

Drug Class Review on Newer Drugs for Insomnia

Update #3: Preliminary Scan Report #1

October 2009

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 Report

October 2008 (searches through January 2008).

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 patients with insomnia?
2. What is the comparative tolerability and safety of Newer Drugs for Insomnia when used to treat patients with insomnia?
3. Are there subgroups of patients for which one Newer Drug for Insomnia is more effective or associated with fewer adverse events based on
 - a. demographics (age, racial groups, and gender)?
 - b. other medications (e.g., stimulants)?
 - c. co-morbidities (including obstructive sleep apnea, other mental disorders)?
 - d. pregnancy?
 - e. history of substance abuse?

Inclusion Criteria***Population:***

Adults and children with insomnia, including (DSM-IV-TR diagnoses):

- Primary insomnia
- Breathing-related sleep disorder (e.g., obstructive sleep apnea)
- Insomnia related to another mental disorder
- Substance-induced sleep disorder, insomnia type
- Sleep disorder due to a general medical condition, insomnia type

Interventions

Zaleplon (Sonata[®])

Zolpidem (Ambien[®])

Zolpidem extended release (Ambien CR[®])

Eszopiclone (Lunesta[®])

Ramelteon (Rozerem[®])

Zopiclone (Imovane[®], Canada only)

Effectiveness outcomes

Sleep latency

Sleep duration

Number of awakenings

Sleep quality

Wake time after sleep onset

Daytime alertness

Tolerance

Rebound

Wherever possible, data on duration of therapy (time to tolerance) will be evaluated within the context of comparative effectiveness.

Safety outcomes

Overall adverse effect reports

Withdrawals due to adverse effects

Serious adverse events

Specific adverse events including, but not limited to

- Abuse potential
- Withdrawal symptoms
- Dependency
- Impairment of memory/daytime functioning

Study designs

Effectiveness:

- Controlled clinical trials of an included drug versus placebo or versus any active comparator (including, but not limited to, another included drug, benzodiazepines, trazodone, diphenhydramine, and amitriptyline).
- Good-quality systematic reviews

Adverse Events (dependency and withdrawal symptoms):

- Controlled clinical trials
- Observational studies (case-control, case series, case reports, cohort studies, surveys).

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 January 2008 through September Week 3 2009, using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical 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/index-eng.php>) web sites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote X1) 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 131 citations. Of those, there are 5 potentially relevant new trials (see Appendix A, attached). The characteristics of these studies are shown in Table 1.

Table 1. Potentially relevant new trials

Study	Comparison	Duration	Population/Notes
Blumer 2009	Zolpidem vs placebo	8 weeks	Children (ages 6 to 17) with insomnia associated with ADHD
Morin 2009	Zolpidem + CBT vs CBT alone	6 months	Adults with insomnia
Fava 2009	Zolpidem extended release vs placebo	8 weeks	Adults with comorbid generalized anxiety disorder and insomnia; all were taking escitalopram 10 mg
Mayer 2009	Ramelteon vs placebo	6 months	Adults with insomnia
Omvik 2008	Zopiclone vs CBT vs placebo	6 months	Adults age 55 and older with insomnia; secondary outcomes (daytime functioning) from a trial already included.

CBT=cognitive behavioral therapy

New Drugs/Indications

A sublingual form of zolpidem tartrate (Edluar®) was approved by the FDA in March 2009 for the treatment of insomnia characterized by difficulty with sleep initiation.

An oral spray form of zolpidem tartrate (Zolpimist®) was approved by the FDA in December 2008 for the treatment of insomnia characterized by difficulty with sleep initiation.

In February 2009, the FDA denied approval of the drug Silenor® (doxepin 3 mg and 6 mg, marketed by Somaxon Pharmaceuticals) for the treatment of insomnia. The company resubmitted the NDA in June 2009 after further data analysis. They will seek approval for the treatment of insomnia characterized by sleep maintenance and the prevention of early morning awakenings. The anticipated action date relating to the resubmission is December 2009.

No new indications for currently included drugs were identified.

New Safety Alerts

No new safety alerts for currently included drugs were identified.

APPENDIX A. Potentially Relevant New Trials (n=5)

Blumer, J. L., R. L. Findling, et al. (2009). "Controlled clinical trial of zolpidem for the treatment of insomnia associated with attention-deficit/ hyperactivity disorder in children 6 to 17 years of age." Pediatrics **123**(5): e770-6.

OBJECTIVE: The goal was to evaluate the hypnotic efficacy of zolpidem at 0.25 mg/kg per day (maximum of 10 mg/day), compared with placebo, in children 6 through 17 years of age who were experiencing insomnia associated with attention-deficit/hyperactivity disorder. **METHODS:** An 8-week, North American, multicenter, double-blind, placebo-controlled, parallel-group study was conducted. Patients underwent stratification according to age (6-11 years [N = 111] or 12-17 years [N = 90]) and were assigned randomly to receive treatment with the study drug or placebo (in a 2:1 ratio). The primary efficacy variable was latency to persistent sleep between weeks 3 and 6. Secondary efficacy variables also were assessed, and behavioral and cognitive components of attention-deficit/hyperactivity disorder were monitored. Safety was assessed on the basis of reports of adverse events, abnormal laboratory data, vital signs, and physical examination findings. The potential for next-day residual effects also was assessed. **RESULTS:** The baseline-adjusted mean change in latency to persistent sleep at week 4 did not differ significantly between the zolpidem and placebo groups (-20.28 vs -21.27 minutes). However, differences favoring zolpidem were observed for the older age group in Clinical Global Impression scores at weeks 4 and 8. No next-day residual effects of treatment were associated with zolpidem, and no rebound phenomena occurred after treatment discontinuation. Central nervous system and psychiatric disorders were the most-frequent treatment-emergent adverse events (>5%) that were observed more frequently with zolpidem than with placebo; these included dizziness, headache, and hallucinations. Ten (7.4%) patients discontinued zolpidem treatment because of adverse events. **CONCLUSION:** Zolpidem at a dose of 0.25 mg/kg per day to a maximum of 10 mg failed to reduce the latency to persistent sleep on polysomnographic recordings after 4 weeks of treatment in children and adolescents 6 through 17 years of age who had attention-deficit/hyperactivity disorder-associated insomnia.

Fava, M., G. M. Asnis, et al. (2009). "Zolpidem extended-release improves sleep and next-day symptoms in comorbid insomnia and generalized anxiety disorder." Journal of Clinical Psychopharmacology **29**(3): 222-30.

A multicenter, double-blind, parallel-group study was designed to assess the efficacy and safety of zolpidem extended-release coadministered with escitalopram in patients with insomnia and comorbid generalized anxiety disorder. Patients (N = 383) received open-label escitalopram 10 mg/d and were randomized to either adjunct zolpidem extended-release 12.5 mg or placebo. The primary efficacy measure was change from baseline to week 8 in subjective total sleep time. Secondary efficacy measures included subjective sleep onset latency, number of awakenings, wake time after sleep onset, sleep quality, the Hamilton Rating Scale for Anxiety, the Beck Anxiety Inventory, the Sleep Impact Scale, the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, and the

Sheehan Disability Scale. The last-observation-carried-forward method was used to impute missing values for most efficacy measures. Safety was monitored at each visit. At week 8 and all time points, there was a significant improvement in the zolpidem extended-release/escitalopram group compared with placebo/escitalopram for total sleep time ($P < 0.0001$). Most of the secondary efficacy measures also significantly favored zolpidem at most visits ($P < 0.0001$). The most common treatment-emergent adverse events in both groups were nausea, dizziness, headache, fatigue, and dry mouth. Concurrent zolpidem extended-release/escitalopram, compared with placebo/escitalopram, significantly improved insomnia and sleep-related next-day symptoms, but not anxiety symptoms, in patients with comorbid insomnia and generalized anxiety disorder.

Mayer, G., S. Wang-Weigand, et al. (2009). "Efficacy and safety of 6-month nightly ramelteon administration in adults with chronic primary insomnia." *Sleep* **32**(3): 351-60.

STUDY OBJECTIVES: Long-duration ($> \text{ or } = 6$ months) polysomnographic studies of insomnia medications are lacking. This study evaluated the long-term efficacy of ramelteon, a selective MT1/MT2 melatonin-receptor agonist used for insomnia treatment. **DESIGN:** Six-month, randomized, double-blind, placebo-controlled study. **SETTING:** Forty-six investigative sites in the United States, Europe, Russia, and Australia. **PARTICIPANTS:** Four hundred fifty-one adults (age $> \text{ or } = 18$ years) with chronic primary insomnia. **INTERVENTIONS:** Ramelteon, 8 mg, or placebo 30 minutes before bedtime nightly for 6 months. **MEASUREMENTS:** Sleep was evaluated by polysomnography and morning questionnaires on the first 2 nights of Week 1; the last 2 nights of Months 1, 3, 5, and 6; and Nights 1 and 2 of the placebo run-out. Next-morning residual effects as well as adverse effects and vital signs were recorded at each visit. Rebound insomnia and withdrawal effects were evaluated during placebo run-out. **RESULTS:** Over the 6 months of treatment, ramelteon consistently reduced latency to persistent sleep compared with baseline and with placebo; significant decreases were observed at Week 1 and Months 1, 3, 5, and 6 ($P < 0.05$). Ramelteon significantly reduced subjective sleep latency relative to placebo at Week 1, Month 1, and Month 5 ($P < 0.05$), with reductions nearing statistical significance at Months 3 and 6 ($P < \text{ or } = 0.08$). No significant next-morning residual effects were detected during ramelteon treatment. No withdrawal symptoms or rebound insomnia were detected after ramelteon discontinuation. Most adverse events were mild or moderate in severity. **CONCLUSIONS:** In adults with chronic insomnia, long-term ramelteon treatment consistently reduced sleep onset, with no next-morning residual effects or rebound insomnia or withdrawal symptoms upon discontinuation.

Morin, C. M., A. Vallieres, et al. (2009). "Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: a randomized controlled trial." *JAMA : the journal of the American Medical Association* **301**(19): 2005-15.

CONTEXT: Cognitive behavioral therapy (CBT) and hypnotic medications are efficacious for short-term treatment of insomnia, but few patients achieve complete remission with any single treatment. It is unclear whether combined or maintenance therapies would enhance outcome. **OBJECTIVES:** To evaluate the added value of

medication over CBT alone for acute treatment of insomnia and the effects of maintenance therapies on long-term outcome. **DESIGN, SETTING, AND PATIENTS:** Prospective, randomized controlled trial involving 2-stage therapy for 160 adults with persistent insomnia treated at a university hospital sleep center in Canada between January 2002 and April 2005. **INTERVENTIONS:** Participants received CBT alone or CBT plus 10 mg/d (taken at bedtime) of zolpidem for an initial 6-week therapy, followed by extended 6-month therapy. Patients initially treated with CBT attended monthly maintenance CBT for 6 months or received no additional treatment and those initially treated with combined therapy (CBT plus 10 mg/d of zolpidem) continued with CBT plus intermittent use of zolpidem or CBT only. **MAIN OUTCOME MEASURES:** Sleep onset latency, time awake after sleep onset, total sleep time, and sleep efficiency derived from daily diaries (primary outcomes); treatment response and remission rates derived from the Insomnia Severity Index (secondary outcomes). **RESULTS:** Cognitive behavioral therapy used singly or in combination with zolpidem produced significant improvements in sleep latency, time awake after sleep onset, and sleep efficiency during initial therapy (all $P < .001$); a larger increase of sleep time was obtained with the combined approach ($P = .04$). Both CBT alone and CBT plus zolpidem produced similar rates of treatment responders (60% [45/75] vs 61% [45/74], respectively; $P = .84$) and treatment remissions (39% [29/75] vs 44% [33/74], respectively; $P = .52$) with the 6-week acute treatment, but combined therapy produced a higher remission rate compared with CBT alone during the 6-month extended therapy phase and the 6-month follow-up period (56% [43/74 and 32/59] vs 43% [34/75 and 28/68]; $P = .05$). The best long-term outcome was obtained with patients treated with combined therapy initially, followed by CBT alone, as evidenced by higher remission rates at the 6-month follow-up compared with patients who continued to take zolpidem during extended therapy (68% [20/30] vs 42% [12/29]; $P = .04$). **CONCLUSION:** In patients with persistent insomnia, the addition of medication to CBT produced added benefits during acute therapy, but long-term outcome was optimized when medication is discontinued during maintenance CBT. **TRIAL REGISTRATION:** clinicaltrials.gov Identifier: NCT00042146.

Omvik, S., B. Sivertsen, et al. (2008). "Daytime functioning in older patients suffering from chronic insomnia: treatment outcome in a randomized controlled trial comparing CBT with Zopiclone." *Behaviour Research and Therapy* **46**(5): 623-41.

The paper presents data from a randomized controlled trial comparing treatment effects of cognitive behavioural therapy (CBT), hypnotic treatment (Zopiclone), and placebo in a sample of insomnia patients. Data from the same trial have already demonstrated that CBT was more efficient in improving sleep than Zopiclone. The novel outcomes that are reported here concern daytime functioning. Forty-six older patients (age ≥ 55) qualifying for a diagnosis of primary insomnia were recruited to participate. Assessments were completed at baseline, post-treatment, and at a 6-months follow-up, and measures of worry, anxiety, depression, interpersonal relationships, subjective alertness, vigilance, and quality of life were used. The participants in both treatment conditions scored within the normal range on the outcome measures at baseline with the exception of reporting less alertness, relative

to a group of good sleepers. One interaction effect indicated that subjective alertness improved more in the Zopiclone group than the CBT group from baseline to post-treatment, and another that CBT was more effective than Zopiclone in reducing trait anxiety from baseline to follow-up. It was concluded that the treatments yielded only minor effects on the measures of daytime functioning, and that none of them was clearly superior to the other.