Pharmacological Treatment of Insomnia

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INTRODUCTION

People experience two forms of sleep: rapid eye movement (REM) and nonrapid eye movement (NREM). Sleep typically begins with the NREM phase, which is followed by the REM phase. NREM sleep is subdivided into three stages in which brain activity, eye movement, and skeletal muscle tone progressively decrease, placing the individual in a deeper state of sleep. Later in the cycle, when the individual enters REM sleep, electrical activity in the brain increases, contributing to increased blood flow to the brain, changes in respiratory and cardiac rates, and dreaming.[1] REM sleep correlates with activities of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system in healthy humans.[2]

Sleep is regulated by a variety of chemicals in the body. In the forebrain and hypothalamus, neurons release gamma-aminobutyric acid (GABA) and histamine. These neurotransmitters have opposing actions on the sleep–wake cycle. Increased GABA and decreased histamine release induce NREM sleep by deactivating the cortex and thalamus. The sleep–wake cycle is also affected by neurotransmitters released by reticular activating system (RAS) neurons, such as norepinephrine, acetylcholine, and serotonin. These neurotransmitters contribute to maintaining wakefulness and significantly decrease during REM sleep. Orexin, which is produced in the hypothalamus, is a neuropeptide that plays an important role in maintaining wakefulness. It is hypothesized that the action of orexin changes the activity of the neurotransmitters involved in the regulation of sleep/wake states. Melatonin is a hormone that plays an integral role in diurnal rhythms. It synchronizes the body with the environment's light–dark cycle, peaking during the night and dipping during the day, to stabilize the body's natural circadian rhythm.[1,3]

According to the *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition (DSM-5), insomnia is defined as dissatisfaction with sleep quantity or quality that results in clinically significant distress or impairment in social, occupational, or other important areas of functioning. Insomnia is associated with one or more of the following symptoms: difficulty initiating sleep (sleep-onset insomnia or initial insomnia); difficulty maintaining sleep (sleep-maintenance insomnia or middle insomnia); and early-morning awakening with the inability to return to sleep (late insomnia).[4]

An estimated 50 million to 70 million adults in the U.S. have chronic sleep and wakefulness disorders.[5] Insomnia is more common in women (25%) than in men (18%), and its prevalence increases with age, affecting approximately 50% of the elderly population.[6] Data from the years 2008 through 2010 from the National Health Interview Survey indicated that 62% of adults in the U.S. slept seven to eight hours and that 28% slept six or fewer hours in a 24-hour period.[7] In the National Health and Nutrition Examination Survey (2005–2010), approximately 4% of U.S. adults 20 years of age and older reported that they had taken prescription sleep aids during the previous 30 days.[8]

PATHOPHYSIOLOGY

Investigators have characterized insomnia as a disorder of hyperarousal that manifests as hypervigilance during the day and difficulty initiating and maintaining sleep at night.[9–11] This hyperarousal may result from chronic activation of the neuroendocrine system's stress response. Studies have found high levels of urinary free cortisol in poor sleepers.[12] Moreover, high levels of both cortisol and adrenocorticotropic hormone (ACTH) in insomniacs suggest that the HPA axis is associated with the pathology of chronic insomnia.[13] Dysregulation of corticotropin-releasing factor (CRF) has also been implicated in the mediation of hyperarousal seen in primary insomnia.[14]

Several comorbid medical conditions can contribute to insomnia. These include obstructive sleep apnea, fibromyalgia, restless legs syndrome, cardiovascular diseases, diabetes, arthritis, migraine, asthma, chronic obstructive pulmonary disease, and chronic pain.[1,13,15,16]

CLASSIFICATION

Insomnia consists of three basic types: acute insomnia, primary chronic insomnia, and associated insomnia.[13] Acute insomnia results from a triggering causal factor that is easily identifiable in an individual who has not had insomnia before. By definition, the acute form does not last longer than four months.[17]

Primary chronic insomnia may be caused by several predisposing (genetic and constitutional) factors, including hyperactivity of stress response mechanisms or of the HPA axis; anxiety and depression; and abnormalities in the circadian rhythm (circadian sleep-wakefulness control).[12,14,17–19] Precipitating and perpetuating factors, such as psychosocial features (e.g., fatigue and irritability), behavioral changes, and cognitive characteristics, also contribute to insomnia.[13]

Associated insomnia is primarily related to an underlying mental or mood disorder, such as depression, dysthymia, cyclothymia, bipolar disorder, anxiety, or schizophrenia.[17,20–23] This form of insomnia may also be caused by inadequate sleep hygiene (i.e., habits that are inappropriate for good quality of sleep), such as psychologically stressful activities; the consumption of caffeine, nicotine, alcohol, or heavy meals; or vigorous

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Disclosure: The authors report no commercial or financial interests in regard to this article.

physical activity near bedtime.[17] Other potential causes of associated insomnia include concomitant medical conditions (e.g., infections and metabolic diseases) and the use of substances or medications (e.g., alcohol, stimulants, and antidepressants).[17]

The Centers for Disease Control and Prevention further classifies insomnia as episodic (lasting at least one month but less than three months); persistent (lasting three months or longer); or recurrent (two or more episodes within one year).[24]

DIAGNOSIS

To qualify for a diagnosis of insomnia, patients must have at least one of the following complaints for at least three nights per week: difficulty initiating and/or maintaining sleep; sleep that is poor in quality; trouble sleeping despite adequate opportunity and circumstances for sleep; or waking up too early.[17,24] In addition, patients must have at least one of the following types of daytime impairment related to sleep difficulty: attention, concentration, or memory impairment; concerns or worries about sleep; daytime sleepiness; errors or accidents at work or while driving; fatigue or malaise; gastrointestinal symptoms; lack of motivation; mood disturbance or irritability; social or vocational dysfunction or poor school performance; or tension headaches.[17]

TREATMENT OVERVIEW

Regardless of the type of therapy used, the treatment of chronic insomnia has two primary objectives: improving sleep quality and quantity, and improving daytime impairments. Initial approaches to treatment usually include at least one behavioral intervention, such as stimulus control therapy or relaxation therapy. Biofeedback therapy is also used. When pharmacotherapy is required, the choice of a specific drug within a class should be directed by: 1) symptom pattern; 2) treatment goals; 3) past treatment responses; 4) patient preference; 5) cost; 6) the availability of other treatments; 7) comorbid conditions; 8) contraindications; 9) concurrent medication interactions; and 10) potential adverse effects. [25]

The recommended sequence of medication trials is:[25]

- Short- or intermediate-acting benzodiazepine receptor agonists (BzRAs) or the melatonin agonist ramelteon.
- Alternative short- or intermediate-acting BzRAs or ramelteon if the initial agent was ineffective.
- Sedating antidepressants (e.g., trazodone, amitriptyline, doxepin, or mirtazapine).
- The combination of a BzRA or ramelteon with a sedating antidepressant.
- Other sedating agents, such as antiepilepsy medications or atypical antipsychotics.

In the following sections, we will discuss prescription medications approved by the Food and Drug Administration (FDA), off-label treatments, over-the-counter drugs, and herbal therapies for patients with insomnia.

BENZODIAZEPINE RECEPTOR AGONISTS

BzRAs include both benzodiazepine (BZD) and non-BZD agents. Although all of these drugs bind to the gamma aminobutyric acid ($GABA_A$) receptor complex, they differ in their affinity for binding sites. BZDs have similar selectivity for alpha subunits 1, 2, 3, and 5, whereas non-BZDs bind more selectively to the alpha 1 subunit. The various subunits of the $GABA_A$ receptors are responsible for the sedative–hypnotic, muscle-relaxant, anxiolytic, and anticonvulsant effects of the BzRAs. Moreover, the selectivity of non-BZDs for the alpha 1 subunit is believed to result in fewer adverse effects on the central nervous system (CNS) and in a reduced potential for abuse compared with BZDs.[26]

Benzodiazepines

Currently, five BZDs are FDA-approved for the treatment of insomnia: triazolam (Halcion, Pfizer), estazolam (ProSom, Abbott), temazepam (Restoril, Mallinckrodt), quazepam (Doral, Questcor), and flurazepam. All of these agents are Schedule IV controlled substances because of their potential for abuse or dependence. The primary difference among them is their duration of action. Triazolam is short-acting; estazolam and temazepam are intermediate-acting; and quazepam and flurazepam are long-acting. Temazepam is the most commonly prescribed BZD for insomnia. The choice of a BZD should be based on the desired onset and duration of action. Patients have developed rapid tolerance to the sedative effects of BZDs; therefore, long-term use of these drugs is not recommended.[27]

In a meta-analysis of 45 randomized controlled trials, BZDs decreased sleep latency and significantly improved total sleep duration in more than 2,600 subjects. All of the studies, however, were of short duration (14 days or less), which prevented the investigators from analyzing tolerance to the drugs' hypnotic properties.[28]

In addition to the potential for tolerance and dependence, BZDs have been associated with psychomotor retardation, memory impairment, paradoxical inhibition (e.g., increased excitement, irritability, and impulsivity), depression, and teratogenic effects in pregnant women.[29] BZDs should be avoided in elderly patients because of the potential for cognitive impairment, delirium, falls, and fractures.[30]

Nonbenzodiazepines

Non-BZDs, also called "Z drugs," were developed to minimize the adverse effects and abuse potential associated with BZDs. A meta-analysis of 13 studies involving more than 4,000 subjects showed that the currently available Z drugs—zolpidem, zaleplon, and eszopiclone—provided small but statistically significant reductions in subjective and polysomnographic sleep latency compared with placebo. The degree to which sleep latency was reduced was greater in studies involving larger doses, longer treatment durations, and greater proportions of younger and/or female patients.[31]

Zolpidem

Zolpidem was the first Z drug to be developed. It is currently available as immediate- and modified-release tablets (Ambien and Ambien CR, respectively [both Sanofi]); as sublingual tablets (Edluar [Meda Pharmaceuticals] and Intermezzo [Transcept Pharmaceuticals]); and as an oral spray (ZolpiMist, NovaDel Pharma). In studies comparing the pharmacokinetics of the zolpidem sublingual tablets and oral spray with that of immediate-release zolpidem tablets, the sublingual formulations maintained

bioequivalence while offering a shorter onset of action.[32,33] Treatment costs should be considered, since some zolpidem formulations are available only as brand-name products.

In studies of zolpidem, treatment-emergent adverse events, such as drowsiness, nausea, dizziness, nightmares, and agitation, have resulted in discontinuation of the drug.[34] Similar adverse-event profiles have been noted between controlled-release and immediate-release formulations.[35] In clinical studies, zolpidem did not alter retrograde memory, a hallmark adverse effect of the older BZD treatments used for insomnia. However, anterograde amnesia was seen in some patients.[36,37] Based on its pharmacokinetic profile (i.e., its extended half-life), greater effects on anterograde amnesia may be expected with controlled-release zolpidem.[38]

Drugs with CNS-depressant effects could potentially enhance the CNS-depressant effects of zolpidem. In addition, the coadministration of cytochrome P450 3A4 (CYP3A4) inhibitors may increase exposure to zolpidem. The drug should be used with caution in combination with imipramine, chlorpromazine, rifampin, or ketoconazole.[39]

In January 2013, the FDA recommended that clinicians use lower doses of zolpidem because new data had shown that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. The FDA informed the manufacturers that the recommended dose of zolpidem for women should be lowered from 10 mg to 5 mg for immediate-release products (Ambien, Edluar, and ZolpiMist) and from 12.5 mg to 6.25 mg for extended-release products (Ambien CR). The FDA also informed the manufacturers that, for men, the labeling should recommend that health care professionals consider prescribing the lower doses ~~5~~ mg for immediate-release products and 6.25 mg for extended-release products. The recommended doses of Intermezzo, a lower-dose zolpidem product approved for middle-of-the-night awakenings, did not change.[40]

Zaleplon

Zaleplon (Sonata, Pfizer) was the second non-BZD to become available. Its rapid onset of action and significantly shorter duration of action offer advantages for patients with middle-of-the-night awakenings.[41] In a randomized, double-blind, placebo-controlled study, both zaleplon and zolpidem effectively shortened sleep latency and lengthened sleep duration when administered during nighttime awakening. The duration of residual sedation, however, was shorter with zaleplon than with zolpidem.[42]

Headache and dizziness were the most common adverse events in clinical studies of zaleplon. The percentages of patients who withdrew from these studies because of adverse events were similar between the zaleplon and placebo groups.[43,44]

Unlike the other non-BZDs, which are extensively metabolized by CYP3A4, zaleplon is primarily metabolized by aldehyde oxidase. Although the coadministration of potent CYP3A4 inhibitors and inducers may alter zaleplon levels, routine dosage adjustments are not usually required.[45]

The absorption of zaleplon is delayed by approximately two hours and is reduced by 35% if the drug is taken with high-fat or heavy meals. Zaleplon is a pregnancy category C drug and should be used with caution in pregnant women. The typical dosing range for nonelderly adults is 10 mg to 20 mg. A 5-mg dose is recommended for specific populations, such as older, debilitated, or hepatically impaired patients. Zaleplon is not recommended for patients with severe hepatic impairment.[45]

Eszopiclone

Eszopiclone (Lunesta, Sunovion) is a non-BZD hypnotic agent approved for the long-term treatment of insomnia.[46] A six-month, double-blind, placebo-controlled, parallel-group study of approximately 800 patients demonstrated that eszopiclone was effective for the treatment of insomnia as measured by sleep latency, total sleep time, and wake time after sleep onset.[47] Because of its longer half-life, eszopiclone should be used only in patients who can have at least seven to eight hours of sleep before the planned time of awakening.[46]

The adverse events most commonly observed with eszopiclone include an unpleasant taste, headache, somnolence, and dizziness.[48,49] In a six-week study of patients with primary insomnia, there was no evidence of tolerance to eszopiclone during therapy or of rebound insomnia after the drug was discontinued.[49]

Eszopiclone is primarily metabolized by CYP3A4. Concurrent use of potent inhibitors or inducers of CYP3A4 enzymes may affect exposure to the drug. Dose reductions are recommended in patients receiving eszopiclone along with a potent CYP3A4 inhibitor, such as ketoconazole. The use of eszopiclone with CYP3A4 inducers, such as rifampin, may reduce its efficacy.[46]

Eszopiclone is absorbed rapidly, with a time to peak concentration of approximately one hour. Taking eszopiclone with or immediately after a heavy meal results in slower absorption and a subsequent reduction in the drug's effect on sleep onset. Eszopiclone is FDA pregnancy category C and should be used with caution in pregnant women. Nonelderly adults may take a maximum dose of 3 mg if clinically indicated. The dose should not exceed 2 mg in patients taking potent CYP3A4 inhibitors or in special populations, such as older, debilitated, or hepatically impaired patients.[46,50]

In May 2014, the FDA issued a warning regarding next-day impairment of driving and other activities after the use of eszopiclone. As a result, the recommended starting dose was reduced to 1 mg at bedtime.[51]

MELATONIN AGONIST: RAMELTEON

Ramelteon (Rozerem, Takeda) is approved for the treatment of insomnia characterized by difficulty with sleep onset, and it is the only melatonin (MT) agonist with this indication.[52] As a targeted MT_1 and MT_2 receptor agonist, ramelteon does not have an affinity for GABA receptors, which negates the potential for abuse.[53] Studies have shown that ramelteon is effective in reducing both polysomnographic and subjective sleep latency in patients with chronic insomnia.[54–57]

The most common ramelteon-related adverse events include dizziness, nausea, and fatigue.[52,58] Unlike zolpidem and eszopiclone, ramelteon does not affect patients' balance, thereby reducing the risk of falls. In addition, the drug is not associated with cognitive or psychomotor effects.[59]

Although ramelteon is absorbed rapidly, it has limited bioavailability as a result of extensive first-pass metabolism. The absorption of ramelteon is delayed and reduced when it is

taken with food. Because of its short half-life (1.36 hours), ramelteon should not be used to treat patients with difficulty maintaining sleep.[52]

Ramelteon is metabolized by several CYP enzymes. The combination of ramelteon and fluvoxamine, a potent CYP1A2 inhibitor, should be avoided. Moreover, ramelteon should be used with caution in patients taking potent CYP3A4 inhibitors, such as ketoconazole, or potent CYP2C9 inhibitors, such as fluconazole. The use of ramelteon with potent CYP3A4 inducers, such as rifampin, may reduce its efficacy.[52]

Ramelteon is a pregnancy category C drug and should be used with caution in pregnant women. Although the drug is cleared more slowly from older adults compared with younger ones, with a 70% greater area under the curve (AUC), no dose adjustments are required in the elderly. Ramelteon should be used with caution in patients with mild-to-moderate hepatic impairment and is contraindicated in those with severe hepatic impairment.[52]

TRICYCLIC ANTIDEPRESSANT: DOXEPIN

Doxepin (Silenor, Pernix Therapeutics) is a sedating tricyclic antidepressant (TCA) with a high affinity for histamine (H_1) receptors. It is approved for the treatment of insomnia characterized by difficulty with sleep maintenance.[60]

Headache and somnolence are the most common adverse events associated with doxepin. Minimal to no adverse effects are reported with the lower doses approved for sleep compared with the higher doses used for depression.[60] A review of nine randomized, placebo-controlled studies found that low-dose doxepin provided modest improvements in sleep maintenance and sleep duration but had no effect on sleep initiation. No significant residual (next-day) sedative effects were reported.[61] In a four-week, randomized, double-blind, placebo-controlled study involving 254 elderly subjects, treatment with doxepin resulted in improved sleep time and fewer awakenings after sleep onset without causing anticholinergic adverse events or memory impairment.[62]

The absorption of doxepin is increased by approximately 40% and the time to peak plasma concentration is delayed by approximately three hours when the drug is taken after a high-fat meal. For that reason, doxepin should not be administered within three hours after eating.[60]

Doxepin is a pregnancy category C drug and should be used with caution in pregnant women. It is extensively metabolized by CYP2C19 and CYP2D6. Therefore, concomitant use of doxepin with inhibitors of these enzymes may increase drug exposure. The dosage for nonelderly adults is 6 mg taken 30 minutes before bedtime. The initial dose in older patients is 3 mg, which may be titrated to 6 mg if clinically indicated. The dose should not exceed 3 mg in patients with hepatic impairment.[60]

BARBITURATES

The CNS depression achieved with barbiturates can range from mild sedation to general anesthesia. In addition, hypnotic doses of these drugs can decrease sleep latency and the number of awakenings.[26,63] As a class, barbiturates are FDA-approved for the treatment of patients with insomnia. They are not recommended for use in that setting, however, because of their significant adverse effects, including the potential for fatal overdose, their low therapeutic index, and the potential for tolerance and dependence.[25]

OREXIN RECEPTOR ANTAGONIST: SUVOREXANT

Suvorexant (Belsomra, Merck) is the first marketed drug in a new category of insomnia medications known as orexin receptor antagonists. Orexins are neurotransmitters that regulate wakefulness and sleep. Suvorexant was approved in August 2014 for the treatment of insomnia characterized by difficulty with sleep onset and/or sleep maintenance. It is a Schedule IV controlled substance.[64,65]

A 12-month, randomized, placebo-controlled, parallel-group trial evaluated suvorexant in subjects with primary insomnia. Suvorexant (n = 517) showed greater efficacy than placebo (n = 254) in improving subjective total sleep time (38.7 minutes versus 16.0 minutes, respectively; $P < 0.0001$) and subjective time to sleep onset (–18.0 minutes versus –8.4 minutes; $P = 0.0002$). The most common adverse event, somnolence, occurred in 13% of the suvorexant group and in 3% of the placebo group.[66]

The recommended starting dosage for suvorexant in insomnia patients is 10 mg administered once per night within 30 minutes of going to bed. The dose may be increased to a maximum of 20 mg as tolerated. The drug should be administered no later than seven hours before the planned time of awakening.[65]

Suvorexant is a pregnancy category C drug. Dose adjustments are not necessary in patients with hepatic or renal impairment. No clinically significant differences in safety and efficacy have been observed in individuals more than 65 years of age compared with younger, healthy subjects. Suvorexant is mainly metabolized by the CYP3A enzyme; therefore, concomitant use with strong CYP3A inhibitors is contraindicated. These drugs can significantly decrease suvorexant levels, thus reducing the drug's efficacy. When used with moderate CYP3A inhibitors, the initial dose of suvorexant should be reduced to 5 mg, which may be increased to 10 mg as tolerated.[65]

Based on clinical trial data and on the drug's mechanism of action, the potential for abuse and adverse events may be lower with suvorexant than with BzRAs. The higher cost of suvorexant and the availability of less-expensive generic options, however, will likely hinder its widespread use. [67]

OFF-LABEL TREATMENTS FOR INSOMNIA

Antidepressants

Trazodone

Approved by the FDA more than 30 years ago, trazodone is used to treat depression at high doses. However, because of its modulating effect on serotonin (5-HT_A) receptors, the drug is also used off-label as a hypnotic at low doses. Studies have shown that trazodone inhibits approximately 50% of the 5-HT_A receptors in the brain at doses as low as 10 mg. In patients with insomnia, a starting dose of 25 to 50 mg at bedtime is recommended. This may be titrated to a dosage of 100 mg per night as indicated. Higher doses may result in anticholinergic adverse effects and orthostatic hypotension, which, in turn, may increase the risk of falls and resulting injury.[68]

Mirtazapine

Mirtazapine (Remeron, Merck), a member of the piperazinoazepine group of compounds, has sedative properties that may benefit patients with insomnia. Sedation is achieved through the drug's potent antagonistic effects on histamine (H_1) receptors. Mirtazapine is currently approved only for the treatment of major depressive disorder.[69] A dosage of 30 mg per day is typically used in insomnia patients; increasing doses may diminish the drug's sleep-enhancing effects.[70] Mirtazapine has been associated with anticholinergic effects and may negatively affect treatment with triglycerides.[69]

Other TCAs

Doxepin is FDA-approved for the treatment of insomnia marked by difficulty with sleep maintenance, but other sedating TCAs (such as amitriptyline, nortriptyline, and imipramine) have been used off-label to treat insomnia patients. The broad neurotransmitter effects of these drugs, however, confer an increased risk for anticholinergic effects, orthostatic hypotension, and slowed cardiac conduction, and safer treatment options have diminished their usefulness. TCAs have been listed as potentially inappropriate for use in older adults.[30]

Atypical Antipsychotics

Although not FDA-approved for the treatment of insomnia patients, atypical antipsychotic medications, such as quetiapine, olanzapine, and risperidone, are commonly prescribed for sleep disorders. The sedation associated with these drugs results from their antagonistic effects on multiple neurotransmitter systems, particularly serotonin ($5\text{-}HT_2$) and histamine (H_1) receptors. Quetiapine is the most commonly prescribed antipsychotic for insomnia.[71,72]

Although the effects of antipsychotics on sleep have been studied in patients with comorbid conditions, such as depression and psychosis, they have not been evaluated in subjects with primary insomnia. Serious adverse events, such as metabolic syndrome and extrapyramidal effects, make these drugs less attractive than agents approved by the FDA for this indication.[73]

OVER-THE-COUNTER MEDICATIONS

Antihistamines

Because of their sedating properties, the first-generation antihistamines diphenhydramine and doxylamine are available over the counter as sleep aids. Diphenhydramine, for example, is contained in Benadryl, Unisom SleepGels, and others, and doxylamine is contained in Unisom Sleep Tabs.[74] The clinical use of these agents as insomnia treatments lacks supporting data.[75]

A randomized, double-blind, crossover study demonstrated that tolerance quickly develops to the sedative effect of diphenhydramine. Fifteen healthy men (ages 18 to 50 years) received either diphenhydramine 50 mg or placebo twice a day for four days. Both objective and subjective measures of sleepiness showed significantly higher levels on day 1 for diphenhydramine compared with placebo. By day 4, however, levels of sleepiness achieved by diphenhydramine were indistinguishable from those associated with placebo. The subjects' tolerance to diphenhydramine was complete by the end of three days of administration.[76]

In addition to the potential for rapid tolerance, studies have indicated that diphenhydramine and doxylamine are only minimally effective in inducing sleep, may reduce sleep quality, and may cause residual drowsiness. Therefore, the use of these drugs in insomnia patients is not recommended.[77]

Moreover, antihistamines are associated with potent anticholinergic effects, such as dry mouth, constipation, and confusion. Older individuals are particularly susceptible to these effects and should generally avoid the use of antihistamines.[30]

Melatonin

Melatonin, a pineal-gland hormone involved in sleep regulation,[78] is available over the counter primarily as a nutritional supplement, but it is also used to treat insomnia related to secondary causes, such as jet lag and shift work.[79]

In a randomized, double-blind, placebo-controlled study, a prolonged-release formulation of melatonin was associated with improvements in sleep and daytime parameters, including sleep latency, sleep quality, and morning alertness, after three weeks of treatment in adults with primary insomnia. The improvements were maintained in a subset of patients who continued treatment for a total of six months.[80]

In another short-term (one week), randomized, double-blind, placebo-controlled investigation, a physiological dose of melatonin (0.3 mg) restored sleep efficiency ($P < 0.0001$) and elevated plasma melatonin levels ($P < 0.0008$) to normal in adults with insomnia. A pharmacological dose (3.0 mg) also improved sleep, but it induced hypothermia and caused plasma melatonin to remain elevated during the day.[81]

In general, however, the evidence suggests that melatonin is not effective in treating most primary sleep disorders with short-term use (four weeks or less).[82] Because of the relative lack of robust efficacy and safety data, melatonin is not recommended for the treatment of chronic insomnia.[25]

HERBAL TREATMENTS

Valerian

Valerian, an herbal product consisting of the root of *Valeriana officinalis*, has been used to treat insomnia since ancient Greek and Roman times.[83] It appears to interact with GABA-ergic neurotransmission, thereby producing a sedative effect.[84]

Although some studies have indicated that valerian is useful for the treatment of patients with insomnia, others have not.[85–89] Interpretation of the available clinical data is complicated by small sample sizes, by the use of different amounts and sources of valerian, by the different outcomes measured, and by high withdrawal rates.[83] Overall, the evidence for valerian as an insomnia treatment remains inconclusive,[85] and it is not recommended for use in these patients.[25]

Kava

The herbal product kava, derived from a shrub (*Piper methysticum*) cultivated in the Pacific islands, appears to act on both GABA and BZD binding sites, resulting in sedative, anticonvulsive, antispasmodic, and central muscular-relaxant effects.[90,91] Over-the-counter kava-containing products are used as alternative therapies for anxiety, stress, and restlessness—major causes of chronic insomnia.[91] However, as with other herbal substances, kava is not recommended for the treatment of

Table 1 FDA-Approved Medications for the Treatment of Insomnia[93,94]

Name	Recommended Dose Before Retiring	Half-Life (hours)	Primary Indication	Adverse Drug Reactions	Additional Considerations	Cost Per Dose*
Benzodiazepines						
Flurazepam	• Initial dose: 15 mg (women); 15 or 30 mg (men) • 15-mg dose may be increased to 30 mg if needed	47–100	Sleep-onset and sleep-maintenance insomnia	• Dizziness • Drowsiness • Lightheadedness • Staggering • Ataxia • Falling	• 15 mg for older or debilitated patients • Caution with alcohol use • Excreted mainly in urine; observe usual precautions in patients with renal or hepatic impairment • Contraindicated in pregnancy (not classified) • Schedule IV controlled substance	Generic: 15 mg, $0.73; 30 mg, $2.92
Temazepam (Restoril)	• Usual adult dose: 15 mg • 7.5 mg may be sufficient for some patients; some may need 30 mg	3.5–18.4	Sleep-onset and sleep-maintenance insomnia	• Drowsiness • Headache • Fatigue	• Initiate 7.5 mg in patients more than 65 years of age or debilitated patients • Caution with alcohol use • 80% to 90% of dose excreted in urine; use caution in patients with renal or hepatic impairment • Pregnancy category X • Schedule IV controlled substance	Brand: 15 mg, $24.98 Generic: 15 mg, $0.73
Triazolam (Halcion)	• Recommended adult dose: 0.25 mg • 0.125 mg may be sufficient for some patients • Dose should not exceed 0.5 mg	1.5–5.5	Sleep-onset and sleep-maintenance insomnia	• Drowsiness • Dizziness • Lightheadedness	• Older adults are at increased risk of ADRs because of higher plasma concentration and reduced clearance • CI with medications that significantly impair CYP3A metabolism (e.g., ketoconazole, nefazodone, protease inhibitors) • Caution with alcohol use • Observe usual precautions in patients with renal or hepatic impairment • Pregnancy category X • Schedule IV controlled substance	Brand: 0.25 mg, $4.27 Generic: 0.25 mg, $2.74
Estazolam	• Initial dose: 1 mg (adults) • Some patients may need 2 mg • Small or debilitated elderly patients: 0.5 mg	10–24	Sleep-onset and sleep-maintenance insomnia	• Somnolence • Hypokinesia • Dizziness • Abnormal coordination	• Eliminated through hepatic metabolism and excreted primarily in urine (87%); influence of hepatic or renal impairment on pharmacokinetics has not been studied • Caution with alcohol use • Pregnancy category X • Schedule IV controlled substance	Generic: 1 mg, $0.89
Quazepam (Doral)	• Initial dose: 7.5 mg • May be increased to 15 mg if necessary	39–73	Sleep-onset and sleep-maintenance insomnia	• Drowsiness • Headache • Fatigue • Dizziness • Dry mouth • Dyspepsia	• May cause confusion and oversedation in older adults • CI in established or suspected sleep apnea or in chronic pulmonary insufficiency • Caution with alcohol use • Extensive hepatic metabolism; only trace amounts of unchanged drug present in urine • Pregnancy category C • Schedule IV controlled substance	Brand: 15 mg, $4.60 Generic: 15 mg, $9.25 (split tablet for 7.5 mg)
Nonbenzodiazepines						
Zolpidem (Ambien)	• Initial dose: 5 mg (women); 5 or 10 mg (men) • 5-mg dose may be increased to 10 mg if needed • Total daily dose should not exceed 10 mg	2.6	Sleep-onset insomnia	• Drowsiness • Dizziness • Diarrhea	• Take after meal • 5 mg for older adults to minimize ADRs related to impaired motor and/or cognitive performance • Dose adjustment for hepatic impairment, but not for renal impairment • Caution with alcohol use • Pregnancy category C • Schedule IV controlled substance	Brand: 5 mg and 10 mg, $17.42 Generic: 5 mg and 10 mg, $4.57

Table 1 FDA-Approved Medications for the Treatment of Insomnia[93,94] (continued)

Name	Recommended Dose Before Retiring	Half-Life (hours)	Primary Indication	Adverse Drug Reactions	Additional Considerations	Cost Per Dose*
Zaleplon (Sonata)	• Initial dose: 10 mg (nonelderly adults) • 5 mg may be sufficient for some patients; others may need 20 mg • Dose should not exceed 20 mg	~1.0	Sleep-onset insomnia	• Headache • Dizziness • Drowsiness • Paresthesia • Nausea • Abdominal pain • Memory impairment	• Risk of abnormal thoughts or behavior, and memory loss • CYP3A4 high first-pass metabolism; dose adjustment for mild-to-moderate hepatic impairment; not recommended for patients with severe hepatic impairment • No dose adjustment for renal impairment • Caution with alcohol use • Pregnancy category C • Schedule IV controlled substance	Brand: 10 mg, $8.23 Generic: 10 mg, $3.60
Eszopiclone (Lunesta)	• Initial dose: 1 mg • May be increased to maximum of 3 mg • Elderly or debilitated patients: dose should not exceed 2 mg	6	Sleep-onset and sleep-maintenance insomnia	• Headache • Somnolence • Unpleasant taste	• CYP3A4 and CYP2E1 metabolism. Dose adjustment only for patients with severe hepatic impairment • 75% excreted in urine, primarily as metabolites; no dose adjustment for renal impairment • Caution with alcohol use • Pregnancy category C • Schedule IV controlled substance	Brand: 1 mg, $14.90 Generic: 1 mg, $11.67
Melatonin Agonist						
Ramelteon (Rozerem)	• Recommended dose: 8 mg • Total daily dose should not exceed 8 mg	1.0–2.6	Sleep-onset insomnia	• Somnolence • Dizziness • Fatigue • Nausea • Exacerbated insomnia	• CI in patients who have had angioedema while on ramelteon and in patients who are taking fluvoxamine concomitantly • Take within 30 minutes before bedtime • Should not be taken immediately after a high-fat meal • Avoid alcohol use • Exposure increased in patients with mild or moderate hepatic impairment; not recommended for patients with severe hepatic impairment • No dose adjustment for renal impairment • Pregnancy category C • Drug schedule: nonscheduled	Brand: 8 mg, $12.23
Orexin Receptor Antagonist						
Suvorexant (Belsomra)	• Recommended dose: 10 mg • Total daily dose should not exceed 20 mg	10–22	Sleep-onset and sleep-maintenance insomnia	• Daytime somnolence • Headache • Dizziness	• CI in patients with narcolepsy • Time to effect may be delayed if taken with food • Half-life increased in patients with moderate hepatic impairment; not recommended for patients with severe hepatic impairment • Caution with alcohol use • No dose adjustment for renal impairment • Pregnancy category C • Schedule IV controlled substance	Brand: 10 mg, $10.52

* Average wholesale price per Red Book Online as of October 15, 2015

ADR = adverse drug reaction; CI = contraindicated; CYP = cytochrome P450

table continues

Table 1 FDA-Approved Medications for the Treatment of Insomnia[93,94] (continued)

Name	Recommended Dose Before Retiring	Half-Life (hours)	Primary Indication	Adverse Drug Reactions	Additional Considerations	Cost Per Dose*
Tricyclic Antidepressant						
Doxepin (Silenor)	• Initial dose: 6 mg (adults); 3 mg (elderly) • Total daily dose should not exceed 6 mg	15.3	Sleep-maintenance insomnia	• Somnolence • Sedation • Nausea • Upper respiratory tract infection	• CI in patients who are using or have used monoamine oxidase inhibitors within the past 2 weeks, as well as patients with untreated narrow-angle glaucoma or severe urinary retention • Take within 30 minutes before bedtime • Should not be taken within 3 hours of meal • Extensive CYP2C19 and CYP2D6 metabolism; dose reduction for hepatic impairment; only small amount excreted in urine • Caution with alcohol use • Pregnancy category C • Drug schedule: nonscheduled	Brand: 6 mg, $12.62
Barbiturates						
Butabarbital (Butisol Sodium)	• Initial dose: 50 to 100 mg (non-elderly adults) as bedtime hypnotic	100	Short-term treatment of sleep-onset and sleep-maintenance insomnia	• Somnolence • Confusion • Agitation	• CI in patients with a history of manifest or latent porphyria • Limit treatment to 2 weeks because of loss of effectiveness • Dosage reduction in elderly or debilitated patients and patients with renal or hepatic impairment • Caution with alcohol use • Pregnancy category D • Schedule III controlled substance	Brand: 50 mg, $5.91 Generic: 50 mg, $5.91; 100 mg, $11.82
Secobarbital (Seconal Sodium)	• Initial dose: 100 mg (non-elderly adults) as bedtime hypnotic	15–40	Short-term treatment of sleep-onset and sleep-maintenance insomnia	• Somnolence	• CI in patients with a history of manifest or latent porphyria, marked impairment of liver function, or respiratory disease in which dyspnea or obstruction is evident • Limit treatment to 2 weeks because of loss of effectiveness • Dosage reduction in elderly or debilitated patients and patients with renal or hepatic impairment • Caution with alcohol use • Pregnancy category D • Schedule II controlled substance	Brand: 100 mg, $38.53
Antihistamines						
Diphenhydramine (Benadryl)	• Adults: 50 mg as a sleep aid	8–17	Sleep-onset and sleep-maintenance insomnia	• Somnolence • Dry mouth • Dizziness • Dyskinesia	• Elderly patients may be susceptible to ADRs • Take within 30 minutes before bedtime • Reduce dosing frequency in patients with renal impairment • No dose adjustment for hepatic impairment • Caution with alcohol use • Pregnancy category B • Drug schedule: over the counter	Brand: Two 25-mg tablets, $0.30 Generic: 50 mg, $0.03
Doxylamine (Unisom SleepTabs)	• Adults: 25 mg	10–12	Sleep-onset and sleep-maintenance insomnia	• Somnolence	• Take within 30 minutes before bedtime • Dose reduction for renal impairment • Caution in patients with hepatic impairment • Caution with alcohol use • Pregnancy: not classified • Drug schedule: over the counter	Not available

* Average wholesale price per Red Book Online as of October 15, 2015

ADR = adverse drug reaction; CI = contraindicated; CYP = cytochrome P450

chronic insomnia because of the relative lack of clinical efficacy and safety data.[25] In 2002, the FDA warned that severe liver injury may result from the use of kava-containing products.[92]

CONCLUSION

The FDA has approved an array of prescription medications for the treatment of insomnia, including BZD and non-BZD drugs, the melatonin agonist ramelteon, the sedating antidepressant doxepin, and the orexin receptor antagonist suvorexant. In addition, several agents approved for other indications, such as the antidepressants trazodone and mirtazapine, are used in this setting. Over-the-counter alternative therapies include antihistamines, melatonin, and the herbal products valerian and kava. Table 1 summarizes the FDA-approved insomnia treatments.[93,94]

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