Strategies for Treating Chronic Insomnia

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Abstract

Insomnia is a prevalent condition that remains underdiagnosed and undertreated. Recognizing and treating insomnia are important in decreasing morbidity and restoring quality of life for those who experience sleep disturbances. Appropriate treatment of insomnia should involve multiple interventions designed to address not only the symptoms of insomnia itself, but also any coexisting factors that may be contributing to the sleep disturbances. A combination of pharmacologic and nonpharmacologic therapies may be particularly efficacious in those with chronic and debilitating insomnia. Pharmacotherapy is the most frequently used intervention for insomnia in cases where the goal of therapy is immediate relief of symptoms, insomnia is accompanied by significant distress or impairment, nonpharmacologic approaches alone are ineffective, or the patient prefers medication. The ideal hypnotic has the following characteristics: rapid absorption, rapid sleep induction, optimal duration of action, preservation of sleep architecture, and a favorable safety profile. This review will discuss currently available treatment options for insomnia, the benefits of each, and appropriate treatment regimens.

(Am J Manag Care. 2006;12:S230-S245)

Characterized by disorders of initiating or maintaining sleep, or nonrestorative sleep, insomnia is a prevalent condition that can coexist with psychiatric and medical illness and cause significant impairment of social and occupational functioning.[1] Patients may experience several symptoms of insomnia at one time, and the pattern of symptoms may change over time.[1] In studies evaluating the outcomes of treatments of sleep disturbances, insomnia is often defined by a sleep latency (SL) and/or wake after sleep onset (WASO) time period greater than 30 min, with a corresponding sleep efficiency (total amount of sleep time divided by the total amount of time spent in bed with the intent to sleep) of less than 85%.[2,3] Insomnia is often further classified in clinical practice, based on the duration of symptoms, as follows: transient insomnia, lasting 1 to 3 nights; short-term insomnia, lasting 3 nights to 1 month; and chronic insomnia, lasting more than 1 month.[1,2,4,5] The severity and treatment of insomnia take into account the frequency, intensity, duration, and consequences associated with the sleep disturbances.[1,4]

Chronic insomnia may exist in isolation (primary insomnia) or coexist with other medical and psychiatric illnesses, medication and substance misuse, behavioral or environmental factors, or other primary sleep disorders, such as obstructive sleep apnea.[6] Although the direct consequences of insomnia have not been fully identified, chronic insomnia has been associated with a higher risk for the development of depression, cardiovascular disorders, chronic obstructive pulmonary disease, back and hip problems, osteoarthritis, rheumatoid arthritis, and peptic ulcer disease.[6-8] Although prevalence estimates of insomnia vary depending on the definitions and criteria used, epidemiologic studies indicate that approximately 30% to 35% of the general population experience at least occasional or intermittent sleep disturbances.[6,7,9,10] Twenty-five percent of these individuals, or 10% of the population, report chronic insomnia symptoms accompanied by daytime consequences of fatigue, irritability, and impaired concentration, which can lead to negative effects on overall health, mood, and functioning.[6,7,10] Costs associated with insomnia can include related medical expens-

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es, more frequent use of healthcare resources, a higher rate of absenteeism, reduced subjective productivity, and an increased risk of accidents relative to those without insomnia.[6,11] As a result, the overall economic burden of insomnia is estimated to exceed $100 billion annually.[6,10,12] Populations at particular risk for insomnia may include women, elderly persons, people with medical and psychiatric comorbidities, and shift workers.[2,6,13-15]

However, despite the fact that insomnia is a prevalent condition that can be associated with negative consequences, it remains underdiagnosed and undertreated. Recognizing and treating insomnia are important in decreasing morbidity and restoring quality of life for those who experience sleep disturbances. A comprehensive assessment of an individual's medical, psychiatric, and pharmacologic history, sleep and wakefulness patterns, and family history of sleep disorders is necessary before a diagnosis of insomnia can be made and a treatment plan implemented. Appropriate treatment of insomnia should involve multiple interventions designed to address not only the symptoms of insomnia itself but also any coexisting factors that may be contributing to the sleep disturbances.

Many people with insomnia complain about difficulties in falling asleep, and, as a result, sleep onset has long been the focus of both pharmacologic and nonpharmacologic treatment interventions. Sleep maintenance (staying asleep) can also be a significant problem, particularly in the elderly and in individuals with insomnia coexisting with psychiatric and medical disorders.[6,14] Although many individuals may benefit from pharmacologic intervention, evidence also supports the use of nonpharmacologic treatments in the management of insomnia. A combination of pharmacologic and nonpharmacologic therapies may be particularly efficacious in those with chronic and debilitating insomnia.

Nonpharmacologic Interventions for Treating Insomnia

Nonpharmacologic interventions in the treatment of insomnia primarily include behavioral and cognitive techniques that focus on modifying factors that precipitate and perpetuate sleep disturbances. Several behavioral techniques (ie, sleep hygiene [SH] education, relaxation therapies, stimulus control, sleep restriction) and cognitive therapy have been shown to be effective in the treatment of insomnia.[2-4,14,16-19] Clinical data demonstrate that behavioral techniques, particularly stimulus control and sleep restriction, are superior to placebo and as effective as pharmacotherapy in the short-term treatment of sleep initiation problems associated with insomnia.[2,3,17,19] Most behavioral and cognitive interventions are compatible with one another and can be combined to optimize outcome. In general, advantages of these behavioral and cognitive interventions are minimal adverse effects and documented improvement in sleep sustained over 6 to 24 months.[2,17,19,20] Limitations to the implementation of these interventions include a shortage of personnel trained in the provision of these techniques, high cost and limited or no insurance reimbursement, patient preferences for pharmacologic interventions, and the fact that these techniques are time intensive and require motivation on the part of the individual experiencing insomnia symptoms.[3,4,16-18] Furthermore, some research has suggested that the efficacy of behavioral and cognitive interventions decreases with increasing age.[14,19] Behavioral and cognitive interventions are typically implemented when pharmacotherapy is contraindicated as augmentation to pharmacotherapeutic interventions or as a result of patient preference.

First outlined in 1977 and based on clinical observations of patients with sleep disturbances, SH recommendations have evolved into a list of behaviors, environmental conditions, and other sleep-related factors that are believed to be instrumental in promoting improved quantity and quality of sleep.[16] The assumption that accompanies SH education in patients with insomnia is that sleep disturbances arise, to some extent, when these patients deviate from SH behaviors.[16,18] Although commonly used as an approach to the treatment of insomnia, definitions of SH in the scientific literature vary, depending on investigator and study focus. However, common components of SH

recommendations include limiting the use of the bedroom only for sleep and intimacy; keeping a regular bedtime and wake-up schedule; avoiding alcohol, tobacco, caffeine, large meals, and vigorous exercise near bedtime; eliminating or minimizing daytime napping; and modifying the sleep environment to eliminate or remove sleep-disturbing elements, such as bright lights, extremes in temperature and noise levels, and bedroom clocks.[4,16,18] Evidence supporting SH education as a stand-alone approach to the treatment of insomnia is limited.[2,16,19] Although these factors are rarely the primary cause of chronic insomnia, individuals should always be educated about good SH and proper sleep habits, regardless of the etiology of the sleep disturbance.

Relaxation therapies for insomnia specifically target the arousal system and focus on reducing factors, such as tension and stress, that may precipitate sleep disturbances.[17,18] Many individuals, however, do not recognize the significance of stress reduction in the treatment of their insomnia and do not invest the time required to learn progressive muscle relaxation, meditation, simple breathing retraining, guided imagery, or other forms of relaxation. There is currently no evidence to support the use of relaxation techniques as the sole intervention in the management of insomnia.[2,18]

The basis for the use of stimulus control is to associate the bedroom and bedtime with sleep rather than wakefulness.[2-4,18,19] To increase sleep efficiency and decrease frustration that occurs with extended time awake in bed, individuals are instructed to go to sleep only when drowsy, to keep a regular sleep-wake cycle, to use the bed only for sleep and sex, to avoid napping during the day, and to get out of bed if unable to fall asleep within 20 min.[2,18] Equally important, individuals should be encouraged to engage in relaxing activities until they feel drowsy or sleepy again, and to repeat this last step as often as necessary. Often used in conjunction with stimulus control, sleep restriction limits the amount of time spent in bed to only the time actually spent sleeping.[17,18] Maintenance of a consistent wake time, even after a poor night's sleep, is necessary to synchronize the endogenous circadian rhythm that regulates sleep and wakefulness.[17,18] The allowable time spent in bed is increased or decreased by 15 to 20 min each week until a goal of 80% to 90% sleep efficiency is met.[2,18] Because gains in total sleep time are not seen immediately, both stimulus control and sleep restriction require patient motivation and encouragement. Both techniques have been shown to be highly efficacious as single or combined therapies for sleep-onset and sleep-maintenance insomnia.[2,19]

Cognitive approaches used in the treatment of insomnia involve restructuring techniques that address maladaptive thought patterns and attitudes that exacerbate and amplify sleep disturbances.[2,3,18] The goal is to recognize, challenge, and change patient-specific unrealistic sleep expectations, misconceptions about the causes of insomnia, and apprehension and anxiety about bedtime. Cognitive therapy has not been evaluated as a stand-alone treatment for chronic insomnia, but treatment approaches that incorporate cognitive restructuring techniques have shown positive outcomes.[2,3]

Pharmacologic Interventions for Treating Insomnia

Pharmacotherapy is the most frequently used intervention for primary and secondary insomnia when immediate symptom relief is needed, when the sleep disturbances produce significant distress or impairment, when behavioral and cognitive interventions alone are insufficient in treating the insomnia, or when a patient prefers the use of medication.[2,18,21]

Characteristics of a desirable hypnotic include rapid absorption, rapid sleep induction, optimal duration of action, preservation of sleep architecture, and being free from unwanted effects and drug interactions.[21] The desired hypnotic agent should not cause residual daytime effects or memory loss, should not interact synergistically with ethanol to produce respiratory depression, and should not produce tolerance, dependence, or rebound insomnia.

Currently available hypnotic agents (both benzodiazepines and nonbenzodiazepines) have sedative effects that are mediated via activity at the gamma-aminobutyric acid type A ($GABA_A$) receptors, leading to

enhancement of the activity of GABA. GABA is the major inhibitory neurotransmitter of the mammalian central nervous system (40% of central nervous system [CNS] neurons are estimated to be GABAergic) and is thought to play the pivotal role within the sleep-inducing and maintenance systems.[21,22] These agents differ in their pharmacokinetic profiles, safety profiles, and degree of selectivity for $GABA_A$ receptor subtypes. Most GABA receptors are composed of α, β, and γ subunits that combine to form pentameric channels, which open secondary to the binding of GABA or an agonist.[23,24] The result is an influx of negative chloride ions into the neuronal cell, neuronal cell hyperpolarization, and subsequent action potential inhibition. The $GABA_A$ receptor subtype accounts for greater than half of all GABA receptors and consist primarily of 2 α_1-subunits, 2 β_2-subunits, and 1 γ_1-subunit.[23-27] $GABA_A$ receptors containing the α_2- or α_3-subunits are considerably less abundant and α_4-, α_5-, and α_6-subunits account for less than 5% of all $GABA_A$ receptor subtypes.[24,27-29] The heterogeneity of $GABA_A$ receptor subtypes is responsible, in part, for the various pharmacologic effects of benzodiazepines and other GABA agonists.

Based on their elimination half-lives ($t_{1/2}$), hypnotic agents may be divided into 4 categories: (1) ultrashort-acting agents with a $t_{1/2}$ of 1 hr, such as zaleplon; (2) short-acting agents, with a $t_{1/2}$ of 2.5 to 6 hr, including triazolam, and the nonbenzodiazepines zolpidem tartrate and eszopiclone; (3) intermediate-acting agents, with a $t_{1/2}$ of 9 to 24 hr, including estazolam and temazepam; and (4) long-acting agents, with a $t_{1/2}$ greater than 24 hr, including flurazepam, diazepam, and quazepam.[18,22] These differences in half-life, along with time for onset of action, which is based, in part, on the time to maximal concentration and $GABA_A$ receptor subtype activity, may be useful in determining which hypnotic agent to employ for a specific sleep complaint.[18] For example, for a primary complaint of difficulty falling asleep, an agent with a short half-life and rapid onset of action may be the most appropriate choice; administration of a longer-acting agent may increase the risk of residual daytime effects. An agent with a longer half-life might be more appropriate for a patient experiencing numerous awakenings throughout the sleep cycle or early awakening with an inability to return to sleep, provided that the agent does not produce significant next-day residual effects.

The use of hypnotics and other sedating agents for chronic insomnia is less straightforward. Eszopiclone is approved for the long-term treatment of sleep-onset and sleep-maintenance insomnia and is the only hypnotic that has been studied in two 6-month, double-blind, placebo-controlled, randomized trials of nightly administration.[30-32] Ramelteon, a melatonin receptor agonist that binds to receptors regulating circadian rhythms, has recently received US Food and Drug Administration (FDA) approval and is indicated for the long-term treatment of sleep-onset insomnia, as evidenced in two 5-week, placebo-controlled trials of nightly administration.[33] Zolpidem tartrate extended-release formulation was also recently approved for the treatment of insomnia without any limitation in the length of use, based on two 3-week, placebo-controlled studies of nightly administration.[34] Other FDA-approved hypnotics in the marketplace are indicated for the short-term treatment of insomnia.

Benzodiazepines. The benzodiazepine site in the $GABA_A$ receptor is located on the interface of the α- and γ-subunits, and the effects of benzodiazepines are determined by the $GABA_A$ receptor subtype.[24,28] The α_1-subunit appears to mediate the sedative and, in part, the anterograde amnesia and anticonvulsant effects of benzodiazepines.[25,26,35] The α_2-subunit mediates anxiolysis, and the α_3- and α_5-subunits share anticonvulsant and ataxic properties.[25,27] The muscle relaxant and ethanol potentiation effects of benzodiazepines appear to be mediated by the α_2- and α_4-subunits, respectively.[25,27] The α-subunit of the $GABA_A$ receptor appears to be benzodiazepine insensitive.[26] Previous receptor terminology corresponds to the $GABA_A$ receptor α-subunit, with the α_1-subunit reflecting benzodiazepine$_1$ (BZ_1, or omega$_1$) pharmacology and a heterogeneous set of $GABA_A$ receptor subtypes containing α_2-, α_3-, or α_5-subunits reflecting benzodiazepine$_2$ (BZ_2, or omega$_2$) pharmacology.[28,36]

Supported by extensive studies confirming safety and efficacy at recommended doses, benzodiazepines have been the first-line option in the pharmacologic short-term management of insomnia.[19,23] Benzodiazepines that are approved by the FDA for use in insomnia include estazolam, flurazepam, quazepam, temazepam, and triazolam. A meta-analysis of 22 studies reviewing the benefits and risks associated with the short-term use (≤14 days) of benzodiazepines or zolpidem to treat insomnia in adults reported significant improvements in SL onset, number of awakenings, total sleep duration, and sleep quality compared with placebo.[37] A second meta-analysis that included short-, intermediate-, and long-acting benzodiazepines showed improvements in total sleep duration but not SL onset.[38] The use of benzodiazepines for the long-term treatment of chronic insomnia, however, remains controversial, because no data have been gathered to evaluate the long-term use of these agents.[4,38]

Adverse effects associated with the use of benzodiazepines, such as alteration of sleep architecture, tolerance, next-day residual effects, cognitive and psychomotor impairment, anterograde amnesia, and rebound insomnia, are dose dependent and vary according to the pharmacokinetics of the individual agent.[4,22,38,39] The next-day hangover effect is the most common complaint associated with the use of the longer-acting benzodiazepines, with many patients experiencing headache, dizziness, decreased mental alertness, and diurnal sedation.[22,30] In addition to tolerance to the hypnotic and sedative effects, physiologic dependence accompanied by withdrawal symptoms on discontinuation can occur with long-term use of benzodiazepines, but not to the extent seen with older sedatives and recognized drugs of abuse.[4,22,38,39] Discomfort associated with benzodiazepine withdrawal symptoms may be minimized by avoiding abrupt discontinuation and employing a gradual tapering of the benzodiazepine dose.[22,39,40] This physiologic dependence does not appear to be associated with psychological dependence or accompanying inappropriate drug-seeking and drug-taking behaviors.[40]

Benzodiazepine dependence is considered more likely with use of high doses, daily dosing of more than 4 months' duration, advanced age, current or previous history of sedative hypnotic and/or alcohol dependence, and use of high-potency, short–half-life benzodiazepines.[41] Furthermore, abuse potential of a particular benzodiazepine is linked to both greater lipophilicity and shorter elimination half-life. All benzodiazepines, however, have abuse potential and all potentiate the effects of alcohol.[22] Given the pharmacology of the benzodiazepines, none of these adverse effects are unexpected. However, despite their adverse effects, benzodiazepines are considered relatively safe in the general population, and even excessive doses are rarely fatal unless other CNS depressants (ie, ethanol) are taken concomitantly.[22,40] Benzodiazepine hypnotics are approved for the short-term (7-14 days) treatment of insomnia and, like all sedative hypnotics, should be used with caution in individuals with a history of substance abuse and in the elderly, who may metabolize these medications more slowly, placing them at risk for greater cognitive impairment and sedative effects.[18,38,39]

Nonbenzodiazepines. In an attempt to minimize the adverse effects associated with the use of benzodiazepines, the development of nonbenzodiazepine agents has been pursued. Not surprisingly, since the introduction of the nonbenzodiazepine hypnotic medications, use of benzodiazepines has steadily declined.[18] The 4 currently available nonbenzodiazepines (zolpidem tartrate, zolpidem tartrate extended-release, zaleplon, and eszopiclone) promote sedation via the inhibitory neurotransmitter GABA, but possess distinct pharmacologic profiles, profiles of receptor specificity, and clinical activity.[32,42]

Zolpidem tartrate and zolpidem tartrate extended-release. Zolpidem tartrate, an imidazopyridine derivative, is indicated for the short-term treatment of insomnia and has a rapid onset of action and short elimination half-life ($t_{1/2}$ ~2.5 hr).[43] It appears to possess a very high affinity for the $GABA_A$ receptor α_1-subunit, with significantly less affinity for

the α_2- and α_3-subunits than do the benzodiazepines.[26] Zolpidem has almost no activity at the α_5-subunit and, as a result of its preferential α_1-subunit–binding affinity, has minimal muscle relaxant and anticonvulsant effects.[26,44] The recommended doses are 10 mg in healthy adults and 5 mg in older patients, debilitated patients, and in those with hepatic dysfunction.[43] Adverse events most commonly associated with discontinuation from US trials were daytime drowsiness (0.5%), dizziness (0.4%), headache (0.5%), nausea (0.6%), and vomiting (0.5%).[43] Adverse events reported statistically significantly more often than placebo in short-term (up to 10 nights) clinical trials of zolpidem tartrate (up to 10 mg) were drowsiness (2%), dizziness (1%), and diarrhea (1%).[43] During longer-term treatment (28-35 nights) of zolpidem tartrate (up to 10 mg), adverse effects reported statistically significantly more often than placebo were dizziness (5%) and a "drugged feeling" (3%).[43] Overall, adverse effects associated with zolpidem tartrate are dose related, occurring more frequently with ≥20 mg per night. When used at recommended doses, zolpidem tartrate does not appear to negatively affect next-day psychomotor or cognitive function. Several trials have evaluated consecutive nightly use of zolpidem tartrate.[45-49] The longest placebo-controlled trial of nightly administration is 5 weeks; therefore, the potential for dependence, tolerance, or rebound insomnia on discontinuation after longer use is uncertain.[45]

In a large study of consecutive, nightly treatment, zolpidem tartrate 10 mg was found to significantly decrease SL and increase total sleep time during the active treatment time period of 28 nights versus placebo.[47] No improvement in the number of sleep awakenings was seen for zolpidem tartrate versus placebo, and WASO was not assessed. On the first night after discontinuation of 4 weeks of treatment, a statistically significant higher number of patients who had received zolpidem tartrate 10 mg showed an increase in SL ($P \geq .05$) and an increase in number of awakenings ($P \geq .01$) relative to baseline versus those who had received placebo.[47] Withdrawal effects (defined as 3 or more new symptoms) on the first night after treatment discontinuation were significantly higher ($P \geq .05$) in the zolpidem tartrate 10-mg group versus placebo.[47]

Similar findings with regard to the lack of ability of zolpidem tartrate to demonstrate a decrease in the number of awakenings or improvement in sleep maintenance have been noted in other randomized, double-blind, placebo-controlled trials. Results of some of these studies showed that zolpidem tartrate 10 mg improved sleep maintenance initially but not by the end of the study period.[46,49,50] Other studies did not find an improvement in sleep maintenance.[45,49,51] Results from studies of the effects of zolpidem tartrate 10 mg on total sleep time have not been consistent.[47-50] Discontinuation treatment effects evaluated 2 to 3 days post-therapy include cases of tolerance, rebound effects, and withdrawal reactions.[45,47,48,51]

Because of concern about potential tolerance and/or abuse with nightly use, several studies of the effects of nonnightly (intermittent) use of zolpidem tartrate have been conducted. In 1 study, intermittent dosing with zolpidem tartrate 10 mg on all treatment nights of the study had a statistically significant impact on total sleep time during weeks 1 to 4, but no effect for weeks 5 to 8.[52] No difference in SL was seen for zolpidem tartrate 10 mg versus placebo when examining intermittent dosing during the entire treatment period. Also, although there was a statistically significant lower number of awakenings during weeks 1 to 2, weeks 3 to 8 showed no improvement in the number of awakenings for zolpidem tartrate 10 mg. It was recommended that patients receive education during intermittent dosing. Specifically, they should be informed that relatively poor sleep could occur on the nights that the medication is not taken compared with nights that the medication is taken. Other studies have shown similar improvements in sleep onset and sleep maintenance with intermittent dosing of zolpidem.[53-55]

In studies in which quality of life has been measured, the impact of zolpidem tartrate on these measures has been equivocal.[52-54] In 2 trials, patients reported improved sleep quality when treated with zolpidem

tartrate.[53,54] However, another study using the 36-item short-form health survey to document quality-of-life changes across various domains has not demonstrated any significant improvement with zolpidem tartrate treatment compared with baseline.[55]

Zolpidem tartrate extended-release is formulated to provide extended plasma concentrations beyond 3 hr after administration.[34] It is indicated for treatment of sleep-onset and/or sleep-maintenance insomnia based on 2 double-blind, randomized, placebo-controlled polysomnogram (PSG) studies of 3 weeks' duration. For the 12.5-mg daily dose in adults, adverse events exceeding 5% were headache (19% vs 16% with placebo), somnolence (15% vs 2% with placebo), dizziness (12% vs 5% with placebo), and nausea (7% vs 4% with placebo). For the 6.25-mg daily dose in elderly patients, adverse effects with a greater than 5% incidence were headache (14% vs 11% with placebo), dizziness (8% vs 3% with placebo), somnolence (6% vs 5% with placebo), and nasopharyngitis (6% vs 4% with placebo).[34]

Zaleplon. Classified as a pyrazolopyrimidine derivative, zaleplon has an ultrashort elimination $t_{1/2}$ of approximately 1 hr. It can be administered up to 4 hr before the anticipated wake time, when difficulty falling asleep is experienced.[56] Similar to zolpidem, zaleplon preferentially binds to the GABA receptor α_1-subunit but possesses less affinity for the α_2-, α_3-, and α_5-subunits than does zolpidem.[25,26]

Zaleplon, at recommended doses of 10 mg in adults and 5 mg in the elderly, has been shown to decrease SL with little to no effects on total sleep time or number of nocturnal awakenings.[42,56,57] Headache is the most commonly reported adverse effect with recommended doses.[56] The few studies that have specifically evaluated the residual effects of middle-of-the-night use of zaleplon have reported little or no next-morning memory impairment.[58-61] Whether administered during the day, at bedtime, or in the middle of the night, zaleplon was associated with less psychomotor and memory impairment and more rapid resolution of adverse effects than zolpidem tartrate.[6,57-62] It is important to note that no studies have looked at middle-of-the-night zaleplon dosing beyond 2 nights' total duration or in elderly individuals with insomnia.

A large, multicenter, placebo-controlled trial in adult patients with insomnia indicated favorable effects of zaleplon on SL when given at the recommended 10-mg dose.[47] Effects were maintained throughout the duration of the 4-week study and, in contrast to the findings with zolpidem tartrate, there was no evidence of rebound insomnia or withdrawal symptoms after discontinuation when given at the recommended doses. In addition, a number of studies in elderly patients with insomnia have also demonstrated significant decreases in SL with short-term (≥2 weeks) use of zaleplon.[63-65] Given the safety and efficacy data in promoting sleep initiation, zaleplon appears to be particularly useful in those whose only sleep disturbance is difficulty falling asleep or for sleep maintenance when the patient is expected to get at least 4 hr of additional sleep.

Eszopiclone is a cyclopyrrolone derivative and an enantiomer of zopiclone, a sedative hypnotic not marketed in the United States. Although not fully elucidated, zopiclone, and presumably eszopiclone, show similar binding profiles to the α_1-subunit of the $GABA_A$ receptor as benzodiazepines, but with α-subunit specificity and affinity lying somewhere between those of zaleplon and zolpidem.[66,67] Of the 6 known α-subtypes, α_1 and α_3 have been associated with the brain systems that control sleep. In vitro studies with functional recombinant $GABA_A$ receptors suggest that (R,S)-zopiclone (racemic zopiclone) and its S-isomer (eszopiclone) display considerable activity at $GABA_A$ receptors containing the α_3-subtype, as well as activity at receptors of the α_1-subtype.[29,68]

With an elimination $t_{1/2}$ of approximately 6 hr, eszopiclone is approved for the treatment of sleep-onset and sleep-maintenance insomnia, and has demonstrated efficacy and safety in patients with primary insomnia using both PSG and patient-reported measures of sleep.[30,31,69,70] Improvement in patient-reported next-day function was also

noted.[69] Eszopiclone has been studied in both transient and chronic conditions, showing improvement in sleep onset, sleep maintenance, and total sleep time.[30,31,71] It is the first sedative-hypnotic agent to be approved without a limitation of short-term use only.[32]

The most commonly reported adverse events of eszopiclone versus placebo, administered at recommended adult (2- and 3-mg) doses were headache (21% and 17%, respectively, vs 13% with placebo), unpleasant taste (17% and 34%, respectively, vs 3% with placebo), somnolence (10% and 8%, respectively, vs 3% with placebo), dizziness (5% and 7%, respectively, vs 4% with placebo), infection (5% and 10%, respectively, vs 3% with placebo), dry mouth (5% and 7%, respectively, vs 3% with placebo), dyspepsia (4% and 5%, respectively, vs 4% with placebo), nausea (5% and 4%, respectively, vs 4% with placebo), nervousness (5% and 0%, respectively, vs 3% with placebo), and rash (3% and 4%, respectively, vs 1% with placebo).[32] Infection appeared to be primarily due to the common cold in both eszopiclone groups, and taste disturbances were attributed to the liquid formulation used in many studies. In the elderly patient (1- and 2-mg) doses, the most common adverse events were headache (15.3% and 15.2%, respectively, vs 15.0% with placebo), unpleasant taste (8.3% and 11.4%, respectively, vs 1.3% with placebo), somnolence (6.9% and 3.8%, respectively, vs 8.8% with placebo), and dyspepsia (5.6% and 1.3%, respectively, vs 2.5% with placebo).[70]

Eszopiclone use in the long-term treatment of insomnia was studied in a double-blind, placebo-controlled trial evaluating the long-term safety and efficacy of eszopiclone 3 mg administered nightly over a 6-month period to adults with chronic primary insomnia.[30] Eszopiclone demonstrated sustained (week 1 through 6 months) clinically and statistically significant improvements in all self-reported measures of sleep initiation, sleep maintenance, sleep duration, sleep quality, and daytime functioning. There was no evidence of physiologic tolerance or diminished efficacy over the entire 6 months of the study for all endpoints measured. Eszopiclone was generally well tolerated, with headaches and unpleasant taste reported more often in the eszopiclone group.

This initial 6-month controlled study was followed by a 6-month open-label extension phase in which all patients were administered eszopiclone 3 mg nightly.[31] Overall, patients randomized to placebo in the first 6 months and switched to eszopiclone for the open-label extension experienced improvements in all measures of sleep studied. The improvement was evident at every time point throughout the entire 6-month period without any evidence of loss of therapeutic effect or increase in eszopiclone dose. In this open-label phase of the study, patients switched from placebo to eszopiclone reported significant improvements in sleep and daytime functioning relative to the final month of double-blind treatment. These improvements were comparable with those experienced and sustained by patients who received eszopiclone for all 12 months. Eszopiclone was well tolerated throughout the 12-month period, and there was no evidence of withdrawal on discontinuation of treatment or any worsening rates of adverse effects across time. In summary, these studies demonstrate that long-term use of eszopiclone is safe and leads to sustained efficacy without tolerance in the long-term management of insomnia.[30,31]

Similar results have been observed in elderly patients with chronic insomnia. In a multicenter, placebo-controlled study, elderly patients were treated with nightly eszopiclone 1 or 2 mg over a 2-week period. Patients receiving the 2-mg dose experienced significant improvements in patient-reported measures of sleep onset, WASO, and total sleep time, and in several next-day efficacy measures (eg, improvements in daytime alertness, morning sleepiness, daytime ability to function, and overall sense of well-being) compared with those taking placebo.[70] The 1-mg group had significantly shorter SL compared with placebo. Patients receiving the 2-mg dose who napped also reported a significant reduction in the median number of naps and in the 2-week cumulative total nap time. In a second double-blind, placebo-controlled study, elderly patients with

chronic insomnia received eszopiclone 2 mg nightly for 2 weeks.[72] Compared with placebo, eszopiclone significantly reduced average objective SL and WASO, and increased average sleep efficiency over the 2-week, double-blind treatment period. Similar to the previous study, in patients who napped, the cumulative number of naps was reduced relative to placebo.

Ramelteon. The hypnotic ramelteon is a melatonin receptor agonist with affinity predominantly for melatonin 1 (MT_1) and melatonin 2 (MT_2) receptors.[33,73] Ramelteon is indicated for the treatment of sleep-onset insomnia.[33] Clinical trials supporting efficacy and safety of ramelteon included two 35-night, randomized, double-blind, placebo-controlled PSG trials of patients with chronic insomnia: 1 study in adults aged 18 to 64 years (using single, nightly ramelteon 8 or 16 mg), and a 3-period crossover trial in subjects aged 65 years or older (using ramelteon 4 or 8 mg or placebo).[33] PSG was performed on the first 2 nights in each of weeks 1, 3, and 5 of treatment. In these studies, all doses reduced SL to persistent sleep (PSG results) compared with placebo. The second study in subjects aged 65 years or older reported subjective efficacy measures with 4 or 8 mg or placebo for 35 nights, and both doses reduced SL compared with placebo.[33] A similarly designed study in adults aged 18 to 64 years using 8 and 16 mg of ramelteon did not replicate the finding of reduced patient-reported SL compared with placebo.[33] In a published clinical trial evaluating the efficacy, safety, and dose response of ramelteon, patients with chronic primary insomnia were randomized into a double-blind dosing sequence of 4, 8, 16, and 32 mg of ramelteon and placebo.[74] This 5-period crossover study included a 5- to 12-day washout period between treatments, and patients served as their own controls. All doses of ramelteon resulted in statistically significant decreases in latency to persistent sleep and increases in total sleep time. No next-day residual effects and no differences in the number or type of adverse events were apparent at any dose of ramelteon compared with placebo.[74] The most frequent adverse reactions in phase 1 to 3 studies of ramelteon 8 mg were headache (7% vs 7% with placebo), somnolence (5% vs 3% with placebo), dizziness (5% vs 3% with placebo), and fatigue (4% vs 2% with placebo).[33] Unlike the other pharmacologic options, ramelteon is not a controlled substance.[33,73]

Other Drugs Used to Promote Sleep. *Trazodone* is a triazolopyridine antidepressant with sedating properties that, although not FDA approved for this indication, is widely used for the treatment of insomnia.[75] A review of the clinical trials for trazodone showed that over half of the studies were conducted over a period of 3 weeks or less, and no trial exceeded 6 weeks of active treatment.[76] The majority of the studies in this review involved depressed patients, not those with primary insomnia, and enrolled fewer than 30 patients in the trazodone treatment groups. The most common adverse events seen at dosages of 75 to 500 mg/day in these studies included drowsiness, dry mouth, nausea, vomiting, constipation, headache, and blurred vision.

Only 1 randomized, double-blind, parallel, placebo-controlled study has evaluated the benefit of trazodone for patients with primary insomnia.[46] This study evaluated the efficacy of trazodone in nondepressed patients with insomnia and was a randomized, double-blind, placebo-controlled comparison of trazodone 50 mg and zolpidem tartrate 10 mg administered nightly for 2 weeks.[46] During the first week, patients in both the trazodone and zolpidem tartrate groups reported significant improvements in subjective SL, sleep duration, WASO, and sleep quality relative to placebo, but trazodone was significantly less effective than zolpidem tartrate with respect to self-reported SL and sleep duration. During week 2, the trazodone group did not significantly differ from the placebo group on any of the sleep efficacy endpoints. The zolpidem tartrate group, however, continued to report significant improvement in SL and sleep duration compared with placebo throughout the entire 2-week period but not in WASO during the second week. Estimated total sleep time did not significantly differ across groups at any time during the study period.

Compared with tricyclic antidepressants, the cardiovascular risk profile of trazodone

is relatively benign.[76] However, a review of trazodone studies in patients with depression revealed reports of hypotension, syncope, and exacerbation of ischemic attacks associated with trazodone administration.[76,77] In addition, torsades de pointes, characterized by prolongation of the QT_c interval, and other arrhythmias have been reported with trazodone administration.[78,79] Trazodone is metabolized almost exclusively by the hepatic cytochrome P-450 3A4 (CYP3A4) isoenzyme system and is therefore subject to elevation of serum levels when it is coadministered with potent CYP3A4 inhibitors such as ketoconazole.[77] These adverse effects could be of particular concern in elderly individuals and in those with preexisting cardiovascular disease. Because no randomized controlled trials have evaluated trazodone use in elderly patients with insomnia, careful consideration should be given when prescribing trazodone or any other hypnotic. Cases of priapism, related to the α-adrenergic antagonist properties of trazodone, have also been reported.[76,77] Serotonin syndrome has been reported when trazodone, even at low doses, has been used in combination with other antidepressants.[80] It is important to note that dosages of trazodone used in insomnia are typically lower (25-100 mg before bedtime) than dosages used to treat depression (100-600 mg/day).[76] Because so few studies have been conducted in nondepressed patients with insomnia, it is difficult to assess the risk associated with the use of trazodone in the treatment of insomnia. In clinical trials evaluating trazodone in nondepressed patients with insomnia, patients experienced significant CNS adverse effects (eg, headache and somnolence) versus placebo.[46,76]

According to Mendelson's review, the majority of studies evaluating the efficacy of trazodone in depressed or dysthymic patients with secondary insomnia reported improvements in subjective sleep assessments, including sleep onset, sleep quality, and sleep duration.[76] However, as pointed out previously, these studies used a wide range of doses, were small (involving <20 patients), and were not randomized or placebo controlled; in addition, trazodone was associated with a high study discontinuation rate, impaired next-day functioning, and impairments in "ease of awakening" and "feelings on/after awakening"—key measures used in the Leeds Sleep Evaluation Questionnaire.[76]

Studies evaluating tolerance associated with the use of trazodone in primary insomnia are nonexistent; therefore, no conclusions can be reached at this time. In the study by Walsh et al described previously, the efficacy relative to placebo observed during week 1 was lost at week 2, but this effect was primarily related to improvements in the placebo group rather than decrements in the trazodone group.[46]

Over-the-counter (OTC) Products. Although some patients with insomnia seek and follow medical advice in addressing their sleep disturbances, many choose to self-medicate with OTC sleep aids. The major categories of OTC sleep aids include antihistamines and the dietary supplements melatonin and valerian. First-generation antihistamines (eg, diphenhydramine, brompheniramine, or chlorpheniramine) induce sedation and confusion via central antihistaminergic and anticholinergic mechanisms.[81] Diphenhydramine is the most commonly used antihistamine in OTC sleep aids, and studies evaluating its sedative effects have produced data to support the clinical observation of sedation after administration.[82,83] Only 1 double-blind, randomized, placebo-controlled study evaluating subjective reports of sleep parameters with nightly administration of diphenhydramine 50 mg over a 2-week period indicated some improvement in SL, sleep duration, quality of sleep, and number of awakenings.[84] This study, however, demonstrated evidence of tolerance, and efficacy was not sustained. The adverse effects of diphenhydramine were notable compared with placebo and included tiredness, drowsiness, dizziness, and grogginess.

The limitations of antihistamines for treating insomnia include a negative adverse-effect profile, including changes in sleep architecture (ie, a reduction in rapid eye movement [REM] sleep secondary to their anticholinergic effects); next-day seda-

tion and cognitive impairment; the development of tolerance after only a few days of use; the potential for abuse; and significant drug interactions.[81,85] Studies in elderly patients have shown that they are at particular risk for cognitive impairment and altered consciousness associated with diphenhydramine use.[86,87]

Dietary supplements, such as the hormone melatonin and the herb valerian, appear to have some sedative properties, and many patients with insomnia perceive these products as being a safer or more natural alternative to drugs. However, melatonin and herbal preparations are marketed as dietary supplements, which can be sold without premarket review or approval by the FDA.[88] These preparations, therefore, are not standardized regarding active ingredients, nor are they screened for possible unapproved ingredients.

Melatonin is an endogenous hormone that plays a major role in the circadian sleep process. It promotes a behavioral state resembling quiet wakefulness, which allows for normal sleep initiation, rather than sleepiness or profound sedation.[89] The role of melatonin in the treatment of chronic insomnia is not entirely clear, but studies suggest that melatonin may be helpful in those with sleep disturbances associated with reduced endogenous melatonin and circadian disorders.[89-92]

Valerian is used in many cultures for its purported calming and relaxing effects that help initiate sleep and decrease anxiety in those with insomnia.[93] The mechanisms of valerian's effects on sleep are unclear, but GABAergic activity has been suggested. A systematic review of randomized clinical trials evaluating valerian for insomnia found great inconsistency in terms of study design, and the quality of these studies from a methodological viewpoint is questionable. Overall, the meta-analysis showed contradictory and inconclusive results of valerian with respect to sleep improvement, indicating a need for rigorous trials to determine its efficacy.[94] Clinical trials have not evaluated tolerance, dependence, or withdrawal and rebound symptoms on discontinuation. Because dietary supplements are not required to be standardized in the United States, the nature of valerian preparations and their constituents may differ, depending on when and where the plant was harvested.[95]

Comparison of Nonpharmacologic and Pharmacologic Interventions

Few studies have directly compared the separate and combined effects of behavioral and pharmacologic therapies for the treatment of insomnia. One meta-analysis compared the short-term efficacy of benzodiazepines and nonbenzodiazepines (zolpidem tartrate and zaleplon) versus behavioral interventions (primarily stimulus control with or without sleep restriction) in the short-term treatment of primary insomnia.[17] Both interventions demonstrated similar improvements in SL, number of awakenings per night, WASO, total sleep time, and sleep quality. The authors of the meta-analysis concluded that, overall, behavioral therapy for persistent primary insomnia was as effective in the short term (2-4 weeks) as pharmacotherapy.[17] The authors also stated that pharmacotherapy may be a choice when symptom reduction is an immediate requirement, with behavioral treatment indicated in cases where drugs are contraindicated. When costs were considered, sedative hypnotics were more cost-effective over a 5-week period, but the authors indicated that it was possible that long-term use of behavioral treatment might reduce indirect costs, thus offsetting the short-term cost benefit.[17]

A randomized, placebo-controlled trial involving adults with chronic sleep-onset insomnia compared the clinical efficacy of cognitive behavioral therapy (CBT) and pharmacologic (zolpidem tartrate) therapy, alone and in combination.[3] The behavioral components of the CBT included a combination of sleep restriction, stimulus control, and relaxation training. The primary sleep outcome measured was SL; secondary sleep outcomes measured were sleep efficiency, total sleep time, and measures of daytime functioning. CBT alone produced the greatest improvements in SL and sleep efficiency, and the combined pharmacotherapy-CBT treatment provided no advantage over CBT alone. The positive effects of CBT alone and in combination with pharmacotherapy on SL and sleep efficiency were maintained at long-term follow-up (up to 12 months).

In a placebo-controlled study in elderly patients with sleep-maintenance insomnia, the efficacy of CBT and pharmacotherapy (temazepam), alone or in combination, was evaluated using sleep efficiency measurements.[20] All 3 active-treatment groups were more effective than placebo in improving sleep efficiency during the treatment period. Follow-up data obtained at 12 and 24 months after treatment discontinuation showed that only the CBT group maintained a sleep efficiency of ≥85%. Both the pharmacotherapy-alone group and the combined-intervention group reported a significant loss of therapeutic benefit at follow-up after discontinuation.

Findings from other studies suggest that although pharmacotherapy may produce a more rapid improvement in sleep disturbances compared with CBT interventions, use of nonpharmacologic therapies may improve insomnia in as many as 70% to 80% of cases; however, treatment response can be highly variable.[2] Therapeutic gains are often seen after 4 to 8 weeks of therapy for pharmacotherapy alone, after CBT interventions alone, or after a combination of pharmacotherapy and CBT.[2,3,17,20] However, these findings should be evaluated in view of more recent data on the long-term use of pharmacotherapy.[31] Furthermore, the long-term clinical effects of CBT appear to be maintained after treatment discontinuation, although these results warrant further investigation. Despite the important findings of studies comparing pharmacotherapy and CBT, CBT remains underused in clinical practice, perhaps owing to real and presumed barriers, such as practitioner time constraints, patient nonadherence, and a reluctance to reimburse or underreimbursement of psychosocial interventions.[96,97] In addition, practitioners may view treatments such as CBT as being far less cost-effective than pharmacotherapy; other limitations of CBT include the fact that most family practitioners are not trained to administer it, the daily time constraints that most family practitioners face, and insurance reimbursement constraints. However, newer abbreviated forms of CBT may be more cost-effective and easier to administer.[12,98]

Treatment of Insomnia With Comorbid Conditions

Patients with depression and chronic pain syndromes may be at increased risk for the development of chronic sleep disturbances that may further increase the severity of the comorbid condition.[15,99] Few studies, however, have evaluated the treatment of insomnia in patients with comorbid medical or psychiatric illnesses. Before the start of treatment of insomnia associated with depression or chronic pain, underlying sleep disorders, such as sleep apnea and restless legs syndrome, should be ruled out. Insomnia coexisting with other conditions responds similarly to benzodiazepines and nonbenzodiazepines as does primary insomnia.[99,100] Appropriate pharmacologic and nonpharmacologic therapy targeted at the sleep disturbances themselves may also improve the comorbid condition, and vice versa. A careful evaluation of the risk-benefit ratio for any treatment modality employed should be carefully considered in patients with insomnia and comorbid conditions.

Many antidepressants have been linked to changes in sleep architecture, particularly delayed onset of REM sleep, reduced amount of REM sleep, and increased slow-wave sleep.[101] Although trazodone does not produce any of these changes, it may increase REM sleep.[15,99] Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), venlafaxine, and bupropion, are considered to be activating, and benzodiazepine receptor agonists or sedating antidepressants (eg, trazodone) are often coprescribed.[99] As previously discussed, studies have documented improvements in clinical parameters of depression and its accompanying sleep disturbance with trazodone monotherapy.[76] In addition to trazodone, doxepin, amitriptyline, nefazodone, and mirtazapine have been used for their sedative effects associated with histamine or serotonin postsynaptic receptor blockade.[99]

The effects of zolpidem tartrate nightly for 4 weeks were evaluated in SSRI-treated patients with depression in a 6-week, double-blind, placebo-controlled study with first- and last-week single-blind placebo periods.[102] Compared with placebo, zolpidem tartrate significantly improved total sleep

time, reduced the number of awakenings, and improved self-rated sleep measures, such as sleep quality, daytime functioning, improved concentration, and overall well-being. No evidence of improved depression during the period of zolpidem tartrate–SSRI coadministration was reported. The most common adverse events during the double-blind period included headache (33.7%), dysmenorrhea (11.6%), and dyspepsia, somnolence, and back pain (9.5% each). Post-treatment adverse events reported included headache (13.3%) and dysmenorrhea and sinusitis (4% each). No tolerance developed during the 4-week double-blind period. After substitution of placebo for zolpidem, the zolpidem-treated patients reverted to pre-treatment insomnia symptoms, with significant subjective rebound sleep disturbances for 1 night.

Chronic pain appears to worsen sleep difficulties, and, in turn, sleep difficulties worsen the perception of the severity of pain.[15,100] Triazolam was evaluated in the treatment of patients with insomnia and comorbid rheumatoid arthritis.[103] This double-blind, placebo-controlled, crossover study found that nighttime triazolam doses (titrated from 0.125 to 0.5 mg) significantly improved SL and total sleep time, and decreased the number of awakenings. Furthermore, daytime alertness and duration of morning stiffness improved during treatment with triazolam.[103] Similarly, zolpidem has been found to improve sleep quality in patients with fibromyalgia.[104] However, large-scale studies to support these findings are lacking.

In patients with rheumatoid arthritis and coexisting insomnia, a double-blind, placebo-controlled study showed that eszopiclone significantly improved all sleep efficacy measures (SL, WASO, nocturnal awakenings, total sleep time, and sleep depth).[105] Sleep quality was also significantly improved, as were daytime alertness, ability to function, and ability to concentrate. Changes in scores on the Arthritis Self-Efficacy Scale were clinically and statistically significant for overall score, pain, and pain plus other symptoms. Patient assessment of pain severity, assessed using a Likert scale ranging from 0 to 10, was significantly reduced in the eszopiclone group.

In patients experiencing chronic pain, sedative antidepressants may be useful in alleviating the coexisting depression, anxiety, and/or insomnia.[100] Amitriptyline has been well studied in pain syndromes; trazodone, nefazodone, and mirtazapine can also be used.[100]

Before the use of sedative hypnotic agents or antidepressants, nonpharmacologic strategies should be considered. Nonpharmacologic methods that have been found to be useful in patients with rheumatoid arthritis, fibromyalgia, and chronic fatigue syndrome include CBT, SH, and exercise.[15,100]

Summary

As the primary disorder or a comorbidity associated with other disorders, insomnia is a common yet complex problem that can result in serious consequences.[6-9] Despite its high prevalence, insomnia is often misunderstood by both physicians and patients and, as a result, is not well managed.[10] The management and treatment of insomnia should be multifactorial and include both nonpharmacologic and pharmacologic interventions.[3,4,17] Nonpharmacologic strategies should focus on the various psychological, environmental, behavioral, and lifestyle factors that precipitate and perpetuate sleep disturbances.[17-19] Studies indicate that nonpharmacologic interventions, alone or in combination with pharmacotherapy, can be effective for insomnia.[17]

The most common approach to the treatment of insomnia is pharmacologic intervention; pharmacologic options include benzodiazepines, nonbenzodiazepine sedative-hypnotic agents, melatonin and melatonin receptor agonists, sedating antidepressants, sedating antihistamines, and herbal products.[4,18,96] No single pharmacologic agent currently available meets criteria for the ideal hypnotic.[21] Therefore, the choice of pharmacologic agent should be based on the type and duration of the sleep disturbance and the patient's current medical conditions, age, and concomitant drug therapy.[4,18,96] Furthermore, the pharmacokinetic and the adverse event profiles of the hypnotic agent should be considered. Treating insomnia in the presence of comorbid conditions, such as depressive disorders

and chronic pain syndromes, may also improve the symptoms of the comorbid condition.[99,100,103,104]

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