

# Continuing Education for Pharmacists

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## Insomnia and New Drugs to Treat It: Lunesta and Rozerem

**Thomas A. Gossel, R.Ph., Ph.D.**  
Professor Emeritus  
Ohio Northern University  
Ada, Ohio

and

**J. Richard Wuest, R.Ph.,  
Pharm.D.**  
Professor Emeritus  
University of Cincinnati  
Cincinnati, Ohio

**Goals.** The goals of this lesson are to provide background information on insomnia, and discuss Lunesta and Rozerem, new drugs for its treatment.

**Objectives.** At the conclusion of this lesson, successful participants should be able to:

1. describe the etiology, classification, and management of insomnia;
2. identify pharmacologic principles and therapeutic considerations for Lunesta and Rozerem; and
3. select from a list, the indications, mechanisms of action, adverse effects, warnings and toxicities, drug interactions, and benefits and limitations of Lunesta and Rozerem.

FDA recently approved two new molecular entity (NME) drugs for treatment of insomnia: Lunesta (eszopiclone) and Rozerem (ramelteon). See Table 1. This lesson discusses them and provides



Gossel



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information for patients on insomnia and its management.

### Insomnia

Characterized by difficulty initiating or maintaining sleep, insomnia is a significant health concern. An estimated 20 to 40 percent of all adults complain of occasional short-term insomnia, while another 10 to 15 percent complain of chronic insomnia. The economic impact is enormous with direct costs associated with lost productivity.

Insomnia is the most common of all sleep disturbances. Affected individuals approaching bedtime often become anxious. In the morning, they continue to feel mentally and physically tired, anxious, depressed, and irritable. Throughout the day they may

experience serious adverse consequences that negatively impact their performance, including persistent fatigue, low motivation, disturbance of judgment, and reduced coordination.

### Etiology

The precise biochemical and pathophysiological reasons for the various forms of insomnia are not clear; however, the balance in concentrations of sleep-controlling neurotransmitters including acetylcholine, dopamine, gamma-aminobutyric acid (GABA), serotonin, and melatonin is very important. Disruption of circadian rhythms (e.g., resulting from jet lag or alternating work shifts), change of environment, sleep apnea, periodic limb movements, stimulant drugs, drug dependence, and drug withdrawal may contribute to insomnia.

Medical causes of insomnia include pain that may interfere with the ability to fall asleep and also lead to lighter sleep and increased nocturnal awakenings. Nocturia (excessive nighttime urination) may be the result of consuming foods,

**Table 1**  
**New Drugs for Treatment of Insomnia**

| Trade / Generic Name<br>(Sponsor / Manufacturer) | Dosage<br>Form           | FDA<br>Class | Date<br>Approved   |
|--|--------------------------|--------------|--------------------|
| Lunesta/Eszopiclone<br>(Sepracor)                | tablets, 1, 2, &<br>3 mg | 1S*          | 12/04 <sup>±</sup> |
| Rozerem/Ramelteon<br>(Takeda)                    | tablet, 8 mg             | 1S*          | 7/05               |

\*New molecular entity drug approved via Standard Review. The drug appears to have therapeutic qualities similar to those of one or more previously marketed drugs.

<sup>±</sup>Not marketed until 2005.

beverages, or medications with diuretic action too late in the day.

### **Classification**

Insomnia can be categorized according to the nature of sleep disruption or the duration of the complaint. Insomnia is classed as *sleep onset* insomnia (difficulty falling asleep), *sleep maintenance* insomnia (frequent or sustained awakenings), *sleep offset* insomnia (early morning awakenings), or *nonrestorative* sleep (persistent sleepiness despite sleep of adequate duration).

Insomnia is also categorized according to the duration of symptoms as transient (acute), short-term, or chronic (long-term or persistent). *Transient* insomnia occurs in an otherwise normal sleeper. Its duration is usually one to several nights (within a single episode), and is associated with acute stress or disruption of the person's biological clock. Hypnotic therapy may or may not be indicated. When chosen, drugs should be prescribed at their lowest doses and administered only for several consecutive nights, or periodically when needed. These medications should not be taken chronically.

*Short-term* insomnia is similar to transient insomnia except that it may persist a few days to three weeks. It, too, is associated with situational stress (e.g., loss of a loved one), but it can also be due to more protracted stress such as a medical illness. Patient education relative to sleep hygiene is especially valuable. Hypnotic medication is indicated, to be used at the lowest dosage for periods normally not exceeding three weeks.

*Chronic* insomnia continues beyond four weeks, and accounts for 6 to 10 percent of all cases of insomnia. It often waxes and wanes, and is associated with medical or psychiatric conditions or use of alcohol and/or other drugs. Treatment of the underlying cause is paramount. Hypnotic therapy is indicated only if treatment of the underlying condition fails.

About 10 to 15 percent of patients with chronic insomnia have an underlying problem with substance abuse, especially alcohol or other sedatives, or stimulants. Stimulant drugs, including caffeine, can disrupt sleep, especially if taken late in the day. CNS depressants, including alcohol, can cause dependence and, upon withdrawal, disturbed, restless sleep. Although alcohol may help the individual feel relaxed and able to fall asleep, its short duration of action may incite mild withdrawal during the night. The person, therefore, may have disrupted sleep and increased dreaming due to REM (rapid eye movement; period of dreaming) rebound.

Alcohol can also potentiate sleep-related breathing disorders (e.g., sleep apnea) by decreasing muscle tone in the upper airways to result in airway obstruction, hypoxemia (below-normal oxygen concentration in the blood), hypercapnia (excessive carbon dioxide in the blood), and fragmented sleep. Sleep disturbance may continue for months or years in recovering alcoholics. It is unwise to treat this insomnia with benzodiazepines or barbiturates since they are cross-tolerant with alcohol.

Psychophysiologic insomnia is a conditioned insomnia that the person has associated with his own bed, bedroom, or sleep process. It can be transient, short-term, or chronic. The harder the patient tries to sleep, the more difficult it is to do so. Such a person often sleeps remarkably well in the sleep laboratory or a hotel room, and other areas away from the causes of insomnia.

An occasional night of sleep disruption in the setting of life stresses or excitement about external occurrences is common and without lasting consequences. Persistent insomnia can impose important adverse consequences in the form of impaired daytime function. There is also clear evidence of increased risk of major depression with insomnia.

### **Management**

Management of insomnia depends on its type and frequency of symptoms. Primary interventions, including sleep hygiene and relaxation training, should be recommended first. Sleep hygiene refers to the measures an individual can take to promote or maximize sleep (Table 2). Relaxation techniques such as meditation or yoga may reduce psychic and muscular tension that will interfere with sleep onset.

The ideal sleep-aid should have a quick onset, and duration of action of sufficient length to maintain sleep for the entire night but not too prolonged to cause next-day sedation. It should neither produce serious adverse effects, nor cause tolerance, withdrawal, or rebound.

### **Lunesta (eszopiclone)**

Lunesta is a stereoselective isomer of zopiclone, a nighttime sleep-aid that has been widely used in Europe and other parts of the world for more than a decade. Eszopiclone is the [S]-isomer of racemic zopiclone, which is responsible for the hypnotic effects of zopiclone; whereas the [R]-isomer has no hypnotic properties.

Eszopiclone is a non-benzodiazepine hypnotic indicated for chronic use in insomnia. It differs in this respect from zolpidem (Ambien) and zaleplon (Sonata) and other sleep-aids that are limited to short-term use. Eszopiclone was approved for use over a longer period because its manufacturer sponsored a six-month clinical trial showing efficacy and safety, while manufacturers of the other products did not. Its precise mechanism of action is unknown; however, its effect to promote sleep is believed to result from agonistic interaction with GABA-receptor complexes. These receptor complexes are located close to or coupled with benzodiazepine receptors in the brain. Whether there are differences between various hypnotic drugs in binding to subtypes of the receptors is unclear.

A landmark clinical trial that earned the drug's credibility and FDA approval for chronic use

included patients aged two to 69 years who reported less than 6.5 hours of sleep per night, and/or a sleep latency of more than 30 minutes each night for at least one month before screening. Interventions included eszopiclone 3 mg (n = 593) and placebo (n = 195) nightly for six months. Endpoints included sleep latency; total sleep time; number of awakenings; wake time after sleep onset; quality of sleep; and next-day ratings of ability to function, daytime alertness, and overall sense of physical well-being.

At the first week and each month throughout the study, eszopiclone produced significant and sustained improvements in sleep latency, number of awakenings, wake time after sleep onset, number of nights awakened per week, total sleep time, and quality of sleep compared with placebo. Monthly ratings of next-day function, alertness, and sense of physical well-being were also significantly better with eszopiclone than with placebo.

**Adverse Effects.** The most common adverse effects in pre-marketing clinical trials were unpleasant taste, headache, somnolence, dizziness, and dry mouth. Some patients reported memory impairment the next day. This was usually mild and often reported only during the first week of treatment. Some patients taking 3 mg doses performed less well than their placebo controls on certain measures of psychomotor function, when measured 9.5 hours after taking the drug.

**Drug Interactions.** Lunesta alone does not produce a dangerous degree of central sedation when taken in usual doses. It is metabolized by CYP3A4 and CYP2E1 enzymes. Co-administration with a potent inhibitor of CYP3A4 such as ketoconazole (Nizoral), itraconazole (Sporonox), clarithromycin (Biaxin) or ritonavir (Norvir) can prolong its duration of action. If one of these drugs is taken concurrently, the dose of Lunesta should be reduced. Rifampin (Rifadin), a potent inducer of CYP3A4 enzymes, can decrease

serum concentrations and effectiveness of Lunesta. Lunesta does not alter the clearance of drugs metabolized by common CYP450 enzymes.

Lunesta is not highly bound to plasma proteins, so it is not expected to interact with drugs that are highly bound. In clinical trials, Lunesta did not interact pharmacodynamically or pharmacokinetically with warfarin (Coumadin), digoxin (Lanoxin), or paroxetine (Paxil).

#### **Indications and Uses.**

Lunesta is indicated for treatment of insomnia. In controlled outpatient and sleep laboratory studies, Lunesta administered at bedtime decreased sleep latency and improved sleep maintenance. Lunesta should only be taken immediately before going to bed, or after the patient has gone to bed and experienced difficulty falling asleep.

Lunesta is a Schedule IV controlled substance under the Controlled Substances Act. Even though its chemical structure is unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties, Lunesta shares some of the pharmacologic properties of the benzodiazepines.

#### **Dosage and Administration.**

The recommended starting dose of Lunesta for non-elderly adults is 2 mg immediately before bedtime. Dosing can be initiated at or raised to 3 mg if clinically indicated. The recommended starting dose for elderly patients whose primary complaint is difficulty falling asleep is 1 mg immediately before bedtime. The dose may be increased to 2 mg if indicated. For elderly patients whose primary complaint is difficulty remaining asleep, the recommended dose is 2 mg immediately before bedtime. Taking Lunesta with or immediately after a heavy/high-fat meal slows drug absorption and reduces its effect on sleep latency. Individuals with severe hepatic impairment should start with 1 mg doses. No dose adjustment is necessary for subjects with mild or moderate hepatic impairment. Table 3 summarizes patient information for Lunesta.

**Table 2**  
**Suggestions for Improving Sleep**

- Determine the optimal sleep-time for maximal efficiency during the next day.
- Maintain regular times to go to bed and arise each day. Time in bed should not exceed 8 hours per night.
- Select a time to go to bed and one to get up each day, and stick to your routine, even on weekends and holidays.
- Refrain from daytime napping.
- Avoid caffeine after midafternoon and nicotine before bedtime and during the night.
- Abstain from alcoholic beverages, and do not ingest large quantities of any liquid late in the evening.
- Avoid eating too much during the evening. Avoid heavy or spicy foods.
- Exercise regularly, preferably 6 hours before bedtime, but avoid exercise within 3 hours of bedtime.
- Establish a relaxing routine in preparation for sleeping. Avoid frustrating activities just before bedtime.
- Avoid using the bedroom for nonsleep activities such as watching TV.
- If unable to fall asleep within 20 to 30 minutes, get up and go to another room. Do not return to the bedroom until sleepy.
- Control the room temperature (slightly cool is better than too warm), and minimize environmental noise.

Lunesta is available as film-coated tablets containing 1, 2, or 3 mg eszopiclone.

#### **Rozerem (ramelteon)**

Rozerem is the first and only prescription sleep medication that is not a controlled substance. It is a melatonin receptor agonist with high affinity for melatonin MT<sub>1</sub> and MT<sub>2</sub> receptors. This affinity is believed to contribute to its sleep-promoting properties.

Three subtypes of melatonin receptors have been identified, designated as MT<sub>1</sub>, MT<sub>2</sub>, and MT<sub>3</sub>. MT<sub>1</sub> and MT<sub>2</sub> are involved in the regulation of sleep. An area within the hypothalamus called the

**Table 3**  
**Patient Information for**  
**Lunesta and Rozerem**

**Lunesta**

- Lunesta is used to help you sleep, including helping you fall asleep, remain asleep during the night, and keep you from waking up too early in the morning.

- Take this medicine exactly as directed by your doctor. Take it immediately before going to bed. Do not take it unless you are able to get at least 8 hours of sleep before you must be active again.

**Rozerem**

- Rozerem is used to help you fall asleep more quickly. It is not indicated to help you stay asleep during the night or to keep you from waking up early in the morning.

- Take this medicine within 30 minutes of going to bed.

**Both Lunesta and Rozerem**

- Do not drink alcohol or take other sedative drugs at the same time as taking this or any sleep-aid.
- For this medicine to work best, do not take it with or immediately after a high-fat, heavy meal.
- Tell your doctor about any prescription or nonprescription medicine, vitamin/mineral supplements, or herbal remedies you are taking.
- Tell your doctor if you are pregnant or planning to become pregnant, or are breastfeeding.
- Do not engage in hazardous activities such as operating a motor vehicle or heavy machinery after taking this medicine.
- Call your doctor if you experience worsening of your insomnia or any disturbing thoughts or behavior, or any bothersome side effects.
- Observe good sleep hygiene measures. Your doctor or pharmacist can explain these to you.

suprachiasmatic nucleus functions as the body's "master clock," and regulates the 24-hour sleep-wake cycle. MT<sub>1</sub> is believed to regulate sleepiness. MT<sub>2</sub> is thought to be involved in the readjustment of circadian rhythms.

Results from animal studies have demonstrated a selectivity of ramelteon for MT<sub>1</sub> over MT<sub>2</sub> receptors, which was more than 1,000-fold greater than that of melatonin.

This strongly suggests that ramelteon may act more specifically on the sleep-onset process than melatonin itself. Ramelteon also has a 3- to 6-fold higher affinity for human MT<sub>1</sub> and MT<sub>2</sub> receptors in comparison to melatonin.

Rozerem is devoid of appreciable affinity for other receptor sites within the brain. These include the GABA receptor complex, and receptors that bind neuropeptides, cytokines, serotonin, dopamine, norepinephrine, acetylcholine, or opiates.

Rozerem was evaluated in two randomized, double-blind trials in subjects with chronic insomnia using polysomnography to objectively assess results. The first study enrolled adults (aged 18 to 64 years) with chronic insomnia. Subjects received a single, nightly dose of Rozerem 8 mg or 16 mg or placebo for 35 days. Polysomnography was performed on the first two nights during Weeks 1, 3, and 5 of treatment. Both doses of Rozerem reduced the average latency to persistent sleep at each of the time points when compared to placebo.

The second study was a three-period crossover trial in subjects aged 65 years or older with a history of chronic insomnia. Subjects received Rozerem 4 mg or 8 mg, or placebo, and underwent assessment in a sleep laboratory for two consecutive nights in each of the three study periods. Both doses of Rozerem reduced latency to persistent sleep compared to placebo.

**Adverse Effects.** Five percent of the 3594 subjects exposed to Rozerem in premarketing clinical studies discontinued treatment owing to an adverse event, compared with 2 percent of 1370 subjects receiving placebo. The most frequent adverse events that had greater than 2 percent incidence in subjects receiving Rozerem were somnolence, dizziness, and fatigue.

**Drug Interactions.** Rozerem is metabolized primarily by CYP1A2, with secondary detoxification by CYP3A4 and CYP2C isoforms. It should not be used in

combination with strong CYP1A2 inhibitors (e.g., fluvoxamine, Luvox). It should be used with caution in patients taking other CYP1A2 inhibiting drugs since less potent CYP1A2 inhibitors have not been adequately studied. Rozerem should be administered with caution in persons taking ketoconazole, a strong CYP3A4 inducer, or fluconazole (Diflucan), a strong CYP2C9 inhibitor.

**Indications and Uses.**

Rozerem is indicated for the treatment of insomnia characterized by difficulty with sleep onset. Rozerem is not a controlled substance.

**Dosage and Administration.**

The recommended dose of Rozerem is 8 mg taken within 30 minutes of going to bed. It is recommended that Rozerem not be taken with or immediately after a high-fat meal. Rozerem should not be used by persons with severe hepatic impairment, and should be used with caution in patients with moderate hepatic impairment. Table 3 lists patient information for Rozerem.

Rozerem is marketed as tablets containing 8 mg ramelteon.

**Overview and Conclusions**

Many people experience temporary insomnia. It is only when insomnia persists or begins to interfere with normal daytime activities that affected individuals seek help.