Sedative / Hypnotic Review

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FDA-Approved Indications

Drug	Manufacturer	Adjunct to anesthesia and perioperative sedation	Short-term treatment of insomnia*	Treatment of insomnia
chloral hydrate (Somnote®)[1]	generic	X	X	
estazolam (Prosom™)[2]	generic		X	
eszopiclone (Lunesta™)[3]	Sepracor			X
flurazepam (Dalmane®)[4]	generic		X	
quazepam (Doral®)[5]	Questcor		X	
ramelteon (Rozerem™)[6]	Takeda			X
temazepam (Restoril®)[7]	generic		X	
triazolam (Halcion®)[8]	generic		X	
zaleplon (Sonata®)[9]	generic		X	
zolpidem (Ambien®)[10]	generic		X	
zolpidem sublingual (Edluar®)[11]	Meda		X	
zolpidem ER (Ambien® CR)[12]	Sanofi-Aventis			X

Overview

Insomnia is a significant public health problem in the United States. The Surgeon General has estimated that chronic sleep loss and untreated insomnia cost the United States $15 billion in health care expenses and $50 billion in productivity losses each year.[13]

Insomnia is a symptom complex that comprises difficulties falling asleep, staying asleep, or nonrefreshing sleep, in combination with daytime dysfunction or distress. The symptom complex can be an independent disorder (primary insomnia) or the result of another condition (secondary

insomnia).[14] Insomnia is commonly divided into three types based on duration. Transient insomnia lasts up to one week and is often referred to as adjustment sleep disorder, because it is caused most often by an acute situational stress, such as a test or deadline. It is often recurrent with the same or similar stresses. The second type, short-term insomnia, by definition lasts one to six months, and is usually associated with more persistent stressful situational (death or illness) or environmental (noise) factors. Finally, chronic insomnia is insomnia lasting more than six months. Chronic insomnia is usually primary.

Treatment for insomnia should first consist of identification and treatment/control of secondary sources. Whenever possible, use of nonpharmacological measures should be used to treat insomnia. Stimulus control, progressive muscle relaxation, paradoxical intention, and biofeedback have been shown to be beneficial and are all recommended by the American Academy of Sleep Medicine.[15] When such measures fail to address the condition, use of pharmacologic hypnotics may be indicated.

Chloral hydrate was introduced as a sedative in 1869 followed by paraldehyde in 1882. After their introduction in the early 1900s, barbiturates were the drugs most often used for sleep and sedation. In an effort to improve on the safety profile of the barbiturates, pharmaceutical manufacturers introduced several non-barbiturate sedatives (ethclorvynol, glutethimide, methprylon, etc.) in the 1940s and 1950s. The use of all of these agents declined significantly upon the introduction of the safer benzodiazepines in the late 1950s.[16]

Benzodiazepines dominated the sedative-hypnotic market for a quarter century. From 1987 to 1996, however, prescribing of benzodiazepine hypnotics for the treatment of insomnia declined by 150 percent. During this same time, off-label prescribing of sedating antidepressants for insomnia increased by more than 150 percent.[17] More significant, however, was the release of the non-benzodiazepine hypnotic agent, zolpidem (Ambien), in 1993.

At present, benzodiazepines and newer non-benzodiazepine agents are the drugs primarily recommended and used for the treatment of insomnia. An expert panel convened by the National Institutes of Health (NIH) in June 2005 noted in their draft consensus statement that most antidepressants have not been adequately tested in randomized clinical trials for the treatment of insomnia and that only doxepin and trazodone have even been minimally investigated.[18] The panel noted that all antidepressants “have potentially significant adverse effects, raising concerns about the risk: benefit ratio” for the treatment of patients with chronic insomnia, especially the elderly. Antipsychotics are also widely used off-label for treatment of insomnia. The NIH panel noted in their draft document that: “Studies demonstrating the usefulness of these medications for either short- or long-term management of insomnia are lacking” and that “all of these agents have significant risks and thus their use in the treatment of chronic insomnia cannot be recommended.”

This review will focus on those agents indicated for insomnia and identified by the NIH expert panel as having a role in the contemporary treatment of insomnia in adults as well as one agent approved for use in younger children, chloral hydrate.

Pharmacology

Chloral hydrate is a nonspecific central nervous system (CNS) depressant. It is thought that its CNS effects are due primarily to its active metabolite, trichloroethanol. Hypnotic doses produce mild cerebral depression, while higher doses of chloral hydrate induce respiratory and vasomotor depression. Unlike barbiturates and benzodiazepines, chloral hydrate has little effect on the electroencephalogram.

Benzodiazepines are believed to potentiate gamma aminobutyric acid (GABA) neuronal inhibition. The sedative and anticonvulsant actions of these drugs involve GABA receptors located in the limbic, neocortical, and mesencephalic reticular systems. At least two benzodiazepine receptor subtypes have been identified in the brain, BZ-1 and BZ-2. BZ-1 is thought to be associated with sleep mechanisms while BZ-2 is thought to be associated with memory, motor, sensory, and cognitive functions. Benzodiazepines generally decrease the time to onset of persistent sleep (sleep onset latency, SOL) and reduce the number of awakenings.[19]

Although structurally different from the benzodiazepines and from one another, the cyclopyrrolone hypnotics, eszopiclone (Lunesta), zaleplon (Sonata), and zolpidem (Ambien, Ambien CR), are all active at the GABA-BZ receptor complex.[20] Unlike the benzodiazepines, these newer agents bind selectively to the BZ-1 receptor. Eszopiclone (Lunesta) is the S-isomer of zopiclone, an agent that is available in Canada and Europe.[21,22] Ambien CR, zolpidem extended release (ER), is a modified dosage form of zolpidem (Ambien) that releases drug in a biphasic manner.[23,24] Edluar is a sublingual dosage form of zolpidem.[25]

Ramelteon (Rozerem) is a highly selective and potent agonist of the MT1 and MT2 melatonin receptors, which are believed to be involved in the regulation of the circadian rhythm.[26] The MT1 receptor is believed to regulate sleepiness, whereas the MT2 receptor is thought to help the body shift between day and night. Ramelteon has been reported to have greater affinity, selectivity, and potency than melatonin for the MT1 receptor, resulting in a better ability to induce sleep onset. Ramelteon has shown no affinity for the GABA-receptor complex which is the primary target area for most of the other agents in this class.[27]

Pharmacokinetics

Drug	Onset of Action (minutes)	Duration of Action (hours)	Half-Life of Parent Compound (hours)	Active Metabolite(s) (Half-Life)	Metabolism
chloral hydrate[28,29]	30-60	4-8	short	trichloroethanol (8-11 hrs)	chloral hydrate dehydrogenase alcohol dehydrogenase
estazolam[30,31]	15-120	6-8	14.4-15	None	CYP 3A4
eszopiclone (Lunesta)[32,33]	≤30	6-8	6	zopiclone-N-oxide N-desmethylzopiclone	CYP 3A4 CYP 2E1
flurazepam[34]	30-60	7-10	2.3	desalkylflurazepam (47-100 hrs; up to 160 hrs in elderly) N-1-hydroxyethylflurazepam (2-4 hrs)	oxidation
quazepam (Doral)[35]	20-60	7-10	39	2-oxoquazepam (39 hrs) N-desalkyl-2-oxoquazepam (73 hrs)	hepatic
ramelteon (Rozerem)[36]	≤30	nr	1-2.6	MII (2-5 hrs)	oxidation CYP 1A2
temazepam[37]	15-120	6-8	3.5-18.4	None	conjugation
triazolam[38]	15-30	1.7-3	1.5-5.5	None	oxidation CYP 3A4
zaleplon (Sonata)[39,40]	10-30	4	1	None	aldehyde oxidase CYP 3A4
zolpidem (Ambien)[41] zolpidem ER (Ambien CR)[42]	<30-96 (delayed in presence of food)	8	2.5-2.6 1.6-4.1	None	CYP 3A4
zolpidem sublingual (Edluar)[43]	30-180 (delayed in presence of food)	8	1.65-6.73	None	CYP 3A4

Zolpidem ER (Ambien CR) is a coated two-layer tablet with one layer that releases the drug content immediately and another layer that slowly releases additional drug beyond three hours after administration.[44] Compared to the immediate release formulation, the peak concentration of zolpidem ER is reached at later time (2.4 versus 2.0 hours; $p<0.004$) and is approximately 13 percent lower.[45]

Contraindications/Warnings[46,47,48,49,50,51,52,53,54,55]

These drugs should all be administered immediately before going to bed or after the patient has gone to bed and experienced difficulty falling asleep. These agents may result in short-term memory impairment, hallucinations, impaired coordination, dizziness, and light-headedness. The FDA-approved labeling of these drugs includes a warning regarding complex sleep-related behaviors such as sleep-driving, making phone calls, sexual activity, and preparing and eating food while asleep. These behaviors are more likely to occur when the sedative-hypnotic is taken concurrently with alcohol or other CNS depressants. Patients often have no memory of these events. The drugs in this class should all be used at the lowest effective dose and only after careful assessment of sleep disturbances for cause, emergence, or worsening of psychiatric or physical disorders, behavioral changes, amnesia, and withdrawal symptoms. Patients whose insomnia fails to remit after seven to 10 days of treatment with a sedative-hypnotic may have a primary psychiatric or medical illness that should be evaluated.

All of the agents in this class have a warning about their potential for anaphylaxis and angioedema, which can occur as early as the first dose.

Benzodiazepines are contraindicated in patients with suspected or established sleep apnea. Ramelteon also has not been studied in subjects with severe sleep apnea or severe COPD and is not recommended for use in those populations.

Ramelteon (Rozerem) is not a controlled substance. No difference in subjective responses indicative of abuse potential was found between ramelteon and placebo at doses up to 20 times the recommended therapeutic dose.[56]

Ramelteon and zaleplon (Sonata) should not be used in patients with severe hepatic impairment. Chloral hydrate is metabolized rapidly by the liver to an active metabolite that is renally excreted and should be avoided in severe hepatic impairment and moderate or severe renal insufficiency.

All sedative/hypnotics should be administered with caution to patients exhibiting signs and symptoms of depression. Suicidal tendencies may be present in such patients, and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the smallest amount of drug that is feasible should be prescribed for the patient at any one time.

Drug Interactions[57,58,59,60,61,62,63,64,65,66,67]

Drugs in this class should be used with caution in patients receiving other CNS depressants as the effects may be additive, resulting in decreased alertness and impaired psychomotor performance.

Benzodiazepines: Increased CNS depressant effects of the benzodiazepines that are metabolized by oxidation have been reported when coadministered with isoniazid, oral contraceptives, cimetidine, and disulfiram.

Chloral hydrate: Chloral hydrate may potentiate the effect of warfarin. Concomitant use with alcohol may cause a vasodilation reaction (flushing, tachycardia, etc.).

Estazolam, eszopiclone (Lunesta), ramelteon (Rozerem) and its active MII metabolite, triazolam, zaleplon (Sonata), and zolpidem (Ambien, Ambien CR, and Edluar) are substrates for the CYP450 3A4 enzyme. As such, inducers of CYP450 3A4 (e.g., rifampin) increase the clearance and reduce the bioavailability of these agents by approximately 80 percent. Inhibitors of CYP450 3A4 (e.g., cimetidine, clarithromycin, ketoconazole) increase the bioavailability of these drugs by up to 84 percent.

Ramelteon (Rozerem): Ramelteon is contraindicated for concomitant use with fluvoxamine, a strong CYP1A2 inhibitor. It should be used with caution in patients taking less strong CYP1A2 inhibitors. Administration of ramelteon with fluconazole increases the bioavailability of ramelteon and the MII metabolite by approximately 150 percent.

Triazolam: Concurrent administration with efavirenz, delavirdine, azole antifungals, nefazodone, protease inhibitors, and any drugs that significantly impair the CYP3A mediated oxidative metabolism are contraindicated. Caution is recommended when administering triazolam with grapefruit juice, fluvoxamine, diltiazem, verapamil, amiodarone, nicardipine, nifedipine, and ranitidine, because these agents can increase plasma concentration of triazolam.

Adverse Effects

Drug	Headache	Myalgia	Amnesia	Dizziness	Daytime Drowsiness/ Somnolence
chloral hydrate[68]	reported	nr	nr	reported	reported
estazolam[69]	16 (27)	≤1	≤1	7 (3)	3 (2)
eszopiclone (Lunesta)[70]	13-21	nr	nr	1-7	8-10
flurazepam[71]	reported	nr	reported	reported	reported
quazepam (Doral)[72]	4.5 (2.2)	nr	reported	1.5 (<1)	12 (3.3)
ramelteon (Rozerem)[73]	7 (7)	2 (1)	nr	5 (3)	5 (3)
temazepam[74]	8.5 (9.1)	nr	<0.5	4.5 (3.3)	2.5 (1.1)
triazolam[75]	9.7 (8.4)	nr	reported	7.8 (3.1)	nr
zaleplon (Sonata)[76]	30-42 (35)	7 (4)	2-4 (1)	7-9 (7)	reported
zolpidem (Ambien)[77]	19 (22)	7 (7)	1 (0)	5 (1)	nr
zolpidem ER (Ambien CR)[78]	14-19 (11-16)	<1-4 (0)	1-3 (0)	8-12 (3-5)	6-15 (2-5)
zolpidem sublingual (Edluar®)[79]	7 (6)	nr	1 (0)	5 (1)	8 (5)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses. nr = not reported.

For eszopiclone (Lunesta), eight to 34 percent of patients reported a dose-related unpleasant taste as compared to ≤ 5.6 percent of placebo patients. Dose-related respiratory infection has been reported in five to 10 percent of patients taking eszopiclone compared to three percent of patients taking placebo. Anxiety has been reported in one to 3.7 percent of patients receiving eszopiclone compared to ≤ 2.1 percent of patients taking placebo.

Special Populations[80,81,82,83,84,85,86,87,88]

Pediatrics

The incidence of insomnia in children ranges from one to six percent; in children with neurodevelopmental or psychiatric comorbidities, the incidence is as high as 50 to 75 percent.[89,90,91] Insomnia in children may result in irritability, restlessness, lack of concentration, suicide risk, and poor memory.[92]

Chloral hydrate is the only agent in this class indicated for treatment of insomnia in children of

all ages. Flurazepam is indicated for treatment of insomnia in children older than 14 years old.

The American Academy of Sleep Medicine's task force on Pharmacotherapy in Pediatric Sleep Medicine published guidelines in 2005 that do not recommend any one hypnotic over another for use in children.[93] Rather, the consensus statement urges caution when using any of these drugs for the pediatric patient and calls for additional research to be done in this area.

Guidelines from the 2006 National Sleep Foundation, state that there is a need for pharmacologic management of pediatric insomnia.[94] Acknowledging that there is an absence of pharmaceuticals indicated for hypnotic use in the pediatric population, this organization stated that there is a need for trials to confirm the safety and efficacy of such agents in these patients.

A survey of 671 primary care pediatricians found that more than 75 percent had prescribed nonprescription medications, and more than half had prescribed prescription medications for pediatric insomnia.[95] Most commonly, these agents were prescribed for acute pain and travel, followed by children with special needs. Antihistamines were the most common nonprescription medications for sleep, followed by melatonin and herbal remedies. Alpha-agonists were the most frequently prescribed sleep medication.

Pregnancy

The immediate release dosage form of zolpidem is Pregnancy Category B. Zolpidem ER, zolpidem sublingual, eszopiclone, ramelteon, and zaleplon are Pregnancy Category C. Flurazepam is Pregnancy Category D, while the other benzodiazepine hypnotics are Pregnancy Category X.

Hepatic Impairment

In patients with severe hepatic impairment, the bioavailability of eszopiclone is increased two-fold compared with healthy volunteers; time-to-peak and peak concentrations remain unchanged.

The bioavailability of zaleplon is increased up to 400 percent in patients with compensated cirrhosis and 700 percent with decompensated cirrhosis.

In patients receiving zolpidem who have chronic hepatic insufficiency, the AUC is two times higher and Cmax is five times higher than baseline.

Japanese patients

In Japanese adults, the bioavailability of zaleplon is increased by 64 percent. This may also occur in other Asian populations.

Geriatrics[96,97,98]

Patients over the age of 65 years may demonstrate an increase in total exposure to sedative/hypnotic agents. Dosing for the benzodiazepines should commonly begin at the lowest effective dose for these patients. Ramelteon may be an exception as it did not show any overall differences in safety and efficacy between elderly and younger adult patients.

Dosages[99,100,101,102,103,104,105,106,107,108,109,110]

Drug	Bedtime Dose	Dose Adjustment	Availability
chloral hydrate	0.5-1 g	Elderly: 250-500 mg Children: 25-50 mg/kg/day or 1.5 g/m^2 orally or rectally up to a maximum of 1 g per single dose at bedtime	500 mg suppository 500 mg/5 mL liquid
estazolam	1-2 mg	Elderly, underweight or debilitated: 0.5-1 mg	1, 2 mg tablet
eszopiclone* (Lunesta)	2-3 mg	Elderly: 1-2 mg for difficulty falling asleep; 2 mg for difficulty staying asleep Severe hepatic impairment: 1 mg Concurrent use with strong CYP 3A4 inhibitor: 1-2 mg	1, 2, 3 mg tablet
flurazepam	15-30 mg	Elderly and adolescents: 15 mg	15, 30 mg capsule
quazepam (Doral)	15 mg, dose may be reduced to 7.5 mg in some patients based on individual response	Elderly: 7.5 mg, dose may be increased to 15 mg if 7.5mg is ineffective after one to two nights	7.5 mg, 15 mg tablet
ramelteon (Rozerem)**	8 mg	--	8 mg tablet
temazepam	7.5-30 mg	Elderly and debilitated: start at 7.5 mg initially until individual responses are determined	7.5, 15, 22.5, 30 mg capsule
triazolam	0.125-0.5 mg maximum: 0.5 mg	Elderly or debilitated: 0.125 - 0.25 mg; maximum: 0.25 mg	0.125, 0.25 mg tablet
zaleplon (Sonata)***	10-20 mg may also be given after attempt to fall asleep, provided that at least 4 hours of sleep remain	Elderly, low-weight or hepatic impairment: 5-10 mg Concurrent use of cimetidine: Initial dose: 5 mg Mild to moderate hepatic impairment: 5 mg	5, 10 mg capsule
zolpidem* (Ambien, Edluar)	10 mg	Elderly, concurrent CNS depressants, debilitated or hepatic insufficiency: 5-10 mg	5, 10 mg tablet 5, 10 mg sublingual tablet
zolpidem ER (Ambien CR*)	12.5 mg	Elderly, debilitated, or hepatic insufficiency: 6.25 mg	6.25, 12.5 mg tablet

* Should be taken on empty stomach to avoid delayed onset of action.
**Due to a 31 percent increase in bioavailability when given with a high-fat meal, ramelteon (Rozerem) should not be taken with or immediately after such a meal.
***Taking zaleplon (Sonata) or eszopiclone (Lunesta) with or immediately after a heavy, high fat meal results in slower absorption and would be expected to reduce its effect on sleep latency.

Since many of the adverse effects to the sedative/hypnotics appear to be dose related, usually therapy should be initiated with a low dose and then maintained at the lowest effective dose, especially in the elderly. Continuous use should be avoided, and patients should be encouraged to use these medications only when necessary. Use for more than three weeks should be avoided and monitored if a longer duration is necessary. These drugs should never be combined with alcohol consumption.

Clinical Trials

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance. Many of the trials with agents in this class were performed in an open-label manner; introduction of bias must be considered when evaluating study findings.

COMPARISONS OF BENZODIAZEPINES

estazolam and flurazepam

The hypnotic efficacy of estazolam 1 mg and 2 mg was compared to flurazepam 30 mg and placebo in a randomized, double-blind, seven night study that involved 223 patients with insomnia.[111] On subjective assessments of the patients, no differences were noted between estazolam 2 mg and flurazepam 30 mg on any of six sleep parameters. Patients who received estazolam 1 mg rated their sleep significantly better than did patients who were receiving placebo on all parameters except SOL. Global evaluation of the physicians indicated significant improvement in quality of sleep, sleep duration, and nocturnal awakenings in all three active treatment groups; estazolam 2 mg and flurazepam 30 mg decreased SOL significantly. Adverse events were reported by 54 percent of patients receiving estazolam 1 mg, 58 percent of those receiving estazolam 2 mg, and 68 percent of those receiving flurazepam 30 mg. The incidence of adverse events in the placebo group was 43 percent.

In a double-blind trial, 229 patients with insomnia were randomized to receive estazolam 2 mg, flurazepam 30 mg, or placebo for seven consecutive nights.[112] The analysis of efficacy was based on patients' daily assessments of sleep and investigators' global evaluations. The patient subjective questionnaire indicated that estazolam and flurazepam significantly improved all parameters ($p<0.05$) as compared to placebo. A marked or moderate improvement in sleep was reported by 81, 78 and 36 percent estazolam, flurazepam, and placebo recipients, respectively. There were no significant differences in hypnotic effect between estazolam and flurazepam. All efficacy parameters of the investigators' global evaluation, except quality of sleep, improved

significantly more ($p<0.05$) for patients receiving estazolam or flurazepam than for those receiving placebo. The percentage of patients reporting any adverse experience was 59 percent for estazolam, 72 percent for flurazepam, and 43 percent for placebo. Somnolence and hypokinesia were the most commonly reported adverse events. An analysis of the global evaluation of side effects showed that flurazepam had a significantly worse side effect profile than estazolam ($p<0.05$) or placebo ($p=0.001$).

flurazepam and quazepam

Daytime residual drowsiness and psychomotor performance were assessed for quazepam and flurazepam in two randomized, parallel, double-blind studies in insomniacs.[113] In the first study, 17 middle-aged patients took quazepam 15 or 30 mg or flurazepam 30 mg nightly for four weeks. Subjects were given placebo for four nights before and 15 nights after active treatment. In the second study, 48 geriatric patients took quazepam 15 mg, flurazepam 15 mg, or placebo nightly for one week. Subjects were given placebo for one night before and seven nights after active treatment. In the first study, flurazepam patients were significantly ($p<0.05$) sleepier the day after the seventh and fourteenth treatment nights when compared to baseline, whereas quazepam patients were not. In the second study, flurazepam patients were sleepier in the late afternoon ($p<0.05$) after the seventh treatment night than were quazepam and placebo patients. There were no significant differences among the groups in the performance test results.

quazepam and triazolam

In a double-blind study, 45 patients were randomized to receive either quazepam 15 to 30 mg (median 15 mg) or triazolam 0.25 to 0.5 mg (median 0.25 mg) for four weeks.[114] The subjects, who had insomnia based on a mild to moderate generalized anxiety disorder, received placebo for one week before and two weeks after treatment with active drug. Anxiety improved significantly with both drugs and remained improved throughout the two-week post-drug placebo phase; quazepam was slightly superior to triazolam. Polysomnography, an objective measure of SOL, demonstrated a shortened sleep onset only after quazepam. Sleep efficiency improved after acute administration of both drugs, but improvement was maintained only by quazepam as tolerance developed to triazolam. Rebound insomnia was observed only in the first post-triazolam placebo night. Subjective sleep quality behaved very similarly to objective sleep efficiency. Awakening quality improved after acute therapy with both drugs. Somatic complaints were reported only with quazepam.

A randomized, double-blind, three-compartment, parallel-group study comparing quazepam 15 mg, triazolam 0.5 mg, and placebo was conducted in 65 insomniac subjects over five weeks.[115] Using sleep questionnaires for evaluation, no differences were noted between quazepam and triazolam on treatment nights. Evidence of carryover effectiveness with quazepam and rebound effects with triazolam was noted on off-treatment nights.

COMPARISONS OF BENZODIAZEPINES AND NON-BENZODIZAPINES

temazepam and zolpidem (Ambien)

A randomized, double-blind trial compared zolpidem 10 mg to temazepam 20 mg with respect to subjective rebound insomnia after cessation of four weeks of treatment of 163 patients with chronic insomnia.[116] Both agents improved total sleep time (TST) as well as SOL significantly during the four treatment weeks. Prevalence rates for rebound insomnia, defined as a worsening of TST or SOL of more than 40 percent compared to baseline, were 27 percent for

TST and 53 percent for SOL in the zolpidem group and 26 and 58 percent, respectively, in the temazepam group. No significant differences were found between the agents for rebound insomnia, nor with respect to their efficacy or safety.

triazolam and zaleplon (Sonata)

Zaleplon and triazolam were compared in a double-blind, placebo-controlled trial enrolling 132 patients with primary insomnia.[117] Patients received zaleplon 5 mg or 10 mg, triazolam 0.25 mg, or placebo for 14 nights. Median SOL was shorter in both zaleplon groups and triazolam group compared to placebo during the first week of therapy, but not during the second week due to a significant placebo effect. The effects of zaleplon on SOL were similar in the first and second weeks. Total sleep time did not differ between zaleplon and placebo groups. Total sleep time was increased during the first week of triazolam treatment, but not the second. On subjective assessment of SOL, zaleplon 10 mg and triazolam were more effective than placebo during the first week. Only zaleplon 10 mg produced lower subjective SOL during the second week. On the last night of assessment, none of the active treatments were judged more effective than placebo. Negative residual morning psychomotor or memory effects were not observed in any treatment group.

triazolam and zolpidem (Ambien)

In a parallel-group, double-blind, placebo-controlled, polysomnographic study, the possible occurrence of rebound insomnia was evaluated in 24 patients suffering from moderate to severe chronic insomnia. Patients were randomized to either triazolam 0.5 mg, zolpidem 10 mg, or placebo.[118] Treatment duration was 27 nights, followed by three placebo-controlled withdrawal nights. Both drugs showed significant efficacy compared to placebo during the active treatment period. A trend toward tolerance was noted in the triazolam group but not in the zolpidem group. The increase in total sleep time in the zolpidem group was accompanied by an increase in the number of sleep cycles. When active treatment was discontinued, clear rebound insomnia was present in the triazolam group while it was not possible to observe any rebound in the placebo and zolpidem groups. Subjective feelings of the patients assessed by means of visual analog scale correlated well with polysomnographic data.

COMPARISONS OF NON-BENZODIZEPINES

zaleplon (Sonata) and zolpidem (Ambien)

In a double-blind study, 615 patients were randomized to receive zaleplon 5 mg, zaleplon 10 mg, or zaleplon 20 mg, zolpidem 10 mg, or placebo.[119] The four-phase study consisted of a prestudy washout period (one to three weeks), a single-blind placebo run-in period (seven nights), a double-blind treatment period (28 nights), and a single-blind placebo run-out period (three nights). In the 574 patients who completed the study, zolpidem significantly reduced SOL during weeks one through three, as did zaleplon 5 mg. Zaleplon 20 mg and zolpidem 10 mg significantly increased sleep duration during all four weeks of the double-blind treatment. No significant differences were observed in number of awakenings between the placebo and active treatment groups during the double-blind treatment periods. Scores for sleep quality were significantly better than placebo during week one with zaleplon 10 and 20 mg and for all weeks with zolpidem 10 mg. On the first night after treatment discontinuation, significantly more patients who received zolpidem experienced longer SOL relative to baseline and reported withdrawal effects (depressed mood, pain in muscles, peculiar taste, loss of memory, olfactory sensitivity). The most common adverse event in all treatment groups was headache. There

were no significant differences in the frequency of treatment-emergent adverse events among the active treatment groups and the placebo group.

A randomized, double-blind, placebo-controlled, three-period, crossover design was used to study 37 adults with insomnia who received treatment during an experimental awakening four hours after bedtime.[120] The study objective was 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 four to seven hours after dosing using sleep latency testing. Latency to persistent sleep and total sleep time before and after awakening were recorded. 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. Significant differences from placebo were not found with zaleplon in daytime sedation measures. At four, five, and seven hours after zolpidem, sleep onset, measured by sleep latency testing, was shorter than after placebo. Self report measures of concentration and alertness and Digit Symbol Substitution Test scores after zolpidem were also lower than placebo. 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 four hours after zaleplon 10 mg but was detected with zolpidem 10 mg up to seven hours after treatment.

PLACEBO CONTROLLED TRIALS OF NON-BENZODIAZEPINES

<u>eszopiclone (Lunesta) and placebo</u>

A double-blind study enrolled 308 patients, 21 to 64 years of age, with primary chronic insomnia.[121,122] Patients were randomized to receive eszopiclone 2 mg, eszopiclone 3 mg, or placebo for 44 consecutive nights followed by two nights of single-blind placebo. Treatment with either dose of eszopiclone resulted in an approximate 45-minute improvement in the primary endpoint of SOL (placebo 58 minutes; $p<0.001$ for both doses). Eszopiclone also significantly improved the secondary endpoint of sleep efficiency ($p<0.0001$ for both doses compared to placebo). Another secondary endpoint, wake time after sleep onset (WASO), was reduced only by the higher dose of eszopiclone (41.2 minutes) compared to placebo (49.1 minutes; $p=0.02$). There was no evidence of tolerance or rebound insomnia after therapy discontinuation. There was no decrement in psychomotor performance relative to baseline, nor was there a difference between eszopiclone and placebo. The most common adverse event related to eszopiclone was unpleasant taste.

A double-blind study randomized 231 patients, 65 to 85 years of age, with chronic insomnia to receive either eszopiclone 1 mg, eszopiclone 2 mg, or placebo nightly for two weeks.[123,124,125] In the study, the higher dose of eszopiclone improved sleep maintenance ($p<0.05$), total sleep time (by 40 minutes; $p<0.001$), quality of sleep ($p<0.001$), depth of sleep ($p<0.002$), and reduced the number of naps (median 0 versus 2, $p<0.05$) compared to placebo. Patients receiving the higher dose also reported significant improvements in daytime alertness, daytime ability to function, sense of well being, and reduced morning sleepiness ($p<0.05$ for all comparisons to placebo). Both doses of eszopiclone were effective at decreasing SOL ($p<0.004$ compared to placebo) and reducing total nap time ($p<0.05$ compared to placebo).

In a double-blind study, 264 patients, 65 to 85 years of age, with a diagnosis of primary insomnia were randomized to receive eszopiclone 2 mg or placebo nightly for two weeks.[126] Compared with placebo, eszopiclone 2 mg significantly reduced objective (polysomnographic) and subjective SOL [($p<0.0001$ for both measurements) and ($p<0.05$ and $p=0.0019$,

respectively)]. Subjective improvement was also noted in sleep efficiency ($p<0.04$), total sleep time ($p<0.0001$), and the cumulative number and duration of naps among patients who napped ($p=0.03$) compared to placebo. Eszopiclone also produced improvements in the quality of sleep and in physical functioning. There was no rebound insomnia after treatment withdrawal, and the most common adverse event was unpleasant taste.

In a double-blind study, investigators randomized 545 patients with insomnia and major depressive disorder to receive, in addition to daily fluoxetine, eszopiclone 3 mg or placebo nightly.[127] In the eight-week study, patients treated with eszopiclone showed improvements in the primary endpoint, wake time after sleep onset ($p\leq0.002$), compared to those receiving placebo. The active treatment was also more effective than placebo in improving the secondary endpoints of SOL ($p\leq0.0001$) and TST ($p\leq0.0004$). Patients in the eszopiclone group reported superior subjective improvements in sleep quality ($p\leq0.0002$), depth of sleep ($p\leq0.0007$), daytime alertness ($p=0.03$), clarity of thought and concentration ($p=0.02$), and ability to function ($p=0.007$). Patients in the eszopiclone group demonstrated significantly greater improvement in symptoms of depression, as measured by HAM-D17 (Hamilton Depression Rating Scale), at weeks four ($p=0.01$) and eight ($p=0.002$). HAM-D17 response were noted in 59 percent of patients in the eszopiclone group compared to 48 percent of patients in the placebo group; remission rates were 42 and 33 percent, respectively ($p=0.03$). Study completion rates and treatment tolerability were similar between groups.

A multicenter, randomized, double-blind, placebo-controlled trial evaluating eszopiclone treatment upon patient-reported sleep, fatigue and sleepiness, insomnia severity, quality of life, and work limitations for six months.[128] A total of 830 patients with primary insomnia, who reported mean nightly total sleep time $\leq$ 6.5 hours/night and/or mean nightly sleep latency >30 minutes were randomized to eszopiclone 3 mg or matching placebo for six months. Patient-reported sleep and daytime function, Insomnia Severity Index, Physical Functioning, Vitality, and Social Functioning, and Work Limitations Questionnaire domain scores were improved with eszopiclone versus placebo (all $p<0.05$).

ramelteon (Rozerem) and placebo

In a double-blind study, investigators randomized 829 elderly patients (mean age 72.4 years) with chronic primary insomnia to either ramelteon 4 mg, ramelteon 8 mg, or placebo nightly for five weeks.[129] Administration of ramelteon resulted in a reduction in subjective SOL and an increase in TST at weeks one, three, and five of the study. Ramelteon did not change subjective sleep quality, the number of nighttime awakenings, or the ease of falling back to sleep. Withdrawal effects, including rebound insomnia, were not observed.

In a double-blind study, 405 patients (mean age 39.3 years) with primary insomnia were randomized to receive ramelteon 8 mg, ramelteon 16 mg, or placebo nightly for 35 nights.[130] Polysomnography indicated that both doses of ramelteon were associated with a reduction in SOL at each assessment starting on nights one and two. Ramelteon was also associated with an improvement in TST and sleep efficiency on nights one and two.

A six-month, randomized, double-blind, placebo-controlled, multicenter study evaluated the long-term efficacy of ramelteon for insomnia in 451 adults (age ≥ 18 years) with chronic primary insomnia.[131] Patients were randomized to receive either ramelteon 8 mg or placebo 30 minutes before bedtime nightly for six months. Sleep was evaluated by polysomnography and morning questionnaires on the first two nights of week one; the last two nights of months one, three, five, and six; and nights one and two 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. During the six months of treatment, ramelteon consistently reduced latency to persistent sleep compared with baseline and with placebo; significant decreases were observed at week one and months one, three, five, and six ($p<0.05$). Ramelteon significantly reduced subjective sleep latency relative to placebo at week one, month one, and month five ($p<0.05$), with reductions nearing statistical significance at months three and six ($p\leq0.08$). 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.

zolpidem ER (Ambien CR) and placebo

Two similar three-week studies of zolpidem ER were conducted in patients with primary insomnia.[132,133] One study randomized 205 elderly patients (mean age 70.2 years) to zolpidem ER 6.25 mg or placebo while the other randomized 212 adults (mean age 44.3 years) to zolpidem ER 12.5 mg or placebo. In each study, zolpidem ER was found to lead to significant improvement compared to placebo in polysomnographic WASO in the first six hours of the night as well as improvement in SOL and TST. Subjects did not report any residual impairment or sedation.

zolpidem sublingual (Edluar) and placebo

A randomized, double-blind, placebo-controlled, three-way crossover study evaluated the efficacy and safety of low-dose, sublingual zolpidem tartrate when taken during a scheduled middle-of-the-night (MOTN) awakening in subjects with insomnia characterized by difficulty returning to sleep following MOTN awakenings.[134] The study was performed at five sleep laboratories and enrolled adults (24 males, 58 females, mean age 45.9 years) with a diagnosis of DSM-IV primary insomnia and a history of prolonged MOTN awakenings. Baseline difficulties with MOTN awakenings were confirmed by a 10-day screening sleep diary and polysomnography (PSG) screening. Each treatment period consisted of two consecutive nights of dosing separated by a washout period of five to 12 days. Subjects were awakened four hours after lights out, dosed with sublingual zolpidem 3.5 mg, zolpidem 1.75 mg, or placebo, kept awake for 30 minutes, and then returned to bed for an additional four hours. Sleep parameters were assessed by PSG and post-sleep questionnaires. Results demonstrated that low-dose sublingual zolpidem tartrate demonstrated significant dose-related decreases in latency to persistent sleep and total sleep time ($p<0.001$) compared to placebo after MOTN dosing. All subject reports paralleled PSG observations. Neither dose showed next-morning impairment on the digit symbol substitution test (DSST) or ratings of sleepiness. The 3.5-mg dose produced improvements in reports of sleep quality ($p<0.001$), ability to function, and level of refreshed sleep ($p<0.05$ for both dosages) compared to placebo. Sublingual zolpidem tartrate lozenges were generally safe and well tolerated.

Summary

The selection of a specific hypnotic is based in large part on whether the patient has problems with initiation or maintenance of sleep, co-morbid conditions, side effect tolerance, and availability.

There are no direct comparisons of the effectiveness of the newer non-benzodiazepine agents and the benzodiazepines; only indirect comparisons for each medication against a placebo are available. The assumed increased risk with benzodiazepine medications over non-

benzodiazepines is based on indirect comparisons, and there is evidence of publication bias as both groups have increased incidence of adverse risks in patients over 60 years of age.

In general, the benzodiazepines decrease the time for sleep onset and prolong the duration of sleep, although dependence, tolerance, and abuse may occur. Among the benzodiazepines, the duration of action is the primary variable that may make one preferable to another in a given patient. Triazolam has the shortest duration of action, while temazepam and estazolam have intermediate durations. Flurazepam and quazepam have long durations of effect, and as a result, should be avoided in the elderly or others in whom daytime sedation may be a concern.

Rebound insomnia may develop when benzodiazepines are abruptly withdrawn and is more likely to occur with the short-acting benzodiazepines. Rebound insomnia can be minimized by using smaller doses and tapering the dosage. Some studies have highlighted concerns with increased falls and hip fractures in the elderly following benzodiazepine use; however, others have found that untreated insomnia itself increases the risk of falls.

Similar to the benzodiazepines, the BZ-1 selective agents decrease sleep latency with duration of action again being the primary difference among these agents. Although dependence, tolerance and abuse may occur with these agents, next day sedation, rebound insomnia, and drug interactions are generally lessened. For the BZ-1 selective agents, zaleplon is more rapid acting with a shorter duration than zolpidem. Eszopiclone has a longer half-life than either zaleplon or zolpidem.

The melatonin receptor agonist, ramelteon (Rozerem), has demonstrated reduction in sleep latency, but not in sleep maintenance. Patient evaluations are inconsistent, and there are no direct comparative studies. There is a low likelihood of dependence or abuse, and adverse effects are rare.

Chloral hydrate is effective when used for a very short term but is associated with tolerance in as little as two weeks. Dependence, GI effects, drug interactions, and fatalities in overdose may also occur. It offers no advantage over the currently available choices for treating insomnia.

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