnia can be associated with medical conditions, psychiatric disorders, neurologic disorders, primary sleep disorders, and drugs. In fact, drugs are a common cause of insomnia, a fact often overlooked.

Nonbenzodiazepine hypnotics are an excellent alternative to traditional benzodiazepines, offering comparable efficacy and a lower risk of adverse effects such as amnesia, daytime sleepiness, respiratory depression, orthostatic hypotension, and falls.

Sedating antihistamines should be used conservatively for insomnia due to limited efficacy and the potential for significant adverse effects.

*Dr. Budur has indicated that he has received honoraria from Takeda Pharmaceuticals. Dr. Foldvary-Schaefer has indicated that she has received honoraria and consulting fees from GlaxoSmithKline and honoraria from UCB corporation.

INSOMNIA IS AN UNDERAPPRECIATED public health issue. Its consequences are staggering when we consider its effects on social and occupational performance, health care costs, comorbidities, and quality of life.[1,2] Women and the elderly are particularly vulnerable, as are patients with mood disorders and substance abuse. Too often, it is dealt with as a symptom without attention to its cause.

In recent years, insomnia treatment has advanced beyond the routine use of benzodiazepines, and newer drug options are less likely to cause tolerance, dependence, and withdrawal. Cognitive behavioral therapy, in some cases coupled with drug therapy, is the most effective treatment of chronic insomnia once underlying disorders affecting sleep are addressed. With careful diagnosis and treatment, we can improve the quality of nighttime sleep, daytime performance, and quality of life for patients with insomnia.

THE COSTS OF INSOMNIA

The total direct cost of insomnia, including visits to physicians and psychologists and hospital care, is estimated at $13.9 billion.[3] Walsh and Engelhardt[3] estimated the total cost of substances used to treat insomnia in 1995 at $1.97 billion, with prescription drugs accounting for less than half of this cost.

Other costs of insomnia are due to decreased productivity, absenteeism, and occupational and motor vehicle accidents.[3,4] These indirect costs are difficult to estimate, but one survey found that persons reporting 7 or more nights of poor sleep per month missed 5.2 days of work per year more than persons who reported sleeping well.[5] In a 1991 Gallup poll, 5% of people with chronic insomnia (vs 2% of those without insomnia) reported having had a motor vehicle accident related to fatigue at some time in their life.[6]

TABLE 1

Primary and comorbid insomnia

PRIMARY INSOMNIA

Idiopathic insomnia
Long-standing complaint of insomnia with onset during infancy or childhood

Psychophysiologic insomnia
Heightened arousal and learned sleep-preventing associations that result in insomnia and associated decreased functioning during wakefulness

Paradoxical insomnia
Complaints of severe insomnia without any objective sleep disturbance

COMORBID INSOMNIA

Psychosocial stressors

Psychiatric disorders
Mood disorders: depression, bipolar disorder, dysthymia

Anxiety disorders: generalized anxiety disorder, panic disorder post-traumatic stress disorder

Psychotic disorders: paranoia, schizophrenia, delusional disorder

Medical disorders
Cardiovascular: angina, congestive heart failure

Respiratory: chronic obstructive pulmonary disease, asthma

Neurologic: Alzheimer disease, Parkinson disease

Rheumatologic: fibromyalgia, chronic fatigue syndrome, osteoarthritis

Gastroenterologic: gastroesophageal reflux disease, irritable bowel syndrome

Sleep disorders: restless legs syndrome, sleep apnea, circadian rhythm disorders

Drug and substance abuse
Alcohol, tobacco, recreational drugs, caffeine

Other costs

Insomnia can cause significant emotional distress, fatigue, sleepiness, and impairment of daytime functioning. Impaired social and occupational functioning adversely affects quality of life: people with insomnia have higher rates of mental health problems, drug and alcohol abuse, cardiac morbidity, painful musculoskeletal conditions, and health care utilization.[7] The evidence linking insomnia and major depressive disorder is strong, while the evidence linking it with anxiety disorders is less robust.[8] Insomnia is associated with a significantly greater incidence of occupational injury, motor vehicle accidents, and death.[3,4]

NORMAL SLEEP PATTERNS

A night's sleep in normal adults consists of four to five cycles of approximately 90 minutes each. Sleep is divided into rapid eye movement (REM) sleep and non-REM sleep (stages I, II, III, and IV). Normal sleep latency (the time it takes to fall asleep) is less than 30 minutes, and sleep progresses from light stages (I and II) to deep stages (III and IV). The normal REM latency (time to achieve REM sleep from sleep onset) is 90 to 110 minutes. About 5% of sleep time is spent in stage I, 45% to 50% in stage II, and 25% to 30% in stages III and IV, while REM sleep accounts for 20% of total sleep time. Stages III and IV (also referred to as slow-wave sleep) and REM sleep have important roles in restoring physiologic functions and in consolidating memory.

CLASSIFYING SLEEP DISORDERS

The second edition of the International Classification of Sleep Disorders defines insomnia as difficulty initiating or maintaining sleep, early awakening, or nonrestorative sleep despite adequate opportunity, accompanied by at least one of the following forms of daytime impairment[9]:

- Fatigue or daytime sleepiness
- Impairment of attention, concentration, or memory
- Poor social, occupational, or academic performance
- Mood disturbance or irritability
- Less motivation, energy, or initiative
- Proneness to errors or accidents at work or while driving
- Tension headaches or gastrointestinal distress due to sleep loss
- Worries about sleep.

Insomnia has been classified in a variety of ways,[10–12] for example, according to cause (primary, secondary), symptoms (difficulty falling asleep, difficulty staying asleep, nonrestorative sleep), or duration (acute = less then 1 month, chronic = 1 month or longer). While all of these classifications are clinically

TABLE 2

Commonly used drugs that can cause insomnia

Antihypertensives	Beta-blockers
Antidepressants	Selective serotonin reuptake inhibitors, venlafaxine (Effexor), bupropion (Wellbutrin, Zyban), duloxetine (Cymbalta), monoamine oxidase inhibitors, atomoxetine (Strattera)
Hormones	Oral contraceptive pills, cortisone, thyroid supplements
Stimulants	Methylphenidate (eg, Ritalin), dextroamphetamine (Dexedrine), modafinil (Provigil)
Sympathomimetics	Albuterol (eg, Proventil, Ventolin), salmeterol (Serevent), theophylline, pseudoephedrine (eg, Sudafed)
Steroids	Cortisone
Over-the-counter drugs	Excedrin, Anacin

useful in the diagnosis of insomnia, none is sufficient on its own.

The International Classification divides insomnia into two broad categories of primary or secondary, although many experts now prefer the term "comorbid" rather than secondary[13] (TABLE 1).

Primary insomnia

Psychophysiologic insomnia is the most common type of primary insomnia. These patients have insomnia lasting at least 1 month and conditioned sleep difficulty with or without heightened arousal in bed as indicated by one or more of the following[9,14,15]:

- Excessive focus on sleep, heightened anxiety about sleep
- Difficulty falling asleep in bed at desired time, but not during monotonous activities when not intending to sleep
- More able to fall asleep when away from home
- Mental arousal in bed (intrusive thoughts, perceived inability to cease sleep-preventing mental activity)
- Heightened somatic tension in bed (perceived inability to relax).

Secondary insomnia

Comorbid insomnia (TABLE 1) can be associated with medical conditions (eg, chronic pain, thyroid dysfunction, esophageal reflux), psychiatric disorders (anxiety, depression, bipolar disorder), neurologic disorders (Parkinson disease, Alzheimer disease), primary sleep disorders (sleep apnea, restless legs syndrome), and drugs. In fact, drugs are a common cause of insomnia, a fact often overlooked (TABLE 2).

A symptom or a disease?

Whether insomnia is a symptom or a disease has long been debated.[16] Traditionally, it has more often been considered a symptom due to its association with various medical and psychiatric disorders, and since treatment of the primary disorder often leads to remission of the sleep complaint. Although comorbid insomnia is a more common diagnosis than primary insomnia, whether the insomnia is primary or comorbid is not always clear, and this confusion may lead to inadequate or inappropriate treatment.[16,17]

5% of people with chronic insomnia reported a fatigue-related motor vehicle accident

Which type is more common?

Estimates of prevalence vary depending on the method used to diagnose and monitor patients.[18] According to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, 20% to 49% of US adults have intermittent insomnia.[19] An estimated 10% to 20% of adults have chronic insomnia.[20–22] Approximately 25% of people with chronic insomnia have primary insomnia.[7] In the 2005 National Sleep Foundation's Sleep in America poll, about half of those surveyed reported insomnia,[23] and the respondents reported at least one symptom of insomnia for at least a few nights per week within the previous year.

The prevalence of insomnia is higher in women and the elderly (over age 65).[10,11] Females are 1.5 times more likely to be affected.[24] From 20% to 40% of elderly adults report insomnia at least a few nights every month.[25]

The prevalence of different types of insomnia is not known due to methodologic variations across studies. Buysse et al[17] studied 216 patients assessed at five different sleep disorder centers; 20.2% had primary insomnia and, most strikingly, 44% were diagnosed with secondary insomnia related to a mental disorder. Insomnia secondary to a breathing-related sleep disorder accounted for 5.4% of cases. Also surprising was the low prevalence of insomnia related to a medical condition, accounting for only 3.9% of cases.[17]

MANAGEMENT OF INSOMNIA

The management of insomnia requires detailed sleep, medical, and psychiatric histories, including medications, drug and alcohol use, and occupational factors (eg, shift work), as well as a survey of the sleep environment and sleep-related attitudes and beliefs. Included in the sleep history are habitual sleep times and wake times during workdays and non-workdays, time to sleep onset, number of nocturnal awakenings and their cause, activities done in bed during periods of wakefulness (watching television, worrying, eating), daytime consequences of insomnia, and symptoms of other sleep disorders, such as sleep apnea and restless legs syndrome.

20-49% of adults have intermittent insomnia; 10-20% have chronic insomnia

It is often helpful for patients to keep a sleep diary for 1 to 2 weeks noting bedtime, wake time, nighttime awakenings, and daytime naps.

A general physical examination and neurologic examination should be performed. People with severe sleep deprivation typically appear sleepy or tired and may have reduced head control (nodding), repeated yawning, nystagmus, tremor, ptosis, and dysarthria.

An upper airway examination is important in patients with suspected sleep apnea to look for nasal patency, posterior pharyngeal obstruction, palate position, and tonsil size.

The neurologic examination should include an assessment of sensory and motor systems and deep tendon reflexes in the lower extremities to identify peripheral neuropathy.

The general physical examination is likely to be normal in most cases. Patients with comorbid conditions such as sleep apnea, endocrine disorders, and cardiac problems are more likely to exhibit abnormalities on general examination.

In most cases, patient education and nondrug treatment, sometimes combined with drug therapy, can markedly improve sleep quality and daytime functioning.

GENERAL PRINCIPLES OF TREATMENT

Identify and treat the underlying cause

The most effective approach to comorbid insomnia is to treat the comorbid condition: ie, optimizing management of medical and psychiatric disorders and pain syndromes, diagnosing and treating primary sleep disorders, addressing substance abuse, and, whenever possible, discontinuing or reducing drugs known to adversely affect sleep.

Sleep hygiene

Patients with insomnia, whether it is primary or secondary, acute or chronic, should be educated about good sleep hygiene—healthy habits and rituals that promote a good night's sleep:

- Think positive
- Establish fixed bed and wake times
- Relax before going to bed
- Maintain a comfortable sleep environment
- Avoid clock-watching
- Follow a 20-minute "toss and turn" rule (ie, if you don't fall asleep within 20 minutes, get up)
- Use the bedroom only for sleep and sex
- Avoid daytime naps
- Avoid caffeine, alcohol, and nicotine within 6 hours of sleep
- Exercise regularly, but not within 3 hours of sleep.

NONDRUG TREATMENTS

Nondrug treatments such as cognitive behavioral therapy (CBT) are effective for both primary and comorbid insomnia. However, the paucity of trained professionals, the need for repeat visits, cost, and variable insurance cov-

erage limit the availability of these options for many patients. Failure to provide instant relief limits the success of CBT in some cases.

The aims of cognitive behavioral therapy

The goal of CBT is to correct the maladaptive thought patterns and behaviors that can cause or worsen insomnia, regardless of the underlying cause. CBT is a very structured and focused treatment. The patient is expected to play an active role, and the eventual goal is to make the patient his or her own therapist.

A typical CBT session lasts 40 to 60 minutes and is conducted by a psychologist. The course of treatment varies from six to 10 sessions depending on the intensity of the problem and the progress made. Some patients benefit from additional, "reinforcing" sessions once every few months.

Proven benefits

CBT has been shown to produce positive changes in polysomnographic variables,[26–28] including an increase in total sleep time (time in minutes spent asleep from lights out to lights on) and sleep efficiency (total sleep time divided by time in bed in minutes, expressed as a percentage) and a decrease in sleep latency (time in minutes to the first epoch of sleep from lights out) and wake time after sleep onset (time in minutes awake after the first epoch of sleep). Sleep latency is reduced from 61 minutes to 30 minutes, total sleep time is increased by 20 to 65 minutes, and sleep efficiency is increased from 61% to 85%.[26–28] Its benefits outlast those of drug therapy.[26,27]

The cognitive component

The cognitive component of CBT focuses on correcting dysfunctional beliefs and attitudes about insomnia.[29] The goal of the technique is to empower the patient by providing a sense of control over sleep. CBT seeks to educate patients about the variation in nightly sleep requirement between individuals, the effects of sleep deprivation, and the influence of physical or mental illness on sleep.[28]

The behavioral component

The behavioral component of CBT focuses on reducing conditioned arousals. The most common techniques are as follows:

Relaxation therapy includes progressive muscle relaxation, deep-breathing exercises, and guided imagery and meditation. Progressive muscle relaxation trains the patient to recognize and control tension by performing a series of exercises that consist of first tensing and then relaxing a series of muscle groups. In deep-breathing exercises, patients inhale and exhale slowly as the abdomen expands and contracts. The goal is to train the patient to breathe slowly and relax in situations that provoke anxiety. Guided imagery and meditation are used to focus the patient on pleasant and restful images rather than racing images.[28,29]

Biofeedback trains the patient to develop a greater awareness and voluntary control over the physiologic processes affected by stress and anxiety. Depending on the technique, electrodes or sensors are placed on the scalp and forehead, around the chest and abdomen, and on the fingertips.

In neurofeedback, electroencephalographic activity recorded from the scalp is displayed on a computer screen. As the patient relaxes, his or her brain waves slow down, facilitating the initiation of sleep.

Cognitive behavioral therapy is proven to be beneficial in insomnia

In respiratory biofeedback, sensors are placed around the chest and abdomen and measure respiratory rate, rhythm, and volume. The patient sees and hears the signals from these sensors and uses them to modify breathing patterns indicative of elevated stress and anxiety, such as hyperventilation.

Similar techniques are used in thermal biofeedback (measuring blood flow changes), muscle tension biofeedback, and other such tests. Relaxation is the key component in biofeedback, with the therapist acting as coach.

Stimulus control therapy aims at reassociating the bed with sleep instead of arousal by incorporating good sleep hygiene strategies, as previously discussed. For example, patients are instructed not to lie in bed for more than 20 minutes if they cannot sleep, to use the bed only for sleep and sex, and to avoid thoughts and behaviors such as watching the clock that lead to mental activation or frustration while trying to fall asleep.[28,29]

Sleep restriction is based on the premise that time spent awake in bed is counterpro-

ductive and promotes the insomnia cycle. The goal is to improve sleep efficiency to at least 85%. Initially, patients are advised to stay in bed only when asleep. They are then allowed to increase the time spent in bed by 15 to 20 minutes per night each week, provided that sleep efficiency exceeds 90%. The time in bed is decreased by 15 to 20 minutes per night if sleep efficiency falls below 90%.[28]

THE RATIONALE FOR DRUG TREATMENT OF INSOMNIA

Basic principles

Some basic principles of drug treatment of insomnia are as follows[30–32]:

- Do not use hypnotic drugs by themselves: treatment should include sleep hygiene and behavioral therapies.
- Start hypnotics at low doses and titrate upward slowly as needed, especially in the elderly.
- Avoid long-term use of benzodiazepines.
- Use hypnotics (especially benzodiazepines) cautiously in patients with a history of substance abuse or dependence.
- Monitor patients regularly for signs of tolerance, dependence, and withdrawal.
- Advise patients of the potential for hangover effects and for accidents while driving or working, especially with long-acting preparations.
- Taper hypnotics gradually to avoid withdrawal symptoms and rebound insomnia—ie, the worsening of insomnia relative to baseline for 1 or 2 nights after stopping the drug. This is a problem with short- and intermediate-acting preparations and also with larger doses.

Relaxation is the key component in biofeedback

Drug categories

Drug treatments for insomnia are broadly classified into benzodiazepines, nonbenzodiazepine hypnotics, and miscellaneous sleep-promoting agents.

BENZODIAZEPINE HYPNOTICS

For many years, benzodiazepines were the drugs of choice for insomnia. Their ease of administration and relative safety compared with the barbiturates led to a huge surge in their use in the 1980s. However, in the last several years, tolerance, dependence, and withdrawal associated with benzodiazepines and the availability of safer alternatives have resulted in a significant decline in their use for insomnia.

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system. Benzodiazepines bind to specific sites on postsynaptic $GABA_A$ receptors, potentiating the effects of GABA and resulting in sedation, sleep, and various other effects such as anxiolysis and muscle relaxation.

Various benzodiazepines, including triazolam (Halcion), temazepam (Restoril), lorazepam (Ativan), and flurazepam (Dalmane), have been used to treat insomnia.

Safety issues

As a class, benzodiazepines have a potential for dependence and significant adverse effects, including hangover, dizziness, hypotension, and respiratory depression. They should be used cautiously in patients with a history of substance abuse, in the elderly, and in patients with respiratory problems such as chronic obstructive pulmonary disease and sleep apnea.[30,32,33]

Benzodiazepines are contraindicated in patients with severe respiratory disorders. In the elderly, benzodiazepines are associated with an increased incidence of hip fractures secondary to orthostatic hypotension and falls. Although some studies suggest a higher risk of fractures with long-acting benzodiazepines, other studies have shown that the short-acting benzodiazepines are associated with similar complications.[34]

NONBENZODIAZEPINE HYPNOTICS

Nonbenzodiazepine hypnotics (TABLE 3) are an excellent alternative to traditional benzodiazepines. They offer comparable efficacy and a lower incidence of amnesia, daytime sleepiness, respiratory depression, orthostatic hypotension, and falls.

Zolpidem

Zolpidem (Ambien), a nonbenzodiazepine hypnotic of the imidazopyridine class, was approved by the US Food and Drug

TABLE 3

Nonbenzodiazepine hypnotic drugs to treat insomnia

DRUG	METABOLISM	HALF-LIFE (HOURS)	DOSE (MG)	ADVERSE EFFECTS	WARNINGS
Zolpidem (Ambien) (Ambien CR)	CYP3A4	 2.5 6.25–12.5	5–10	Drowsiness, dizziness, headaches, rash, gastrointestinal distress	Reduce dose by 50% in hepatic impairment and the elderly; contraindicated in severe hepatic impairment
Zaleplon (Sonata)	Aldehyde oxidase	1	5–10	Dizziness, headache anxiety, amnesia, malaise	Reduce dose by 50% in hepatic impairment and the elderly; contraindicated in severe hepatic impairment
Eszopiclone (Lunesta)	CYP2E1 and CYP3A4	6	1–3	Headache, unpleasant taste, somnolence, dizziness	Maximum of 2 mg in the elderly; decrease dose to 1–2 mg if given with a strong CYP3A4 inhibitor
Ramelteon (Rozerem)	CYP1A2	1.5	8	Somnolence, dizziness, fatigue	Contraindicated in severe hepatic impairment; avoid using with a CYP1A2 inhibitor (eg, fluvoxamine)

Administration (FDA) in 1992 for the short-term treatment of insomnia. Zolpidem selectively binds to the alpha-1 subunit of $GABA_A$ receptors and produces strong sedative and hypnotic effects without the anxiolytic, myorelaxant, and anticonvulsant effects of benzodiazepines.[35]

In clinical trials, zolpidem decreased sleep latency and increased the duration of sleep for up to 5 weeks.[36–38] Furthermore, Maarek et al[39] followed patients taking zolpidem for 360 days in an open-label study and found persistent improvements in measures of sleep (decreased sleep latency and nocturnal awakenings and increased sleep duration) without rebound or withdrawal effects upon discontinuation.[39]

Due to its rapid onset and short duration of action, zolpidem is particularly useful in sleep-onset insomnia. A controlled-release form of zolpidem (Ambien CR) was released recently and is useful for sleep-onset and sleep-maintenance insomnia.

Zaleplon

Zaleplon (Sonata), a pyrazolopyrimidine, was approved for short-term treatment of insomnia in 1999. It is rapidly and almost completely absorbed after oral administration and has a very short half-life of 1 hour. It selectively binds to the alpha-1 subunit of $GABA_A$ receptors.[40]

Zaleplon is indicated for the short-term treatment of insomnia and has been shown to decrease the time to sleep onset in a 5-week polysomnographic study in subjects with primary insomnia. Tolerance and rebound insomnia after discontinuation were not observed.[41] Zaleplon increases total sleep time and decreases awakenings. It is particularly useful for sleep-onset insomnia and, due to its short half-life, has no hangover effects.

A study of zaleplon in doses of 25 mg, 50 mg, and 75 mg—several times greater than the recommended doses—in patients with known drug abuse found the abuse potential of zaleplon to be comparable to that of the benzodiazepine triazolam.[42] Another study investigating memory, learning, and psychomotor performance found zaleplon superior to zolpidem and triazolam.[43]

Eszopiclone

Eszopiclone (Lunesta), the *S*-isomer of the racemic zopiclone, is a cyclopyrrolone used extensively in Europe since 1987 for the treat-

Benzodiazepines are contraindicated in people with severe respiratory disorders

ment of insomnia and approved by the FDA in December 2004. Its exact mechanism of action is not known, but it is thought to interact with the GABA receptor complex at binding domains located close to or allosterically coupled to benzodiazepine receptors.

In two multicenter trials,[44,45] a dose of 3 mg significantly decreased sleep latency and wake time after sleep onset and increased sleep efficiency for 6 months compared with placebo. Significant and persistent improvement in sleep and daytime function was evident in patients treated for 12 months, with few adverse effects and no development of tolerance.[46]

Eszopiclone has a longer half-life (5–6 hours) than the other nonbenzodiazepine hypnotic agents and therefore it should be prescribed to patients who expect to spend at least 8 hours in bed. The recommended dose is 3 mg before bedtime in adults, 1 mg for sleep-onset insomnia, 2 mg for sleep-maintenance insomnia in the elderly, and 1 to 2 mg in patients with hepatic impairment.

Ramelteon

Alternative agents have not undergone rigorous scrutiny

Ramelteon (Rozerem) is the first and only nonscheduled drug approved by the FDA for the treatment of insomnia. It was approved in July 2005 for sleep-onset insomnia and can be prescribed for long-term use.

Ramelteon is a melatonin receptor agonist with high selectivity to MT1 and MT2 receptors in the suprachiasmatic nucleus of the hypothalamus.[47] These receptors are believed to be involved in sleep promotion and maintenance of the circadian rhythm.

Ramelteon has no appreciable binding to GABA receptors and, hence, has no anxiolytic or muscle-relaxant properties and no abuse potential. Its half-life is short and variable (1–6 hours), making it more suitable for sleep-onset insomnia than for sleep-maintenance insomnia. Ramelteon significantly improved latency to persistent sleep and total sleep time in healthy adults with transient and chronic insomnia and in elderly patients with chronic insomnia.[48–50]

The recommended dose is 8 mg given 30 minutes before the habitual bedtime. It should not be taken with or immediately after a high-fat meal, as this could delay the time to maximum plasma concentration.

MISCELLANEOUS SLEEP-PROMOTING AGENTS

Many over-the-counter agents are purported to reduce sleep onset and nocturnal awakenings. In 1995 alone, people spent more than $300 million on nonprescription drugs for the treatment of insomnia.[3] Many of these products contain antihistamines and herbs. Unfortunately, despite the popularity of these products, we still lack evidence that they are effective in the treatment of insomnia.

Melatonin

Melatonin, available in both natural and synthetic forms, is one of the most popular over-the-counter sleep aids,[51] with sales of about $50 million in 1995.[3] It is a naturally occurring hormone secreted by the pineal gland. In humans, melatonin secretion increases shortly after darkness, peaks between 2:00 AM and 4:00 AM, and then decreases gradually in the morning.[52]

Melatonin is thought to promote sleep in humans by attenuating the wake-promoting signals in the suprachiasmatic nucleus of the hypothalamus—hence the theory that melatonin given during normal waking hours has hypnotic properties.[53] Since melatonin decreases the core body temperature, it is postulated that melatonin also regulates the sleep-wake cycle through thermoregulatory mechanisms.[54]

The sedative effects of melatonin are observed at supraphysiologic and pharmacological doses.[55] Melatonin decreases the time to sleep onset and to stage II sleep without altering sleep architecture.[56] However, other randomized, placebo-controlled trials have not shown improvements in subjective or objective measures.[57,58]

The pharmacokinetics of melatonin have not been well established due to differences in dosing, large variations in absorption (up to 25-fold), and the diversity of study subjects.[51,59] Plasma concentration and half-life vary by dose, time of administration, and type of preparation.[60]

Natural melatonin is extracted from animals, so the purity of the preparation cannot always be guaranteed.

Melatonin is available in various strengths ranging from 50 μg to 20 mg. The recommended dose is typically 3 mg, although 1 mg produces concentrations equivalent to nocturnal physiologic levels.[61] It is not uncommon, however, to increase melatonin in 3-mg increments to a maximum of 12 to 15 mg.

A dose-response relationship has not been determined for melatonin. It is typically taken 30 minutes before the usual bedtime, although the benefit may be improved when taken 4 to 5 hours before bedtime, if insomnia is associated with delayed sleep phase syndrome.

Data about its adverse effects are limited. Dizziness, headache, fatigue, and irritability were reported in one study.[62] Megadoses (300 mg/day) of melatonin inhibit ovarian function.[63] Pregnant and lactating women should not use melatonin, as safety data are not available. The FDA does not regulate the safety, efficacy, or purity of melatonin preparations.

ANTIHISTAMINES

Advise patients not to use alcohol to promote sleep

Antihistamines are the major ingredient in many over-the-counter sleep aids (see **drugstore.com** for a list of commonly used products). Three—diphenhydramine hydrochloride, diphenhydramine citrate, and doxylamine succinate—are currently approved by the FDA for this purpose.[51] Adverse effects can be troublesome and include dizziness, fatigue, and morning hangover in as many as 10% to 25% of people who take them.[30]

Studies investigating the efficacy of antihistamines for insomnia are inconclusive. A recent study[64] showed rapid development of tolerance to the sedating effects of antihistamines. They have not been rigorously studied for insomnia, and safety and efficacy data are limited.

ALCOHOL

Many people with insomnia self-medicate with alcohol to fall asleep. Although the prevalence of alcohol use for insomnia is unclear, a survey in the Detroit metropolitan area showed that 13.3% of people ages 18 to 45 used alcohol to promote sleep in the past year. Of these, 6.2% used alcohol at least every other night for this reason.[65] A 1995 survey estimated that people spent more than $780 million on alcohol for sleep induction in that year alone.[3]

Patients should be strongly warned against using alcohol to promote sleep: its effects on sleep are variable, and it more often causes sleep fragmentation and a reduction in REM sleep. Regular use for this purpose also carries a risk of abuse, tolerance, and dependence, as well as the worsening of chronic obstructive pulmonary disease and sleep apnea.[66]

ANTIDEPRESSANTS

Low doses of sedating antidepressants such as trazodone (Desyrel), amitriptyline (Elavil), doxepin (Sinequan, Adapin), and mirtazapine (Remeron) are often prescribed to nondepressed patients for the treatment of insomnia.[67] However, a recent evidence-based review[68] offered little support for their use in nondepressed patients. We have even less evidence for the use of other antidepressants in this setting. However, antidepressants continue to be prescribed for insomnia because they are unscheduled, are relatively inexpensive, and have little abuse potential. Nevertheless, they should be used conservatively for insomnia due to limited efficacy and the potential for significant adverse effects.

ALTERNATIVE TREATMENTS

A number of alternative treatments are thought to be effective in promoting sleep onset and maintenance. However, none has undergone rigorous scrutiny, and published work on herbal hypnotics is limited.

Kava-kava

Kava-kava is an extract of the roots of the Polynesian plant *Piper methysticum*. It contains a number of active compounds, all of which are believed to produce counter-excitation at the cellular level, which in turn results in anxiolytic and hypnotic actions.

Kava-kava has a rapid onset of action, with minimal hangover effect.[69] However, reports of severe hepatotoxicity led to its ban

in parts of Europe,[70] and the FDA has issued an advisory regarding the potential risk for serious liver injury.[71] The Food Standards Agency in the United Kingdom banned kava-kava in 2002, due to purported causal links with serious hepatotoxicity, requiring liver transplantation in some cases.[72]

Kava-kava is an inhibitor of CYP 1A2, 2C9, 2C19, 2D6, 3A4, and 4A9/11 isoenzymes. Therefore, taking it along with an agent metabolized by the P450 system, such as diazepam (Valium), warfarin (Coumadin), haloperidol (eg, Haldol), and fluoxetine (Prozac), can lead to toxicity.[73,74]

Valerian

Valerian is derived from *Valeriana officinalis*. Its exact mechanism of action is unknown. There is some evidence that it interacts with the GABA receptor, producing sedative effects.[75]

Valerian has been shown to increase slow-wave sleep, but its slow onset of action (2 to 3 weeks) makes it unsuitable for the acute treatment of insomnia. The dosage most often used is 600 mg/day. Aside from headaches and hangover effects, no serious adverse effects have been reported. It is thought to be helpful for chronic insomnia and in the elderly, but efficacy data are lacking.[39]

Aromatherapy

Aromatherapy with lavender, chamomile, and ylang-ylang induces a state of mind conducive to sleep. However, there is no evidence of any direct hypnotic effect.

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