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New Medications for the Treatment of Insomnia

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Insomnia is a common disorder affecting 10-34% of general medical practice patients, with a range of 10-15% meeting the criteria for chronic insomnia.[1,2] In 2004, Americans filled more than 35 million prescriptions for sleeping pills, spending $2.1 billion on these medications.[3] Evidence suggests that nearly half of chronic insomnia patients who take sleeping pills derive little or no subjective benefit from hypnotic usage, although they continue to take them for years.[4] The objective of this article is to examine the relative benefits and limitations of the newest nonbenzodiazepine sedative eszopiclone (*Lunesta*) and the novel melatonin receptor agonist ramelteon (*Rozerem*).

Eszopiclone

Eszopiclone (*Lunesta*), FDA approved December 2004, is the s-isomer of zopiclone, a sedative/hypnotic that has been available outside the United States since 1987. It is a nonbenzodiazepine, similar to zaleplon and zolpidem, thought to work via interaction with GABA-receptor complexes, at binding domains near or allosterically-coupled to benzodiazepine receptors. Its approval was based on six randomized, controlled trials for transient and chronic insomnia.[5-10]

Transient Insomnia: Rosenberg et al. evaluated the efficacy and safety of eszopiclone in healthy sleepers in an insomnia-inducing environment.[5] The primary efficacy measure was the mean objective sleep latency to persistent sleep (time to fall asleep) determined via polysomnography. Patients treated with 2 and 3mg of eszopiclone had significantly less sleep latency compared to placebo. The median objective latency reported for placebo was 12.5 minutes. Sleep latency was decreased to 6.5 minutes for the 2mg dose ($p<0.0001$) and approximately 5.5 minutes for the 3mg and 3.5mg doses ($p<0.0001$). The 1mg dose was no better than placebo.

Chronic Insomnia: The safety and efficacy of eszopiclone for chronic insomnia (symptoms of insomnia for at least 1 month) was evaluated in four randomized, double-blind, placebo-controlled studies.[6-9] In all of these studies, patients with a history of substance abuse/dependence or Axis I or II psychiatric disorders were excluded. Zammit et al. [6] compared eszopiclone 2 or 3mg to placebo in 308 patients (age 21 to 64 years) for 44 consecutive nights. The mean objective sleep latency (average from nights 1, 15 and 29) was 33.0 minutes for placebo and 23.0 and 18.0 minutes, for the 2 and 3mg doses respectively ($p<0.01$). Of the three treatment arms, however, only placebo improved at each evaluation and a difference of only 12 minutes separated mean sleep latency of placebo on the last night of objective evaluation from the highest dose of eszopiclone.

Krystal et al.[7] conducted a 6-month double-blind, placebo-controlled study to evaluate the safety and efficacy of eszopiclone 3mg in 788 adult patients (age 21-65 years). At the end of the sixth months, the mean self-reported (subjective) sleep latency was 63.1 minutes for placebo and 47.0 minutes for eszopiclone 3mg ($p<0.0001$), as compared to baseline values of 96.1 minutes and 90.6 minutes, respectively. Although patients did not report tolerance to the effects of eszopiclone (or placebo) over the course of the 6 month study, there were no objective measures to support this finding. The results of an open-label eszopiclone 3mg extension phase have also been published.[10] The subjective nature of this open-label portion, in particular, make the results of this study less useful.

Two additional 2-week randomized, double-blind, placebo-controlled studies evaluated the safety and efficacy of eszopiclone in elderly patients (age 65-85 years).[8,9] Scharf et al.[8] evaluated the subjective improvement in sleep outcomes of eszopiclone 1 and 2mg versus placebo in elderly patients. The study demonstrated that eszopiclone 2mg significantly improved all primary and secondary subjective sleep measures, but while eszopiclone 1mg improved sleep latency it did not improve measures related to sleep maintenance. Erman et al.[9] used objective measures (polysomnography) to evaluate the efficacy of eszopiclone in 265 elderly patients. Sleep latency (primary endpoint) was significantly improved in the eszopiclone group compared to placebo ($p<0.0001$). Results were available in abstract form only.

Class/Drug	Dose (mg)	Onset (min)	Effect on Sleep Structure	Adverse Effects	Cost/ 15 days*
BENZODIAZEPINES					
Temazepam (Restoril)	15-30	45-60	↓ sleep latency ↑ total sleep time ↓ delta sleep ↓ REM sleep	rebound insomnia dependence, hang over, daytime sedation, anterograde amnesia	$2
Triazolam (Halcion)	0.125 -0.25	15-30			$4
NON-BENZODIAZEPINES					
Zolpidem (Ambien)	5-10	30	↓ sleep latency ↑ total sleep time ↑ delta sleep ↓ ↔ REM sleep	headache, dizziness, tolerance/ withdrawal	$45
Zaleplon (Sonata)	5-10	15-30			$40
Eszopiclone (Lunesta)	1-3	20-50	↓ sleep latency ↑ total sleep time ↔ delta sleep ↔ REM sleep	unpleasant taste, headache, dizziness, dry mouth, dyspepsia, nausea	$45
MELATONIN RECEPTOR AGONIST					
Ramelteon (Rozerem)	8	12-70	↓ sleep latency ↑ total sleep time ↔ delta sleep ↔ REM sleep	dizziness, insomnia, hyperprol-actiemia	$36
ANTIDEPRESSANTS					
Amitriptyline (Elavil)	10-100	60-240	↓ sleep latency ↑ delta sleep ↓ REM sleep	antichol-inergic side effects, hypo-tension	$1
Trazodone (Desyrel)	25-150	30-120	↓ sleep latency ↑ total sleep time ↔ delta sleep ↔ REMsleep		$3

*Average retail cost for 15 days to OHP; excludes rebate

Table 1. Sedative hypnotic class comparison.

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There are no fully published head-to-head or active control trials that compare eszopiclone to the other nonbenzodiazepines. The only available comparative data comes from a poster presentation at a 2005 meeting of the American Psychiatric Association.[11] While the study's sponsor (Sepracor) states that this study was not prospectively designed to compare eszopiclone with zolpidem, the report from the Drug Effectiveness Review Project on newer sedative hypnotics found that objective sleep latency was slightly shorter for zolpidem 10mg compared to eszopiclone 1mg, but there was no difference between zolpidem 10mg and eszopiclone 2mg or 3mg.[12] In addition, there were no differences between zolpidem and eszopiclone on subjective measures of next-day effects. Separately, data compiled by Griffiths and Johnson found that the likelihood for abuse was higher for eszopiclone (50%) compared to zolpidem (33%) and trazodone (0%).[13] Relative toxicity also varied between these drugs from 56% for eszopiclone and zolpidem to 42% for trazodone. Further comparative studies of effectiveness and safety are needed in order to distinguish eszopiclone from other sedative hypnotic agents. A comparison of pharmacologic properties and cost information across sedative hypnotic drug classes is available in table 1.

Ramelteon

Ramelteon (*Rozerem*) is a melatonin agonist approved for the treatment of insomnia associated with a difficulty in sleep onset. It is highly selective for melatonin type 1 (MT1) and type 2 (MT2) receptors. Melatonin receptors, when activated, inhibit adenylate cyclase and lead to a decrease in cyclic AMP. One study in animals indicates that the MT1 receptor regulates sleepiness, while the MT2 receptor may mediate the phase-shifting effects of melatonin on the 24-hour biological clock.[14] Melatonin itself is available as a "dietary supplement," but its effectiveness as a sedative hypnotic remains uncertain.

While a number of studies evaluating the use of ramelteon in transient and chronic insomnia have been conducted, currently there is very limited data available for review.

Roth et al.[15] performed a one-night study of ramelteon 16 or 64mg in healthy normal sleeping adults. While the latency to persistent sleep decreased by 10.5 minutes and 9.1 minutes for the 16 and 64mg doses respectively ($p<0.001$), the maintenance of sleep was no better for ramelteon than for placebo. Longer duration studies of various doses in patients with chronic insomnia have similar findings, suggesting there is no benefit to using ramelteon in patients with problems maintaining sleep, nor is there benefit to using doses greater than 8mg.[16] Currently there are no head-to-head trials to compare ramelteon to other sedative hypnotic medications.

The most common adverse effects seen in clinical trials were somnolence, dizziness, nausea, fatigue, headache and insomnia. In one 6-month study, 32% of patients had an increase in serum prolactin.[17] Some CYP isoenzyme inducers (e.g. rifampin) have been found to decrease the serum concentration of ramelteon by up to 80%. The manufacturer advises against the coadministration of ramelteon and strong CYP1A2 inhibitors (e.g. fluvoxamine) that can markedly increase serum ramelteon concentrations. High dose ramelteon in rats was found to cause hepatic carcinoma. In light of this, ramelteon is contraindicated in patients with severe hepatic impairment and should be used with caution in moderate hepatic impairment.

In comparison to placebo, ramelteon has been found to objectively reduce the latency to persistent sleep by an average of 7.5-15.7 minutes and increase total sleep time by 11.6 to 19.0 minutes.[18] The clinical significance of these findings is suggested to be minimal.

Sedative Use in the Elderly

Sedative hypnotic medications are commonly used by elderly patients. In the first 11 months of 2005, there were 6,036 Oregon Health Plan fee-for-service (open card) patients over the age of 65 that received a sedative hypnotic medication. A recent meta-analysis published in the *British Medical Journal* reviewed the risks and benefits of sedative hypnotics in older people.[19] Their findings suggest that while improvements in sleep may be statistically significant, their clinical benefit is modest. The number needed to treat for one patient to have improvement in quality of sleep was 13. In addition, the authors found that the number needed to harm for sedative hypnotics compared to placebo was 6. Psychomotor-type side effects such as dizziness and loss of balance are commonly reported by the elderly. The authors noted that studies comparing benzodiazepines to the newer sedative hypnotics have not found any significant difference in cognitive adverse events. These findings suggest that the benefits of sedating medications in elderly patients may not justify the increased risk.

Conclusion

The two newest sedative hypnotic medications, eszopiclone and ramelteon do not appear to offer additional benefit and are high cost alternatives to the older agents. Further studies with active comparators are necessary prior to identifying their ideal place in therapy. Intermittent treatment with all sedating medications is preferred to chronic therapy. If long-term therapy is required, the lowest effective dose should be prescribed. All sedative hypnotic medications need to be used cautiously in elderly patients with the benefit of treatment outweighing the known risk associated with these drugs.

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References

1. Sateia MJ. Insomnia. *Lancet*. 2004;364(9449):1959-1973.
2. Silber MH. Chronic insomnia. *NEJM*. 2005;353(8):803-810.
3. Medco Health Solutions, Inc. Sleep deprivation driving drug use and cost, new research finds increased use of prescription sleep aids. www.medco.com. Accessed 11/3/2005.
4. Sateia MJ, Doghramji K, Hauri PJ, Morin CM. Evaluation of chronic insomnia. *Sleep*. 2000;23(2):243-308.
5. Rosenberg R, Caron J, Roth T, Amato D. An assessment of the efficacy and safety of eszopiclone in the treatment of transient insomnia in healthy adults. *Sleep Med*. 2005; 6():15-22.
6. Zammit GK, McNabb LJ, Caron J, et al. Efficacy and safety of eszopiclone across 6-weeks or treatment for primary insomnia. *Curr Med Res Opin*. 2004;20(12):1979-1991.
7. Krystal AD, Walsh JK, Laska E, et al. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. *Sleep*. 2003;26(7):793-799.
8. Scharf M, Erman M Rosenberg R, et al. A 2-week efficacy and safety study of eszopiclone in elderly patients with primary insomnia. *Sleep*. 2005;28(6):720-727.
9. Erman M, Rosenberg R, Caron J, et al. Polysomnographic and patient-reported evaluation of the efficacy and safety of eszopiclone in elderly subjects with chronic insomnia (poster presentation). *Sleep*. 2004;27(suppl.):A257-A258.
10. Roth T, Walsh JK, Krystal A, et al. An evaluation of the efficacy and safety of eszopiclone over 12 months in patients with chronic primary insomnia. *Sleep Med*. 2005;6(6):487-95.
11. Erman MK, Walsh JK, Wessel TC, Caron J, Amato D. A crossover study of eszopiclone in the treatment of primary insomnia (poster). American Psychiatric Association Meeting Poster Session. 2005.
12. Center for Evidence Based Medicine. Drug class review of newer sedative hypnotics. http://www.ohsu.edu/drugeffectiveness/reports/final.cfm. Accessed December 15, 2005.
13. Griffiths RR, Johnson MW. Relative abuse liability of hypnotic drugs: a conceptual framework and algorithm for differentiating among compounds. *J Clin Psychiatry*. 2005;66 Suppl 9:31-41.
14. Cajochen C. TAK-375 Takeda. *Curr Opin Investig Drugs*. 2005;6(1):114-121.
15. Roth T, Stubbs C, Walsh JK. Ramelteon (TAK-375), a selective MT1/MT2-receptor agonist, reduces latency to persistent sleep in a model of transient insomnia related to a novel sleep environment. *Sleep*. 2005;28(3):303-307.
16. Erman M, Seiden D, Zammit G, et al. An efficacy, safety, and dose-response study of ramelteon in patients with chronic primary insomnia. *Sleep Med*. 2005, in press.
17. Rozerem Package Insert. Takeda Pharmaceuticals. 2005.
18. Ramelteon for insomnia. *Med Lett Drugs Ther*. 2005;47(1221):89-91.
19. Glass J, Lanctot KL, Herrmann N, et al. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ. 2005 Nov 19;331(7526):1169-1176.

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