Insomnia

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OVERVIEW

Insomnia is defined as a complaint of disturbed, inadequate or poor-quality sleep that interferes with daytime functioning. Individuals with insomnia may have difficulty falling or staying asleep, or feel unrefreshed from sleep despite having adequate opportunity to sleep. Up to half of all adults complain of occasional trouble sleeping in any given year. About 10-25% have chronic symptoms with serious daytime consequences, including fatigue, difficulty concentrating, irritability, and memory impairment. Insomnia is more common among women, the elderly, and patients with medical or psychiatric conditions. People with chronic insomnia have lower motivation and productivity, are more likely to have depression or anxiety, and are at greater risk for injury (falls, traffic accidents) and substance abuse than people without insomnia. Early recognition and treatment of insomnia can reduce its physical and emotional toll, as well as healthcare costs related to its complications.

Management of insomnia varies widely and depends on the cause, duration and frequency of symptoms. Recognizing and mitigating any underlying cause is an essential first step in successful treatment. Nondrug therapies include sleep hygiene measures (correcting poor sleep habits) and cognitive-behavioral therapy, which combines correcting negative beliefs and attitudes about sleep with behavioral changes that improve sleep. If necessary, medications are added. Drugs used for insomnia include over-the-counter antihistamines, benzodiazepines, selective benzodiazepine receptor agonists, sedating antidepressants, and the melatonin receptor agonist ramelteon.

The Bottom Line

- Nondrug therapy is the preferred treatment for chronic insomnia. Sleep medications are often used in addition to nondrug therapies and in patients who do not respond to these methods.
- Sleep medication should be selected based on the underlying sleep problem (e.g., difficulty falling asleep vs. staying asleep) and any underlying medical causes of insomnia.
- Medications with a fast onset and short duration are the best choices for difficulty falling asleep (sleep onset insomnia). Appropriate drugs may include zaleplon, zolpidem immediate-release, triazolam and ramelteon. Rebound insomnia can be a problem, however, with short acting benzodiazepines like triazolam.
- Individuals who have difficulty staying asleep (sleep maintenance insomnia) are most appropriately treated with drugs that have an intermediate duration and no active metabolites (to minimize daytime effects). Zolpidem extended-release, eszopiclone, temazepam, oxazepam, lorazepam and estazolam may be appropriate choices. Zaleplon can be taken after awakening in the night.
- Sedative-hypnotics should be used intermittently, in the lowest effective doses, for a short duration, with gradual discontinuation to avoid rebound insomnia, dependence, and withdrawal symptoms.

Benzodiazepines are effective and safer than older hypnotics (e.g., barbiturates, chloral hydrate) but have several disadvantages including residual daytime sedation, tolerance, dependence and withdrawal symptoms, rebound insomnia and abuse potential. The newer benzodiazepine receptor agonists (zolpidem, zaleplon, eszopiclone) are generally the preferred agents for uncomplicated insomnia, since they have a

Continuing Education Objectives
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- Describe the difference between sleep onset and sleep maintenance insomnia, and primary and secondary insomnia.
- List the drugs commonly used for the treatment of insomnia. Describe the efficacy and most concerning adverse effects of each drug class.
- Describe nondrug therapies for the treatment of insomnia.
- Given a patient’s symptoms, recommend a medication for insomnia.
lower risk of dependence, withdrawal symptoms and abuse. The newer agents are comparable to benzodiazepines in the treatment of sleep onset insomnia (difficulty falling asleep). Few comparative studies in sleep maintenance insomnia (wakefulness after sleep onset) have been published. The newer drugs are more expensive than benzodiazepines. Ramelteon is modestly effective for sleep onset insomnia and has no potential for dependence or abuse. Sedating antidepressants (e.g., trazodone, amitriptyline) are often prescribed off-label to avoid the potential for dependence, withdrawal and abuse with benzodiazepine agonists, however, their value has been demonstrated mainly in patients with depression.

**Background**

Insomnia may be transient (lasting < 1 week), short term (lasting 1-4 weeks) or chronic (lasting > 1 month). Transient and short-term insomnias are usually related to emotional or physical discomfort from stressors such as acute illness, environmental changes (noise, light, temperature), anticipation of a stressful event, or sleeping at a time inconsistent with the daily biological rhythm (e.g., jet lag or shift work).

Chronic insomnia often has multiple underlying causes and is more challenging to treat. Symptoms may wax and wane over time. **Primary** chronic insomnia arises from no identifiable environmental, medical or psychiatric cause and accounts for 12-15% of people with chronic insomnia. Secondary or comorbid insomnia develops as a consequence of an underlying medical problem (e.g., pain, immobility, difficulty breathing), psychiatric illness (e.g., dementia, anxiety, depression), or specific sleep disorder (e.g., restless legs syndrome, periodic limb movement disorder, sleep apnea). Medications, social drugs such as alcohol and caffeine, and drugs of abuse may also cause insomnia. (Table 1)

**Nondrug Management**

Sleep experts recommend nondrug approaches as the preferred treatment for insomnia because of their efficacy, long lasting benefits, and lack of side effects. Nondrug approaches include both behavioral and cognitive therapy. Behavioral therapies such as stimulus control, sleep restriction, sleep hygiene education, and relaxation training have been in use for decades. An analysis of 48 clinical trials of behavioral therapies found that 70-80% of patients with primary chronic insomnia have improvements in sleep onset, sleep maintenance and total sleep time. The most effective behavioral strategies appear to be stimulus control and sleep restriction. Behavioral control is aimed at reassociating the bedroom with the rapid onset of sleep.

More recently, researchers have tested cognitive methods designed to correct anxiety-producing and erroneous beliefs about sleep (e.g., “I can’t sleep without medication.”). There is evidence that combined cognitive and behavioral therapy (CBT) can be as effective as prescription drugs for the treatment of chronic insomnia. In contrast to sleep medications, the benefits of CBT persist for 6 months or more after treatment is completed and no adverse effects have been identified. Potential drawbacks are the need for a trained therapist and a motivated patient, the cost of therapy, and a delayed onset of effect (several weeks) compared to sleep medication.

### Table 1. Some Drugs That May Worsen Insomnia

<table>
<thead>
<tr>
<th>Drugs That May Cause Insomnia</th>
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<tbody>
<tr>
<td>Alcohol</td>
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<tr>
<td>Antidepressants</td>
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<tr>
<td>Bupropion</td>
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<tr>
<td>Monoamine oxidase inhibitors</td>
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<td>Serotonin reuptake inhibitors</td>
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<td>Tricyclic antidepressants</td>
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<td>Venlafaxine</td>
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<td>Antihypertensives (cont.)</td>
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<td>Diuretics (at bedtime)</td>
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<td>Methyldopa</td>
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<td>Reserpine</td>
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<td>Hypnotic use (chronic)</td>
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<tr>
<td>Sympathomimetic amines</td>
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<td>Amphetamines</td>
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<tr>
<td>Appetite suppressants</td>
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<tr>
<td>Beta-adrenergic agonists</td>
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<tr>
<td>Decongestants</td>
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<tr>
<td>Phenytoine</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
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<tr>
<td>Miscellaneous</td>
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<tr>
<td>Anabolic steroids</td>
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<tr>
<td>Antineoplastics</td>
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<tr>
<td>Caffeine</td>
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<tr>
<td>Corticosteroids</td>
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<td>Histamine2-receptor antagonists</td>
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<tr>
<td>Levodopa</td>
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<tr>
<td>Methylphenidate</td>
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<td>Methysergide</td>
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<tr>
<td>Nicotine</td>
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<tr>
<td>Oral contraceptives</td>
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<tr>
<td>Phenytoin</td>
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<tr>
<td>Quinidine</td>
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<tr>
<td>Theophylline</td>
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<td>Thyroid preparations</td>
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### Table 2. Some Drugs That May Produce Withdrawal Insomnia

<table>
<thead>
<tr>
<th>Drugs That May Produce Withdrawal Insomnia</th>
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<tbody>
<tr>
<td>Alcohol</td>
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<tr>
<td>Antihistamines</td>
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<tr>
<td>Hypnotics</td>
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<tr>
<td>Barbiturates</td>
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<tr>
<td>Benzodiazepines</td>
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<tr>
<td>Chloral hydrate</td>
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<tr>
<td>Ethchlorvynol</td>
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<tr>
<td>Monoamine oxidase inhibitors</td>
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<tr>
<td>Miscellaneous</td>
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<tr>
<td>Amphetamine</td>
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<tr>
<td>Cocaine</td>
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<tr>
<td>Marijuana</td>
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<tr>
<td>Opiates</td>
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<td>Phencyclidine</td>
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Patients should also be encouraged to have proper sleep hygiene. (See inset, Patient Connection) Since nondrug treatments require behavioral change and can take several weeks to work, the risk of low compliance should be evaluated. Drug therapy may be added in the interim if necessary. Combination therapy with a sedative-hypnotic plus CBT or behavioral therapy is common, but has not been well studied.

**Prescription Sleep Medications**

**Benzodiazepine Receptor Agonists**

Benzodiazepines work by binding to GABA (gamma-aminobutyric acid) receptors in the central nervous system and enhancing its effects. Benzodiazepines have been shown to increase total sleep time by about 1 hour with short-term use (e.g., up to two weeks) for the treatment of insomnia. The evidence for improvement in sleep onset is mixed, with one large analysis of benzodiazepine trials showing improvement while two others found no significant benefit.

Five benzodiazepines (estazolam, flurazepam, temazepam, quazepam, triazolam) are FDA approved for the short-term treatment of insomnia, but all benzodiazepines have similar effects on sleep. Benzodiazepines differ in their pharmacokinetic profiles (onset, duration, elimination half-life) and can be selected for individual patients based on the type of sleep disturbance being treated and the physiologic characteristics of the patient (Table 2). Agents with a rapid onset and a relatively short duration, such as triazolam (Halcion®), are most effective for reducing the time to sleep onset, but may be more likely to cause transient rebound insomnia and withdrawal reactions after discontinuation.

Intermediate-acting agents (e.g., temazepam [Restoril®], estazolam [ProSom®]) are more effective for maintaining sleep throughout the night. The long-acting agents flurazepam (Dalmane®) and quazepam (Doral®) may be useful in patients who have both insomnia and high levels of daytime anxiety.

Residual daytime effects are a major concern with benzodiazepine use. Daytime sedation, confusion, dizziness, motor incoordination and cognitive impairment (reduced memory, reaction time and thought processing speed) are thought to be related to the increased risks of traffic accidents, work-related errors and falls seen with benzodiazepine use. These adverse daytime effects are most common with long-acting agents and uncommon with short-acting agents. Long-acting agents may accumulate with repeated administration, particularly in elderly or debilitated individuals and those with liver disease.

Older people are more susceptible to benzodiazepine side effects. The use of long-acting agents such as flurazepam has been linked with an increased risk of falls and hip fractures in the elderly. The use of sedative-hypnotics in older people with insomnia generally results in modest benefits and a relatively high risk of side effects. These include cognitive impairment, daytime fatigue and psychomotor dysfunction, which may lead to falls and traffic accidents. The benefits of sedative-hypnotics may not outweigh the risks in older adults. If benzodiazepine are used, treatment should be limited to low doses of short or intermediate-acting agents with no active metabolites, for the shortest duration possible. The risk of falls remains, however.

Anterograde (after the dose) amnesia, wandering at night and paradoxical reactions (e.g., stimulation) have been reported with benzodiazepine use. Amnesic effects appear to be related to the dose (more frequent with higher doses, such as triazolam 0.5 mg), the drug, and the route of administration. Benzodiazepines may also worsen symptoms of primary snoring and sleep apnea, and their use is contraindicated during pregnancy.

Tolerance to the hypnotic effect of benzodiazepines may develop after several weeks of therapy. It is often characterized by decreased effectiveness at the end of the night (early morning insomnia). Early morning insomnia is more common with short-acting agents such as triazolam.

Rebound insomnia, dependence and withdrawal symptoms are also concerning complications. Rebound insomnia is rare after discontinuation of long-acting agents and mild following withdrawal of intermediate-acting agents. Significant rebound insomnia lasting 1 to 3 nights may occur after triazolam withdrawal. Benzodiazepines may cause physical dependence and abrupt discontinuation may result in withdrawal symptoms ranging from anxiety to seizures. With intermediate-acting agents, withdrawal symptoms are more likely following daily use for more than one month, while short-acting agents (e.g., triazolam) can lead to withdrawal effects after as little as 1 week of use. Gradual dose reduction is recommended to minimize possible withdrawal effects. The rate of reduction depends on the benzodiazepine dose and half-life, the duration of therapy, and the type of insomnia (acute or chronic). Patients who experience withdrawal symptoms can resume taking the drug at the previous dose, then slowly reduce the dose until the drug is discontinued.

Benzodiazepines should generally be prescribed for no
more than two to four weeks. Although long term use is common, efficacy and safety remain unclear. Guidelines proposed for the long term (off-label) use of benzodiazepine and selective benzodiazepine receptor agonists (see below) for insomnia include:

- Use only for persistent insomnia that is not caused by a correctable psychiatric or medical condition and is not responsive to nondrug therapies;
- Periodic assessment of the patient for continued need for sleep medication, continued effectiveness without dose escalation, and side effects;
- Continued assessment of sleep hygiene measures and any contributing medical or psychiatric conditions.

**Selective Benzodiazepine Receptor Agonists**

Selective benzodiazepine receptor agonists include zolpidem (*Ambien®, Ambien CR™*), zaleplon (*Sonata®*) and eszopiclone (*Lunesta®*). A fourth short-acting benzodiazepine receptor agonist, indiplon, is currently under FDA review. These agents bind to the same GABA receptor complex as benzodiazepines, but are more selective for the omega-1 receptor subunit, which is thought to be involved with sedation. Because of their selectivity and relatively short half-lives, these agents have a lower risk for side effects, tolerance, dependence, and withdrawal reactions compared to benzodiazepines. (See Table 3 for a comparison of all non-benzodiazepine agents.)

**Zaleplon (Sonata®) and Zolpidem (Ambien®)**

Zaleplon is an ultra-short acting sedative-hypnotic with an onset of action of about 30 minutes and a duration of about 4 hours. Next day residual effects are unlikely due to its short half-life and duration of action, however, some patients may experience early morning awakening as the effects wear off. According to the manufacturer, zaleplon is so short-acting that it may be taken in the middle of the night without causing morning grogginess, as long as the patient has at least 4 hours to devote to sleep. In controlled clinical studies of up to 30 days duration, zaleplon reduced the time to sleep onset by about 10-20 minutes but did not decrease nighttime awakenings or increase total sleep time. 

Zolpidem is a short-acting sedative-hypnotic, with a similar onset and longer duration of action (6-8 hours) than zaleplon. In controlled clinical trials, zolpidem has been shown to reduce the time to sleep onset and increase total sleep time for periods up to 35 days. Zolpidem 10 mg has been similar to triazolam 0.25 mg in improving sleep maintenance (i.e., decreasing nighttime awakenings and increasing total sleep time). In 2 small studies, zolpidem 10 mg was similar to triazolam 0.25 and 0.5 mg in reducing the time to sleep onset. Minimal residual daytime effects were reported in a large postmarketing survey of zolpidem. Zolpidem is also available as an extended-release preparation (*Ambien CR™*). *Ambien CR™* has a dual layer design; the first layer releases 5 mg or 10 mg immediately to initiate sleep and the second layer releases the remain-

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**Table 2. Commonly Used Benzodiazepine Sedative-Hypnotics**

<table>
<thead>
<tr>
<th>Drug (brand name)</th>
<th>Usual Dose Range</th>
<th>Elderly Dose</th>
<th>Onset</th>
<th>Half-life</th>
<th>Duration</th>
<th>Active Metabolites</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>estazolam (Prosom®)</td>
<td>1 - 2 mg</td>
<td>0.5 - 1 mg</td>
<td>60-120 min</td>
<td>10-20 hrs</td>
<td>intermediate</td>
<td>No</td>
<td>May interact with drugs that inhibit CYP3A4*</td>
</tr>
<tr>
<td>flurazepam (Dalmane®, others)</td>
<td>15 - 30 mg</td>
<td>15 mg</td>
<td>30-60 min</td>
<td>50-100 hrs</td>
<td>long</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>lorazepam § (Ativan®, others)</td>
<td>1 - 4 mg</td>
<td>0.25 - 1 mg</td>
<td>30-60 min</td>
<td>10-20 hrs</td>
<td>intermediate</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>oxazepam ** (Serax®, others)</td>
<td>15 - 30 mg</td>
<td>10 - 15 mg</td>
<td>45-60 min</td>
<td>5-20 hrs</td>
<td>short-intermediate</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>quazepam (Doral®)</td>
<td>7.5 - 15 mg</td>
<td>7.5 mg</td>
<td>30-60 min</td>
<td>20-100 hrs</td>
<td>long</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>triazolam (Halcion®, others)</td>
<td>0.125 - 0.25 mg</td>
<td>0.125 mg</td>
<td>15-30 min</td>
<td>2-5 hrs</td>
<td>short</td>
<td>No</td>
<td>May cause amnesia; may interact with drugs that inhibit CYP3A4†</td>
</tr>
<tr>
<td>temazepam (Restoril®, others)</td>
<td>15 - 30 mg</td>
<td>7.5 - 15 mg</td>
<td>60-120 min</td>
<td>10-20 hrs</td>
<td>intermediate</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

* short: about 2-4 hrs; intermediate: about 8-12 hrs; long: about 10-30 hrs (depending on metabolite)  
† 3A4 inhibitors include ketoconazole, itraconazole, clarithromycin, telithromycin, erythromycin, protease inhibitors (e.g., ritonavir, lopinavir), nefazodone, diltiazem, verapamil and grapefruit juice (especially in large quantities). Coadministration may slow benzodiazepine metabolism and increase sedation.  
º Depending on the metabolite  
§ Lorazepam is not FDA approved for insomnia.  
** Oxazepam is FDA approved for insomnia caused by anxiety.
der of the dose three hours later to help maintain sleep. Among adults younger than 65, zolpidem ER 12.5 mg daily reduced the time to sleep onset by about 10 minutes early in treatment and by about 5 minutes after two weeks of use. In addition, the number of nighttime awakenings during the first 6 hours of the night decreased from 2-3 to less than 1. Similar results were seen in elderly adults (>65 years) who took zolpidem ER 6.25 mg daily for three weeks. The advantages and disadvantages (e.g., daytime effects) of zolpidem ER relative to other sedative-hypnotics, including zolpidem immediate release, are unclear; comparative studies have not been published.

Common side effects of zolpidem and zaleplon include headache, dizziness, drowsiness and nausea. Rebound insomnia has been reported on the first night after discontinuation. Tolerance, dependence and withdrawal symptoms have also been reported, however, these effects are infrequent. Gradual tapering upon discontinuation is recommended with these agents, particularly after several weeks of use.

There have been recent reports of zolpidem causing sleepwalking activities, such as driving, eating or drinking, with no memory of the event. The side effect resolved when zolpidem was discontinued. While it is known that sedative-hypnotics can cause sleepwalking and dose-related amnesic effects, it is not known if zolpidem is particularly prone to causing these events or if certain patients are more susceptible to experiencing them when taking sedative-hypnotics in general. Either way, patients should be warned about the possibility of sleepwalking and told to report any unusual behavior while taking zolpidem or any other sedative hypnotic.

**Eszopiclone (Lunesta®)**

Eszopiclone is similar to zolpidem in onset of action but has a longer half-life and a weakly active metabolite, rendering it effective for both sleep onset and sleep maintenance insomnia. Eszopiclone and zolpidem extended-release are the only benzodiazepine receptor agonists that are not restricted to short term use for insomnia in the FDA approved labeling. Several clinical studies have shown that eszopiclone reduces the time to sleep onset and improves subjective measures of daytime functioning compared to placebo when taken for up to 6 months in doses of 2-3 mg per night by adults younger than 65 years old and 1-2 mg per night by elderly adults. Only the higher doses significantly improved sleep maintenance. Specifically, eszopiclone 3 mg per night reduced the median time to sleep onset from 60 to 30 minutes and reduced wake time after sleep.

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**Table 3. Non-Benzodiazepine Hypnotics**

<table>
<thead>
<tr>
<th>Drug (brand name)</th>
<th>Usual Dose Range</th>
<th>Elderly Dose</th>
<th>Onset</th>
<th>Half-life</th>
<th>Duration*</th>
<th>Active Metabolite</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective Benzodiazepine Receptor Agonists</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>zolpidem (Ambien®)</td>
<td>5 - 10 mg</td>
<td>5 mg</td>
<td>30 min</td>
<td>2.5 hrs</td>
<td>short</td>
<td>No</td>
<td>Occasional anterograde amnesia with high doses (&gt;10 mg/day); may interact with drugs that inhibit CYP3A4†</td>
</tr>
<tr>
<td>(Ambien CR™) 6.25-12.5 mg</td>
<td>6.25 mg</td>
<td>30 min</td>
<td>2.5 hrs</td>
<td>intermediate</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>zaleplon (Sonata®)</td>
<td>10 - 20 mg</td>
<td>5 mg</td>
<td>30 min</td>
<td>1.1 hrs</td>
<td>very short</td>
<td>No</td>
<td>May cause unpleasant taste, dry mouth; may interact with drugs that inhibit CYP 3A4†</td>
</tr>
<tr>
<td>eszopiclone (Lunesta®)</td>
<td>2 - 3 mg</td>
<td>1 - 2 mg</td>
<td>30 min</td>
<td>6 hrs</td>
<td>intermediate</td>
<td>Yes (weak)</td>
<td></td>
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<tr>
<td><strong>Other Agents</strong></td>
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<td></td>
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<tr>
<td>ramelteon (Rozerem®)</td>
<td>8 mg</td>
<td>8 mg</td>
<td>15-30 min</td>
<td>1-2.6 hrs</td>
<td>short</td>
<td>Yes</td>
<td>Do not take with high fat meal. May interact with drugs that inhibit CYP 1A2, 3A4; reduce dose if receiving a potent 3A4 inhibitor</td>
</tr>
<tr>
<td>trazodone (Desyrel®)</td>
<td>50-200 mg</td>
<td>25-60 mg</td>
<td>30-60 min</td>
<td>5-9 hrs</td>
<td>NA</td>
<td>No</td>
<td>May interact with drugs that inhibit CYP 3A4; reduce dose if receiving a potent 3A4 inhibitor</td>
</tr>
</tbody>
</table>

* very short: about 2-4 hrs; short: about 6-8 hrs; intermediate: about 8-12 hrs; long: about 10-30 hrs (depending on metabolite)
† Patients with liver dysfunction should begin treatment with a lower dose (e.g., zolpidem 5 mg, zolpidem ER 6.25 mg; zaleplon 5 mg [do not use if impairment is severe]; eszopiclone 1 mg [adjust for severe impairment only]). Liver function and hypnotic side effects should be closely monitored.
‡ 3A4 inhibitors include ketoconazole, itraconazole, clarithromycin, telithromycin, erythromycin, protease inhibitors (e.g., ritonavir, lopinavir), nefazodone, diltiazem, verapamil and grapefruit juice (especially in large quantities).
§ after fasted oral administration  † trazodone is not FDA approved for the treatment of insomnia.
onset from 60 to 20 minutes after six months of treatment.39 These benefits were sustained in some patients for up to one year in a large open label study.30 Tolerance was not observed in the studies.

Side effects included unpleasant taste, headache, and cold-like symptoms. Residual daytime effects may occur, particularly with higher doses. With nightly doses of 3 mg in younger adults and 2 mg in the elderly, next day confusion was reported by 2-3% and memory impairment by 1-1.5% of patients.26 Mild rebound insomnia was reported on the first night after eszopiclone was discontinued following 6 weeks of use. Serious withdrawal symptoms were not observed after abrupt discontinuation of eszopiclone, however, anxiety, abnormal dreams and upset stomach occurred in up to 2% of patients within 48 hours of drug discontinuation.26

Drug Interactions
The CNS depressant effects of all benzodiazepine receptor agonists are additive with those of other CNS depressants, including alcohol, anticonvulsants, antipsychotics and antidepressants. Alcohol should be avoided. If other CNS depressants are prescribed concurrently, patients should be cautioned about increased sedation.

The sedative effects of eszopiclone and some benzodiazepines (e.g., triazolam, alprazolam, estazolam) may be increased and prolonged by potent inhibitors of CYP450 3A4 (e.g., ketoconazole,itraconazole, nefazodone, clarithromycin, some protease inhibitors). Zolpidem is less likely than eszopiclone to be affected by 3A4 inhibitors and no effect on zaleplon is expected. Inducers of 3A4 such as rifampin may decrease the concentration and effects of zolpidem, eszopiclone, zaleplon and the benzodiazepines mentioned above. Cimetidine may increase zaleplon levels and a reduced zaleplon dose (5 mg) is recommended during concurrent use.

Ramelteon (Rozerem®)
Ramelteon (Rozerem®) is a selective melatonin receptor agonist effective in the treatment of sleep onset insomnia. Unlike benzodiazepines and selective benzodiazepine receptor agonists, ramelteon appears to have no potential for abuse and is not a controlled substance.

Melatonin is a neurohormone naturally excreted by the pineal gland. Endogenous melatonin is thought to regulate the circadian rhythm underlying the normal sleep-wake cycle. Its synthesis and release are stimulated by darkness and suppressed by light.

Ramelteon has been shown to be modestly effective in reducing the time to sleep onset.37 Nightly doses of ramelteon 8 mg for 5 weeks decreased the time to sleep onset by about 8-16 minutes in both younger (<65 years) and older (>65 years) adults with chronic insomnia.33,34 The effect on total sleep time was inconsistent. In general, total sleep time increased modestly in the first week of use but was not significantly improved after several weeks of treatment with an 8 mg dose.25,34 Ramelteon does not appear to decrease the number of night-time awakenings.

The most common side effects of ramelteon are drowsiness, fatigue and dizziness. Small, transient increases in measures of next day residual effects (e.g., fatigue, immediate word recall) are reported in the prescribing information.35 Decreased testosterone and increased prolactin levels have also been reported, although the clinical implications of these effects are unclear. Assessment of prolactin and testosterone levels should be considered in patients who experience unexplained amenorrhea, galactorrhea, decreased libido or problems with fertility. Neither rebound insomnia nor withdrawal effects have been observed after discontinuing use.

The recommended dose of ramelteon is 8 mg taken within 30 minutes before going to bed. Ramelteon should not be taken with or immediately after a high-fat meal to avoid delayed absorption. No dose adjustment is needed for elderly patients. Ramelteon is not recommended for use in patients with severe liver disease or in women who are pregnant or nursing. It has not been studied in patients with severe sleep apnea or severe COPD and is not recommended for use in these groups.

Ramelteon may interact with medications that inhibit or induce CYP1A2, 3A4, or 2C9. Patients who are taking fluvoxamine (Luvox®), a strong CYP1A2 inhibitor, should not take ramelteon. Other inhibitors of 1A2, 3A4 (e.g., ketoconazole) or 2C9 (e.g., fluconazole) should be used with caution, as they may increase ramelteon levels and the risk of side effects. Co-administration with rifampin, a CYP inducer, dramatically reduced ramelteon levels and may reduce its effects.

Antidepressants
Recent surveys identify trazodone as one of the most frequently prescribed drugs for the treatment of insomnia11 and the use of other sedating antidepressants is common. These agents may be selected instead of sedative-hypnotics because of concerns about dependence and abuse, however, published evidence to support antidepressant use in nondepressed insomniacs is limited. Certain sedating antidepressants (e.g., amitriptyline [Elavil®], imipramine [Tofranil®], paroxetine [Paxil®]) are used to relieve depression-associated insomnia or prevent early morning awakening caused by panic attacks. Trazodone is often prescribed for sleep in patients with depression, although evidence for its efficacy is limited.
to a few small studies. Side effects of tricylic antidepressants are concerning and include dry mouth, postural hypotension, constipation, urinary retention, and cardiac toxicity (e.g., arrhythmias). These agents are also potentially lethal in overdose. Paroxetine may cause sexual dysfunction, while trazodone may cause postural hypotension and rarely, priapism. Sleep experts recommend reserving antidepressants for patients whose sleep disturbances are caused by major depression or other mood disorders.

**Nonprescription Drugs, Herbs, and Dietary Supplements**

**Antihistamines**

Over-the-counter (OTC) sleep aids containing sedating antihistamines (diphenhydramine, doxylamine) are widely used to self-treat insomnia. The efficacy of antihistamines in insomnia has not been established, however, and side effects can be significant. Daytime sedation is common, increasing the risk of traffic accidents and falls. Cognitive impairment and anticholinergic effects (dry mouth, urinary retention, constipation, blurred vision, delirium) are also problematic, particularly for the elderly. Tolerance to the sedating effects of diphenhydramine may develop after as little as 3 days of use. Sleep experts generally do not recommend sedating antihistamines for the treatment of insomnia.

**Dietary and Herbal Supplements**

While several dietary supplements have been studied for the treatment of insomnia, none are clearly safe and effective. Valerian has been shown to have mild sleep-inducing, anxiolytic and tranquilizing effects. Valerian may reduce the time to sleep onset and improve sleep quality if taken nightly for several weeks. However, the published evidence evaluating efficacy is inconclusive. It is generally well tolerated, with occasional reports of headache, excitability, stomach upset, uneasiness, dizziness, unsteadiness and low body temperature. Melatonin is widely used to self-treat insomnia, however, a recent analysis of studies evaluating its use in secondary insomnia (i.e., due to an underlying disorder) and insomnia due to jet lag or shift work found no evidence that it is effective. While these studies support the safety of melatonin, a benefit has not been clearly established.

Other dietary supplements that may have sleep inducing effects include kava kava, passion flower, hops, chamomile, 5-hydroxytryptophan and L-tryptophan. Consumers should be advised that kava kava has been linked with rare cases of liver toxicity.

**References**

Test Questions

This copy of the issue was generated online. To submit your test answers, return to the website and follow the links to the "Take The Test button".

Questions are based on information provided in the text, tables and Patient Connection insert.

Look for this symbol in the issue to find the text related to key information.

1. Which of the following may cause secondary (comorbid) insomnia?
   a. alcohol and nicotine  c. diazepam and enalapril
   b. vitamin A and simvastatin  d. a low-fat diet

2. What is the preferred treatment for insomnia?
   a. over-the-counter sleep aids
   b. a benzodiazepine sedative-hypnotic
   c. a nonbenzodiazepine sleep medication
   d. nondrug therapies that improve sleep

3. Which of the following is a component of good sleep hygiene?
   a. exercising regularly right before going to bed
   b. going to bed only when sleepy
   c. eating large meals just before bedtime
   d. sitting in bed & watching T.V.

4. Which of the following is true regarding long-acting benzodiazepines?
   a. they are likely to cause insomnia
   b. they are more likely than short-acting agents to cause dependence
   c. they produce more severe rebound insomnia than short-acting agents
   d. sitting in bed & watching T.V.

5. If a patient complains of rebound insomnia after stopping an insomnia medication, which of the following should be avoided in the future?
   a. temazepam  c. triazolam
   b. quazepam  d. flurazepam

6. Which of the following has the shortest duration of action?
   a. ramelteon (Rozerem®)  c. zaleplon (Sonata®)
   b. zolpidem (Ambien®)  d. eszopiclone (Lunesta®)

7. Which of the following may interact with drugs that inhibit CYP3A4?
   a. zaleplon (Sonata®)  c. eszopiclone (Lunesta®)
   b. doxylamine (Unisom Nighttime®)  d. temazepam (Restoril®)

8. Which of the following would be an appropriate starting dose for an elderly individual?
   a. zaleplon (Sonata®) 5 mg  c. eszopiclone (Lunesta®) 3 mg
   b. zolpidem (Ambien®) 10 mg  d. trazodone (Desyrel®) 200 mg

9. Which sleep medication may cause an unpleasant taste?
   a. zolpidem (Ambien®)  c. zaleplon (Sonata®)
   b. eszopiclone (Lunesta®)  d. ramelteon (Rozerem®)

10. Which of the following is affected by fatty meals and should be taken on an empty stomach?
    a. triazolam (Halcion®)  c. temazepam (Restoril®)
    b. ramelteon (Rozerem®)  d. trazodone (Desyrel®)

11. A 35-year-old patient complains that he falls asleep quickly, but frequently wakes up after an hour or two, and then has difficulty falling asleep again. Which agent would be the most appropriate recommendation?
    a. trazodone (Desyrel®)  c. zaleplon (Sonata®)
    b. ramelteon (Rozerem®)  d. temazepam (Restoril®)

12. What is a good reason to recommend against the use of sedating antihistamines (e.g., diphenhydramine) for self-treating insomnia?
    a. rash occurs frequently
    b. diarrhea and frequent urination are common side effects
    c. tolerance to the sedating effect can develop in as few as 3 nights
    d. individuals often become dependent on antihistamines

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**What causes insomnia?**

Insomnia can be caused by stress (for example, major life changes like a new job, new home, or loss of a loved one), a medical condition such as chronic pain, obesity, or reflux disease, a mental illness such as depression or anxiety, and medications (for example, steroids, caffeine or caffeine-like drugs, antidepressants, certain drugs for high blood pressure). When an underlying condition is identified as a possible cause, it should be treated first. In some cases, no underlying cause for insomnia can be identified.

**How is insomnia diagnosed and treated?**

Diagnosis begins when an individual, bed partner, or doctor recognizes the possibility of a sleep disorder. A full medical history, sleep and waking history, and physical examination must be done before a diagnosis can be made. A 1-2 week sleep diary (writing down things like usual bedtimes, how much time it takes to fall asleep, total sleep time, number of awakenings, and use of medications) may help both the patient and provider discover what disrupts the sleep/wake cycle and how to best treat the problem.

Insomnia is treated first with recommendations for behavioral change, which can include relearning sleep habits, eliminating noise and other disruptions from the sleep environment, and working with a sleep therapist on other measures that improve sleep. These approaches can be at least as effective as sleep medication and have more long-lasting benefits. Medications may be helpful in addition to behavioral changes and “sleep therapy”.

**Does behavioral therapy for insomnia work?**

Three to six 1-hour sessions with qualified sleep therapists have been shown to reduce insomnia symptoms for at least 6 months after therapy is completed. In contrast sleep medications only work while you are taking them. Behavioral therapy has also been effective in helping long term users of prescription sleep medication improve their sleep and stop taking medication.

**What are some ways to improve sleep without taking medication?**

All individuals with insomnia, whether it’s short term or chronic, should know about the elements of good “sleep hygiene” outlined in the box at right. These are steps you can take to improve sleep without medication.

**How much sleep do I need?**

The right amount of sleep varies from person to person. Most people need between 7 and 9 hours of sleep each night. Some people can function on less, while others need more.

**How do I know if I should see a healthcare professional about my insomnia?**

You should see a professional for help if your sleep problem (trouble falling asleep or staying asleep; waking up too early) affects how you feel and what you do during the day. Either your family healthcare provider or a sleep specialist should be able to help you.

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**Steps To Improve Sleep Without Medication**

<table>
<thead>
<tr>
<th><strong>Stimulus Control Measures</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Develop a bedtime routine. Keep a regular bedtime and wake up at the same time each day. Begin to slow down and unwind at least 30 minutes before bedtime.</td>
</tr>
<tr>
<td>- Do not use your bed for anything except sleeping and sexual activity (no eating, watching TV, or working in bed).</td>
</tr>
<tr>
<td>- Lie down to go to sleep only when you are sleepy. If you are unable to fall asleep, get up and go to another room. Do something relaxing until you are drowsy, then return to the bed.</td>
</tr>
<tr>
<td>- Avoid daytime naps.</td>
</tr>
</tbody>
</table>

**Good Sleep Habits (Sleep Hygiene)**

- Do not consume caffeine during the 4 to 6 hours before bedtime, and minimize your total daily intake.
- Avoid nicotine, especially near bedtime and during night awakenings; it is a stimulant.
- Do not use alcohol to help you fall asleep. Alcohol can cause awakenings later in the night.
- Avoid heavy meals too close to bedtime. Also avoid hunger; a light snack may help you fall asleep.
- Regular exercise in the late afternoon may deepen sleep; vigorous exercise within 3-4 hours of bedtime may interfere with sleep.
- Move the alarm clock away from the bed if it is a source of distraction.
- Eliminate or minimize environmental stimuli such as noise, light, or extreme temperatures during your sleep time.
• **What is sleep apnea?**

Sleep apnea is a breathing disorder that usually includes loud snoring. It consists of short periods throughout the night when breathing stops or is very shallow. People with sleep apnea wake up repeatedly so they will start breathing again and as a result, don’t get enough sleep. Sleep apnea has been linked to heart disease, strokes and even death. If you or your sleep partner suspect sleep apnea, ask your healthcare provider to refer you to someone who can diagnose and treat the problem.

• **Is it safe to take over-the-counter or herbal sleep medications?**

The most common OTC sleep aids are the antihistamines diphenhydramine (Benadryl®, Nyquil®) and doxylamine (Unisom®, Nytol®). These drugs are also found in OTC pain relievers such as Tylenol PM®. While they are safe for occasional use by most people, antihistamines are not very effective for insomnia and stop working fairly quickly with regular use (tolerance develops). Individuals with heart conditions, high blood pressure, breathing problems, glaucoma, thyroid disease or prostate or bladder conditions should not take these medications without the advice of a healthcare professional. Side effects, which can be pronounced in elderly people, include next-day drowsiness, mental slowness, dry mouth, constipation and trouble urinating.

Dietary supplements used for insomnia include melatonin, kava and valerian. Melatonin, which is a hormone, may be useful in some people with insomnia due to work-shift changes or jet lag. Whether it is useful for other types of insomnia is unclear. The effectiveness of valerian is also unclear and several weeks of use are needed before any benefit is noticeable. Kava may be useful for insomnia, but severe liver disease has been linked to its use. Since the FDA does not regulate or approve dietary supplements, the quality and purity of these products cannot be guaranteed. In addition, the appropriate doses for insomnia are unclear.

• **When should I take my prescription sleeping pill?**

Prescription medications for insomnia should be taken at bedtime and only when you can devote at least 8 hours to sleep. Taking sleep medication when you need to be awake in a few hours, or even up to 6-7 hours later, may result in reduced mental alertness and memory problems when you get up. Ramelteon (Rozerem®) can be taken within 30 minutes of going to bed. zaleplon (Sonata®) can be taken after going to bed and having difficulty falling asleep. Ramelteon, zolpidem (Ambien®), zaleplon (Sonata®) and eszopiclone (Lunesta®) should not be taken with or right after a meal.

• **What precautions do I need to be aware of with prescription sleeping pills?**

Prescription sleeping pills (zolpidem [Ambien®, Ambien CR™], zaleplon [Sonata®], eszopiclone [Lunesta®] and benzodiazepines such as triazolam [Halcion®] and temazepam [Restoril®]) can cause drowsiness, decreased mental alertness, and memory problems the day after taking them. Elderly individuals, in particular, are more likely to fall, be confused, and have memory problems. You should be aware that your ability to drive and perform other tasks that require full alertness can be reduced. Do not take more than the prescribed dose. Benzodiazepines are more likely than the newer medications to cause side effects and unpleasant symptoms (withdrawal) when you stop taking them. Report any unusual side effects to your healthcare provider.

• **What is the new drug that is like melatonin?**

Ramelteon (Rozerem®) reduces the time it takes to fall asleep by about 10-15 minutes. It does not appear to be helpful for individuals who wake up during the night. Unlike other prescription sleep medications, ramelteon does not appear to cause dependence, withdrawal symptoms or memory problems. However, it can cause drowsiness, tiredness and dizziness.

• **Why do I have a prescription for an antidepressant for insomnia?**

Trazodone (Desyrel®), an antidepressant, has been widely used to relieve insomnia in depressed as well as non-depressed people. However, there is very little information available about whether it works in non-depressed patients or what dose is most effective. Other antidepressants that cause sedation as a side effect have also been used to treat insomnia. Like trazodone, there is little information available about their effectiveness.

**Resources for More Information**

- **American Academy of Sleep Medicine** (708) 492-0930
  http://www.aasmnet.org
  Includes:
  - American Insomnia Association
  - American Sleep Apnea Association
  - Find a Sleep Center
  - http://www.sleepcenters.org
- **National Sleep Foundation** (202) 347-3471
  http://www.sleepfoundation.org
- **The National Center on Sleep Disorders Research** (301) 435-0199
  http://www.nhlbi.nih.gov/about/ncsdr
- **American Sleep Apnea Association** (202) 293-3650
  http://www.sleepapnea.org/info/index.html