Beyond Benzodiazepines: Alternative Pharmacologic Agents for the Treatment of Insomnia

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OBJECTIVE: To review the epidemiology, etiology, and classification of insomnia and provide an overview of the pharmacologic therapy of insomnia. Novel nonbenzodiazepine hypnotics including zolpidem, zopiclone, and zaleplon, as well as nonprescription products such as valerian and melatonin, are reviewed in detail.

DATA SOURCES: A MEDLINE search was performed to identify relevant clinical studies, case reports, abstracts, and review articles published between April 1992 and December 1997. Key search terms included insomnia, benzodiazepines, zolpidem, zopiclone, zaleplon, Cl 284,846, melatonin, and valerian. Additional references were obtained from the lists of review articles and textbooks.

DATA EXTRACTION AND SYNTHESIS: Data concerning the safety and efficacy of the hypnotic agents were extracted from all available clinical trials and abstracts. Background information regarding insomnia, benzodiazepines, and other hypnotics was extracted from the most current literature, including review articles and textbooks.

CONCLUSIONS: New developments in benzodiazepine receptor pharmacology have introduced novel nonbenzodiazepine hypnotics that provide comparable efficacy to benzodiazepines. Although they may possess theoretical advantages over benzodiazepines based on their unique pharmacologic profiles, they offer few, if any, significant advantages in terms of adverse effects. Over-the-counter agents such as valerian and melatonin may be useful in alleviating mild, short-term insomnia, but further clinical trials are required to fully evaluate their safety and efficacy.

KEY WORDS: insomnia, hypnotics.

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INSOMNIA IS THE SUBJECTIVE COMPLAINT of poor sleep quality or inadequate quantity of sleep that adversely affects daily functioning.[1] People with insomnia may present with one or several sleep disturbances including difficulty initiating sleep (taking >30 min to fall asleep) or difficulty maintaining sleep (frequent nocturnal awakenings, early morning awakenings). These difficulties may result in daytime problems such as fatigue, diminished concentration, memory difficulty, and inability to perform complex tasks. Poor sleep has been associated with an increased incidence of traffic accidents, depression, alcohol abuse, and mortality.[2] As a result, the total direct and indirect cost of insomnia amounts to approximately $100 billion a year.

The incidence of insomnia has remained relatively stable for the past 20 years based on regional and national surveys. Approximately 30–35% of adult Americans experience insomnia in 1 year, with 10–15% considering their sleeplessness to be serious or chronic.[3] According to a national Gallup Organization survey (1995),[4] 49% of adults had difficulty sleeping an average of at least 5 nights per month. Insomnia is even more prevalent among the elderly, affecting more than one-half of those over the age of 65 years.[5] The most frequent populations with disturbed sleep include women, individuals of lower socioeconomic status, and patients with chronic medical and psychiatric disorders.[1]

Despite the fact that insomnia is so widespread, only 5% of adults have visited their physician specifically for insomnia, while 69% have never reported their sleep problems to a healthcare professional.[6] The lack of attention given to insomnia may be explained by the fact that many patients and physicians do not believe that it is a serious medical problem or that the physician may not have adequate interest or training in sleep medicine. The small proportion of patients seeking medical management suggests that there may be many more individuals who require proper evaluation and treatment of their sleep problems. Proper therapy may reduce overall morbidity, mortality, and expenditures attributed to insomnia.

Normal Sleep Physiology

Normal sleep consists of two phases, rapid eye movement (REM) sleep and non-REM sleep.[7,8] Non-REM sleep

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is further subdivided into four stages. Stage 1 sleep, the lightest stage of sleep, is very brief. Stage 2 sleep is a light stage of sleep, making up 50% of total sleep time. Stages 3 and 4, collectively called slow-wave sleep or delta sleep, are characterized by a deep, restorative sleep. They have a rejuvenating function and a decrease in these stages is associated with poor sleep quality. REM sleep is associated with high levels of neuronal activity and dreaming. Although its exact purpose is unknown, REM sleep is believed to play a role in memory and learning.[9] REM rebound occurs upon abrupt discontinuation of agents that suppress REM sleep (i.e., barbiturates, benzodiazepines, tricyclic antidepressants), resulting in vivid and frightening dreams in some individuals.[10]

Sleep involves cycling (~4–6 cycles per night) between the non-REM and REM stages.[7] Delta sleep dominates early in the night, but as the night progresses, less time is spent in delta sleep while REM periods become longer and more prevalent. The elderly frequently experience more frequent and prolonged awakenings with changes in their sleep cycle, resulting in decreased delta sleep, more stage 1 sleep, and less total sleep time.

Objective and Subjective Sleep Studies

Sleep stages are measured objectively in a sleep laboratory using polysomnography, which includes data recorded from the electroencephalogram (EEG), electrooculogram, chin electromyogram, and respiratory monitor.[11] Sleep parameters commonly measured in sleep studies include sleep latency (time measured from "lights out" to the initiation of sleep), the percentage of time spent in each sleep stage, the number of night awakenings, and sleep efficiency (ratio of total sleep time to total time spent in bed).[12] The data recorded are useful for evaluating the effects of various drugs on sleep.[7] In addition, polysomnography measures physiologic variables such as respiratory effort and airflow, oxygen saturation, leg movements, and heart rate during sleep. These data aid in the detection of sleep disorders such as periodic limb movement disorder (PLMD) or sleep apnea.

Subjective evaluation of sleep quality using a questionnaire provides a sensitive means of detecting mild sedative effects of a compound, as well as its effects on daytime functioning. Subjective measurements are important for assessing the efficacy of a hypnotic because, even when electrophysiologic measurements indicate detectable changes in sleep, if the drug does not produce a subjective sensation of improved sleep, its usefulness is somewhat limited. Clinical studies using subjective assessments can also include a larger sample size, thereby providing a more comprehensive picture of the drug's safety and efficacy in a wide variety of individuals.[7]

Etiology and Classification of Insomnia

Insomnia can result from a variety of physical, physiologic, psychological, psychiatric, and pharmacologic factors.[13] The most recently revised International Classification of Sleep Disorders[14] classifies 84 sleep disorders into four major categories and describes some of their major causes. These classifications include: dyssomnias, which are comprised of disorders in initiating or maintaining sleep (insomnia), or excessive sleepiness (hypersomnia); parasomnias, which are abnormal behaviors during sleep; sleep disorders associated with medical/psychiatric disorders; and proposed sleep disorders, which include conditions that cannot yet be classified as sleep disorders due to insufficient data.

Dyssomnias are further divided into extrinsic sleep disorders, intrinsic sleep disorders, and circadian rhythm sleep disorders. Extrinsic insomnia is attributed to external factors such as inadequate sleep hygiene, drug or alcohol dependency, or situational stress. Intrinsic insomnia develops from causes within the body and includes psychophysiologic insomnia, idiopathic insomnia, obstructive sleep apnea, restless legs syndrome, or PLMD. Circadian rhythm disorders consist of jet lag syndrome, shift work sleep disorder, advanced sleep phase syndrome, and delayed sleep phase syndrome.

Insomnia is also commonly classified based on the duration of symptoms.[15] This categorization is used to guide both diagnosis and treatment. Transient insomnia, lasting 2–3 days, is associated with an acute stressor (e.g., hospitalization, public speaking) or disruption of circadian rhythms (e.g., shift work, jet lag). Short-term insomnia is attributed to an ongoing stress usually related to work and family life (e.g., loss of a job, illness) and may last up to 3 weeks. Long-term or chronic insomnia lasts longer than 3 weeks. It is often the result of an underlying psychiatric disorder (e.g., depression, anxiety, psychosis), medical condition (e.g., peptic ulcer disease, asthma, Parkinson's disease), or chronic drug and alcohol abuse.

Treatment Guidelines for Insomnia

To properly treat insomnia, the clinician should evaluate the patient by obtaining a complete medical and psychiatric history and by performing a physical examination with pertinent laboratory tests.[16] If the assessment discloses an underlying cause for the insomnia, that should be addressed first, followed by consideration of both nonpharmacologic and pharmacologic therapy.

Transient insomnia is expected to subside upon resolution of the acute stressor.[16] Nonpharmacologic therapy consisting of adherence to good sleep hygiene should be emphasized (Table 1).[1,17,18] Drug therapy is not advocated, but if the insomnia occurs in a predictable fashion, short-acting hypnotics may be used for 2–3 nights only.[16] In addition to encouraging proper sleep habits, short-term insomnia may be managed with 7–10 days of pharmacotherapy with hypnotics given intermittently (i.e., 1 of 3 nights or skipping a dose after 1–2 nights of good sleep).

In the case of long-term or chronic insomnia, recommendations for therapy are not as well defined and referral to a sleep specialist may be warranted.[6] If medical or psychiatric causes have been ruled out, nonpharmacologic therapy consisting of both behavioral and cognitive approaches (Table 1) may be tried initially. If this is insufficient to relieve the patient's symptoms, drug therapy may

be used as an adjunct to the nonpharmacologic therapy.[16] In most cases, hypnotics should be used intermittently and for short periods (≤3 wk) to prevent the development of tolerance and dependence. The recommended duration of therapy for chronic insomnia has not been established since benzodiazepines are indicated only for intermittent and short-term insomnia. Clinicians should use professional judgment based on the patient's complaints, response to therapy, and development of adverse effects. The patient may monitor progress by keeping nightly sleep diaries. If the sleep problem improves, the hypnotic dosage should be gradually tapered (i.e., reduce the dose by 25% of the original dose every 5 d) and nonpharmacologic therapy continued.[19] If the patient has not responded after an adequate trial of drug therapy, he should be reevaluated for any additional medical or psychiatric causes of insomnia. Certain conditions, such as PLMD and REM sleep behavior disorder, may require long-term use of benzodiazepines.[20,21]

Pharmacologic Therapy

Drug therapy is indicated when nonpharmacologic measures are insufficient to relieve a patient's insomnia. Table 2[1,22-31] summarizes the effects of various medications on sleep parameters.

Table 1. Nonpharmacologic Therapy for Insomnia[1,17,18]

THERAPY	DESCRIPTION
Sleep hygiene instructions	maintain a regular sleep–wake schedule go to bed only when sleepy; participate in a relaxing activity until tired use the bed and bedroom only for sleep and sexual activity avoid daytime and midafternoon naps avoid stimulants (e.g., caffeine, nicotine) and alcohol before bedtime avoid poor sleep environment (e.g., uncomfortable temperature, noisy) avoid heavy exercise or stimulating activity in the late evening do not eat heavy meals before going to bed
Stimulus control	prepare a set of instructions designed to establish the bedroom as cues for sleep instead of wakefulness
Sleep restriction	limits the length of time spent in bed, thereby creating partial sleep deprivation, which results in deeper, more continuous sleep improves sleep efficiency (total sleep time/time spent in bed) and helps consolidate sleep
Relaxation training	biofeedback: teaches relaxation by conditioning specific muscular and electroencephalographic activity autogenic training: teaches relaxation by associating pleasant visual images with relaxing sensations progressive muscular relaxation: teaches relaxation by tensing and relaxing muscle groups hypnosis
Cognitive therapy	psychotherapy aimed at changing the patient's assumptions and perceptions about the insomnia

BARBITURATES AND DERIVATIVES

Older hypnotics such as barbiturates and nonbarbiturate nonbenzodiazepines (i.e., glutethimide, ethchlorvynol, chloral hydrate) have fallen out of favor due to the high incidence of adverse effects, rapid development of tolerance, and dependence with long-term use.[32]

ANTIDEPRESSANTS

Low doses of sedating antidepressants such as amitriptyline[23] or trazodone[24,25] have also been used to treat insomnia. Trazodone 50–100 mg has been used successfully in patients experiencing insomnia induced by antidepressant therapy with selective serotonin-reuptake inhibitors[24] and in depressed insomniacs receiving no other medication (trazodone 150–400 mg).[25] Although antidepressants may improve sleep in patients with underlying depression, more data are needed regarding their use in nondepressed individuals.

BENZODIAZEPINES

Benzodiazepines remain the mainstay of therapy due to their proven efficacy and relative safety.[13,15,16] The selection of the proper agent is determined by the patient's age, insomnia symptom (inability to fall asleep, nocturnal awakening, early morning awakening), concurrent disease states, and the pharmacokinetics of the drug (time of onset, half-life, duration of action, active metabolites). In general, short-acting agents are preferred; however, longer-acting agents may be helpful for patients with daytime anxiety.

Despite their safety, benzodiazepines are associated with several adverse effects, particularly with high doses and long-term use (Table 3).[26-31,33-38] These include residual daytime sedation or "hangover," rebound insomnia, and anterograde amnesia. The abuse potential of benzodiazepines is relatively low when used in small dosages for brief periods. However, if taken regularly for a longer duration, tolerance may develop to their hypnotic effects and withdrawal symptoms may appear upon abrupt discontinuation. Tolerance may develop within 1–2 weeks for short- and intermediate-acting agents, whereas long-acting agents may retain efficacy for longer periods of time.[33] In addition, benzodiazepines have respiratory depressant effects and should not be used in patients with sleep apnea or chronic obstructive pulmonary disease (COPD).

NOVEL PHARMACOLOGIC AGENTS

The unsatisfactory adverse effect profile of benzodiazepines has spurred new research in γ-aminobutyric acid $(GABA)_A$–benzodiazepine receptor pharmacology. Two central benzodiazepine receptor subtypes (BZ_1/BZ_2 or ω_1/ω_2) and one peripheral benzodiazepine receptor have been identified.[39] BZ_1 receptors are located in areas of the brain that are involved in sedation; BZ_2 receptors are highly concentrated in areas responsible for cognition, memory, and psychomotor functioning.[40] Most benzodiazepines act nonselectively at these sites, which may account for their

hypnotic effects as well as unwanted central nervous system (CNS) adverse effects. The newer nonbenzodiazepine agents attempt to overcome some of the adverse effects of benzodiazepines by acting at selective benzodiazepine receptor sites on the $GABA_A$-receptor complex, acting at nonbenzodiazepine sites on the complex, or by being nonspecific partial agonists at the benzodiazepine receptor.

This review examines novel nonbenzodiazepine hypnotics in terms of their unique characteristics, mechanisms of action, and potential therapeutic advantages, if any, over the traditional benzodiazepines. Zolpidem and zopiclone are currently in widespread use; another potential candidate, zaleplon, is still in clinical development. Table 3 compares the adverse effect profiles of the nonbenzodiazepines with those of the benzodiazepine hypnotics.

Table 2. Effects of Medications on Sleep Parameters

DRUG	SLP LTNCY[a]	TOT SLP TIME	DELTA SLP %[b]	REM SLP %[c]	SLEEP QLTY[d]	COMMENTS
Antidepressants tricyclics[22,23]	↓	NA	↑	↓	NA	anticholinergic and cardiovascular adverse effects; exacerbate PLMD, do not worsen sleep apnea, have low abuse potential
trazodone[24,25]	↓	↑	↔[e]	↔	↔	may cause priapism in men; daytime sedation reported
Barbiturates[22]	↓	↑	↓	↓	NA	severe withdrawal symptoms; daytime sedation; lethal upon overdose
Benzodiazepines[22]	↓	↑	↓	↓	↑	increased stage 2 accounts for increased sleeping time; relative to barbiturates, benzodiazepines have a mild capacity to reduce REM sleep %; individual response influenced by type of drug, dose, duration of treatment; withdrawal ↓ total sleep time
Chloral hydrate[1,22]	↓	↑	↔	↔	NA	avoid in patients with hepatic, renal, or cardiac disease because it may cause direct organ toxicity; displaces warfarin and oral hypoglycemics from binding sites
Zaleplon[26-28,f]	↓	↑ or ↔	↑[g]	↓[g]	NA	studies available only in abstract form
Zolpidem[29]	↓	↑	↑	↔	↑	variable effects on decreasing number of nighttime awakenings
Zopiclone[30,31,h]	↓	↑	↑	↔	↑	decreases number of nighttime awakenings

↑ = increase; ↓ = decrease; ↔ = no effect; LTNCY = latency; NA = not assessed; PLMD = periodic limb movements disorder; QLTY = quality; REM = rapid eye movement; SLP = sleep; TOT = total.
[a]The time from lights out to the initiation of stage 1 sleep.
[b]The percentage of total sleep time spent in delta sleep (slow-wave sleep).
[c]The percentage of total sleep time spent in REM sleep.
[d]Based only on subjective assessments.
[e]Some studies show an increase in stage 3 or 4 sleep.
[f]An investigational agent.
[g]Occurs only with doses of 40 and 60 mg.
[h]Not available in the US.

ZOLPIDEM

Zolpidem (Ambien) is the first nonbenzodiazepine in the US that selectively binds to the BZ_1 (ω_1) receptor subtype.[29] This specificity may account for its minimal anticonvulsant, myorelaxant, and anxiolytic properties at hypnotic dosages, although anticonvulsant and myorelaxant effects are observed at higher doses. It is also hypothesized that this agent's selectivity may be responsible for its lower tolerance and abuse potential, although the mechanism for this phenomenon is not clear.[41] Due to limited experimental data, it is still controversial whether activity at a specific benzodiazepine receptor subtype is responsible for different pharmacologic properties of an agent. For example, quazepam is a long-acting benzodiazepine that also binds specifically to BZ_1 (ω_1) receptors,[40] but it does not have any significant clinical benefits over other nonselective benzodiazepines with similar half-lives (e.g., flurazepam).[42]

Zolpidem has a rapid onset of action and a short elimination half-life ranging from 1.5 to 2.4 hours. This agent has demonstrated similar improvements in sleep latency and total sleep time compared with benzodiazepines (e.g., triazolam, flunitrazepam).[29] However, unlike benzodiazepines, which tend to decrease REM and delta sleep, zolpidem does not adversely alter physiologic sleep architecture. Although in theory this property should be advantageous, its clinical significance remains to be determined.

Zolpidem's adverse effects are dose related, occurring more frequently with 20 mg or more. In a total of 1028 patients, the most common adverse effects of zolpidem 5–50 mg were drowsiness (5%), dizziness (5%), headache (3%), and gastrointestinal distress (4%).[43] One to two percent of the patients also experienced memory disturbances, nightmares, confusion, depression, hangover effects, falls, and asthenia. Recently, there have been several published case reports of unusual CNS adverse effects such as psychotic symptoms,[44] sensory distortions,[45] and sleepwalking[46] that may be linked to zolpidem.

Next-day cognitive functioning and performance are not affected with nighttime zolpidem use, as predicted by its short half-life.[47,48] In comparative clinical trials, equipotent doses of zolpidem and triazolam appear to have similar effects on impairing memory[49,50] and psychomotor functioning.[49] Maximum impairments were seen approximately 1.5 hours after dosing, which is near the time of estimated peak plasma concentrations for both drugs. No

memory or performance deficits were reported 6–8 hours after drug intake.

There have been few studies evaluating the rebound effects of zolpidem based on a night-by-night analysis using objective polysomnographic techniques. From the data available, rebound insomnia, which is defined as a worsening of sleep below baseline levels, does not appear to occur after discontinuation of zolpidem.[29,37,51-54] In one polysomnographic study,[51] 6 patients with insomnia received zolpidem for 14 nights followed by 3 nights of placebo. Sleep was recorded for 3 nights at the beginning and end of the drug period and for the 3 placebo nights. No changes in sleep stages or rebound insomnia occurred upon withdrawal of the drug. A single-blind, placebo-controlled, polysomnographic study[54] in 24 patients with insomnia determined that zolpidem 10 mg was associated with less rebound insomnia than triazolam 0.5 mg. These results are potentially misleading because zolpidem 10 mg is therapeutically equivalent to triazolam 0.25 mg, not 0.5 mg.[55]

Although zolpidem should not be used for longer than 7–10 days, some trials have demonstrated that zolpidem is effective for the long-term treatment of insomnia, with little evidence of tolerance, withdrawal symptoms, or rebound insomnia.[56-58] In a double-blind, placebo-controlled, multicenter sleep laboratory study,[56] zolpidem's effects on improving sleep latency and sleep efficiency were maintained for 35 nights of drug treatment. In a single-blind, flexible-dose, general practitioner study in 107 outpatients, there were no signs of tolerance to zolpidem's hypnotic effects during the entire 6-month study period.[57] Hypnotic efficacy of zolpidem was maintained for 179 nights as determined by polysomnographic evaluations in an open, single-blind trial involving 14 elderly psychiatric hospitalized patients.[58] Since only one of these three trials was well-controlled and double-blind, these results should be interpreted with caution.

The claim that zolpidem is associated with less abuse liability than benzodiazepines remains to be proven. Although clinical trials did not point to any clear evidence of abuse, there have been case reports of chronic abuse, tolerance, and withdrawal symptoms, suggesting that this drug may carry a higher abuse potential than expected.[59,60] As with all psychotropic drugs, individuals with a history of addiction to drugs or alcohol should be monitored carefully while receiving zolpidem.

Zolpidem 10 mg given in a single dose[61,62] or multiple doses[63] does not affect respiratory parameters in patients with COPD. One early study[64] involving patients with sleep apnea showed a decrease in oxygen saturation with zolpidem 20 mg. Although most data suggest that zolpidem will not worsen respiratory function, caution should still be used in patients with respiratory compromise.

Table 3. Adverse Effects of Benzodiazepines and Nonbenzodiazepine Hypnotics

CHEMICAL CLASS	DRUG	HANGOVER EFFECTS	REBOUND INSOMNIA	TIME TO DEVELOPMENT OF TOLERANCE[a]	DEPENDENCE/ ABUSE POTENTIAL	COMMENTS
Benzodiazepines[33-36]						
short-acting (<6 h)	triazolam	0	+++	+++	++	may have less respiratory depressant effects than other benzodiazepines; doses >0.25 mg not recommended because of increased CNS adverse effects; gradual tapering may reduce rebound
intermediate-acting (6–24 h)	estazolam, flunitrazepam,[b] lormetazepam,[b] loprazolam,[b] temazepam	+/++	++/+++	++/+++	++	hangover effects may become more marked with increased dose
long-acting (>24 h)	flurazepam, nitrazepam,[b] quazepam	+++	0	+	++	avoid in elderly because of increased risk of falls and hip fractures
Imidazopyridine[29,37]	zolpidem	+	0	+	+	
Cyclopyrrolone[30,31,38]	zopiclone[b]	++	++	++	+	doses >7.5 mg cause more adverse effects without increasing hypnotic efficacy
Pyrazolopyrimidine[26-28]	zaleplon[c]	NA	NA	NA	NA	due to lack of clinical trials, no comparisons can be made regarding adverse effect profile of zaleplon and other agents; long-term trials are needed to assess tolerance and abuse potential

0 = no effect; + = mild effect; ++ = moderate effect; +++ = marked effect; CNS = central nervous system; NA = not assessed.
[a]0 = tolerance does not develop; + = tolerance develops slowly (3 wk–months); ++ = tolerance develops rapidly (1–2 wk); +++ = tolerance develops very rapidly (few days).
[b]Not available in the US.
[c]Investigational agent.

The usual dose of zolpidem for short-term insomnia is 10 mg given immediately before bedtime.[65] For patients older than 65 years or with hepatic impairment, an initial dose of zolpidem 5 mg is recommended. Like benzodiazepines, zolpidem should be prescribed at the lowest dose for 7–10 nights only. If used for more than 2–3 weeks, the patient should be reevaluated.

The potential benefits of zolpidem appear to be its preservation of normal sleep architecture and its minimal tolerance and abuse potential. Long-term experience in general practice is necessary before any firm conclusions can be made regarding the clinical significance of these advantages. Considering this and its relatively high cost, zolpidem should be reserved as a second-line agent for insomnia.

ZOPICLONE

Zopiclone (Imovane), available only in Europe and Canada, is a nonbenzodiazepine that binds to a site close to, but not directly on, the benzodiazepine binding site of the $GABA_A$ receptor.[30] It is short- to intermediate-acting, with a half-life ranging from 3.5 to 6.5 hours; there are no active metabolites. Compared with benzodiazepines, zopiclone has demonstrated similar improvements in the sleep of people with insomnia.[30,31]

Nighttime administration of zopiclone has been shown to cause a hangover the next morning and impair psychomotor performance similar to that seen with temazepam and nitrazepam.[66,67] Zopiclone 7.5 mg causes memory impairment up to 2 hours after administration, but there are no morning-after effects.[68] Zopiclone is also associated with rebound insomnia when the drug is discontinued.[69,70] One study reported sleep onset latency to be worse upon withdrawal of zopiclone compared to temazepam.[66] Symptoms of anxiety, decreased sleep duration and sleep quality, and increased sleep latency have been observed on the second day of zopiclone withdrawal after 3 weeks of drug use.[71] Although zopiclone has low abuse potential, there have been reports of dependence and withdrawal reactions in patients with a history of substance abuse.[72,73] Finally, regarding respiratory depressant effects, zopiclone either had no effects on respiratory function or caused only mild respiratory depression in patients with COPD.[30,74]

The most common adverse effects seen with zopiclone are bitter taste (3.6%), dry mouth (1.6%), difficulty arising in the morning (1.3%), sleepiness (0.5%), nausea (0.5%), and nightmares (0.5%).[75] The usual dose for the treatment of short-term insomnia is 7.5 mg taken 30–60 minutes before retiring.[31] An initial dose of 3.75 mg is recommended in the elderly and in patients with hepatic impairment.[30]

Zopiclone does not appear to offer significant advantages over benzodiazepines in terms of efficacy or adverse effects. The choice of which agent to use should be based on the clinician's preferences and cost considerations.

ZALEPLON

Zaleplon (Cl 284, 846) is a novel sedative/hypnotic currently undergoing new drug application submission to the Food and Drug Administration (FDA). Similar to zolpidem, zaleplon binds selectively to the BZ_1 (ω_1) receptor subtype.[26] Animal studies suggest that zaleplon possesses benzodiazepine-like sedative properties, but it may have a lower incidence of adverse effects.[76]

Pharmacokinetic analysis demonstrates rapid absorption and a short half-life ranging from 0.9 to 1.1 hours.[77] Very low plasma concentrations of the desethyl metabolite are detected and the three major metabolites do not exhibit pharmacologic effects.[78] These characteristics are desirable because they should prevent next-morning hangover effects.

To date, there have been few clinical studies evaluating the sedative effects of zaleplon in persons with insomnia. One large-scale study[26] demonstrated that zaleplon 5 and 10 mg decreased sleep latency compared with placebo, with the 10-mg dose having effects comparable with those of triazolam 0.25 mg. These results were evident only on nights 4 and 5 of the trial, whereas no significant differences in sleep latency were reported on nights 16 and 17 due to unexplained improvement in the placebo group. Two other trials[27,28] confirmed that escalating doses of zaleplon (5, 10, 20, 40, 60 mg) produced significant reductions in latency to sleep relative to placebo. Total sleep time was increased by 41.9 minutes with zaleplon 20 mg in one trial,[28] whereas another study[27] failed to show any significant changes with doses up to 60 mg. A dose-related increase in the percentage of stage 3–4 sleep, and a decrease in the percentage of REM sleep occurred with 40 and 60 mg.

The most frequently reported adverse effects attributed to zaleplon in doses up to 30 mg were dizziness, headache, and somnolence.[26,28,77] Zaleplon 60 mg produced more CNS detriments including impaired vision and motor skills. Most of these events were of mild to moderate intensity, with peaks occurring 1–2 hours after dosing. Doses up to 15 mg were not associated with any significant psychomotor impairment.[77] Some impairment was produced by zaleplon 30 and 60 mg, but the effects were limited to 2.5 hours after treatment. Zaleplon 60 mg produced impairment on some psychometric tests for up to 25 hours. In contrast, doses of up to 60 mg had no effect on short-term memory recall. Compared with lorazepam 2 mg, zaleplon 20 mg produced similar or slightly less impairment in memory recall and psychomotor functions 1 hour after treatment.[79] Patients recovered functioning within 3 hours of zaleplon administration, whereas recovery with lorazepam occurred 5 or more hours after treatment. These results are not surprising because lorazepam has an intermediate duration of action of 6–8 hours, whereas zaleplon is a short-acting agent. A more appropriate comparison would have been with triazolam, which also has a short duration of activity. Finally, the results did not suggest abuse potential based on analysis of subjective feelings produced by the drug, mean liking scores, and desire to take the drug again.[77]

Zaleplon possesses a favorable pharmacologic profile that warrants further clinical study. It has a dose-related effect on reducing sleep latency and a relatively insignificant effect on increasing total sleep time, thereby finding its greatest usefulness in sleep initiation disorders. The opti-

mal dose that imparts hypnotic activity while minimizing adverse effects remains to be determined.

Over-the-Counter Sleep Aids

As an alternative to prescription hypnotics, over-the-counter sleep aids are becoming more popular. Two antihistamines, diphenhydramine and doxylamine, are currently indicated for promoting sleep. Even though these agents cause daytime sedation, psychomotor impairment, and anticholinergic adverse effects, they continue to have widespread use.[1] The use of alcohol as a hypnotic is discouraged due to its abuse potential and the propensity to increase the number of awakenings throughout the night.[80]

L-Tryptophan, an amino acid precursor of serotonin that had been sold as a "natural" hypnotic, was removed from the market because of its association with eosinophilia–myalgia syndrome, due to a contaminant that was introduced during production.[81]

Other nonprescription medications, valerian and melatonin, are widely used as mild hypnotics. A detailed review of the literature regarding these agents is presented here. Table 4[1,22,80,82-96] describes the effects of common nonprescription sleep aids on various sleep parameters.

VALERIAN

Valerian, an herbal product consisting of the underground parts of the plant *Valeriana officinalis*, continues to be used after hundreds of years as a minor tranquilizer and sleep aid. It was dropped from the US National Formulary approximately 40 years ago due to the increasing use of barbiturates.[97] It is still included in the European Pharmacopoeia, and is a widely used hypnotic and daytime sedative in Germany and Russia.

The active components responsible for valerian's therapeutic effects have yet to be identified. A combination of valepotriates, volatile oils (e.g., valerenic acid), and unidentified aqueous constituents may contribute to the sedative properties of valerian.[98] The amount of active constituents can vary greatly between species as well as within a species.[97] Although originally believed to be the sedating component, the activity of valepotriates alone is questionable since they are highly unstable and are hydrolyzed rapidly by heat and moisture. Moreover, valepotriates are not water soluble and are only minimally present in aqueous extracts. Nevertheless, commercial preparations containing small amounts of valepotriates (0.01% w/v) still showed some hypnotic efficacy.[86] This suggests that some other substance is present in aqueous extracts that may improve sleep. It is still unknown whether the activity of valerian is due to one compound or a combination of ingredients.

The exact mechanism whereby valerian exerts its hypnotic effects has not yet been established, but it causes both CNS depression and muscle relaxation.[98] Data suggest that sedation may result from an interaction of unknown valerian constituents with central $GABA_A$ receptors.[99]

A few investigators have reported valerian's effects on decreasing sleep latency and improving subjective sleep. In a placebo-controlled, crossover trial involving 128 volunteers with a wide range of age and sleep quality, Leath-

Table 4. Effects of Nonprescription Sleep Aids on Sleep Parameters

DRUG	SLEEP LATENCY[a]	TOTAL SLEEP TIME	DELTA SLEEP %[b]	REM SLEEP %[c]	SLEEP QUALITY[d]	COMMENTS
Alcohol[22,80]	↓	↑ (first half of the night) ↓ (second half of the night)	↑	↓ (first half of the night)	NA	acute effects are variable
acute						
chronic	↓	↔	↓	↓	↓	withdrawal symptoms include ↓ total sleep time, ↑ awakenings, ↓ delta sleep
Antihistamine[1]	↓	↑	NA	NA	↑	results based on subjective data only; diphenhydramine doses >50 mg are not recommended; nonaddicting; may lower seizure threshold; rapid development of tolerance
Melatonin						
physiologic doses (0.1–0.3 mg) in healthy subjects[87-89]	↓	↑	↔	↔	NA	↓ sleep latency to stage 2,[88,89] ↑ SE,[89]
pharmacologic doses (1–10 mg) in healthy subjects[87-92]	↓ or ↔	↑ or ↔	↔	↔	↔	↓ sleep latency to stage 2,[88,89] ↑ SE[89] ↑ REM latency with 5 mg[92]
pharmacologic doses (1–5 mg) in insomniacs[93-96]	↓ or ↔	↓[d]	↔	↔	↑ or ↔	↑ REM latency with 1 mg,[93] ↑ SE[94,95]
Valerian[82-86]	↓	↔ or ↑	↑	↔	↑	no reports of tolerance or abuse

↓ = decrease; ↓ = decrease; ↑ increase; ↔ = no effect; NA = not assessed; REM = rapid eye movement; SE = sleep efficiency.
[a]The time from lights out to the initiation of stage 1 sleep.
[b]The percentage of total sleep time spent in delta sleep (slow-wave sleep).
[c]The percentage of total sleep time spent in REM sleep.
[d]Based on subjective assessments only.
[e]In one trial, subjects believed that they slept less.

wood et al.[85] demonstrated that self-proclaimed poor sleepers, particularly those younger than 40 years old and women, showed the greatest improvement in sleep quality, decreased sleep latency, and reduced number of night awakenings with valerian aqueous extract 400 mg. Two studies using valerian in dosages ranging from 400 to 900 mg agreed with these findings,[82,86] while another did not.[83] In a double-blind, crossover, placebo-controlled trial,[84] subjective measurements of sleep latency and wake time after sleep onset were reduced by more than 50% after a 900-mg dose, with smaller effects after 450 mg. There were improvements in sleep when measured in the subjects' homes, but the investigators failed to confirm the hypnotic effect of valerian in a sleep laboratory. This discrepancy can be attributed to the younger subjects and the more stressful sleep environment in the laboratory, which can minimize the mild sedative activity of valerian. One EEG study[83] concluded that valerian aqueous dried extract 135 mg three times daily increased delta sleep and decreased stage 1 sleep.

It is difficult to adequately quantify the sleep-promoting effects of valerian based on these trials because study designs, subject characteristics, dosage, and content of the various preparations differed. The general trend shows that the mild hypnotic effects of valerian decrease sleep latency and improve sleep quality. Although no direct comparisons have been made, one investigator[85] suggested that valerian 400 mg is at least as effective as small doses of benzodiazepines and barbiturates.

Few adverse effects have been reported with valerian. Next-morning hangover was experienced by poor sleepers receiving valerian 900 mg, but not with 450 mg.[86] There have been four case reports[100] of women who sustained liver damage and hepatitis after ingesting combination products of valerian and skullcap (another herbal product) for anxiety. Although it is unclear which compound contributed to the development of hepatotoxicity, valerian preparations should be avoided in patients with liver dysfunction.

There has been some concern over the cytotoxicity of valepotriates, a component found in most valerian preparations only in negligible amounts. These constituents contain an epoxide group and were found to act as alkylating agents in vitro.[101] However, this property has not been demonstrated in vivo due to poor absorption and distribution of the compound.[98] Also, as mentioned previously, valepotriates break down rapidly, and most preparations contain very low concentrations. Nevertheless, since there are many species of valerian that contain variable amounts of chemical constituents, contamination of a product with a species that contains higher concentrations of valepotriates may pose a concern.

The issue of safety and quality control is an important aspect concerning over-the-counter herbal products such as valerian. In 1994, the Dietary Supplement Health and Education Act (DSHEA) was enacted to allow herbs, vitamins, minerals, and amino acids to be marketed as dietary supplements.[102] According to the DSHEA provisions, manufacturers are not required to provide data regarding the safety, purity, and efficacy of a product. Consequently, content and purity may vary from one batch to another and from manufacturer to manufacturer. Despite the lack of strict regulatory control by the FDA, most reliable manufacturers perform assays such as thin-layer chromatography or HPLC to identify active constituents and toxic compounds. Pharmacists and those selling herbal preparations must be aware of reputable manufacturers in order to ensure that they are offering the highest quality to the consumers.

Valerian is available in several preparations that may differ in effectiveness, depending on the type of preparation, age of the herb or extract, species, and growing conditions of the plant.[97] It may be administered in the form of a tea, tincture, capsule, or tablet. Valerian is also commonly found in combination products containing skullcap or hops. The dosage varies depending on the preparation, but it is generally recommended to take one or two tablets or capsules (200–1000 mg *V. officinalis* root) 30–60 minutes before bedtime. Commercial products are most commonly standardized according to the content of the volatile oils (valerenic acid). The characteristic unpleasant odor associated with these products is attributed to enzymatic hydrolysis of some of the plant's constituents.

In conclusion, limited studies provide evidence for the mild hypnotic activity of valerian. The active components, pharmacology, adverse effect profile, and toxicity must be clarified before valerian's role in the pharmacotherapy of insomnia can be more clearly defined.

MELATONIN

Due to recent widespread media attention, melatonin has become one of the most frequently requested over-the-counter sleep aids. This neurohormone, which is synthesized from tryptophan and secreted by the pineal gland, is involved in the regulation of circadian rhythms and the initiation of sleep. It is believed that the physiologic increase in blood melatonin concentrations by 10- to 50-fold,[103] which occurs 1–2 hours before bedtime, may be the final trigger for inducing sleep.[88] Ingestion of small physiologic doses of 0.1 or 0.3 mg of melatonin in the daytime can generate serum concentrations that are within the normal nocturnal range (50–200 pcg/mL).[87] Other findings indicate that melatonin may possess a phase-setting effect instead of, or in addition to, a direct hypnotic effect.[104]

Melatonin's involvement in the regulation of sleep–wake cycles in circadian-based sleep disorders such as jet lag and delayed sleep-phase syndrome is well documented.[104,105] There have been less consistent demonstrations of hypnotic effects of melatonin, although a trend toward improved subjective sleep has been noted.[87,90,91] These inconsistencies may have been due to differences in the melatonin dosages, the timing of administration, experimental approaches, and diversity of the subjects.

Investigators have reported[106,107] sleep-inducing properties in both healthy volunteers and patients with insomnia when melatonin was administered in large pharmacologic doses that elevate serum concentrations to very high, supraphysiologic concentrations. Melatonin has also demonstrated mild soporific effects when given in the daytime or early evening hours, when plasma melatonin concentra-

tions are normally low.[87,90,91] Ingestion of physiologic doses (0.1 or 0.3 mg) or small pharmacologic doses (1 or 10 mg) of melatonin by healthy volunteers at 1145 decreased sleep latency.[87] In another study,[91] melatonin 3 or 6 mg administered to healthy volunteers 30 minutes or 2 hours prior to an early evening nap reduced sleep latency and increased total sleep time.

Reports of the hypnotic properties of low-dose melatonin administered close to bedtime in healthy volunteers or those complaining of poor sleep are varied. In one study[88] involving healthy men, melatonin 0.3 or 1.0 mg given at 1800, 2000, or 2100 decreased sleep latency as measured subjectively and polysomnographically without causing changes in REM sleep. Another investigation[92] involving healthy men yielded no subjective changes in sleep after single doses of melatonin 1 or 5 mg were taken at 2245. An increase in REM latency with the 5-mg dose was the only polysomnographic change noted. Subjects sleeping less than 4 hours per night for the previous 6 months reported that melatonin 1 or 5 mg given 15 minutes before bedtime improved sleep quality, although there were no other improvements in sleep parameters.[93] Polysomnography demonstrated an increase in REM latency with the 1-mg dose.

One difficulty in determining melatonin's efficacy is the fact that most of the trials were conducted with healthy volunteers. The few studies conducted in patients with insomnia (<65 y old) did not yield very favorable results. One investigation[107] showed improvements in patients' subjective assessments of total sleep time, but this occurred with a very large dose of melatonin (75 mg). Two studies[93,96] using low pharmacologic doses (1 or 5 mg) found no changes in sleep onset or duration.

The timing of melatonin administration appears to affect sleep initiation. Data suggest that melatonin is more effective when administered 2 hours before bedtime[88,94,108] than when it is given immediately before bedtime.[92,93] In contrast, one study[91] found that administration of melatonin 2 hours before bedtime is no more effective than administration 30 minutes prior to retiring. It is possible, however, that the absence of hypnotic effect reported in some trials was due to factors other than time of administration. Sleep-inducing properties may become more apparent with repeated doses rather than single doses. In addition, since increased sleepiness is most evident when low-dose melatonin is administered in the daytime or early evening, melatonin may exert hypnotic effects only when endogenous concentrations are low.[87,90]

Melatonin may prove to be particularly effective in elderly patients with insomnia, a population shown to have decreased nocturnal secretions of the hormone.[94,95] One study,[94] which measured sleep parameters using wrist actigraphs, demonstrated that 1 and 2 mg of sustained-release melatonin improves sleep efficiency and sleep maintenance. Sleep initiation was improved with 2 mg of fast-release melatonin. In another study,[95] sustained-release melatonin 2 mg increased sleep efficiency and decreased time awake after sleep onset in elderly people with chronic insomnia, without affecting total sleep time. The use of sustained-release preparations that maintain effective serum concentrations throughout the night and a longer duration of treatment (3 wk) may have been responsible for these beneficial effects. Although these studies appear promising, the analysis of patients' sleep was based on actigraphic parameters, which are less sensitive than polysomnographic measurements.

Melatonin may also be useful in treating multidisabled children with severe insomnia.[109] A series of case reports[110] involving 15 neurologically impaired children with chronic sleep disturbances, including fragmented sleep patterns and delayed sleep onset, showed that bedtime administration of melatonin 2–10 mg resulted in subjective improvements in the children's disrupted sleep.

No adverse effects were reported with the use of melatonin in the trials mentioned. In 300 subjects using melatonin for as long as 1 month, the only adverse reactions were abdominal cramps when as much as 3–6 g were taken.[111] Since melatonin is rapidly absorbed and has a short half-life of 20–50 minutes,[112] patients usually do not experience hangover effects.[88] Some subjects ingesting pharmacologic doses of melatonin have experienced fatigue, headache, dizziness, and increased irritability.[113] The exact incidence of adverse effects is unknown because these data are lacking in clinical trials and manufacturers are not required to report adverse reactions.

There are several precautions regarding the use of melatonin. The National Sleep Foundation warns that self-medication with melatonin may exacerbate the adverse effects associated with insomnia as a result of the phase-shifting effects of the hormone.[114] Melatonin has been found to enhance immune functioning in mice, and it is not recommended in patients with immune disorders, lymphoproliferative disorders, and those taking immunosuppressants or corticosteroids.[115] Since melatonin 300 mg/d was found to inhibit ovarian function, women trying to conceive are discouraged from using it.[116] Pregnant women and nursing mothers should not take melatonin because it has not been adequately tested in this population. Melatonin may also cause vasoconstriction, so caution should be used in patients with vascular disorders.[117] Very large doses (1200 mg) have been shown to exacerbate depression, although the effects of low doses on mood are unknown.[118]

Melatonin supplements in the form of tablets, capsules, and lozenges, in a dose range of 0.3–10 mg, are currently used for short-term insomnia. Dosing guidelines have not been established, but some recommendations can be made regarding proper use. Patients should begin by taking low doses (0.3–1 mg). Manufacturers recommend taking melatonin immediately before retiring, but clinical studies suggest that a more optimal time to take it may be approximately 2 hours before bedtime. If no improvement is noted after several nights, the dosage can be increased gradually. It is recommended that 3 mg or less be used because even doses as low as 1 mg can produce serum melatonin concentrations that are greater than normal nocturnal concentrations.[87] Larger doses may result in high concentrations of melatonin, which will remain elevated into the next day.

Despite melatonin's extensive use in the US, it is still considered to be a "dietary supplement" and the FDA does not regulate its safety, purity, or efficacy. Other countries

have already instituted measures to restrict the use of melatonin. In Canada, melatonin is classified as a new drug, which requires that manufacturers submit an application with supporting scientific evidence of safety, efficacy, quality, and purity before they market the product (personal communication, TC Mueller, PhD, Health Canada, Bureau of Pharmaceutical Assessment, July 1997). Since no manufacturer has yet submitted this application, melatonin is not available for sale. In Britain, melatonin is available only as a prescription product, and the dispensing pharmacist must make every effort to verify that the manufacturer of the product is reliable (personal communication, JB Cole, United Kingdom Department of Health, Medicine Control Agency, July 1997).

Since there is limited information on the product labeling, pharmacists are in an excellent position to counsel patients regarding the proper dosage, potential adverse effects, contraindications, and drug interactions associated with melatonin. The pharmacist should mention that the often-exaggerated claims concerning melatonin have not yet been proven scientifically in large-scale clinical trials and that the long-term safety of the product is not known. Finally, patients should be advised to avoid self-medication with melatonin and all other over-the-counter agents for long periods of time because chronic insomnia may be due to an underlying disease state that should be evaluated by a physician.

Conclusions

The search for the ideal hypnotic, one that induces sleep rapidly, maintains sleep for the entire night, and is devoid of next-morning hangover effects, continues. Nonbenzodiazepines offer hypnotic efficacy similar to that of benzodiazepines, but whether these agents offer any significant advantages will be determined more definitively only with further clinical experience. Meanwhile, research into the area of benzodiazepine receptor pharmacology is proceeding.

Over-the-counter products offer an alternative for individuals with mild insomnia, but they should be used cautiously. Melatonin may have a role in patients with circadian rhythm disorders and low melatonin concentrations, such as the elderly. Although valerian and melatonin are "natural," clinical trials evaluating their safety and efficacy are limited, and indiscriminate long-term use is not recommended.

Although sleepless nights may be considered by many to be just a fact of life, insomnia should not be regarded as a benign condition. All efforts at treatment should be made, first by using nonpharmacologic methods, and then by resorting to appropriate pharmacologic therapy if necessary.

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