Eszopiclone for late-life insomnia

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Abstract: Insomnia, the most common sleep disturbance in later life, affects 20%–50% of older adults. Eszopiclone, a short-acting nonbenzodiazepine hypnotic agent developed for the treatment of insomnia, has been available in Europe since 1992 and in the US since 2005. Although not yet evaluated for transient insomnia in older adults, eszopiclone has been shown to be safe and efficacious for short-term treatment (2 weeks) of chronic, primary insomnia in older adults (64–91 years). Clinical studies in younger adults (mean = 44 years) have shown eszopiclone can be used for 6–12 months without evidence of problems. Because the oldest participant in these longer-term trials was 69, it not known whether eszopiclone is effective for older adults [particularly the old old (75–84 years) and oldest old (85+)] when used over longer periods. This is unfortunate, because older individuals frequently suffer from chronic insomnia. Cognitive-behavioral therapy for insomnia, which effectively targets the behavioral factors that maintain chronic insomnia, represents an attractive treatment alternative or adjuvant to eszopiclone for older adults. To date, no studies have compared eszopiclone to other hypnotic medications or to nonpharmacological interventions, such as cognitive-behavioral therapy for insomnia, in older adults. All of the clinical trials reported herein were funded by Sepracor. This paper provides an overview of the literature on eszopiclone with special emphasis on its use for the treatment of late-life insomnia. Specific topics covered include pharmacology, pharmacodynamics, pharmacokinetics, clinical trial data, adverse events, drug interactions, tolerance/dependence, and economics/cost considerations for older adults.

Keywords: aging, eszopiclone, hypnotics, insomnia, older adults, sedative-hypnotics

Introduction

Insomnia, defined as difficulty initiating and/or maintaining sleep or nonrestorative sleep (American Psychiatric Association 1994), is the most common sleep disturbance in later life. Prevalence estimates for individuals 65 and older range from 20%–50% (compared to 9%–15% for the general adult population), and women have been found to be 40%–60% more likely to suffer from insomnia compared to men (Foley et al 1995; Ohayon 2002; Lichstein et al 2004; Roberts et al 2004). Sleep maintenance difficulties (or unwanted awakenings during the night) are frequently believed to be problematic for older individuals. However, recent epidemiological evidence from the National Sleep Foundation (NSF) (Foley et al 2004) indicates a wider range of difficulties with approximately one-fifth of older adults (defined in this study as individuals aged 55 and over) suffering from difficulty falling asleep, one-third from waking during the night, one-fourth from waking too early with difficulty returning to sleep, and one-third from unrefreshing sleep. Unfortunately, insomnia in older adults is both underdiagnosed and undertreated. Although 50% of the older adults sampled by the NSF reported experiencing at least one symptom of insomnia several times a week, only 4% had been diagnosed with insomnia and only 3% were receiving treatment (Foley et al 2004).

Insomnia is often more severe in the elderly. Older adults with insomnia awaken more frequently and spend a greater percentage of their nights awake than do younger

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people with insomnia (Lichstein et al 2004). Insomnia can be classified as acute/transient (1 month or less), persistent (more than 4 weeks), or chronic (lasting 6 months or more). Unfortunately, older adults are particularly susceptible to developing chronic insomnia (McCrae et al 2003, 2005). Age-related increases in the occurrences of chronic medical conditions such as heart disease, arthritis, stroke, or lung disease contribute to older adults' increased risk of chronic insomnia (Foley et al 2004). Chronic late-life insomnia is associated with a variety of negative consequences, including decreased quality of life, disturbed mood (particularly, depression and anxiety), disturbed quality of social interactions, increased risk of nursing home placement, dependence on sleep medication, and impaired cognitive functioning (Hart et al 1995; Reynolds et al 1999; Roth and Ancoli-Israel 1999).

Agents typically used to treat late-life insomnia include benzodiazepines, sedating antidepressants, and newer nonbenzodiazepine hypnotics. The benzodiazepines, which have been the 'gold standard' for treating insomnia for the past 20–30 years, are starting to be replaced by the nonbenzodiazepine agents. Eszopiclone, a short-acting nonbenzodiazepine hypnotic agent developed for the treatment of insomnia, has been available in Europe since 1992. In the US, eszopiclone received approval from the food and drug administration (FDA) in 2004 and became available in 2005 under the brand name, Lunesta (Sepracor). Eszopiclone's properties are similar to those of zolpidem (Ambien), another popular nonbenzodiazepine hypnotic. While both agents may promote sleep initiation, eszopiclone's longer half-life (6 hours vs 2.6 hours) may provide an advantage for sleep maintenance and early morning awakening.

In the US, eszopiclone has the distinction of being the first hypnotic agent with a controlled substance designation that does not have restrictions on its length of use. This distinction is based on clinical studies demonstrating eszopiclone can be used for 6–12 months without evidence of problems (eg, tolerance/dependence). Unfortunately, these studies contained primarily younger adults (mean age of approximately 44 years). Because the maximum age of participants in these trials was 69, there have been no longer term studies in the old-old (75–84) or oldest-old (85+) age groups. Additionally, eszopiclone has not been evaluated for transient insomnia in older adults. There have been 2 clinical studies in older adults (64–85 years) with chronic primary insomnia (Erman et al 2004; Scharf et al 2005). Neither of these studies have examined eszopiclone use in older adults for longer than 2 weeks. To date, no studies have compared eszopiclone to other hypnotic medications or to nonpharmacological interventions for insomnia in older adults.

Eszopiclone

Methods used to evaluate and select literature

Both the MEDLINE and ISI Web of Science databases were used to conduct the literature search using the following terms: eszopiclone, Lunesta, eszopiclone and behavioral sleep treatments, and eszopiclone and older adults. Abstracts and articles relating to the pharmacology, pharmacodynamics, and pharmacokinetics of eszopiclone that were published between June 2002 and 2006 were retrieved. Clinical trials and letters to the editor were also reviewed. Additionally, the manufacturer (Sepracor, Inc) (Anon 2005a) was contacted for the most up-to-date information about the product. Abstracts from more recent conferences were also reviewed. Overall, 69 articles and abstracts were reviewed.

Description of drug

Eszopiclone (Lunesta) was approved by the Food and Drug Administration on December 15, 2004. Eszopiclone is prescribed for the treatment of insomnia. Eszopiclone, the S-isomer of zopiclone, has been available in Europe since 1992 (Anon 2005a). It is a nonbenzodiazepine hypnotic agent of the cyclopyrrone class (sedative hypnotic class of drugs). Eszopiclone has a single chiral center with an (*S*)-configuration (Sepracor 2005) and is formulated as film-coated tablets to be used for oral administration in 1 mg, 2 mg, or 3 mg tablets (Sepracor 2005). Eszopiclone is classified as a schedule IV drug under the Controlled Substances Act. Identification as a schedule IV drug means that eszopiclone has accepted medical use for treatment within the United States, has a low potential for abuse in comparison to drugs in schedule III, and may lead to limited physical or psychological dependence relative to drugs in schedule III (Chapter 13 of Title 21 of the United States Code, 1970).

Pharmacology/pharmacodynamics

The pharmacology, or mechanism of action, of eszopiclone is unknown. Eszopiclone's effect is believed to result from the interaction of the drug with GABA-receptor complexes that are located close to, or are coupled with, benzodiazepine receptors (Anon 2005d). Once the eszopiclone binds to the GABA-receptor complex, there is an increase in chloride transmission that subsequently depresses the central nervous system, slowing brain activity, and resulting in sedation (Drover 2004). Additionally, eszopiclone binds mini-

mally to plasma proteins. Consequently, the absorption and distribution of the drug is minimally affected by other drugs that may be competing for protein binding sites, resulting in a lowered probability for drug interactions with drugs that strongly bind to plasma proteins (Laustsen 2005).

The chemical structure of eszopiclone is unrelated to imidazopyridines, pyrazolopyrimidines, benzodiazepines, barbiturates, or other drugs with known hypnotic properties (Sepracor 2005).

Pharmacokinetics

The pharmacokinetics (ie, the impact of the body on the drug) of eszopiclone can be discussed in terms of absorption, metabolization, elimination, and considerations for special populations. In healthy subjects (adults and elderly), eszopiclone is rapidly absorbed, with peak concentrations occurring within one hour (Sepracor 2005). There is not a selective reuptake of Eszopiclone by red blood cells as indicated by a blood to plasma ratio of less than one (Sepracor 2005). Absorption of eszopiclone may be reduced if it is taken with or immediately after a high-fat/heavy meal (Sepracor 2005). The metabolization of eszopiclone occurs primarily in the liver through oxidation and demethylation (the removal of a methyl group; Brielmaier 2006). Eszopiclone has a half-life of approximately six hours (Sepracor 2005). Older adults (65+) have a slightly prolonged elimination (approximately nine hours). Therefore, the starting dose of eszopiclone for elderly patients should be decreased to 1 mg and should not exceed 2 mg (Sepracor 2005). The pharmacokinetics of eszopiclone in men and women and all races participating in Phase 1 studies of eszopiclone were similar (Sepracor 2005). Special dosage considerations for elderly patients are further discussed below.

Indications

Eszopiclone is indicated for the treatment of insomnia (Sepracor 2005). It is specifically indicated for patients who experience difficulty falling asleep as well as for those who have sleep maintenance difficulty (ie, difficulty staying asleep) (Anon 2005a).

Dosage considerations for older adults

Starting dosage recommendations for elderly patients who primarily complain of difficulty with sleep onset is 1 mg immediately before bedtime. This contrasts with the recommended starting dose of 2 mg for adults. Since some of the important adverse effects of sedative/hypnotic drugs appear to be related to the dosage (eg, impaired motor or cognitive performance), it is important to monitor the dosage in elderly patients who may be more sensitive to sedative/hypnotic drugs. If the primary complaint of the elderly patient is difficulty maintaining sleep, the recommended dose is 2 mg immediately before bedtime. Studies have shown that the 2 mg dose in elderly patients produces the most consistent improvements in sleep maintenance (Erman et al 2004; Scharf et al 2005).

Specialized dosage recommendations also exist for those patients diagnosed with severe hepatic impairment (severe liver disease). In that case, the recommended starting dosage of eszopiclone is 1 mg as systemic exposure will be doubled in these individuals.

Clinical trial research

Trials in older adults

There are no published trials examining the effect of eszopiclone on transient insomnia in older adults. To date, only two clinical trials (Erman and colleagues (2004) and Scharf and colleagues (2005)) (total n = 495) have been conducted to examine the safety and efficacy of eszopiclone in the treatment of primary and chronic insomnia in older adults (ranging from 64–85 years). Each of these trials were short-term (over a 2-week period), and none compared eszopiclone to another hypnotic or to nonpharmacological interventions. Nonpharmacological interventions for insomnia include cognitive-behavioral therapy, relaxation therapy, or exercise. Much of the data is limited to abstracts, and all clinical trials were funded by Sepracor, the manufacturer of eszopiclone. A brief description of the methods employed by these trials and their key outcomes is provided below. See Table 1 for an even more concise summary of these trials.

Erman and colleagues (2004) conducted a randomized, double-blind, placebo-controlled study of 264 adults 65–85 years old. All participants met DSM-IV diagnostic criteria for primary insomnia. One hundred thirty six older adults were given eszopiclone 2 mg, and 128 received a placebo. Polysomnography was used to assess latency to persistent sleep, sleep efficiency, wake time after sleep onset, and number of awakenings. An interactive voice response system was used in the morning to assess sleep parameters and in the evening to assess daytime function and sleep latency (SL), wake time after sleep onset (WASO), number of awakenings (NWAK), total sleep time (TST), depth and quality of sleep, and morning sleepiness. Quality of life was assessed using the Insomnia Severity Index and SF-36 questionnaires. Eszopiclone significantly reduced objective latency to persistent sleep ($p < 0.001$) and WASO ($p < 0.05$) compared with placebo. Objective

awakenings ($p = 0.16$) were reduced and SE ($p = 0.04$) was also improved with eszopiclone compared to placebo. Patient reported measures of sleep, including SL ($p < 0.0001$), and WASO ($p = 0.002$) were also significantly reduced. The Insomnia Severity Index total score ($p = 0.001$) and the SF-36 domains of overall functioning ($p = 0.045$) and vitality ($p = 0.056$) were improved in the eszopiclone 2 mg group.

Scharf and colleagues (2005) conducted a randomized, double-blind, placebo-controlled, multi-centered 2 week study on the efficacy and safety of eszopiclone. Elderly patients (n = 231) with primary insomnia between the ages of 65 and 85 received 1 mg, 2 mg, or a placebo. An interactive voice response system was used to obtain SL, TST, WASO, NWAK, daytime functioning, and quality of life. Results indicate that the eszopiclone 2 mg group had significantly improved SL ($p = 0.0034$), TST ($p = 0.0003$), WASO ($p \leq 0.05$), and sense of physical well-being ($p < .05$) compared with placebo. The 1 mg group exhibited significantly decreased SL ($p \leq 0.012$) compared with placebo, but was not significant on any other efficacy endpoint.

Four additional studies performed secondary data analysis of clinical trials of eszopiclone containing either older adult only or mixed-age samples.

In an abstract, McCall and colleagues (2004) conducted a pooled analysis of two randomized, double-blind, placebo-controlled evaluations (Erman and colleagues (2005) and Scharf and colleagues (2005)) of adults between 64 and 85 years old (n's = 207 and 215). In both studies, the patients received nightly treatment with eszopiclone 2 mg or placebo for 2 weeks. The pooled analysis found that eszopiclone was well tolerated and patients taking eszopiclone experienced improvements in sleep maintenance, quality, and next day functioning. Patients taking eszopiclone experienced improvements in median SL ($p < 0.0001$), WASO ($p \leq 0.01$), TST ($p < 0.0001$), sleep quality ($p \leq 0.01$), and sleep depth ($p \leq 0.0007$) versus placebo.

In another abstract, Amato and colleagues (2005) conducted Pearson correlation coefficients in an analysis of a randomized, double-blind, placebo-controlled, parallel-group study of 159 people with primary insomnia aged 64–85.

Table 1 Clinical trials in older adults

Author & date	Population	Study design	Treatment dosages	Measurement	Summary
Erman et al (2004)	N = 264 (65–85 y) primary insomnia	R,DB,PC; 2 week duration	Eszopiclone 2 mg; placebo	Assessed with PSG: LPS, SE, WASO, and # of awakenings; twice daily with IVRS: SL,WASO, TST, quality and depth of sleep, and morning sleepiness; with ISI and SF: QoL	Eszopiclone 2 mg significantly decreased objective LPS ($p < 0.0001$) and WASO ($p < 0.05$) and subjective SL ($p < 0.001$) and WASO ($p = 0.0019$). Morning sleepiness was less for the eszopiclone group than with placebo ($p = 0.07$); There were no significant differences between groups on other daytime functioning measures.
Scharf et al (2005)	N = 231 (65–85 y) primary insomnia	R,DB,PC,MC; 2 week duration	Eszopiclone 1 mg; 2 mg; placebo	IVRS: SL,TST,WASO, number of awakenings, daytime functioning, Q-LES-Q : QoL	Eszopiclone 2 mg group had significantly shorter SL ($p = 0.0034$), TST ($p = 0.0003$), WASO ($p \leq 0.05$), and sense of physical well-being ($p < 0.05$) compared with placebo; 1 mg significantly decreased SL ($p \leq 0.012$) compared with placebo, but was not significant on any other efficacy endpoint.

Abbreviations: R, randomized; DB, double-blind; PC, placebo-controlled; PSG, polysomnography; IVRS, interactive voice response system; ISI, Insomnia Severity Index; SF, SF-36 questionnaires; OL, open-label; MC, multicenter; DSST, Digit Symbol Substitution Test; PG, parallel-group; Q-LES-Q, quality of life enjoyment and satisfaction questionnaire; LPS, latency to persistent sleep; SL, sleep latency; SE, sleep efficiency; WASO, wake after sleep onset; TST, total sleep time; QoL, quality of life.

Patients either received eszopiclone 2 mg (n = 79) or placebo (n = 80). The analysis tested the correlation between daytime alertness, ability to function, and physical well-being and sleep quality, total sleep time, wake time after sleep onset, and sleep latency. This study also examined the percent of treatment effect on the next day function variables (daytime alertness, ability to function, and physical well-being) attributable to the effect of eszopiclone on sleep. In both groups, the next day function variables correlated highly with sleep quality ($r \approx 0.5$) and to a lesser extent with TST ($r \approx 0.3$), WASO, and SL ($r \approx 0.2$).

Rosenberg et al (2004) analyzed four studies of eszopiclone use in elderly and non-elderly patients with primary insomnia to determine if results were similar in both populations. The studies were randomized, double-blind, and placebo-controlled. Two 2-week studies of eszopiclone 2 mg in elderly patients and two non-elderly studies of eszopiclone 3 mg were analyzed. The first elderly study used polysomnography and subjective measures (n = 264; Erman, Rosenberg, and Caron, 2004), and the second study used subjective measures only (n = 159). One of the non-elderly studies was a 6-week polysomnographic and subjective study (n = 204), and the second study was a six month subjective study (n = 788; Krystal et al. 2003). In all four studies, patient reports of sleep onset ($p < 0.01$), WASO ($p < 0.05$), and TST ($p < 0.01$) improved compared with placebo. In the objective studies, eszopiclone significantly improved sleep onset, TST, and WASO in both populations ($p < 0.05$) compared to placebo. This study is published as an abstract.

In an abstract, Gary et al (2004) examined pharmacokinetic and pharmacodynamic effects of eszopiclone. They analyzed two studies of healthy adults who were administered eszopiclone. In one study, non-elderly adults (n = 48, ages 18–45) were administered 1, 2, 3, and 5 mg of eszopiclone. In the other study, elderly adults (n = 36, ages 65–79) were administered 1, 3, and 6 mg. Plasma concentrations were measured, and the digit symbol substitution test (DSST), a measure of psychomotor performance, attention and ability to remember and operate on complex symbols) was administered. In both studies, eszopiclone was absorbed rapidly and plasma levels became steady by approximately 48 hours. Peak plasma concentration levels were reached at 1–1.25 hour post-dose. The 2 mg profile in older adults was consistent with the 3 mg profile in non-elderly adults. Based on the pharmacokinetic and pharmacodynamic profiles from these studies, 2 mg for older adults and 3 mg for non-elderly adults are the targeted doses for treatment.

In a poster presentation, Doghramji and colleagues (2006) conducted a mixed-age, open-label, multi-center trial of eszopiclone with 2606 individuals. On day 1, ten tablets of eszopiclone 1 mg, 2 mg, or 3 mg were administered to adults ages 15–91 according to their ages, sleep complaint, and medical condition. The mean age of participants was 50-years-old, 68% were female, 56% presented with secondary insomnia, and 44% had primary insomnia. Unfortunately, the proportion of the sample that was age 65 and older was not reported. Thirty seven percent of participants reported suffering from depression, 26% from anxiety, and 11% from arthritis. Participants used eszopiclone for up to 10 nights over a 10–14 day time span. Participants were given a questionnaire to fill out rating their satisfaction with eszopiclone and its safety and tolerability. Results revealed that 50% of the participants preferred eszopiclone to zolpidem (n = 896) and trazodone (n = 150).

Trials in non-elderly adults

To date, there have been five clinical trials (Krystal et al 2003; Zammit et al 2004; Rosenberg et al 2005; Roth et al 2005) of the safety and efficacy of eszopiclone on non-elderly adults. Three of the trials examined the effect of eszopiclone on chronic insomnia,one study analyzed its effect on transient insomnia, and one study examined eszopiclone's relationship to fluoxetine and depression. The methods employed by these trials and their key outcomes are described in the table below. As with the trials of eszopiclone on older adults, much of the data is limited to abstracts, none of the trials compared eszopiclone to cognitive-behavioral therapy for insomnia, and all clinical trials were funded by Sepracor, the manufacturer of eszopiclone. Table 2 provides a concise summary of these trials.

Rosenberg and colleagues (2005) studied wake time, sleep latency, number of awakenings, and perceptual speed in a sample with normal sleep habits. They found that doses 1–3.5 mg resulted in significantly reduced wake time, all doses ($p \leq 0.05$) except the 1 mg dose significantly reduced SL ($p \leq 0.0001$), and the number of nighttime awakenings was significantly reduced ($p \leq 0.02$) in the 3 and 3.5 mg dose groups. The authors found no decrement in morning DSST scores for any of the dosage groups.

In a sample diagnosed with chronic primary insomnia, Krystal and colleagues (2005) found that a dose of 3 mg of eszopiclone significantly improved SL, TST, NWAK, WASO, and quality of sleep ($p \leq 0.03$) compared to placebo. Additionally, daytime ratings of function, alertness, and physical well being were higher with eszopiclone. Using the

Table 2 Clinical trials in adults

Author & date	Population	Study design	Treatment dosages	Measurement	Summary
Rosenberg et al (2005)	N = 436 (25–50 y) normal sleep habits	MC, R, DB, PC, PG; first-night effect model	Eszopiclone 1, 2, 3, 3.5 mg; placebo	Assessed with PSG, DSST, Self-report: SL, SE, number of awakenings, morning sleepiness	Eszopiclone significantly reduced latency to persistent sleep ($p \leq 0.0001$) in all doses except 1 mg. All doses significantly reduced wake time ($p \leq 0.05$). Number of awakenings was reduced in the 3 and 3.5 mg groups ($p \leq 0.02$). There were no decrements in next morning DSST scores in any treatment group.
Krystal et al (2003)	N = 788 (21–69 y) Primary, chronic insomnia	R, DB, PC; out-patient, monthly visits, 6-month duration	Eszopiclone 3 mg; placebo	Assessed with IVRS: SL, TST, number of awakenings, WASO, quality of sleep, next day ratings of function, daytime alertness, and sense of physical well being	Eszopiclone improved all efficacy parameters ($p \leq 0.03$) versus placebo. Next day function, alertness, and sense of physical well being were better with eszopiclone ($p \leq 0.003$) in monthly ratings.
Roth et al (2005)	N = 471 (21–64 y) Primary, chronic insomnia. (Continuation of Krystal et al study)	OL, 6-month extension phase (for combined total of 12 months)	Eszopiclone 3 mg	continuation of parameters in Krystal et al	Patients previously treated with placebo reported significant and rapid improvements in sleep and day time functioning ($p \leq 0.0001$).
Zammit et al (2004)	N = 308 *M* age = 39.8 y; range 21–64 y); Chronic primary insomnia	R, DB, PC, PG; 44 consecutive nights with 2 nights of single-blind placebo	Eszopiclone 2, 3 mg; placebo	PSG (nights 1, 15, 29) and patient-reports (nights 1, 15, 29 43–44); DSST: next-day effects	SL, TST, SE, and WASO significantly improved with eszopiclone 3 mg versus placebo (all ps ≤ 0.05). Eszopiclone 2 mg improved all of those parameters except WASO. There were no decrements in next morning DSST scores in any treatment group.
Fava et al (2006)	N = 545 *M* age = 40.4 y; range 21–64; Major Depressive Disorder and insomnia	R,DB,PC,PG, OL; 8 weeks then all patients received SB placebo for 2 additional weeks	Fluoxetine hydrocholoride, 20–40 mg; with Eszopiclone 3 mg; or placebo	HAM-D-17; and IVRS (3–7 days for baseline); ISI; CGI-S	Decreased SL ($p \leq 0.001$) and WASO ($p \leq 0.002$) and increase in TST ($p \leq 0.0004$), SQ ($p \leq 0.0002$) , DS ($p \leq 0.0007$) in the eszopiclone and fluoxetine group compared to placebo. Scores also significantly improved on the HAM-D-17 (week 4, $p \leq 0.01$, week 8, $p \leq 0.002$) in the co-therapy group.

Abbreviations: R, randomized; DB, double-blind; SB, single blind; PC, placebo-controlled; PSG, polysomnography; IVRS, interactive voice response system; ISI, Insomnia Severity Index; SF, SF-36, questionnaires; OL, open-label; MC, multi-center; DSST, Digit Symbol Substitution Test; PG, parallel-group; Q-LES-Q, quality of life enjoyment and satisfaction questionnaire; CGI-S, Clinical Global Impression severity; HAM-D-17, Hamilton Depression Scale; LPS, latency to persistent sleep; SL, sleep latency; SE, sleep efficiency; WASO, wake after sleep onset; TST, total sleep time; SQ, sleep quality; DS, Depth of Sleep; QoL, quality of life.

same sample, Roth and colleagues (2005) found that participants who were previously treated with placebo showed rapid improvements in sleep and daytime functioning measures ($p \leq 0.003$) when treated with the 3 mg eszopiclone dose.

In a sample of adults with chronic insomnia, Zammit and colleagues (2004) found that all sleep parameters (SL, TST, WASO, and SE) improved under the 3 mg dose condition, while all parameters except for wake time after sleep onset improved in the 2 mg dose condition. There were no impairments in the DSST observed in any of the treatment groups.

The Fava et al (2006) study examined the effects of eszopiclone and fluoxetine co-administered to individuals 21–64 years. All participants met DSM-IV criteria for Major Depressive Disorder and insomnia. All participants began receiving 20 mg fluoxetine daily for 8 weeks. At week 4, there was the option for an increase from 20 mg to 40 mg depending on depressive symptoms at that time. The 545 participants were randomized into 3 mg eszopiclone or placebo groups at week 4. The majority of participants (n = 373; 68.4%) completed the trial. An interactive voice response system was used daily during baseline and the day of and day after scheduled clinic visits through week 6 and daily from weeks 8 through 10. Participants also completed the insomnia severity index (ISI) and Hamilton depression scale (HAM-D-17) at weeks 0, 4, 8, and 10. They completed the Clinical Global Impression Scale (CGI) at every office visit. An 11-point Likert scale was also used to examine wake time after sleep onset, SL, sleep quality, sleep depth, daytime alertness and ability to function, sense of physical well-being, and ability to concentrate. Participants in the eszopiclone and fluoxetine group reported improvements in SL ($p \leq 0.001$), WASO ($p \leq 0.002$), and TST ($p \leq 0.0004$). Participants in this group also reported improvements in depth of sleep ($p \leq 0.0007$) and sleep quality ($p \leq 0.0002$). The co-therapy group did not report a significant change in sense of well-being ($p = 0.1$); although they did report an increase in daytime alertness ($p = 0.03$), ability to function ($p = 0.007$), and ability to think clearly and concentrate ($p = 0.02$). Participants in this group also had significantly reduced HAM-D-17 scores at Week 4 ($p = 0.01$) and Week 8 ($p = 0.002$). The participants in the eszopiclone and fluoxetine group that were more severely depressed at baseline experienced the most significant changes in depressive symptoms at Week 4 ($p = 0.005$) and Week 8 ($p = 0.0007$).

In an additional study described in the Formulary of the annual North American Menopause Society meeting for 2006, a trial of eszopiclone and menopausal-associated insomnia was conducted with a group of women aged 40 to 60 years. Four hundred and ten peri-menopausal and menopausal women participated and were randomized into a 3 mg eszopiclone or placebo group. At the 4-week follow-up, women who received eszopiclone reported significant reductions in SL and WASO compared to those taking placebo. The median reduction of SL for the eszopiclone group was 18.6 minutes compared to the 8.1 minute reduction in the placebo group. The median reduction in WASO was 30.6 minutes versus 1.6 minutes in the placebo group. The frequency or duration of hot flashes was not affected. The names of the investigators were not provided.

Four additional studies conducted secondary data analyses of the clinical trials of eszopiclone in adults.

Krystal et al (2004) analyzed the Krystal et al (2003) study. Participants were grouped into a low (≤ 30 min; n = 190) and high (≥ 30 min; n = 319) WASO. This analysis found that significant differences were noted in both the low ($p = 0.0035$) and high ($p = 0.030055$) WASO. The amount of WASO reduction was directly related ($p < 0.001$) to baseline wake time after sleep onset impairment. If the Krystal et al (2003) trial had used the WASO >30 minute criteria, which is standard for insomnia research, then approximately 40% of participants would have been excluded from the original study.

Buysse and colleagues (2004) performed a trajectory analysis of the Krystal et al (2003) trial. They analyzed the data using a SAS Traj procedure which calculated the probability of subjects belonging to a trajectory and assigned each subject to a particular trajectory. Buysse and colleagues (2004) tested linear and quadratic mixture models using separate models for the eszopiclone and placebo groups. The eszopiclone subgroups showed rapid treatment response and a stable course or slight improvement over the 6-month study period. The placebo subgroup showed a stable course or slight improvement during the study period. The results of these analyses were consistent with other results in that eszopiclone was associated with rapid and sustained response.

McCall and colleagues (2006) also analyzed the Fava et al (2006) trial. They analyzed the trial study to determine whether baseline sleep severity influenced response to the eszopiclone/fluoxetine co-therapy. Participants were stratified by baseline insomnia severity (moderate = ISI score <18; severe = ISI score ≥ 18). Results found that eszopiclone/fluoxetine co-therapy resulted in significant improvements in sleep and depression measure in participants with moderate and severe insomnia compared to monotherapy.

Krystal and colleagues (2006) analyzed the individual items on the Hamilton Depression Scale in the Fava et al

(2006) study (see the Drug Interactions section for more information) examining eszopiclone and fluoxetine. All tests were two-sided and were conducted at a 5% significance level. The continuous variables were compared using an analysis of covariance model across treatment groups. This analysis found that eszopiclone/fluoxetine co-therapy significantly improved the insomnia items on the HAM-D17. Also, several of the co-depressive symptoms improved with co-therapy as opposed to monotherapy.

See below for information regarding studies examining eszopiclone, drug interactions and adverse effects.

Clinical considerations

Adverse events

After reviewing the literature, the most common adverse effects of eszopiclone are unpleasant taste, headache, somnolence, dizziness and dry mouth. Different adverse effects for the non-elderly and elderly have been reported as shown in Tables 3 and 4. The product packaging information for eszopiclone is the only source which provides the frequency of adverse effects. These frequency levels reveal the most extensive consequences of eszopiclone and were reproduced in table form and supplemented by other published information.

Drug interactions

After reviewing the current literature for drug interactions, no specific contraindications to eszopiclone use could be found (see Table 5). Eszopiclone, like its predecessors – zolpidem, zaleplon, and the benzodiazepines – does not, when working by itself, create a dangerous degree of central nervous system (CNS) depression. However, eszopiclone can be deadly if taken with large doses of other CNS depressants (including alcohol) and may have an addictive effect (Anon 2005b). It is warned that Potent CYP3A4 inhibitors such as ketoconazole, itraconazole (Sporanox), clarithromycin (Biaxin) and ritonavir (Norvir) could increase serum concentrations of eszopiclone and prolong its duration of action (Anon 2005c). So if a potent CYP3A4 is taken concurrently with eszopiclone, the dose of the latter should be reduced. Caution should also be taken when giving eszopiclone to those with compromised respiratory function. However, 7 mg given to healthy volunteers did not cause respiratory-depressant effects (Sepracor 2005). As with all sleeping medications, causes of insomnia, including physical or psychiatric, should be assessed before a drug treatment is started. This assessment should include a thorough history focusing on severity, functional impact, and persistence of complaints. Precautions should be taken when using sleep medications, such as eszopiclone, in the following populations: elderly; debilitated; and those with depression, and concomitant drug therapy; current illnesses, specifically diseases that could affect the liver, metabolism, or hemodynamic responses (Sepracor 2005). Caution should be taken when prescribing eszopiclone to those with depression as suicidal tendencies could be present and intentional overdose may occur. An overdose of 36 mg of eszopiclone did occur in preclinical trials and proved to be nonfatal (Sepracor 2005).

The manufacturers suggest that the starting dose of eszopiclone for older adults should be 1 mg not 2 mg (Sepracor 2005). Polypharmacy is a concern when prescribing eszopiclone, because the number of medications being taken by older adults has been and will likely continue to increase (Vener et al 1979; Stewart et al 1991; Kaufman et al 2002; Lernfelt et al 2003). The most common medications used by older individuals are cardiovascular drugs, analgesics, and drugs for diseases in the central nervous system (Lernfelt et al 2003). Women age 65 and older have the highest prevalence of medication use with 94% taking at least 1 medication; 57% taking at least 5 or more; and 12% taking 10 or more. Rates were similarly high for men with 91% taking at least 1 mediation; 44% taking at least 5; and 12% taking 10 or more (Kaufman et al 2002). Aspirin taken as a cardiovascular prophylaxis was the most commonly used medication (58%-M; 51%-W). The following drugs which have been tested for interactions, see Table 5, were found to be used by older adults: paroxetine (< 1%-both), digoxin (9%-M, 5%-W), warfarin (8%-M, 4%-W), and fluoxetine (< 1%-M, 1%-W) (Kaufman et al 2002). Unfortunately, none of these studies included older adults. In the previously described Scharf and colleagues (2005) study, 92% of the older adults receiving the 1 mg dose of eszopiclone and 89% receiving the 2 g dose were on a concomitant medication. The 5 most frequently reported medications in that study were aspirin, estrogen, calcium, levothyroxine, and acetaminophen (Scharf et al 2005). Because polypharmacy is common in older adults, close attention to potential drug interactions, particularly for other commonly used drugs, may help to prevent adverse events such as accidents, falls, nursing home placements, and even death.

Tolerance/dependence

Use of a sleep medication nightly for greater than a few weeks may cause the medication to lose its effectiveness in engendering sleep, this is called tolerance (tachyphylaxis).

Table 3 Adverse effects reported by non-elderly adult patients

	Frequent AE's at least 1 in 1/100	**Infrequent AE's between 1/100 & 1/ 1,000**	**Rare AE's fewer than 1/1,000**
Body as a whole	Headache, chest pain, viral infection, abdominal pain, abnormal dreams, asthenia, accidental injury, pain	Allergic reaction, cellulitis, face edema, fever, halitosis, heat stroke, hernia, malaise, neck rigidity, photosensitivity, diabetes mellitus,	
Cardiovascular system	Migraine	Hypertension	Thrombophlebitis.
Digestive System	Dry mouth, dyspepsia, nausea, vomiting, diarrhea, pharyngitis	Anorexia, cholelithiasis, increased appetite, melena, mouth ulceration, thirst, ulcerative stomatitis	Colitis, dysphagia, gastritis, hepatitis, hepatomegaly, liver damage, stomach ulcer, stomatitis, tongue edema, rectal hemorrhage
Hemic and Lymphatic System		Anemia, lymphadenopathy	
Metabolic and Nutritional	Peripheral edema	Hypercholesteremia, weight gain, weight loss	Dehydration, gout, hyperlipemia, hypokalemia
Musculoskeletal System	Back pain	Arthritis, bursitis, joint disorder (mainly swelling, stiffness, and pain), leg cramps, myasthenia, twitching,	Arthrosis, myopathy, ptosis
Nervous System	Anxiety, confusion, depression, dizziness, hallucinations, libido decreased, nervousness, somnolence	Agitation, apathy, ataxia, emotional lability, hostility, hypertonia, hypesthesia, incoordination, insomnia, memory impairment, neurosis, nystagmus, paresthesia, reflexes decreased, thinking abnormal (mainly difficulty concentrating), vertigo	Abnormal gait, euphoria, hyperesthesia, hypokinesia, neuritis, neuropathy, stupor, tremor
Respiratory System	Infection, rhinitis, sinusitis	Asthma, bronchitis, dyspnea, epistaxis, hiccup, laryngitis	
Skin and Appendages	Rash,	Acne, alopecia, contact dermatitis, dry skin, eczema, skin discoloration, sweating, urticaria	Erythema multiforme, furunculosis, herpes zoster, hirsutism, maculopapular rash, vesiculobullous rash
Special Senses	Unpleasant taste	Conjunctivitis, dry eyes, ear pain, otitis externa, otitis media, tinnitus, vestibular disorder	Hyperacusis, iritis, mydriasis, photophobia
Urogenital System	Dysmenorrhea (women) (women) gynecomastia (men)	Amenorrhea, breast engorgement, breast engorgement, breast enlargement, breast neoplasm, breast pain, cystitis, dysuria, female lactation, hematuria, kidney calculus, kidney pain, mastitis, menorrhagia, metrorrhagia, urinary frequency, urinary incontinence, uterine, hemorrhage, vaginal hemorrhage, vaginitis	Oliguria, pyelonephritis, urethritis

Adapted from (Krystal et al 2003; Zammit et al 2004; Melton et al 2005; Rosenberg et al 2005; Roth et al 2005; Sepracor 2005). Doses range from 1 to 3.5. Other symptoms for which frequency information could not be obtained include: flu syndrome, myalgia, and a non fatal overdose.

There have been studies testing the sustained benefit of 3 mg of eszopiclone for a 6 week (Zammit et al 2004), 6 month (Krystal et al 2003), and 12 month period (Roth et al 2005). None of these studies showed evidence of pharmacologic tolerance. However, further research is needed to test eszopiclone's discontinuation effects (Roth et al 2005). The worsening of sleep relative to baseline values after discontinuation of the medication is known as rebound insomnia (Gillin et al 1989). Rebound insomnia has been associated with use of benzodiazepines (Hegelbach-Feller et al 1988). Eszopiclone, which shares some pharmacologic properties of benzodiazepines, is under the same classification, schedule IV controlled substance, as benzodiazepines (Sepracor 2005). Most controlled studies with eszopiclone found it was not significantly associated with rebound insomnia (Krystal et al 2003, 2005; Zammit et al 2004; Erman et al 2005; Fava et al 2006). However, this was not exclusively the case (Anon 2005c). One study found rebound insomnia on the first night in patients discontinuing the 2 mg dose of eszopiclone, and patients discontinuing the 3 mg dose had diminished sleep efficiency (time asleep/8 hours) on the first night (Anon 2005c). In addition to tolerance and rebound insomnia, withdrawal following discontinuation is another major concern associated with hypnotic medications. No serious withdrawal effects were seen with eszopiclone. The following adverse events from the DSM-IV criteria for uncomplicated sedative/hypnotic withdrawal were, however, seen within 48 hours after discontinuing eszopiclone usage: anxiety, abnormal dreams, nausea, upset stomach, hyperesthesia, and neurosis (Sepracor 2005). There were no reports of seizures, hallucinations, or perceptual-disturbance; events that are commonly reported withdrawal symptoms following discontinuation of sedative/hypnotic medications (Sepracor 2005). Nonetheless, the manufacturer urges caution when prescribing eszopiclone for patients with history of alcohol or substance abuse and dependence.

The use of benzodiazepines and similar medications, like eszopiclone, could lead to both physical and psychological dependence. This increases with not only the dose and duration of the treatment but also use of other mediations, and in patients with a history of alcohol/drug abuse or history of psychiatric disorders. The term, hypnotic dependent insomnia, is used to describe a special type of dependence characterized by insomnia or excessive sleepiness associated with tolerance to or withdrawal from hypnotic medications. The use of benzodiazepine as hypnotics has been occurring since the 1960s and before that the barbiturates were used as hypnotics. Nonetheless a variety of abnormal thinking and behavior changes have been shown to transpire with the use of sedative/hypnotics (Sepracor 2005). Characteristics of these changes are decreased inhibitions (out of character extraversion and aggression); bizarre behavior agitation; hallucinations; depersonalization; sporadic amnesia and other neuropsychiatric symptoms; and in those with depression, worsening of the disorder including suicidal ideology (Sepracor 2005). Discontinuation or rapid decrease of such mediations produces effects analogous to alcohol and other CNS depressants. To establish the abuse liability of eszopiclone, individuals known to abuse benzodiazepines were given eszopiclone at twice the recommended dose, 6 and 12 mg. This resulted in euphoric effects

Table 4 Adverse effects reported by elderly adults[1]

	Frequent AE's at least 1 in 1/100	**Other AE's [2] reported AE's with missing frequency**
Body as a whole	Accidental injury, headache, pain	Asthenia, impaired psychomotor functioning (9.5 hrs. post drug, compared to placebo), moderate atypical chest pain[3]
Digestive System	Dry mouth, dyspepsia, diarrhea,	Abdominal pain, nausea
Nervous System	Abnormal dreams, dizziness, neuralgia, nervousness,	Somnolence, next day memory impairment
Skin and Appendages	Pruritis	Rash
Special Senses	Unpleasant taste	
Urogenital System	Urinary tract Infection	

[1]More information on this population is required to gain a fuller view of AE's although, the labeling text does report the overall pattern of AE's for elderly subjects was not different from younger adults.
[2]Due to sample size of many studies full frequency information is unavailable.
[3]Reported but deemed unrelated to treatment.

(at both doses) similar to those of diazepam 20 mg as well as amnesia and hallucinations (Sepracor 2005). In older adults, hypnotics may not be associated with an increased mortality risk, but this population may be more sensitive and are more likely to experience adverse effects (McCall 2005). This is particularly true with long durations of use and high dosages. Other restrictions on the use of hypnotics in older adults consist of potential risk of accidents (ie, falls, motor vehicle accidents cause by slowed reactions), anterograde amnesia, and diminished effectiveness over time. The manufacturer suggests careful monitoring for tolerance or dependence in patients on long-term drug therapy.

Economics/cost

Table 6 compares the cost of various dosages of eszopiclone to 2 other popular and relatively new nonbenzodiazepine hypnotic agents – zaleplon and zolpidem (benzodiazepine receptor agonists) and to the newly introduced melatonin receptor agonist hypnotic agent – ramelteon. Although more expensive than older hypnotic agents, eszopiclone is

Table 5 Drug interactions with eszopiclone

Drug	Effect
Ethanol	Coadministration of eszopiclone and ethanol 0.70 g/kg, showed an additive effect on psychomotor performance up to four hours after ethanol administration.
Ketoconazole	Concomitant administration of eszopiclone 3 mg and ketoconazole 400 mg, which is a potent inhibitor of P450 CYP3A4. The total amount of eszopiclone absorbed by the body increased by 2.2 when given ketoconazole for 5 days. The time to peak effectiveness increased by 1.4 and half life increased by 1.3. Other inhibitors of CYP3A4: itraconazole, clarithromycin, nefazodone, ritonavir, nel-finavir, are expected to act the same way although they have not been tested and no specific recommendations for dose adjustments are made in the prescribing information.
Paroxetine	Coadministration of eszopiclone 3 mg and paroxetine 20 mg for 7 days had no clinically significant pharmacokinetic or pharmacodynamic interact there was a small increase in peak effectiveness of paroxetine 1.5% and eszopiclone 12%.
Digoxin	A single dose of eszopiclone 3 mg did not affect the steady state pharmacokinetics of digoxin in healthy volunteers, there was no recommendation of dose adjustment.
Warfarin	Coadminstration of eszopiclone 3 mg and a single warfarin 25 mg oral dose, daily for 5 days did not affect the pharmacokinetics nor the anticoagulant effect of the warfarin.
Lorazepam	Coadministration of eszopiclone 3 mg with lorazepam 2 mg decreased eszopiclone's peak concentration by 22.69% and lorazepan's by 21.1%, this was not considered a clinically relevant difference.
CNS depressant drugs	Caution should used when giving patients a combination of Eszopiclone and CNS drugs (ie, anticonvulsants, antihistamines and psychotropic medication). This combination may cause addictive CNS depression.
Olanzapine	Coadministration of single doses of eszopiclone 3 mg and olanzapine 10 mg formed a pharmacodynamic interaction and produced a decrease in a measure of psychomotor function. The pharmacokinetics of both drugs were unaltered. The manufacturer makes no specific recommendation for dose adjustments of either drug.
Fluoxetine	Among patients with insomnia and co-existing major depressive disorder co-administration of eszopiclone 3 mg in combination with fluoxetine QAM well tolerated and did not seem to undermine the antidepressant response of fluoxetine.
Effect of food	Coadministration of eszopiclone 3-mg after a high-fat meal resulted in no change in total amount of drug absorbed by the body, a reduction in peak concentration of 21% and a 1-hour delayed time to reach peak concentration. Manufacturer warns that eszopiclone's effects maybe reduced if it is taken with or immediate after a high-fat/heavy meal.
Rifampin	Rifampicin significantly decreased exposure to racemic zopiclone by 80% and a similar effect would be expected with eszopiclone. In subjects aged ≥65 years, the total amount of drug absorbed by the body increased by 41% and prolonged elimination of eszopiclone (t1/2 ~9 h) when compared to non-elderly adults, but peak concentration was unchanged. The manufacturer recommends no dose adjustments when the two drugs are coadministered. The starting dose of eszopiclone in geriatric patients should be 1 mg, with a recommended maximum dose of 2 mg.

similar in cost to the newer nonbenzodiazepine hypnotics and less expensive than ramelteon. The cost of 2 weeks of eszopiclone treatment for transient insomnia is approximately US$46.62–US$49.28. The cost for treating chronic late-life insomnia is considerably higher. In two recent community-based surveys of older adults' sleep patterns, individuals with insomnia reported experiencing difficulties for 7–12 years on average (McCrae et al 2003, 2005). Once daily treatment (one tablet per day) for 7 years would cost approximately US$8,500–US$9,000 and for 12 years would cost US$14,600–US$15,400.

Compared to nonpharmocological treatments, such as cognitive behavioral therapy for insomnia, long-term use of eszopiclone is more expensive. For example, the average duration of cognitive-behavioral therapy for insomnia is 6–10 sessions. Typically, each session lasts 50 minutes. At a cost of $150/session, the total cost of cognitive-behavioral therapy ranges from $900–$1500, making it considerably cheaper than on-going treatment with eszopiclone. Specifically, cognitive-behavioral therapy becomes more affordable after 9–15 months of daily eszopiclone treatment. Additionally, as described below, clinical trial evidence supports cognitive-behavioral therapy's effectiveness for insomnia in older adults.

Other treatment considerations for older adults

Because older adults frequently suffer from chronic insomnia, effective treatment needs to provide not only short-term improvement, but also long-term maintenance (6 months or more). Despite the fact that eszopiclone's length of use is not restricted, the available evidence does not address whether it provides the long-term maintenance that many older adults require. Each of the 3 clinical trials that focused on older adults were only 2 weeks in duration. Although other clinical studies have shown that eszopiclone can be used over periods of 6 and 12 months without evidence of problems, the maximum age of participants in those trials was 69. No long-term studies have been conducted in the old-old (75–84) or oldest-old (85+) age groups.

The role of learning (development of sleep preventing behaviors and associations) in the maintenance of chronic insomnia is another reason for caution in the use of eszopiclone or any other hypnotic medication for treating older adults. Insomnia is precipitated by a wide variety of factors, including medical and psychiatric illnesses. Over time, insomnia that begins due to one of these factors often leads to sleep preventing behaviors (ie, spending too much time in bed, trying too hard to sleep, increasing caffeine), associations (ie, associating the bed and bedroom with anxiety over inability to sleep, becoming fearful over awakening during the night), and physiological arousal. Over time, these behaviors and associations often serve to perpetuate the insomnia. Because older adults are likely to experience 1 or more chronic conditions, they are particularly vulnerable to developing these sleep-preventing behaviors and associations. Thus, cognitive-behavioral therapy for insomnia, which is designed to reverse both sleep-preventing associations and behaviors as well as reduce psychophysiological arousal, should always be considered as either an alternative or an adjunct to hypnotic therapy. Many patients rate cognitive-behavioral techniques for insomnia as more

Table 6 30 Day and per pill cost comparisons (in US dollars) for eszopiclone, ramelteon, zaleplon, zolpidem, and zolpidem-cr

Generic name	Brand name (manufacturer)	Dosages	Cost for 30 day supply	Per pill cost[5]
Eszopiclone	Lunesta (Sepracor)	1, 2, & 3 mg	$105.67/$99.95[1,2]	$3.52/$3.33
Ramelteon	Rozerem (Takeda Pharmaceuticals)	8 mg	$139.95/$149.00[3,4]	$4.67/$4.97
Zaleplon	Sonata (King)	5 mg 10 mg	$89.99/$67.95[1,2] $95.81/$89.95[1,2]	$3.00/$2.27 $3.19/$3.00
Zolpidem	Ambien (Sanofi-Aventis)	5 mg 10 mg	$104.99/$72.95[1,2] $104.99/$93.95[1,2]	$3.50/$2.43 $3.50/$3.13
Zolpidem-Extended Release	Ambien CR (Sanofi-Aventis)	6.25, 12.5 mg	$102.99/$88.88[1,2]	$3.43/$2.96

[1]Retail cost information based on US dollars for a 30 day supply (1 pill per day) purchased from drugstore.com (August 8, 2006).
[2]Retail cost information based on US dollars for a 30 day supply (1 pill per day) purchased from drugstoreScripts.com (August 8, 2006).
[3]Retail cost information based on US dollars for a 30 day supply (1 pill per day) purchased from pharmacies4us.com (August 8, 2006).
[4]Retail cost information based on US dollars for a 30 day supply (1 pill per day) purchased from usainternetpharmacy.com (August 8, 2006).
[5]Cost per pill determined by dividing 30 day supply costs by 30 days.

acceptable than sleep medications, and approximately 70%–80% of individuals treated behaviorally show sleep improvements (Morin et al 1999). Specifically, the typical primary insomnia patient reports decreases in sleep onset latency and wake time after sleep onset below or near the 30-minute criteria commonly used to diagnose insomnia (Morin et al 1999).

Although no clinical trials have compared eszopiclone to cognitive-behavioral therapy for insomnia, growing evidence supports the greater effectiveness of behavioral approaches to pharmacological ones for the treatment of late-life insomnia. In their recent review, Irwin et al (2006) emphasized behavioral therapy over pharmacological intervention for older adults (aged 55+). This review of 23 RCTs (>500 participants) found behavioral treatments (cognitive-behavioral treatment for insomnia, relaxation, behavioral only treatment for insomnia) produced improvements in sleep quality, sleep onset latency, and awakenings during the night. Effect sizes ranged from medium to large (0.38–0.73, ps < 0.01) and were comparable to those achieved with sleep medications. Importantly, for frequent nighttime awakenings which are one of the most common complaints of older adults, there was a better than average response with behavioral treatment compared to medications. Previous research comparing behavioral intervention to sleep medications has demonstrated comparable, yet more immediate effects (meaning sleep improvements are often seen the night the medication is taken compared to a potential delay of several days to several weeks for behavioral interventions, which require time for the patient to adopt new habits and behaviors) for pharmacological intervention (McClusky et al 1991), but better maintenance of improvements at 9 week followup for behavioral intervention. Morin and colleagues (1999) compared 8 weeks of behavioral treatment to temazepam (Restoril; initial dosage 7.5 mg increased up to 30 mg per night depending on treatment response and adverse effects) in older insomniacs. Behavioral intervention alone was more effective in sustaining sleep improvements over time (up to 24 months) than either medication alone or the two treatments combined.

Conclusion

Eszopiclone has been shown to be safe and efficacious for short-term treatment (2 weeks) of chronic, primary insomnia in older adults (64–91 years). Whether eszopiclone is safe and effective for older adults when used over longer periods has not been examined. This is unfortunate, because older individuals frequently suffer from chronic insomnia. For this reason, cognitive-behavioral therapy for insomnia, which targets the behavioral factors that can maintain chronic insomnia, represents an attractive treatment alternative or adjuvant to eszopiclone for older adults. To date, no studies have compared eszopiclone to other hypnotic medications or to nonpharmacological interventions, such as cognitive-behavioral therapy for insomnia, in older adults. All of the clinical trials reported herein were funded by Sepracor, the manufacturer of eszopiclone.

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