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LUNESTA™: A NEW NON-BENZODIAZEPINE FOR THE TREATMENT OF INSOMNIA

Kimberly Fleming, Pharm.D. Candidate

Approximately 33% to 55% of adults suffer from insomnia during their lifetime. An estimated 10% to 15% of adults complain of chronic insomnia, while 25% to 35% complain of transient insomnia.[1] Although the diagnosis of insomnia is somewhat subjective, the consequences of untreated insomnia are transparent. Untreated, insomnia can lead to decreased work productivity and health care costs exceeding one billion per year, partly due to increased car accidents and comorbidities, such as depression.[2,4]

The subjective complaints associated with insomnia include daytime drowsiness, increased sleep latency, and/or nighttime awakenings. The number of hours that any given individual sleeps at night may not be enough to correctly diagnose insomnia. The amount of time an average person sleeps varies from 3 to 10 hours.[3] Thus, some persons that meet the recommended eight hours of sleep per night may be sleep deprived due to individual variations in sleep requirements.[1] Insomnia can not be presumptively diagnosed in a patient simply based on a complaint of daytime somnolence or "not getting enough sleep". A patient must also complain of increased sleep latency and/or nighttime awakenings. The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) lists five criteria for the diagnosis of insomnia (Table 1).[11]

Primary insomnia can be further divided into transient or short-term, and long-term or chronic.[3] However, there is much contention about the precise definition of these subtypes. In general, the major distinction is based on the duration of symptoms. Transient insomnia lasts anywhere from a few days to three weeks. According to the DSM-IV criteria, the complaint must last for at least one month in order to fit the diagnosis of chronic insomnia.[4,11] This leaves a gap between three to four weeks of symptoms in which a patient does not fit either category.

Although the best treatment for insomnia is better sleep hygiene through lifestyle modification, pharmacological therapy is indicated in some circumstances. The ideal hypnotic would possess all of the characteristics listed in Table 2; however, all of the medications currently approved by the FDA for treatment of short-term insomnia display one or more limitations. (Table 3)

Diphenhydramine, and other sedating antihistamines which are available over-the-counter, frequently cause daytime drowsiness and xerostomia. In recent studies, diphenhydramine has shown superiority over placebo for treating transient insomnia; how-

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Table 1. DSM-IV Diagnostic Criteria for Primary Insomnia

A. The predominant complaint is difficulty initiating or maintaining sleep, or non-restorative sleep, for at least 1 month.

B. The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia.

D. The disturbance does not occur exclusively during the course of another mental disorder (e.g., major depressive disorder, generalized anxiety disorder, a delirium).

E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Adapted from Reference 11

ever tolerance to its' sedative effects may occur after a few nights of consistent use.[1,5] Therefore, use of diphenhydramine may not be appropriate for chronic insomnia. Barbiturates, such as phenobarbital, have been replaced by benzodiazepines which are less likely to cause tolerance, dependence, and rebound insomnia. Benzodiazepines also decrease sleep latency and increase duration of sleep. However, according to a recent meta-analysis, benzodiazepines also cause daytime drowsiness, respiratory depression, dizziness, and impairment of cognitive function.[6] These effects limit the use of benzodiazepines in many patients. In addition, practitioners should consider the risk of dependence with this class of drugs and the possibility of rebound insomnia when the medication is discontinued.[4] Chloral hydrate has fallen out of favor for the treatment of insomnia due to drug interactions, GI distress, and fatalities associated with overdose. Although not FDA-approved for insomnia, antidepressants that have sedative properties are often utilized in clinical practice. Trazodone has been widely used to treat insomnia associated with depression.[4] However, this class of drugs has anticholinergic side effects that limit their use. A newer class of drugs, non-benzodiazepines such as zolpidem (Ambien®) and zaleplon (Sonata®), have emerged. This class, also known as the selective benzodiazepine agonists, have fewer drug interactions and cause less rebound insomnia. Due to a rapid onset and short half-life, they decrease sleep latency with minimal daytime drowsiness.[1]

Eszopiclone (Lunesta™), a new non-benzodiazepine hypnotic agent marketed by Sepracor, was approved by the FDA in December 2004. In contrast to zolpidem and zaleplon which are approved for short-term insomnia, eszopiclone is approved for long-term use. This article will examine the safety, efficacy, and tolerability of eszopiclone.

Pharmacology/Pharmacokinetics of Eszopiclone

Benzodiazepines bind non-selectively to the omega 1 and 2 sites on the GABA-A chloride ionophore. Binding results in an influx of chloride ions which suppresses excitatory activity. Omega 1 is responsible for the hypnotic effects of the drug, whereas omega 2 is responsible for the CNS effects such as memory loss. Eszopiclone is believed to bind to a location near the GABA receptor complex that is allosterically coupled to benzodiazepine receptors. Its' chemical structure is unrelated to other hypnotic drugs.[7]

Eszopiclone is the S-isomer of the racemic compound, zopiclone. Zopiclone (Imovane®) is currently marketed in Canada by Sanofi-Aventis. Eszopiclone is rapidly absorbed, reaching maximum

Table 2: Characteristics of the Ideal Hypnotic*

Desirable	Undesirable
Rapid and complete absorption	Residual daytime effects
Rapid sleep induction	Memory loss
Preserved physiological sleep architecture	Altered sleep architecture
Optimal duration of action	Respiratory depression
Addresses the underlying condition causing insomnia	Tolerance and/or physical dependence
	Rebound insomnia
	Interaction with ethanol or other medications

*Adapted from Reference 2

Table 3: Drugs Approved by the FDA for the Treatment of Insomnia

Drug Class	Generic Name	Proprietary Name
Barbiturates	Amobarbital	Amytal®
	Aprobarbital	Alurate®
	Butabarbital	Butisol®, Buticaps®
	Pentobarbital	Nembutal®
	Phenobarbital	Luminal®
	Secobarbital	Seconal®
Benzodiazepines	Estazolam	ProSom®
	Flurazepam	Dalmane®
	Lorazepam	Ativan®
	Quazepam	Doral®
	Temazepam	Restoril®
	Triazolam	Halcion®
Antihistamines (H_1 Receptor Antagonists)	Diphenhydramine	Benadryl®
	Doxylamine	Unisom®, Equate®, Nytol®
Nonbenzodiazepines	Eszopiclone	Lunesta™
	Zaleplon	Sonata®
	Zolpidem	Ambien®
Psychotropics	Ethchlorvynol	Placidyl®
	Paraldehyde	Paral®
Sedqative Hypnotic	Chloral Hydrate	Aquachloral ®

concentration in about 1 hour and does not accumulate when given once daily. Eszopiclone is extensively metabolized by CYP3A4 and CYP2E1 via oxidation and demethylation but does not inhibit any of the major CYP450 pathways. Zopiclone is eliminated primarily as metabolites in the urine. It is assumed that eszopiclone follows the same route of elimination. Less than 10% of the parent drug is excreted in the urine. Food delays the onset of action of eszopiclone by about an hour. The half-life, 6 hours, is substantially longer than either zopiclone or zolpidem. This may serve to increase total sleep time by preventing "wearing off" but could also increase residual effects of the drug. Patients greater than 65 years experience a 41% increase in total exposure and a prolonged elimination of about 9 hours, suggesting the importance of a lower starting dose in this population. When administered with paroxetine, digoxin, or warfarin, no apparent pharmacokinetic or pharmacodynamic drug interactions were observed. Co-administration of eszopiclone with olanzapine results in a change in psychomotor function beyond that expected with either agent alone, suggesting that the CNS effects of eszopiclone may be additive with other drugs. Co-administration of lorazepam and eszopiclone resulted in a 22% decrease in the maximum serum concentration (Cmax) of both drugs. Ketoconazole potentiates a 2.2-fold increase in exposure to eszopiclone.[7] Table 4 compares the pharmacokinetics of the non-benzodiazepine hypnotics.

Clinical Trials

Transient Insomnia

Eszopiclone's effect on transient insomnia was evaluated in a randomized, double-blind, placebo-controlled study.[8] Four hundred thirty-six eligible patients aged 25-50 years were randomized to receive either eszopiclone 1, 2, 3, 3.5 mg, or placebo.

Table 4: Pharmacokinetics of the Non-Benzodiazepines

	Eszopiclone	Zolpidem	Zaleplon
Onset	1 hour	1.5 hours	1 hour
t½	6 hours	2.5-2.6 hours	1 hour
Dose Adjustments	Elderly or hepatic impairment	Elderly or hepatic impairment	Elderly or hepatic impairment
Route of elimination	Hepatic	Hepatic	Hepatic
CYP involvement	CYP3A4, CYP2E1	CYP3A4, CYP2C9	CYP3A4 (minor)

The primary endpoint was latency to persistent sleep (LPS), defined as the duration of time from when the participant began trying to fall asleep to the time immediately before 10 minutes of uninterrupted sleep. Secondary endpoints included wake time after sleep onset (WASO), sleep efficiency, number of nighttime awakenings, and amount of time spent in each stage of sleep. Using polysomnography (PSG), a statistically significant shorter LPS ($p < 0.0001$) was found in participants receiving doses of 2, 3, and 3.5 mg of eszopiclone compared to placebo. Those receiving the 2 and 3 mg dose had a mean LPS of 10 minutes, and those receiving the 3.5 mg dose had a mean LPS of 8 minutes. The WASO was significantly shorter ($p < 0.05$) and sleep efficiency was significantly higher ($p < 0.02$) in subjects treated with eszopiclone, where as nighttime awakenings were significantly reduced with the 3 and 3.5 mg doses only ($p < 0.005$). Self-reported sleep efficacy results were similar to objective measures: shorter LPS ($p < 0.05$), fewer nighttime awakenings ($p < 0.05$), shorter WASO (3 and 3.5 mg only, $p < 0.05$), more total sleep time (all except the 1 mg group, $p < 0.01$), more reports of very deep sleep ($p < 0.01$), and more reports of excellent quality sleep (all but 1 mg, $p < 0.0001$). Significant differences in sleep architecture were seen in participants treated with eszopiclone 3.5 mg compared to placebo. This group showed a decrease in Rapid Eye Movement (REM) sleep ($p < 0.05$), a decrease in stage 1 ($p < 0.05$), and an increase in stage 2 ($p < 0.01$). The incidence of adverse events was similar to placebo with the exception of dysguesia, which was reported at a higher frequency in all groups receiving eszopiclone. Somnolence was reported in all groups, ranging from 6.2 % in the 2 mg group to 4.1% in the placebo group.

Chronic Insomnia

Two randomized, double-blind, multicenter, placebo-controlled trials have evaluated eszopiclone in chronic insomnia. Zammit et al.[9] randomized adults, aged 21-64 years old, to either eszopiclone 2 mg, eszopiclone 3 mg, or placebo for 44 days. As compared to placebo, eszopiclone reduced sleep latency (2 mg $p<0.001$, 3 mg $p< 0.0001$), increased total sleep time (2 mg $p<0.01$, 3 mg $p<0.0001$), increased sleep efficiency (2 mg $p<0.001$, 3 mg $p<0.0001$), and increased quality and depth of sleep (2 mg and 3 mg $p<0.05$). The 3 mg dose significantly improved sleep maintenance ($p<0.01$). The results showed no evidence of rebound insomnia, tolerance, or decreased performance in the morning. Sleep architecture was preserved in all stages except for Stage 2, which increased 25 minutes and 37 minutes for the 2 mg and 3 mg dose of eszopiclone, respectively, versus placebo ($p<0.05$). Treatment-related adverse effects that differed from placebo included abnormal dreams, nervousness, back pain, dizziness, xerostomia, somnolence, headache, and dysguesia.

In the study used to justify chronic use, Krystal et al.[10] randomized 788 patients aged 21 to 69 years to eszopiclone 3 mg or placebo every night for 6 months. Compared to placebo, eszopiclone 3 mg decreased sleep latency ($p<0.0001$), WASO ($p=.0032$), nighttime awakenings ($p< 0.001$), and increased total sleep time ($p<0.0001$) and sleep quality scores ($p<0.0001$). There was no evidence of tolerance to eszopiclone and daytime effects, such as alertness and ability to function, were actually improved. Adverse event rates were similar to the aforementioned study with dysguesia being reported most frequently. Table 5 summarizes the clinical trials with eszopiclone.

Dosing and Administration

Eszopiclone should be taken immediately be-

Table 5: Summary of Clinical Trials

Study *	Drug/Dose	Number of patients	Sleep Latency, min (Median)	Total Sleep Time, min (Median)	Nighttime awakenings (Median)
Rosenberg et al.[8]	Placebo	98	15	460	2
	Eszopiclone 1mg	47	10	460	2
	Eszopiclone 2mg	97	10	470	2
	Eszopiclone 3mg	98	10	474.5	1
	Eszopiclone 3.5mg	96	8	478	1
Zammit et al.[9]	Placebo	99	46	366	3
	Eszopiclone 2mg	104	30	400	2.7
	Eszopiclone 3mg	105	27.7	406	2.4
Krystal et al.[10]	Placebo	196	45	345	2
	Eszopiclone 3mg	595	30	382.5	1.6

*The study by Rosenberg et al. enrolled patients wit transient insomnia, whereas the studies by Zammit and Krystal were in patients with chronic insomnia.

fore bedtime and should not be taken with food due to an increased time to peak plasma concentrations. The recommended starting dose for most adults is 2 mg at bedtime, with the option to increase the dose to a maximum of 3 mg if necessary. For elderly patients who are at increased risk of adverse effects, a starting dose of 1 mg/day is suggested in patients with a primary complaint of increased sleep latency, whereas 2 mg can be used if nighttime awakenings are bothersome. In patients with severe hepatic impairment or patients taking potent CYP3A4 inhibitors, the starting dose should be 1 mg at bedtime. A lower dose should be considered in patients with a disease or condition that might decrease the metabolism of eszopiclone, although there is no clinical evidence of such interactions. No dosage adjustment is necessary in patients with renal impairment. Eszopiclone has not been studied in children younger than 18 years old or in pregnant or nursing women.[7]

Table 6: Average Retail Cost of Non-Benzodiazepines

Drug	Dose	Average Montly (30 day) Cost*
Eszopiclone	1 mg	$111.00-$114.90
	2 mg	$111.00-$114.90
	3 mg	$111.00-$114.90
Zolpidem	5 mg	$45.00-$59.70
	10 mg	$45.00-$59.70
Zaleplon	5 mg	$45.00-$59.70
	10 mg	$60.00-$89.70

* Cost represents average retail cost of Lunesta™, Ambien™, and Sonata™ from 3 major retail pharmacies in Gainesville, FL.

Toxicity and Safety

Some of the adverse events associated with eszopiclone are dose related. Viral infection, xerostomia, dizziness, hallucinations, infection, rash, and unpleasant taste were reported more often with the 3 mg dose compared with the 2 mg dose. Other adverse events observed at a higher rate with active drug than with placebo, are headache, nausea, vomiting, anxiety, depression, nervousness, somnolence, dysmenorrhea, and gynecomastia. Bitter taste was the most frequent side effect with a reported incidence of 3% with placebo, 17% with eszopiclone 2 mg/day, and 34% with eszopiclone 3 mg/day. In clinical trials, the discontinuation rate was less than 2%.[7]

Cost

The average retail cost of the non-benzodiazepine hypnotics are depicted in Table 6.

Summary

Eszopiclone is the first agent available in the United States indicated for the long-term treat-

ment of insomnia. In clinical trials, eszopiclone demonstrated efficacy versus placebo for the treatment of short-term and long-term insomnia, especially at the higher end (3 mg) of the dosing range. Studies of eszopiclone have treated patients for up to six months. It appears to be well-tolerated with the most common reported adverse event being unpleasant taste. The discontinuation rate in all three studies was low and not related to adverse events. In many ways, eszopiclone resembles the non-benzodiazepine hypnotics currently on the market; however, the availability of long-term safety and efficacy data with eszopiclone is encouraging. Long-term studies evaluating zaleplon and zolpidem are needed to confirm their safety and efficacy in this setting.

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Labeling Changes

The FDA has asked that manufacturers of all prescription non-steroidal anti-inflammatory drugs (NSAIDs) revise their product labeling to include warnings regarding increased cardiovascular events and gastrointestinal bleeding. The warning will come in the form of a black box warning in the package insert and a medication guide to be dispensed with the product. Over-the-counter NSAIDS will soon add more specific warnings to the product label, reminding patients of such risks.

New Drug Approvals

Menactra (Meningococcal [Groups A, C, Y, and W-135] polysaccharide diphtheria toxoid conjugate vaccine), a tetravalent conjugate vaccine (MCV4), is approved for the prevention of meningococcal disease in adults and adolescents 11-55 years of age. The Advisory Committee on Immunization Practices (ACIP) now recommends routine vaccination of young adolescents with MCV4 at the preadolescent visit (11-12 years old).

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