

# **Drug Class Review on Newer Drugs for Insomnia**

**Update #2  
Preliminary Update Scan Report #2**

November 2007

**The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.**

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## OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

### Date of Last Updated Report

July 2006 (searches through November 2005)

### Date of Last Preliminary Update Scan Report

November 2006

## Scope and Key Questions

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of newer drugs for insomnia in treating adults and children with insomnia?
2. What is the comparative tolerability and safety of newer drugs when used to treat adults and children with insomnia?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one newer drug for insomnia is more effective or associated with fewer adverse events?

## Included populations

We included studies in adults or children with insomnia of any duration. We did not exclude studies that did not specify a definition of insomnia as part of enrollment criteria, but most studies specified a DSM-IV diagnosis of primary insomnia. The DSM-IV criteria for the diagnosis of primary insomnia are "a complaint of difficulty initiating or maintaining sleep or of nonrestorative sleep that lasts for at least one month and causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. The disturbance in sleep does not occur exclusively during the course of another sleep disorder or mental disorder

and is not due to the direct physiological effects of a substance or a general medical condition.”(Anonymous 1994)

### Included interventions

Six nonbenzodiazepine drugs for insomnia have been introduced since 1992 (Table 1). Five are available in the US (eszopiclone, ramelteon, zaleplon, zolpidem and zolpidem extended release) and two in Canada and other countries (zaleplon and zopiclone).

The recommended starting dose in older adults is half the recommended adult dose for all of these drugs except ramelteon because of the theoretical risk of increased adverse events such as somnolence. This is generally based on increased bioavailability observed in older adults.

**Table 1. Newer drugs for insomnia**

Active ingredient	Brand name	Initial dose (given at bedtime)			Half-life (hours)
		Pediatrics	Adults	Older adults	
eszopiclone	Lunesta	NA	2 mg	1 mg	6
ramelteon	Rozerem	NA	8 mg	8 mg	1-2.6
zaleplon	Sonata	NA	10 mg	5 mg	1
zolpidem	Ambien	NA	10 mg	5 mg	2.5
zolpidem extended release	Ambien CR	NA	12.5 mg	6.25 mg	2.8
zopiclone (Canada)	Imovane	NA	5 to 7.5 mg	3.75 mg	5

### Included outcomes

Improvement in insomnia is measured in several ways. Effectiveness outcomes included sleep latency, sleep duration, number of awakenings, sleep quality, daytime alertness, rebound insomnia, and quality of life. Safety outcomes included tolerance, adverse effects, abuse potential, withdrawal symptoms, and dependency.

*Sleep latency* is the time period taken by a person to fall asleep. *Sleep duration* is the time period a person remains asleep. The *number of awakenings* during the night is also frequently measured in insomnia trials. A measure used in some studies is *wake time after sleep onset (WASO)*. This is the total time that a person is awake between sleep onset and final wake-up.

These outcomes can be measured subjectively (e.g., using patient sleep diaries), or objectively, using *polysomnography* (PSG), the testing of sleep cycles and stages through the use of continuous recordings of brain waves and other measures in a sleep laboratory. Most studies report subjective outcomes. While objective measures may give a more accurate indication of sleep duration and other outcomes, subjective outcomes may be more important to patients.

*Sleep quality* is usually measured by patient questionnaire using a Likert or visual analogue scale (e.g., 0=poor to 10=excellent). Similarly, *daytime alertness* and other *next-day effects* are usually measured by patient self-report.

*Rebound insomnia* is worsening of insomnia from baseline (prior to pharmacotherapy) upon treatment discontinuation. This can be measured using any of the outcomes above.

*Quality of life* includes influence upon physical, psychological, and social aspects of the patient.

## **METHODS**

### **Literature Search**

To identify relevant citations, we searched Ovid MEDLINE, Ovid MEDLINE Daily Update, and Ovid MEDLINE In-Process & Other Non-Indexed Citations from October 2006 through October Week 3 2007, using terms for included drugs and limits for controlled trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada ([http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/index\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/index_e.html)) websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0) and duplicate citations were removed.

### **Study Selection**

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

## **RESULTS**

### **Overview**

Searches resulted in 18 citations. Of those, there were 5 potentially relevant new trials (see Appendix A):

- One sleep laboratory study of zolpidem and zaleplon vs placebo in patients with sleep maintenance insomnia
- 3 placebo-controlled trials of eszopiclone: one in peri- and postmenopausal women with insomnia, one examining the effect of discontinuing eszopiclone after co-administration with fluoxetine in patients with depression and insomnia, and a placebo-controlled trial of the effect of 6 months of treatment with eszopiclone on quality of life and work limitations
- A placebo-controlled trial of ramelteon in older adults with insomnia (previously available only as an abstract)

### **New Drugs**

No new drugs were identified.

In April 2007, the FDA approved the first generic versions of Ambien (Zolpidem) immediate release formulation.

### **New Indications**

No new indications were identified.

## New Safety Alerts

### All newer insomnia drugs

3/14/2007: FDA notified healthcare professionals of its request that all manufacturers of sedative-hypnotic drug products, a class of drugs used to induce and/or maintain sleep, strengthen their product labeling to include stronger language concerning potential risks. These risks include severe allergic reactions and complex sleep-related behaviors, which may include sleep-driving. Sleep driving is defined as driving while not fully awake after ingestion of a sedative-hypnotic product, with no memory of the event. FDA also requested that each product manufacturer send letters to health care providers to notify them about the new warnings, and that manufacturers develop Patient Medication Guides for the products to inform consumers about risks and advise them of potential precautions that can be taken.

The warning includes all of the newer insomnia drugs marketed in the US (eszopiclone, zolpidem, zolpidem controlled release, zaleplon, and ramelteon), and these additional drugs used for insomnia: Butisol sodium, Carbrital (pentobarbital and carbromal), Dalmane (flurazepam hydrochloride), Doral (quazepam), Halcion (triazolam), Placidyl (ethchlorvynol), Prosom (estazolam), Restoril (temazepam), and Seconal (secobarbital sodium).

### Zolpidem

3/28/07: the FDA approved safety labeling revisions for zolpidem to warn of adverse events associated with its use in the treatment of insomnia associated with attention-deficit/hyperactivity disorder (ADHD) in patients aged 6 to 17 years. The label reads:

“Safety and effectiveness of zolpidem has not been established in pediatric patients. In an 8-week study in pediatric patients (aged 6-17 years) with insomnia associated with ADHD, zolpidem did not decrease sleep latency compared to placebo. Hallucinations were reported in 7.4% of the pediatric patients who received zolpidem; none of the pediatric patients who received placebo reported hallucinations.”

## Appendix A. Abstracts of potentially relevant new trials of newer drugs for insomnia

Krystal, A., M. Fava, et al. (2007). "Evaluation of eszopiclone discontinuation after cotherapy with fluoxetine for insomnia with coexisting depression." *Journal of Clinical Sleep Medicine* 3(1): 48-55.

**BACKGROUND:** Insomnia and major depressive disorder (MDD) may coexist. This study evaluated hypnotic discontinuation effects following an 8-week placebo-controlled study of eszopiclone/fluoxetine cotherapy in patients with insomnia and comorbid MDD. **METHODS:** Patients meeting DSM-IV criteria for MDD and insomnia received fluoxetine each morning for 8 weeks and were randomized to concomitant treatment with nightly eszopiclone 3 mg (cotherapy) or placebo (monotherapy). Thereafter, patients received 2 weeks of continued fluoxetine plus single-blind placebo. **RESULTS:** Incidence rates of central nervous system (CNS) and potentially CNS-related adverse events (AEs) during the run-out period were similar between treatment groups (8.8% with monotherapy vs 9.8% with cotherapy), and there was no evidence of benzodiazepine withdrawal AEs. Physician-assessed Clinical Global Impression improvements in depressive symptoms were maintained after eszopiclone discontinuation. Improvements in 17-item Hamilton-Depression Rating Scale (HAMD-17) scores with cotherapy versus monotherapy seen at Week 8 ( $p = .0004$ ) were maintained at Week 10 ( $p < .0001$ ) and significantly higher depression response and remission rates were observed after cotherapy at Week 10 ( $p < .02$ ). Patients discontinued from eszopiclone maintained improvements in SL (sleep latency), WASO (wake after sleep onset), and TST (total sleep time) during the 2 weeks following discontinuation ( $p < .05$ ). **CONCLUSIONS:** In this study, eszopiclone discontinuation did not result in significant CNS or benzodiazepine withdrawal AEs, rebound insomnia, or rebound depression; and improvements in sleep and depressive symptoms were maintained.

Roth, T., D. Seiden, et al. (2007). "A 2-night, 3-period, crossover study of ramelteon's efficacy and safety in older adults with chronic insomnia." *Current Medical Research & Opinion* 23(5): 1005-14.

**OBJECTIVE:** To assess the efficacy and safety of ramelteon, a selective melatonin MT1/MT2-receptor agonist, for insomnia treatment in older adults. **METHODS:** In a randomized, 9-week, 3-period crossover trial conducted at 17 sleep centers, older adults ( $N = 100$ ) with chronic primary insomnia (37 men, 63 women; mean age [range], 70.7 [65-83] years) were administered placebo, ramelteon 4 mg, and ramelteon 8 mg in three treatment phases for two consecutive nights. Each phase was separated by 5- to 12-day washout periods. Sleep was monitored via polysomnography. Subjective sleep parameters, using a Postsleep Questionnaire, were recorded, and residual pharmacologic effects were assessed. **RESULTS:** Statistically significant reductions in latency to persistent sleep were observed with both ramelteon 4 mg and 8 mg compared to placebo (28.7 min vs. 38.4 min,  $p < 0.001$ ; 30.8 min vs. 38.4 min,  $p = 0.005$ , respectively). Total sleep time ( $p = 0.036$  and  $p = 0.007$ , respectively) and sleep efficiency ( $p = 0.037$  and  $p = 0.007$ , respectively) were also significantly improved with ramelteon 4 mg and 8 mg compared to placebo. Statistically significant reductions in subjective sleep latency on a Postsleep Questionnaire were reported with ramelteon 4 mg versus placebo ( $p = 0.037$ ), but not ramelteon 8 mg ( $p = 0.120$ ); no significant differences on other subjective sleep assessments were reported. A lack of power limits interpretation of self-reported sleep parameters. Incidences of adverse events considered treatment related were placebo (7%), ramelteon 4 mg (11%), and ramelteon 8 mg (5%). No residual pharmacologic effects were observed via Digit Symbol Substitution Test, memory recall tests (immediate and delayed), visual analog scales (feelings and mood), and Postsleep Questionnaire (level of alertness and ability to concentrate). **CONCLUSIONS:** In older adults with chronic primary insomnia, ramelteon produced significant reductions in latency to persistent sleep and increases in total sleep time and sleep efficacy, and showed no evidence of adverse next-day psychomotor or cognitive effects.

Soares, C. N., H. Joffe, et al. (2006). "Eszopiclone in patients with insomnia during perimenopause and early postmenopause: a randomized controlled trial." *Obstetrics & Gynecology* **108**(6): 1402-10.

**OBJECTIVE:** To evaluate eszopiclone 3 mg for treatment of insomnia in perimenopausal and early postmenopausal women, as well as the impact of insomnia treatment on mood, menopause-related symptoms, and quality of life. **METHODS:** This was a double-blind, placebo-controlled study with 410 women (aged 40-60; perimenopausal or early postmenopausal) who reported insomnia defined as sleep latency of at least 45 minutes and total sleep time less than or equal to 6 hours per night for at least 3 nights per week over the previous month. Patients were randomly assigned to eszopiclone 3 mg or placebo nightly for 4 weeks. Sleep data were collected once a day. Physician global assessments of menopause, menopause-specific questionnaire, Greene Climacteric Scale, the Montgomery Asberg Depression Rating Scale, and the Sheehan Disability Scale were collected at baseline and end of treatment. **RESULTS:** Patients receiving eszopiclone reported improvements in sleep induction, sleep maintenance, sleep duration, sleep quality, and next-day functioning relative to placebo ( $P < .05$ ). Patients receiving eszopiclone reported fewer total awakenings and awakenings due to hot flushes ( $P < .05$ ). Eszopiclone use led to greater improvement in Montgomery Asberg Depression Rating Scale scores ( $P < .05$ ) and physician global assessments of menopause scores ( $P < .001$ ); total Greene Climacteric Scale score and the vasomotor and psychological sub-scores ( $P < .05$ ); vasomotor and physical domains of the menopause-specific questionnaire ( $P < .05$ ); and family life/home domain of the Sheehan Disability Scale ( $P < .05$ ). **CONCLUSION:** In this study, eszopiclone provided significant improvements in sleep and positively impacted mood, quality of life, and menopause-related symptoms in perimenopausal and early postmenopausal women with insomnia. **CLINICAL TRIAL REGISTRATION:** ClinicalTrials.gov [www.clinicaltrials.gov](http://www.clinicaltrials.gov) NCT00366093 **LEVEL OF EVIDENCE:** I.

Walsh, J. K., A. D. Krystal, et al. (2007). "Nightly treatment of primary insomnia with eszopiclone for six months: effect on sleep, quality of life, and work limitations." *Sleep* **30**(8): 959-68.

**STUDY OBJECTIVES:** To evaluate 6 months' eszopiclone treatment upon patient-reported sleep, fatigue and sleepiness, insomnia severity, quality of life, and work limitations. **DESIGN:** Randomized, double blind, controlled clinical trial. **SETTING:** 54 research sites in the U.S. **PATIENTS:** 830 primary insomnia patients who reported mean nightly total sleep time (TST)  $<$  or  $=$  6.5 hours/night and/or mean nightly sleep latency (SL)  $>$ 30 min. **INTERVENTION:** Eszopiclone 3 mg or matching placebo. **MEASUREMENTS:** Patient-reported sleep measures, Insomnia Severity Index, Medical Outcomes Study Short-Form Health Survey (SF-36), Work Limitations Questionnaire, and other assessments measured during baseline, treatment Months 1-6, and 2 weeks following discontinuation of treatment. **RESULTS:** Patient-reported sleep and daytime function were improved more with eszopiclone than with placebo at all months ( $P < 0.001$ ). Eszopiclone reduced Insomnia Severity Index scores to below clinically meaningful levels for 50% of patients (vs 19% with placebo;  $P < 0.05$ ) at Month 6. SF-36 domains of Physical Functioning, Vitality, and Social Functioning were improved with eszopiclone vs placebo for the Month 1-6 average ( $P < 0.05$ ). Similarly, improvements were observed for all domains of the Work Limitations Questionnaire with eszopiclone vs placebo for the Month 1-6 average ( $P < 0.05$ ). **CONCLUSIONS:** This is the first placebo-controlled investigation to demonstrate that long-term nightly pharmacologic treatment of primary insomnia with any hypnotic enhanced quality of life, reduced work limitations, and reduced global insomnia severity, in addition to improving patient-reported sleep variables.

Zammit, G. K., B. Corser, et al. (2006). "Sleep and residual sedation after administration of zaleplon, zolpidem, and placebo during experimental middle-of-the-night awakening." *Journal of Clinical Sleep Medicine* **2**(4): 417-23.

**STUDY OBJECTIVES:** To assess the efficacy of zaleplon 10 mg and zolpidem 10 mg administered during experimental middle-of-the-night awakenings in patients with sleep-maintenance insomnia using objective polysomnographic measures and to assess daytime residual sedation 4 to 7 hours after dosing using sleep-latency testing. **DESIGN:** A randomized, double-blind, placebo-controlled, 3-period, crossover design was used to study 37 adults with insomnia who received treatment during an experimental awakening 4 hours after bedtime. Latency to persistent sleep and total sleep time before and after awakening were recorded. The primary residual sedation measure was a sleep latency test conducted hourly from 4 to 7 hours after treatment. Self-report measure of alertness and concentration and digit symbol substitution tests were examined concurrently. **SETTING:** Sleep disorders centers. **PATIENTS:** Thirty-seven adults with sleep-maintenance insomnia. **Interventions:** Zaleplon 10 mg, zolpidem 10 mg, or placebo. **MEASUREMENTS AND RESULTS:** Thirty-one patients had efficacy-evaluable data; 37 patients received at least 1 dose of study medication and were included in the safety analysis. Compared with placebo, latency to persistent sleep after both zaleplon and zolpidem was shorter and total sleep time after administration of the drugs was longer (overall  $p < .001$ , Dunnett  $p < .001$  for all posthoc comparisons). Significant differences from placebo were not found with zaleplon in daytime-sedation measures. At 4, 5, and 7 hours after zolpidem, sleep onset on sleep latency testing was shorter than after placebo (overall  $p < .001$  for all, Dunnett tests for posthoc comparisons  $p < .001$ ,  $p < .001$ ,  $p < .05$ , respectively). Self-report measures of concentration (4, 5, and 6 hours, overall  $p < .05$ , Dunnett  $p < .05$  for each time point) and alertness (4 hours, overall  $p < .05$ , Dunnett  $p < .05$ ), and Digit Symbol Substitution Test scores (4 and 5 hours, overall  $p < .001$ , Dunnett  $p < .01$  for both time points) after zolpidem were also lower than with placebo. **CONCLUSIONS:** Zaleplon 10 mg and zolpidem 10 mg effectively shorten sleep latency and lengthen sleep duration after dosing, when administered during experimental nocturnal awakening. Residual sedation was not detected as little as 4 hours after zaleplon 10 mg, whereas residual sedation was detected with zolpidem 10 mg up to 7 hours after treatment. These findings suggest that zaleplon may be an appropriate treatment for use when patients awaken during the night and have difficulty reinitiating sleep.