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#### Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Explain the roles of homeostatic sleep control and the circadian pacemaker in controlling the sleep-wake cycle
- Identify risk factors for insomnia and determine the appropriate screening for and diagnosis of insomnia
- Describe the correlation between insomnia and psychiatric disorders, especially depression
- Evaluate current and emerging treatment therapies for acute and chronic insomnia on the basis of efficacy and safety

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#### Target Audience

This newsletter has been designed to meet the educational needs of primary care physicians who are interested in learning about the diagnosis and management of insomnia.

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No real or apparent conflicts to report

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# THE JOURNAL OF FAMILY PRACTICE

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## Understanding insomnia: Diagnosis and management of a common sleep disorder

Insomnia, defined as complaints of disturbed sleep in the presence of adequate opportunity and circumstance for sleep, is the most common adult sleep pathology.<sup>1</sup> A 2004-2005 National Sleep Foundation (NSF) survey of adults aged at least 18 years found that about 21% thought they had a sleep problem, and about the same number (24%) stated that sleep problems negatively affected their daily lives.<sup>2</sup> Among individuals who experience insomnia, 42% reported sleep problems nearly every night and 88% had difficulty sleeping for more than a year.<sup>3</sup> Despite affecting millions of people in the United States, insomnia is underrecognized and many patients do not receive adequate treatment.<sup>1,4</sup> This lack of effective management can result in serious consequences for affected individuals.

The loss of even small amounts of sleep on a daily basis leads to progressive impairment of cognitive performance.<sup>5</sup> Chronic restriction of sleep to 6 hours or less per night for 14 days (short-term partial sleep deprivation) was found to produce cognitive performance deficits equivalent to as much as 2 nights of total sleep deprivation.<sup>6</sup> Thus, even relatively moderate sleep restriction can seriously impair waking neurobehavioral functions in healthy adults, resulting in fatigue, mood changes such as depression and irritability, difficulty with concentration, and impaired daytime functioning.<sup>3,7,8</sup> These symptoms diminish the quality of daily activities, resulting in a reduced ability to accomplish tasks; nodding off and poor concentration; decreased quality of work and increased work absences; relationship problems;

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## Overview of sleep physiology

Understanding the neuronal interactions involved in the sleep-wake cycle can help in explaining the effects of various drug classes on sleep and wakefulness.<sup>1</sup> Sleep in humans is divided into 2 distinct states, identified as rapid eye movement (REM) and non-rapid eye movement (NREM) sleep.<sup>2</sup> NREM sleep is characterized by the slow oscillation of thalamocortical neurons, partly detected as cortical slow waves. Based on characteristic EEG signals, NREM sleep is divided into 4 stages (S1, S2, S3, and S4). The slow-frequency (<4 Hz) S3/S4 cortical waves, known as slow-wave sleep (SWS), provide an indication of sleep depth.<sup>2</sup>

Physiologic control of the sleep-wake cycle is generally believed to involve 2 components: a homeostatic system that seeks to recover a set point when disturbed (eg, sleep deprivation is followed by extra recovery sleep to make up for the sleep deficit), and a circadian pacemaker that is essentially independent of sleep and waking.<sup>1-3</sup> In one model of homeostatic regulation, a sleep-inducing substance that accumulates during waking could enhance the activity of sleep-promoting neurons while reducing the activity of wake-producing neurons.<sup>1</sup> During sleep, concentrations of the sleep-inducing substance would decrease. Adenosine has been proposed as a possible key factor in this process.<sup>1,2</sup>

The circadian pacemaker, set for an approximately 24-hour cycle, is basically independent of the sleep and waking states, and determines the times of sleep onset by changing the threshold of sleep need that will induce sleep.<sup>1-4</sup> The suprachiasmatic nucleus (SCN) serves as the brain's master clock, with some neurons firing in a 24-hour cycle.<sup>1,5</sup> Under normal circumstances, the SCN is reset on a daily basis by light during the day, and by melatonin, which is secreted from the pineal gland, during the dark cycle.<sup>1,5</sup> Therefore, both the sleep homeostat and the circadian pacemaker contribute to the control of the sleep-wake cycle.

### Neurologic pathways of sleep-wake system

Identification of the neurologic pathways involved in the sleep-wake cycle has advanced in the last decade. At present, it is hypothesized that sleep involves the interactions of mutually inhibiting sleep and arousal centers in the brain.<sup>1-3</sup> Wakefulness is promoted by an ascending arousal pathway that begins in the rostral pons and runs through the midbrain reticular formation.<sup>1</sup> Brainstem and hypothalamic neurons that produce acetylcholine, norepinephrine, dopamine, serotonin, histamine, and orexin/hypocretin may be involved.<sup>3</sup> Each of these arousal networks can increase wakefulness, but coordinated activity is required for complete alertness and cortical activation.<sup>2,3</sup> A switch in the hypothalamus shuts off this arousal system during sleep.<sup>1</sup>

Many of the neurons that help produce sleep and shut off the arousal system are located within a small cluster known as the ventrolateral preoptic area (VLPO), but other sleep-active cells also reside within adjacent regions of the preoptic area and the basal forebrain.<sup>1,3</sup> Cell-specific lesions in this region reduced both NREM and REM sleep, causing insomnia.<sup>6,7</sup>

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and less enjoyment of family and social life.<sup>3,9,10</sup> Daily skills such as driving are often impaired; 37% of licensed drivers in the NSF survey reported that they have nodded off or fallen asleep while driving a vehicle, with 13% having done so at least once a month.<sup>2</sup> About 4% have reported an accident or near-accident in the previous year because of dozing off or feeling too drowsy.<sup>2</sup>

Besides cognition, other physiologic processes are also deleteriously affected. For example, both acute total and short-term partial sleep deprivation were found to elevate high-sensitivity C-reactive

protein (CRP) concentrations.<sup>11</sup> Because high-sensitivity CRP concentrations are a stable marker for inflammation and have been found to be predictive of cardiovascular (CV) morbidity, sleep loss has been proposed to be one of the ways that inflammatory processes are activated, contributing to the association of sleep complaints and CV morbidity.<sup>11</sup>

In attempts to manage insomnia and its complications, almost one quarter of adults have reported using sleep aids, including up to 9% who have used over-the-counter (OTC) medications and 7% who have used prescription sleep aids at least a few nights

TABLE 1

## Selected drugs used for insomnia without a US FDA indication

Drug name (generic)	Drug type	Estimated dose (mg)*	Route of metabolism/clearance	Elimination half-life (h)
Trazodone	Antidepressant	50-150	Hepatic/renal, fecal, biliary	3-6
Amitriptyline	Antidepressant	25-50	Hepatic/renal	12-24
Doxepin	Antidepressant	25-150	Hepatic/renal	10-30
Diphenhydramine	Antihistamine	50-100	Hepatic: CYP450/renal, fecal	6-8
Doxylamine	Antihistamine	6.25-25	Unknown	6-12
Hydroxyzine	Antihistamine	25-50	Hepatic/renal	7-25
Olanzapine	Antipsychotic	2.5-5	Hepatic: glucuronidation, CYP1A2, 2D6/renal, fecal	21-54
Quetiapine	Antipsychotic	25-50	Hepatic: sulfoxidation, CYP3A4/renal, fecal	6-7
Melatonin	Hormone	1-10	Hepatic/renal	0.5-1
Valerian	Plant extract	400-900	Not established	Not established

FDA, Food and Drug Administration.

\*Therapeutic dose for insomnia is not established. Listed doses refer to those cited in the literature and used in clinical practice.

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a month.<sup>2,4,12</sup> More than 1 million Americans have reported taking medications for more than 1 year.<sup>2,12</sup>

Primary care physicians (PCPs) play a vital role in diagnosing insomnia, which may affect as many as 69% of their patients.<sup>2</sup> Typically, PCPs are the first clinicians to see patients who seek medical advice for insomnia that affects daily function. A lack of training in both diagnosing and managing insomnia, and misconceptions about the efficacy and risk of hypnotic medications, are barriers to optimal treatment.<sup>3</sup> As a result, fewer than 30% of adults reported that their doctors ever asked about their sleep.<sup>2</sup>

This supplement will present an update on the current understanding of sleep physiology as it relates to insomnia, and use this background to discuss effective strategies for diagnosing and treating patients whose insomnia results from difficulty with sleep onset and sleep maintenance. A comparison of insomnia medications approved by the US Food and Drug Administration (FDA) will be presented.

### ■ Insomnia: classification and causes

Insomnia is a complex disorder that can result from several types of sleep disturbances: difficulty

in falling asleep, difficulty in maintaining or staying asleep, or waking too early. Nearly 25% of people with insomnia experience more than one of these symptoms.<sup>1,3</sup> Nonrestorative or poor quality of sleep is sometimes included, but this complaint may not share a similar pathophysiologic mechanism with the other sleep disturbances.<sup>1</sup> Insomnia may last from several days to a few weeks (acute insomnia), may recur episodically and infrequently (transient insomnia), or it may last for 1 month and often much longer (chronic insomnia).<sup>13</sup> Many people seek treatment when chronic insomnia affects their ability to function properly during the day.

Approximately 10% to 15% of patients with chronic insomnia experience insomnia as a primary condition (ie, not caused by any known physical or mental condition). The remaining 85% to 90% of patients with chronic insomnia experience sleep problems in conjunction with comorbid conditions (ie, resulting from an underlying physical or mental condition).<sup>14-16</sup> Psychiatric disorders (odds ratio [OR] for severe insomnia, 8.2), hip impairment (OR, 2.7), congestive heart failure (OR, 2.5), obstructive airway disease (OR, 1.5), and back

**TABLE 2**  
**FDA-approved insomnia treatment medications**

Drug (generic)	Brand name	Half-life (h)	Available doses (mg)
<b>Benzodiazepines</b>			
Estazolam	ProSom™	8-24	1, 2
Flurazepam	Dalmane®	48-120	15, 30
Quazepam	Doral®	48-120	7.5, 15
Temazepam	Restoril®	8-20	7.5, 15, 22.5, 30
Triazolam	Halcion®	2-4	0.125, 0.25
<b>Nonbenzodiazepines</b>			
Imidazopyridine:			
Zolpidem	Ambien™	1.5-2.4	5, 10
Zolpidem extended-release	Ambien CR™	2.8-2.9	6.25, 12.5
Pyrazolopyrimidine			
Zaleplon	Sonata®	~1	5, 10
Pyrrolopyrazine			
Eszopiclone	Lunesta®	5-7	1, 2, 3
<b>Melatonin Receptor Agonist</b>			
Ramelteon	Rozerem™	1-2.6	8

CR, controlled release; FDA, Food and Drug Administration.  
*Physician's Desk Reference.* Montvale, NJ: Thomson Healthcare; 2006.

problems (OR, 1.5) all have been associated with insomnia.<sup>17</sup> Underlying sleep disorders include obstructive sleep apnea and restless legs syndrome. Other causes of insomnia include use of pharmacologic agents, circadian rhythm disorders, and periodic limb movement disorder that includes nocturnal myoclonus.<sup>16</sup> Further, neurologic conditions (Parkinson's and Alzheimer's diseases) and medical conditions (chronic pain) may contribute to insomnia.<sup>1</sup> Insomnia and comorbid conditions should be treated simultaneously to ensure optimal patient outcomes; in some cases, treatment of the comorbid condition resolves the insomnia.

Hyperarousal, circadian dysrhythmia, and homeostatic dysregulation may all contribute to insomnia.<sup>14,18</sup> Hyperarousal, which makes it difficult to initiate or maintain sleep at any time of day, may result from either an elevated basal level of arousal or as a failure to inhibit or downregulate arousal at

night.<sup>18</sup> Research has shown that increased brain glucose metabolism when awake or asleep, and increased adrenocorticotrophic hormone activity, both can contribute to hyperarousal. Circadian rhythm sleep disorders occur when there is an alteration of the internal timing mechanism, or a misalignment between sleep and the 24-hour social and physical environment, such as occurs with shift work.<sup>19</sup> Homeostatic dysregulation in primary insomnia may contribute to the perpetuation of insomnia as well as the predisposition for, and precipitation of, the disorder; there is evidence that patients with homeostatic dysregulation may have reduced levels of daytime sleepiness despite sleep loss and complaints of fatigue.<sup>18</sup>

Once initiated, insomnia may be perpetuated by cognitive and behavioral mechanisms.<sup>20,21</sup> Misconceptions about normal sleep, misattributions about the causes of sleep disturbances, and catastrophic worry about the daytime effects of inadequate sleep can all contribute to insomnia. These dysfunctional beliefs often promote behaviors that are intended to improve sleep but

are disruptive to sleep homeostasis and a consistent sleep-wake cycle (eg, taking naps and sleeping late). Sleep-disruptive behaviors are further perpetuated by behavioral conditioning, which may produce conditioned arousal to stimuli that would normally be associated with sleep.<sup>22</sup>

### Insomnia and depression

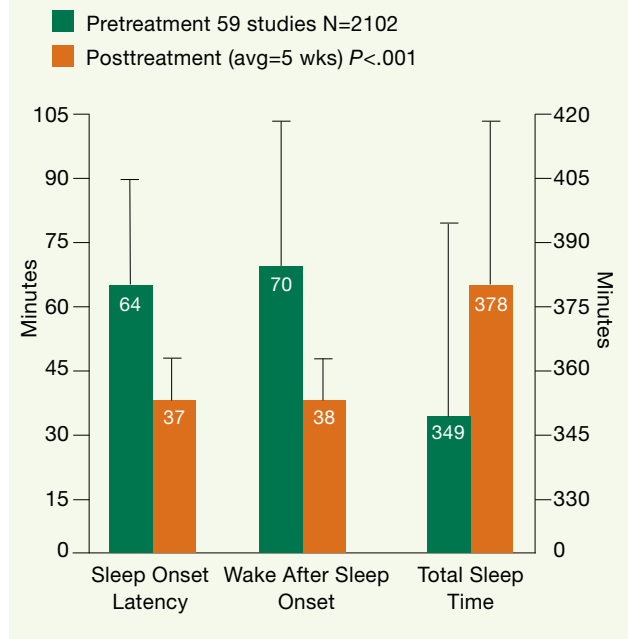
As noted above, there is an especially strong correlation between insomnia and psychiatric disorders, particularly depression. Approximately 40% to 50% of individuals with chronic insomnia meet the criteria for a formal diagnosis of a psychiatric disorder.<sup>23,24</sup> Evidence suggests that primary insomnia and major depressive disorder may have some neuroendocrine and clinical similarities.<sup>25</sup> Abnormal corticotrophin-releasing factor (CRF) activity occurs in major depression, and CRF hyperactivity appears to mediate the hyperarousal seen in primary insomnia.<sup>25</sup> Primary

insomnia may be associated with hypothalamic-pituitary-adrenal axis overactivity and excess secretion of CRF, adrenocorticotrophic-releasing hormone, and cortisol.<sup>25</sup>

Insomnia may be a symptom of depression or may precede the onset of a depressive episode.<sup>26</sup> Breslau and colleagues identified insomnia as a chief predictor of the subsequent development of major depression among young Americans.<sup>27</sup> Specifically, people who experience symptoms of insomnia nearly every day for 2 weeks may be at increased risk for major depression. Although thoughts of suicide and psychomotor changes are examples of predictors of depression, insomnia may be a more useful marker because physicians may more easily recognize and document it.<sup>28</sup>

About 90% of inpatients with depression show evidence of sleep disturbances when examined by EEG, and only about 10% to 15% report normal sleep patterns.<sup>26</sup> Sleep problems among these patients are often typified by increased sleep latency, frequent awakenings and waking too early, and disruption of the REM stage.<sup>26</sup> The S3 and S4 periods are reduced during the first NREM sleep period in these patients.<sup>26</sup> The first REM period is often prolonged, and there is a shorter REM latency and an increased number of eye movements during REM sleep.

The National Institutes of Mental Health (NIMH) Epidemiologic Catchment Area Study indicated that people with chronic insomnia and no psychiatric illness have an increased risk of developing a new psychiatric disorder over time.<sup>26,28</sup> This study, based on interviews with 7954 people, compared rates of psychiatric disorders and insomnia at baseline and 1-year follow-up. The incidence of new cases of major depression and anxiety disorders was higher for respondents with insomnia at both time points compared with respondents whose insomnia resolved at the 1-year follow-up (14% vs 0.6% for major depression; 25.6% vs 7.4% for anxiety disorders, respectively). Additionally, it was found that the incidence of new cases of any psychiatric disorder was almost 3 times as high for respondents who still had insomnia compared with those who no longer experienced insomnia (34% vs 13%, respectively).<sup>28</sup>

**FIGURE 1****Efficacy of cognitive behavioral therapy**

CBT, cognitive behavioral therapy.

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The relationship between psychiatric disorders and insomnia has contributed to off-label treatment of insomnia with an array of antidepressants and antipsychotics (**TABLE 1**).<sup>29</sup>

Whereas insomnia that occurs during a depressive episode might be ameliorated by successful management of the underlying depression, insomnia persists in nearly half of the individuals whose depression has been successfully managed.<sup>21</sup> This persistent insomnia may be either a side effect of the antidepressant medication, or may represent the symptom of a persistent, subsyndromal depression.<sup>21</sup> Therefore, it is important to monitor for persistent insomnia in the depressed patient because it may predict the recurrence of the depression at a later date.<sup>21</sup>

### ■ Risk factors and diagnosis of insomnia

A diagnosis of insomnia is based primarily on patient-derived and family or caregiver complaints

**TABLE 3**

**Indication for newer hypnotics**

Drug (generic)	Brand name	Sleep onset symptoms	Sleep maintenance	Short-term use
Zolpidem	Ambien™	Yes	—	Yes
Zaleplon	Sonata®	Yes	—	Yes
Eszopiclone	Lunesta®	Yes	Yes	—
Ramelteon	Rozerem™	Yes	—	—
Zolpidem ER	Ambien CR™	Yes	Yes	—

CR, controlled release; ER, extended release.

Physician's Desk Reference. Montvale, NJ: Thomson Healthcare; 2006.

during the clinical interview.<sup>1</sup> However, direct queries (“Do you feel that you are sleeping well at nighttime and are fully alert throughout the daytime?”) regarding a patient’s sleep history are important because more than 50% of people who think they have chronic insomnia do not inform their physician.<sup>7</sup> Insomnia may be screened as part of a routine evaluation of patients with sleep problems, and clinicians should consider certain risk factors that have been associated with insomnia.<sup>12,21</sup> Medical (heart, respiratory, and gastrointestinal diseases, as well as Parkinson’s and Alzheimer’s diseases, pain, arthritis, and obesity) and psychiatric conditions (eg, depression, anxiety, mania, and stress) may contribute to sleeplessness. Social conditions, such as unemployment or poor working conditions, may also be risk factors. Older patients have a greater prevalence of insomnia, as do post- and perimenopausal women.<sup>1,12,21</sup> Patients who are divorced, separated, or widowed are also at a greater risk of insomnia. Cigarette smoking, alcohol and coffee consumption, and some prescription drugs that disturb sleep (eg, antidepressants such as selective serotonin reuptake inhibitors) predispose patients to insomnia.<sup>1,13</sup> Sleep environment (such as temperature, lighting, noise, and partner’s sleep habits) should also be considered in assessing sleep problems.

Once it has been established that a patient has insomnia, the chief sleep symptom (eg, problems with sleep onset) should be defined and possible causes identified.<sup>15</sup> PCPs can differentiate acute from chronic insomnia by asking the patient about

the nature of the sleep problem and when the problem began. However, little research is available to indicate the accuracy of self-reported sleep problems, especially when patients judge their own sleep latency or periods of wakefulness during the night. To define more clearly the causes of insomnia, a sleep diary may be kept for 1 or 2 weeks to track accurately the time to sleep onset, number of awakenings, total sleep time (TST), quality of sleep, and the use of sleep medications.<sup>1,7,13</sup> Various questionnaires have been formulated, but there is a lack of standardization.<sup>1</sup> The presence of possible nondiagnosed comorbid syndromes also should be assessed.

The most common difficulty in diagnostic evaluation of a patient is the failure to understand that chronic insomnia has many causes.<sup>15,30</sup> Despite this complexity, however, a systematic, long-term approach to management and to working through sleep disorders can lead to successful treatment.<sup>15</sup>

**■ Treating insomnia**

After evaluation of the medical and psychiatric problems that are associated with a patient’s insomnia, the primary goals of treatment are to remove or mitigate the underlying problems, to prevent the progression of transient to chronic insomnia, and to improve the patient’s quality of life.<sup>15</sup> Due to the possibility of multifactorial insomnia, successful management often requires a care-management approach that utilizes several modes of care, combining nonpharmacologic (educational and

behavioral) approaches along with pharmacologic intervention.<sup>1,15,31</sup> Insomnia and any comorbid conditions should be treated separately and concurrently. For instance, a combination of chronobiotic interventions (such as light exposure), melatonin, hypnotic agents, caffeine and CNS stimulants, and wake-promoting agents have been studied in shift work sleep disorder (SWSD). In 3 randomized, double-blind clinical studies that have evaluated pharmacologic therapies in patients with SWSD, modafinil and armodafinil (wake-promoting agents) significantly improved the ability to sustain wakefulness during waking activities, general clinical condition, and sustained attention or memory.<sup>32</sup> Despite these findings, further research is needed to assess the safety and efficacy of treatment options for individuals afflicted by SWSD. (See discussion of ramelteon, a melatonin receptor agonist, in “Melatonin receptor agonists.”)

### Nonpharmacologic treatments

Nonpharmacologic approaches to treating insomnia essentially reset the physiologic sleep regulation system. These approaches include education about proper sleep hygiene, behavioral modification, and cognitive therapy. It has been suggested that cognitive behavioral therapy (CBT) helps to prime the sleep homeostat by increasing both its input (increased time awake prior to sleep) as well as its output (amount of slow-wave sleep [SWS]).<sup>18</sup> The efficacy of psychological and behavioral treatments for persistent insomnia was examined in a review of 37 studies (N=2246) published between 1998 and 2004.<sup>33</sup> While these therapies showed consistent improvement in several sleep categories in subjects who had either primary or secondary insomnia, more study would be useful in supporting the validity of these findings when the therapies are used by non-sleep specialists in primary care.

In beginning treatment of patients with insomnia, it is important to educate them about the principles of good sleep hygiene, even though these measures by themselves may not resolve insomnia.<sup>9,13</sup> Good sleep hygiene should include a regular sleep-wake cycle with regular exercise in

FIGURE 2a

### Effect of half-life on pharmacokinetic profile

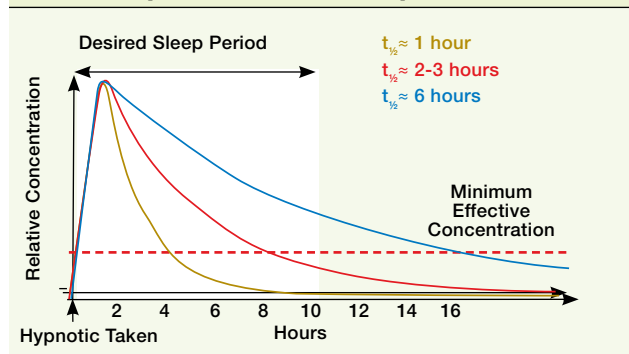
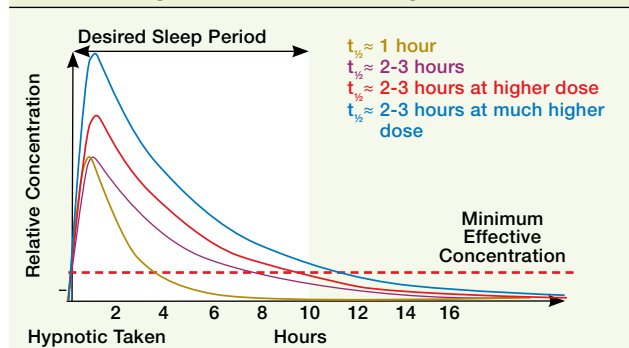


FIGURE 2b

### Effect of increased dose on pharmacokinetic profile

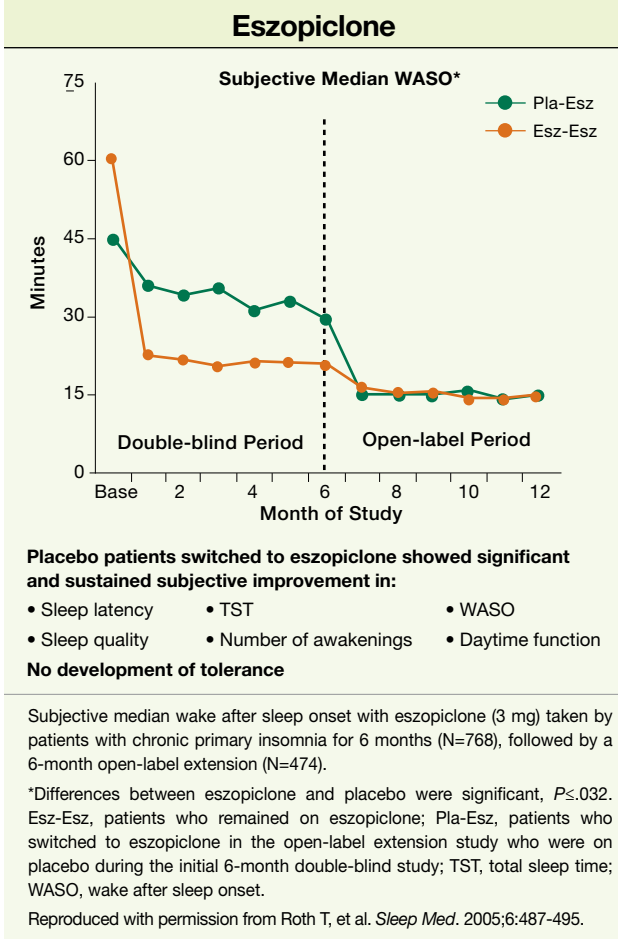


(A) Effect of half-life on pharmacokinetic profile. Longer half-lives lead to increased time of therapeutic action. (B) Effect of increased dose on pharmacokinetic profile. Higher doses lead to increased times of therapeutic action.

the morning or afternoon, but vigorous exercise within several hours of bedtime may interfere with sleep.<sup>7,15,23,34</sup> Bright light exposure should be increased during the day, but decreased at night.<sup>7,34</sup> Heavy meals should be avoided within 3 hours before sleep,<sup>7</sup> and caffeine, alcohol, and nicotine should be avoided at all times.<sup>7,34</sup> A sleep environment enhanced for relaxation and a relaxing routine before bedtime also help to improve sleeping habits.<sup>7,15,34</sup>

Behavioral strategies for treating insomnia include sleep restriction, stimulus control therapy, relaxation training, and cognitive therapy.<sup>35</sup> Sleep restriction creates a mild form of sleep deprivation by having patients limit their time in bed to short periods and gradually increasing sleeping time

**FIGURE 3**



short-term treatment of patients with insomnia, and yields short-term results comparable with prescription medicines (FIGURE 1).<sup>1,7,22,35,36</sup> In a study of 75 subjects with chronic insomnia, patients treated with CBT experienced improvement in TST and middle wake time after sleep onset (WASO) compared with patients treated with muscle relaxation or placebo.<sup>22</sup> CBT has been found to be effective either alone or in combination with pharmacologic therapy,<sup>31</sup> and for older (age 55 years and older; mean age, 69 years) as well as young and middle-aged adults.<sup>20,37</sup> CBT has been a successful technique in managing insomnia caused by sleep onset dysregulation and sleep maintenance problems.<sup>22,37</sup> Although CBT is generally used as a treatment for primary insomnia, it also has been effective in managing comorbid insomnia.<sup>20</sup> Evidence suggests that the effects of this type of therapy will last well beyond its termination.<sup>1</sup> A recent study found that CBT achieves an optimal response when it is provided for 4 weeks.<sup>38</sup> CBT is usually delivered by mental health practitioners or physicians with formal sleep medicine training.<sup>1</sup>

### Pharmacologic therapy

Pharmacologic treatment of insomnia is the use of drugs to help bring about sleep. Over the centuries, many different sleep aids have been tried, but no ideal agent exists. Pharmacologic therapy includes complementary and alternative treatments, off-label use of approved medications, and FDA-approved medications for insomnia. Efficacy has been demonstrated only for the FDA-approved insomnia treatment medications, and significant safety concerns exist with many of the medications used on an off-label basis and with selected over-the-counter and unregulated substances. With increasing knowledge of the neurophysiologic mechanisms that help induce and control sleep, more targeted therapeutic options are becoming available to help manage insomnia. With these newer approaches, the safety profiles of sleep agents also have improved.

### Complementary and alternative treatments

Many people do not seek clinical help for insomnia, choosing instead to self-medicate. As such,

each day. This strategy helps to produce a more rapid sleep onset and overall better sleep quality.<sup>7</sup> Stimulus control includes 5 simple instructions: go to bed only when sleepy, use the bed or bedroom only for sleeping or sexual activity, get out of bed when you are unable to sleep, get up at the same time each day, and do not nap during the day.<sup>35</sup> The objective of relaxation therapy is to reduce autonomic and cognitive arousal.<sup>35</sup> Techniques include muscle relaxation and biofeedback to target muscle tension and other types of physical arousal. Cognitive therapy challenges and seeks to alter the patient's dysfunctional beliefs and misconceptions about sleep and insomnia, thereby helping to improve the quality of sleep.<sup>35</sup>

The combination of cognitive and behavioral methods has been found to be effective for the

use of complementary and alternative pharmaceutical approaches to treat insomnia is considerable in the United States.<sup>1</sup> In 2005, a National Institutes of Health (NIH) consensus panel examined commonly used insomnia treatments and did not endorse any of these preparations for treating insomnia.<sup>1</sup> The panel found that there were safety concerns as well as a lack of efficacy data on the effectiveness of the complementary and alternative approaches. Complicating the use of these preparations, the amount of active ingredient among herbal and dietary preparations varies because nutritional supplements are not regulated by the FDA or by any other agency.

In regard to specific treatments, the NIH panel found that a popular herbal remedy thought to promote sleep, valerian, had limited evidence establishing its effectiveness and has been associated with hepatotoxicity (TABLE 1).<sup>1</sup> Similarly, no systematic evidence was found to support the effectiveness of antihistamines as treatments for insomnia. These commonly used non-prescription agents can cause such adverse effects (AEs) as daytime sleepiness and cognitive impairment.<sup>1</sup> Melatonin, a natural hormone that may affect circadian rhythms, does not have a clearly demonstrated efficacy in treating insomnia.<sup>1</sup> Although short-term use of melatonin is considered safe, no data exist on the safety of long-term use, and it also is not regulated by the FDA.<sup>1</sup>

### Off-label use of psychiatric drugs

Although the FDA has approved several drugs for insomnia, clinicians often turn to many other drugs to manage this disorder (TABLE 1).<sup>29</sup> Regulatory, third-party payor, economic, and clinical influences all contribute to this practice.<sup>29</sup> Whereas off-label use of psychiatric medications to treat symptoms of insomnia is not recommended by the NIH,<sup>1</sup> an analysis of 2002 data found

FIGURE 4

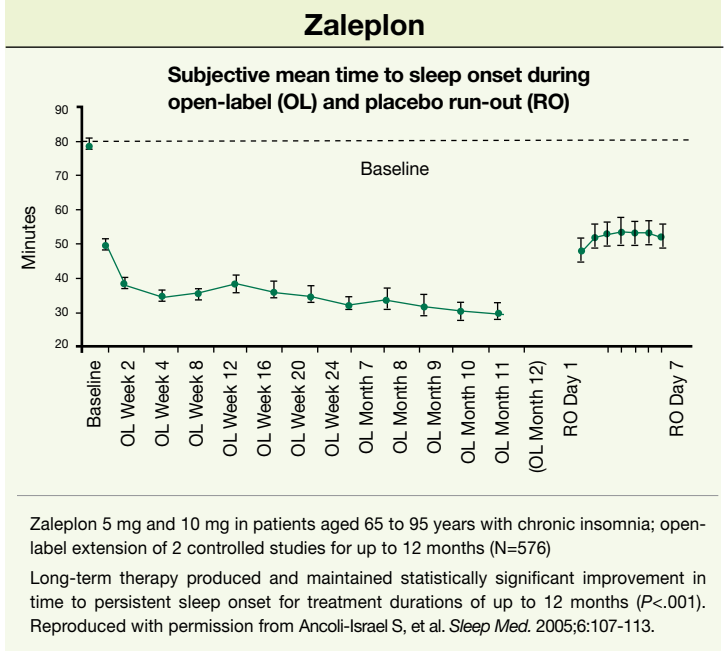
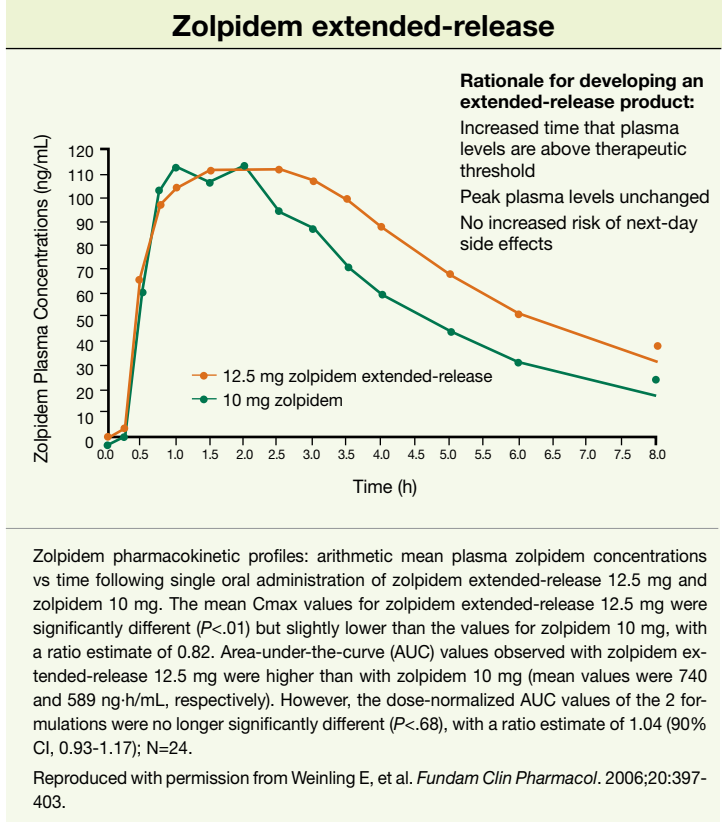
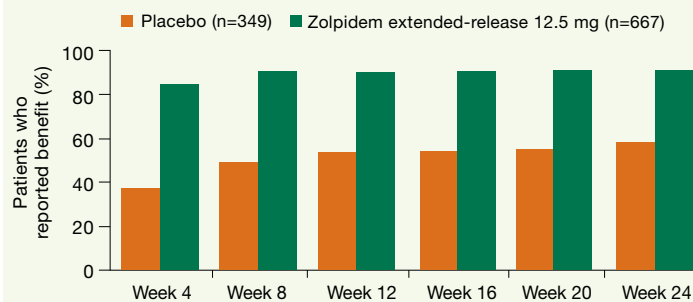


FIGURE 5



**FIGURE 6**

**Zolpidem extended-release: long-term use**

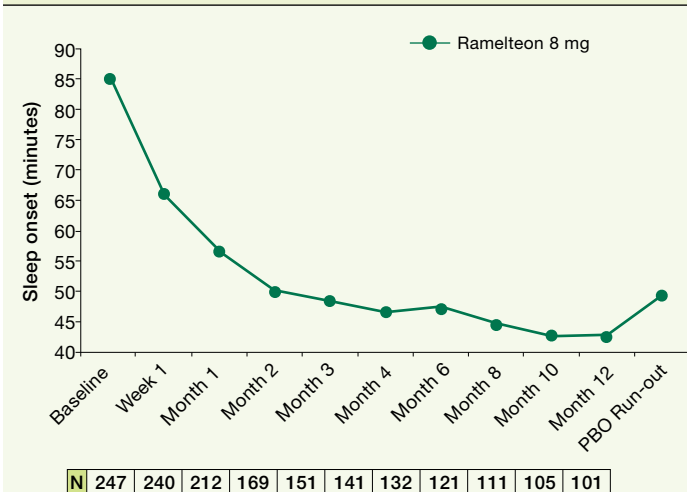


Patient global impression of treatment aid to sleep taken "as needed" 3 to 7 nights per week;  $P < .001$  for each visit.

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**FIGURE 7**

**Ramelteon**



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zolpidem (see following discussion) found that both drugs shortened subjective sleep onset latency after 1 week; however, the effect was not present in the trazodone group after 2 weeks of treatment (zolpidem continued to improve sleep onset after 2 weeks).<sup>41</sup>

Many antidepressants, such as trazodone, have been known to have sedating properties, but their neural mechanisms have not been identified. As discussed, the adrenergic, histaminergic, and cholinergic systems in the brainstem, midbrain, and basal forebrain have been implicated in the promotion and maintenance of wakefulness in the arousal systems of the brain, and antidepressant and antipsychotic medications may antagonize these systems.<sup>29</sup> Trazodone inhibits serotonin reuptake and antagonizes serotonin 2A and serotonin 2C receptors; it also blocks  $\alpha_1$ -adrenergic receptors.<sup>29</sup> Amitriptyline is a tricyclic antidepressant that inhibits the reuptake of both serotonin and norepinephrine almost equally, and also blocks histamine and acetylcholine binding.<sup>29</sup> Mirtazapine blocks presynaptic  $\alpha_2$ -adrenergic receptors, antagonizes serotonin 2A, 2C, and 3 receptors, and is a strong histamine antagonist. The atypical antipsychotics, quetiapine and olanzapine, antagonize histamine receptors and serotonin 2C, and have activity in the adrenergic, muscarinic, and dopaminergic circuits.<sup>29</sup> However, no studies have demonstrated the effectiveness

and safety of antipsychotics such as quetiapine for treatment of patients with insomnia who have no psychiatric comorbidity.

that antidepressant drugs represented 3 of the top 4 drugs prescribed for insomnia, and that only 4 of the top 16 drugs prescribed for insomnia had been approved by the FDA for treating insomnia.<sup>39</sup> Trazodone alone accounts for 22% of the insomnia prescription share in the United States,<sup>12</sup> even though a lack of efficacy data and an AE profile that includes sedation, dizziness, dry mouth, psychomotor impairment, priapism, and CV events, including orthostatic hypotension, do not support its widespread use.<sup>40</sup> A clinical trial comparing trazodone and the FDA-approved nonbenzodiazepine

and safety of antipsychotics such as quetiapine for treatment of patients with insomnia who have no psychiatric comorbidity.

**FDA-approved medications: overview**

FDA-approved medications for insomnia include the hypnotic benzodiazepine receptor agonists (BZRAs), as well as a melatonin receptor agonist, ramelteon (TABLE 2). BZRAs are believed to have a direct effect on the homeostatic regulation of sleep, whereas ramelteon helps to attenuate the evening circadian arousal signal and reset the circadian

pacemaker. The pharmacy prices for the insomnia treatment medications range from inexpensive generic formulations of earlier benzodiazepines to more costly branded products. However, the consumer costs vary considerably due to insurance plans, which place different medications in different tiers. With some pharmacy benefit plans, prior authorization is required for all sleep-related medications; in other plans, only selected products need prior authorization.

As discussed earlier, homeostatic control of the sleep-wake cycle involves separate arousal and sleep mechanisms, with the sleep neurons of the VLPO sending inhibitory GABAergic inputs to the arousal neuronal systems.<sup>42</sup> Decreased inhibition of the arousal system, resulting from GABAergic deficit, has been linked to chronic insomnia and a decrease of SWS.<sup>42</sup> The GABA<sub>A</sub> receptor incorporates a chloride ion channel and normally is composed of 2 alpha, 2 beta, and 1 gamma subunits; each of the subunits may have different subtypes.<sup>42</sup> BZRAs allosterically modulate GABA channels to facilitate the action of GABA. This shifts the GABA concentration-response curves to the left, increasing the amount of chloride current generated and decreasing neuronal excitability.<sup>42-44</sup> BZRAs include both benzodiazepines and nonbenzodiazepines.

Because the BZRAs depend on presynaptic release of GABA, they have a good relative safety profile compared with other drugs that may directly activate the GABA channel (eg, barbiturates).<sup>43</sup> Studies suggest that GABA<sub>A</sub> receptors with an alpha1 subtype are associated with sedation. Whereas both the benzodiazepines and nonbenzodiazepines bind to GABA<sub>A</sub> receptors with this subtype, the benzodiazepines also bind to other non-sleep-mediating receptor subtypes, potentially causing a wider array of non-sleep-related pharmacologic effects.<sup>13,43</sup> Nonbenzodiazepine binding is more specific. Partly due to this nonspecific binding, the benzodiazepines have been reported to alter the architecture of sleep by increasing the amount of time spent in stage 2 sleep, but decreasing the time spent in stage 3 to 4 sleep.<sup>43,44</sup> Additionally, the time spent in REM

sleep is shortened with benzodiazepines, but the number of REM cycles is increased.<sup>43</sup> Overall, benzodiazepines decrease sleep latency and increase TST, but may alter sleep patterns. The nonbenzodiazepines, on the other hand, have been found to have similar effects on sleep latency and TST, but cause little or no change in sleep architecture.<sup>43,44</sup>

Ramelteon enhances sleep onset by a different mechanism, acting as a melatonin receptor agonist and helping to reset the circadian pacemaker in the SCN.<sup>45</sup> It acts by selectively binding to the melatonin receptors MT<sub>1</sub> and MT<sub>2</sub>. Activation of the MT<sub>1</sub> receptor is believed to regulate sleepiness and facilitate sleep onset, while the MT<sub>2</sub> receptor may mediate phase-shifting effects of melatonin on the circadian rhythm.<sup>44,45</sup> Ramelteon facilitates sleep onset, but it does not affect sleep maintenance.

### Pharmacokinetics of FDA-approved insomnia medications

BZRAs and melatonin receptor agonists are among the most studied compounds for the treatment of insomnia. These compounds differ in their sites and durations of action as well as their half-lives, allowing clinicians to match therapeutic options with the specific sleep needs of individual patients.<sup>46</sup> An ideal compound for promoting sleep would be an agent that has an immediate onset of action, a sustained effect for the desired amount of sleep time, and a rapid offset after the time has elapsed.<sup>46</sup> The onset of action is determined by a number of factors, including how quickly the drug can be absorbed into the system and how quickly it can reach its target. How long the drug has a therapeutic effect is determined by how long it maintains a minimal effective therapeutic concentration at its site of action. This factor is determined in part by its half-life. Drugs with longer half-lives are generally expected to have a longer duration of action than drugs with shorter half-lives, dependent on the minimal effective therapeutic concentration (**FIGURE 2A**).<sup>46</sup> Dose also has an effect on the duration of action (**FIGURE 2B**).<sup>46</sup> At higher doses, the medication will have a longer duration of action, but the peak concentration

level also increases, escalating the risk of side effects.<sup>46</sup> Most of the FDA-approved insomnia treatment medications have sufficiently short half-lives so that accumulation will not occur. Several of the benzodiazepines have long half-lives that can lead to steady-state daytime levels.

Based primarily on safety considerations, prescription of hypnotic drugs has shifted away from compounds with long half-lives toward shorter half-life compounds, because faster elimination results in fewer residual effects upon waking.<sup>47</sup> As a group, the benzodiazepines were the first approved insomnia medications, and include estazolam, flurazepam, quazepam, temazepam, and triazolam (TABLE 2). Of these, only triazolam has a relatively short half-life (2 to 4 hours); the others have half-lives of at least 8 to 20 hours, with some as long as 120 hours. The approved nonbenzodiazepines (eszopiclone, zaleplon, zolpidem, and zolpidem extended-release) all have shorter half-lives; zolpidem and zaleplon have half-lives of 1 to 3 hours, whereas eszopiclone has a half-life of 5 to 7 hours. A newer, extended-release formula of zolpidem has shown a more sustained effect compared with the immediate-release formulation, providing both a rapid onset of action as well as maintained sedative effects over 3 to 6 hours postdose, without increasing residual effects.<sup>47</sup> The greater specificity of binding of the nonbenzodiazepines combined with their shorter half-lives leads to a much lower frequency and severity of AEs compared with the older benzodiazepines.<sup>1</sup>

All of the nonbenzodiazepines have a rapid onset of action and are approved for managing symptoms related to sleep onset.<sup>47-49</sup> Eszopiclone, due to its relatively longer half-life compared with the other nonbenzodiazepines, also has been indicated for treating symptoms related to sleep maintenance.<sup>50</sup> Zolpidem extended-release formulation has also been indicated for symptoms of poor sleep maintenance as well as sleep onset. Ramelteon, the melatonin receptor agonist, has been approved for sleep-onset symptoms of insomnia.<sup>44,51</sup> Because there is no risk of addiction, dependence, or withdrawal symptoms, ramelteon is the first nonscheduled hypnotic.

Whereas randomized clinical trials have indicated that all of the FDA-approved insomnia treatments are effective for the short-term management of insomnia (weeks), only the nonbenzodiazepines eszopiclone, zaleplon, and zolpidem extended-release, along with ramelteon, have been examined for long-term (6-12 months) use.<sup>1,50,52,53</sup> In the short term, abuse of these drugs has not been a significant problem, and newer data give no evidence of tolerance or dependency on the medication.<sup>1,49,51,53</sup> A summary of the approved indications for the newer hypnotics is shown in TABLE 3.

### **Benzodiazepines**

As discussed, benzodiazepines are nonselective and bind to both the benzodiazepine receptor involved in sleep as well as other non-sleep-mediating receptor subtypes. In addition, many of these agents have active metabolites and long half-lives (extending for days) that can lead to excessive daytime sedation. In older patients, additional sedation is associated with increased risk for falls and injuries.<sup>54</sup>

Whereas benzodiazepines decrease sleep latency and increase duration of sleep, their nonselective mechanisms of action and their pharmacokinetic properties contribute to the AE profile. Side effects include daytime sedation, cognitive impairment, lack of motor coordination, dependence and abuse, tolerance, and rebound insomnia after withdrawal.<sup>1,55,56</sup>

### **Nonbenzodiazepines**

The emergence of shorter half-life hypnotic drugs, such as zolpidem and zaleplon, and short-to-moderate half-life hypnotic drugs, such as eszopiclone, are important developments in attaining the goal of an ideal hypnotic.<sup>47</sup> In addition to rapid absorption, the drugs offer a fast onset of action, a proven efficacy for sleep onset latency, and rapid elimination that reduces the likelihood of residual effects.<sup>47</sup> Eszopiclone and zolpidem extended-release are approved for longer periods than the earlier BZRAs, which are approved for short-term use. To date, all of the nonbenzodiazepine hypnotics are well tolerated, with no clinical

evidence to suggest significant differences in AEs. Headache at varying rates is a side effect common to all the hypnotics. Other AEs include dry mouth and unpleasant taste with eszopiclone; fatigue and nausea with zaleplon; drowsiness and dizziness with zolpidem; and dizziness with zolpidem extended-release.<sup>13,43,45,49,57</sup>

A review of clinical trials for the nonbenzodiazepine hypnotics demonstrates their efficacy in treating insomnia.<sup>16</sup> A summary of recent clinical trials, with a focus on studies of longer duration, is discussed in the next sections.

### Eszopiclone

Eszopiclone has been approved for long-term use in chronic insomnia, and for treating both sleep onset and sleep maintenance insomnia symptoms. In a 12-month study, adults (aged 21 to 64 years; mean age, 45 years) with chronic primary insomnia who reported sleep duration of less than 6.5 hours/night or sleep latency of more than 30 minutes/night were initially randomized to a 6-month double-blind, placebo-controlled phase, and then the subjects of both groups continued in a 6-month open-label eszopiclone extension (N=111).<sup>50</sup> Both groups—subjects who switched from placebo to eszopiclone 3 mg and individuals who remained on eszopiclone—showed significant and sustained improvement in WASO (FIGURE 3) and other parameters, including sleep latency, number of awakenings, TST, sleep quality, and daytime function.<sup>50</sup> Patients did not develop tolerance.

### Zaleplon

Zaleplon is indicated for the short-term treatment of insomnia to decrease the time to sleep onset. An examination of the results of a 1-year, open-label extension phase of 2 randomized, double-blind trials in patients aged 59 to 95 years in the United States and in Europe indicated that zaleplon was safe and well tolerated in treating insomnia in older patients (FIGURE 4).<sup>58</sup> Patients took zaleplon 5 mg or 10 mg nightly for up to 12 months and were then followed for a 7-day, run-out period. Compared with their baseline, the patients had significantly improved

time to sleep onset, duration of sleep, and number of awakenings.<sup>58</sup> They did not experience rebound insomnia after discontinuation of zaleplon.

### Zolpidem and zolpidem extended-release

Zolpidem is indicated for the short-term treatment of insomnia to decrease the time to sleep onset; zolpidem extended-release is indicated for insomnia characterized by difficulties with sleep onset and/or sleep maintenance, and it may be used on a long-term basis. The biphasic release of zolpidem extended-release provides an immediate release followed by a prolonged release of zolpidem tartrate (FIGURE 5).<sup>59</sup> The extended period of elevated plasma levels, corresponding to the middle of the night, was proposed to improve sleep maintenance without residual effects in patients with insomnia.<sup>59</sup> Pharmacodynamic studies have found that, compared with original zolpidem, zolpidem extended-release improved measures of sleep maintenance (eg, number of awakenings and return to sleep after awakening) in healthy volunteers attempting to sleep in a loud-noise environment that is not conducive to good sleep.<sup>60</sup>

Longer-term studies of zolpidem have been conducted. In a placebo-controlled, double-blind, 12-week study, zolpidem was taken as needed (3 to 5 days per week). The study demonstrated a significant improvement in sleep latency without development of tolerance (increase in pills per week) or evidence of rebound insomnia.<sup>61</sup> Of 199 patients randomly assigned to treatment, 98 received zolpidem. Of that group of 98 patients, 7 discontinued treatment within the first 4 weeks. None of the AEs, which included excessive sleepiness, headache, and drowsiness, was rated as severe.<sup>61</sup>

Zolpidem extended-release used on an as-needed basis has also been studied in a long-term, 24-week, double-blind trial. Adults with chronic primary insomnia took placebo or zolpidem extended-release 12.5 mg 3 to 7 nights per week for 24 weeks.<sup>62</sup> Efficacy was assessed by daily morning questionnaires and Patient Global Impression (PGI) and Clinical Global Impression (CGI) scales every fourth week. Using the PGI, 89.8% and 92.3% of the zolpidem

extended-release group reported the treatment helped them sleep vs 51.4% and 59.7% of placebo patients, respectively, at weeks 12 and 24 (FIGURE 6). The percentage of patients who reported much or very much improved sleep according to CGI was significantly greater at each 4-week treatment interval ( $P<.0001$ , all time points) compared with placebo. For baseline-adjusted analysis at 6 months, zolpidem extended-release significantly improved TST, sleep onset latency, WASO, and number of awakenings compared with placebo. There was no observed tolerance or rebound insomnia on discontinuation. The results support the safety and efficacy of long-term use of zolpidem extended-release for managing long-term insomnia.<sup>62</sup>

### Melatonin receptor agonists

Ramelteon was approved in 2005 for the treatment of sleep onset symptoms of insomnia. Studies of up to 5 weeks' duration have given evidence of the efficacy of ramelteon. For example, in a 5-week study of adults aged 18 to 64 years with chronic insomnia, ramelteon 8 mg significantly reduced sleep latency at weeks 1, 3, and 5 compared with placebo, as measured by polysomnography.<sup>51</sup> Objective TST and sleep efficiency also were significantly improved at week 1 ( $P<.001$ ), but this difference was not maintained at a statistically significant level throughout the 5 weeks. Ramelteon 8 mg was not associated with clinically relevant residual effects.<sup>51</sup> Patients aged 65 years and older with chronic insomnia also experienced significant improvement in sleep latency measured by polysomnography ( $P=.005$ ) but did not report significant differences in subjectively measured sleep latency or TST.<sup>51</sup>

A meta-analysis of 12 randomized controlled clinical trials that examined the efficacy or tolerability of ramelteon found that the mean decrease in latency to persistent sleep ranged from 10 to 19 minutes, and the mean increase in TST was 8 to 22 minutes.<sup>44</sup> The most common AEs observed with ramelteon included headache, dizziness, somnolence, fatigue, and nausea.<sup>44</sup>

More recently, preliminary data obtained during a long-term, 12-month study of ramelteon indicated that the drug remained well tolerated with sustained improvement throughout the trial, and during a placebo washout period (FIGURE 7).<sup>53</sup> Ramelteon has not been associated with withdrawal syndrome or rebound insomnia. Because it lacks the potential for abuse or dependence, ramelteon is not a scheduled controlled substance.<sup>51</sup>

### Summary

Insomnia is a common clinical problem that is chronic for many individuals. It can arise as an independent disorder, or may be linked with comorbid conditions. Left untreated, insomnia can affect the health, safety, and quality of life of patients. Accurate diagnosis of insomnia is critical for effective, individualized treatment strategies. With a thorough assessment of patients' sleep practices and disorders, physicians can distinguish between transient and chronic insomnia, primary and comorbid insomnia related to psychiatric or other illnesses, and insomnia and suspected sleep apnea. Sleep hygiene education should be provided to all patients with sleep disturbances; CBT may benefit some patients. Whereas many treatments have been proposed for insomnia, evidence supports only the efficacy of CBT, benzodiazepine receptor agonists, and a melatonin receptor agonist in treating this disorder. The FDA has approved eszopiclone, zolpidem extended-release, and ramelteon without limiting the duration of treatment, thereby broadening the scope of insomnia management. The nonbenzodiazepine hypnotics have robust efficacy and a low risk of daytime somnolence, development of tolerance, dependence, withdrawal symptoms, and/or rebound insomnia. Clinical trials suggest that use of nonbenzodiazepine hypnotics has not contributed to abuse. Finally, ongoing evaluation and follow-up to assess the effectiveness of therapy will optimize patient outcomes. ■

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**POSTTEST**

Credit will be awarded upon successful completion of assessment questions (70% or better) and completion of program evaluation.

RELEASE DATE: *October 1, 2007* EXPIRATION DATE: *September 30, 2008*

Please circle correct answer for each question

**1. Chronic restriction of sleep to 6 hours or less per night for 2 weeks was found to produce cognitive performance deficits equivalent to:**

- a. 1 night of total sleep deprivation    c. 3 hours of sleep deprivation  
b. 2 nights of total sleep deprivation    d. No sleep deprivation; subjects physiologically adjusted to less sleep

**2. Physiologic control of the sleep-wake cycle is generally believed to involve:**

- a. A homeostatic system                      d. All of the above  
b. Pituitary control of wakefulness        e. Both a and c  
c. A circadian pacemaker

**3. Many of the neurons that help produce sleep and shut off the arousal system are located within:**

- a. The ventrolateral preoptic area        c. The cortex  
b. A pathway that begins in the rostral pons and runs through the midbrain reticular formation    d. The suprachiasmatic nucleus

**4. Inhibitory neurotransmitters involved in inhibiting the arousal system include:**

- a. Acetylcholine                                d. Norepinephrine  
b. GABA    e. Both c and d  
c. Serotonin

**5. People may be at risk for major depression if they experience symptoms of insomnia:**

- a. For at least 2 days                          c. For at least 2 months  
b. For at least 2 weeks                        d. There is no connection between insomnia and depression

**6. Which of the following treatments have been found efficacious in treating insomnia?**

- a. Valerian                                        c. Cognitive behavioral therapy  
b. Antihistamines                              d. Melatonin

**7. FDA-approved pharmacologic treatments for insomnia include:**

- a. Benzodiazepine receptor agonists      c. A melatonin receptor agonist  
b. Nonbenzodiazepine receptor agonists    d. All of the above

**8. Compared with benzodiazepines, nonbenzodiazepine receptor agonists:**

- a. Have shorter half-lives                      c. Have fewer side effects  
b. Bind more specifically to GABA-receptor complexes involved in sleep    d. All of the above

**9. Among the newer hypnotics, which of the following have no restriction for short-term use, and have also been approved for treating sleep onset and sleep maintenance?**

- a. Zaleplon                                        d. Zolpidem extended-release  
b. Eszopiclone                                    e. Both b and d  
c. Ramelteon

**10. The first nonscheduled hypnotic is:**

- a. Ramelteon                                      d. Eszopiclone  
b. Flurazepam                                    e. There are none  
c. Zolpidem

**Understanding insomnia**

**PROGRAM EVALUATION**

*Please complete the evaluation*

**Have objectives for the activity been met?**

Explain the roles of homeostatic sleep control and the circadian pacemaker in controlling the sleep-wake cycle

Yes  No

Identify risk factors for insomnia and determine the appropriate screening for and diagnosis of insomnia

Yes  No

Describe the correlation between insomnia and psychiatric disorders, especially depression

Yes  No

Evaluate current and emerging treatment therapies for acute and chronic insomnia on the basis of efficacy and safety

Yes  No

**Was this publication fair, balanced, and free of commercial bias?**

Yes  No

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