By Harpriya A. (Sonya) Bhagar, MBBS, and Alan D. Schmetzer, MD,
Diplomate of the American Psychotherapy Association



# The Newest Medicines for Sleep

This 1-credit continuing education opportunity is co-sponsored by the American College of Forensic Examiners International (ACFEI) and the American Psychotherapy Association. ACFEI maintains responsibility for all continuing education accreditations. This article is approved by the following for 1 continuing education credit:

APA provides this continuing education credit for **Diplomates**.

The American College of Forensic Examiners is approved by the **American Psychological Association** to offer continuing education for psychologists. ACFEI maintains responsibility for the program and its content.

ACFEI is recognized by the **National Board for Certified Counselors** to offer continuing education for LMFT's, LCSW's, and National Certified Counselors. We adhere to NBCC Continuing Education Guidelines. Provider #5812.

ACFEI is an approved provider of the **California Board of Behavioral Sciences,** approval PCE 1896.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education **(ACCME)** through the joint sponsorship of ACFEI and APA. ACFEI is accredited by the ACCME to provide continuing medical education for physicians. ACFEI designates this educational activity for a maximum of 1 hour(s) in category 1 credit towards the AMA Physicians Recognition Award. Each physician should claim only the number of hours he or she actually spent in the activity. Dr. Schmetzer and Ms. Bhagar have nothing to disclose for CME purposes.

The importance of a good night's rest cannot be over emphasized, yet sleep disorders are often missed or untreated. Patients do not spontaneously report sleep difficulties nor do health care providers routinely inquire about them. They may both feel that it is not a serious illness. This is despite the fact that literature has reported insomnia to be associated with both an increase in psychiatric and medical comorbidity[1] and mortality.[2] Hence, it is no surprise that the newest medicines for sleep are being marketed with late night commercials directed at the sleepless consumer.

Insomnia is defined as difficulty initiating or maintaining sleep or as non-restorative sleep. It is a possible symptom of different medical or mental health disorders or may occur without an underlying cause. Treatment usually involves addressing the causal disorder, if any; non-pharmacological interventions, popularly called "sleep hygiene"; and pharmacotherapy. Sleep hygiene techniques include going to bed only when ready to sleep, avoiding distracting activities in bed such as reading or watching TV, and limiting caffeine intake later in the day. Although several medications are available for insomnia, they have a potential for abuse, dependence, rebound insomnia, and daytime drowsiness. Since the summer 2004 primer "The Medicines for Sleep," in *Annals of the American Psychotherapy Association*,[2] three new medications have received Food and Drug Administration approval for the indication of insomnia. They include the following: eszopiclone (Lunesta) in December 2004, ramelteon (Rozerem) in July 2005, and the modified-release zolpidem (Ambien CR) in September 2005.

The benzodiazepines traditionally used for sleep, such as diazepam (Valium) and temazepam (Restoril), are habit-forming

and have long half-lives. While long half-lives assist in the maintenance of sleep with minimal awakenings, they have a potential to cause daytime sedation. An ideal hypnotic agent would be one that would induce sleep quickly with a fast peak level and have a half-life of sufficient length to promote an adequate duration of sleep but a half-life that is not so long as to cause daytime sedation and/or a hangover effect.

Lunesta, the active S-isomer of the racemic zopiclone, has a chemical structure unrelated to benzodiazepines, but it mediates its sedative effects via interactions at the benzodiazepine receptor complex. It reaches peak concentration in about 1 hour and has an approximate elimination half-life of 6 hours. It has an active metabolite but with a low potency. It is indicated for the treatment of insomnia and improves both sleep latency and maintenance.[3] Ambien CR is a modified release form of zolpidem (Ambien). Like Lunesta, it also has a chemical structure unrelated to benzodiazepines, but it mediates its sedative effects via selective interactions at the benzodiazepine receptor complex. It reaches peak concentration in about 1.5 hours and has a mean elimination half-life of around 2.5 hours. It has a biphasic release that includes an immediate release of zolpidem to promote sleep onset and a more controlled release of the drug to promote sleep maintenance. Ambien CR improves both sleep induction and maintenance.[4] Rozerem is a highly selective melatonin receptor agonist at the melatonin type 1 and type 2 receptors. It reaches peak levels in approximately 0.75 hours, has a short elimination half-life of 1–2.6 hours, and its active metabolite (M-II) is 2–5 hours. Serum levels of Rozerem and M-II are at or below lower limits of quantitation within 24 hours. In clinical trials, Rozerem improved sleep latency. Hence, it is indicated for the treatment of insomnia characterized by difficulty with sleep onset.[5]

Although less pronounced than the benzodiazepines, Lunesta and Ambien CR have a risk of next-day somnolence and dependence [both are Drug Enforcement Administration (DEA) Schedule-IV controlled substances].[3-4] Rozerem is not a controlled substance and clinical trials showed no difference from placebo on residual pharmacological effects, rebound insomnia, or withdrawal. However, it can affect prolactin and testosterone levels, decrease libido, and cause problems with fertility.[5] Sleep agents can produce an additive central nervous system (CNS) depressant effect when co-administered with narcotics, alcohol, and other CNS depressant drugs. Food can delay the absorption and clearance of Lunesta. Rozerem should not be taken immediately after a high fat meal. Other medications that inhibit the cytochrome (CYP) 3A4 enzyme, such as ketoconazole, can result in an increase in serum level of Lunesta. Rozerem should not be taken with fluvoxamine (a strong CYP1A2 inhibitor) and must be used with caution with ketoconazole (a strong CYP 3A4 inhibitor) and fluconazole (a strong CYP2C9 inhibitor).[3-5]

> "An ideal hypnotic agent would be one that would induce sleep quickly with a fast peak level and have a half-life of sufficient length to promote an adequate duration of sleep but a half-life that is not so long as to cause daytime sedation and/or a hangover effect."

The medicines for sleep should be taken just prior to bedtime. Patients are cautioned against engaging in tasks requiring mental alertness such as driving or operating heavy machinery. Lunesta is dosed at 2–3 mg. In elderly or debilitated people and those with hepatic impairment it is dosed at 1–2 mg. Ambien CR is dosed at 12.5 mg and 6.25 mg in elderly and compromised patients. Rozerem is prescribed at 8 mg and also used with caution in elderly or debilitated patients and those with hepatic insufficiency.[3-5]

A recent review found the non-benzodiazepine, benzodiazepine-receptor agonists to have less next-day residual effects than the benzodiazepines themselves.[6] Further, Lunesta and Ambien CR are approved by the FDA without restricted duration of use in the treatment of insomnia. Rozerem, a selective melatonin agonist, is indicated for long term use as well, and it is the first non-scheduled prescription hypnotic.[3-5]

## References

1. Benca, RM. Consequences of Insomnia and Its Therapies. *J Clin Psychiatry.* 2001;62(suppl 10):33-38.
2. Schmetzer, A. Primer for Prescription Medications: The Medicines for Sleep. *Annals of the American Psychotherapy Association.* Summer 2004;No. 2:31.
3. Sepracor, Inc. In: *Physicians' Desk Reference.* 60th ed. Montvale, NJ: Thompson PDR; 2006.
4. Sanofi-Synthelabo, Inc. *Prescribing information on Ambien CR.* September 2005. Available at: http://products.sanofi-aventis.us/ambien_cr/ambienCR.html. Accessed March 24, 2006.
5. Takeda Pharmaceuticals. In: *Physicians' Desk Reference.* 60th ed. Montvale, NJ: Thompson PDR; 2006.
6. Benca, RM. Diagnosis and Treatment of Chronic Insomnia: A Review. *Psychiatr Serv.* 2005;56(3): 332-343.

## About the Authors

**Harpriya A. (Sonya) Bhagar,** MBBS, is an assistant professor of clinical psychiatry at Indiana University School of Medicine and is a member of the American Psychotherapy Association.

**Alan Schmetzer,** MD, is a Diplomate of the American Psychotherapy Association and has been a member since 1998. He is a professor of psychiatry at Indiana University School of Medicine.

**Earn CE Credit**
Take CE questions online at www.americanpsychotherapy.com (click "Online CE") or see the questions for this article on page 49.