

# Management of insomnia in elderly patients using eszopiclone

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**Abstract:** Insomnia is a common sleep complaint in the elderly. The safety and efficacy of eszopiclone, a non-benzodiazepine hypnotic, in elderly patients with chronic insomnia has been established in two 2-week and one 12-week randomized, double-blind, placebo-controlled trials. Eszopiclone 1 mg was effective in reducing sleep latency. Eszopiclone 2 mg was effective in reducing latency to sleep and for increasing sleep maintenance. Eszopiclone doses of 1 mg and 2 mg reduced the number of daytime naps and decreased the duration of naps in elderly patients. Eszopiclone 2 mg improved the quality of life measures for mood, physical health, household activities, medication, leisure activities, and self-report of physical functioning and vitality in the 2-week trials, and vitality and general health in the 12-week trial. The most commonly reported side effects in the elderly included unpleasant taste, dry mouth, dizziness, and somnolence. The concurrent use of drugs that inhibit or induce the cytochrome P450 enzyme CYP3A4 can alter concentrations of eszopiclone and the dose may need to be adjusted. The recommended starting dose of eszopiclone for difficulty falling asleep is 1 mg at bedtime. For elders who complain of difficulty maintaining sleep, eszopiclone should be initiated at 2 mg at bedtime. Overall, eszopiclone is a safe and well-tolerated treatment option for elderly patients with insomnia.

**Keywords:** eszopiclone, insomnia, elderly

## Introduction

It has been estimated that over 50% of the elderly population living at home and up to two-thirds of those who reside in institutions report a sleep disturbance.<sup>1</sup> Insomnia, characterized by difficulty falling asleep or maintaining sleep along with daytime symptoms, is one of the most common sleep complaints of elderly patients. Higher rates of insomnia are reported in elderly patients with concurrent psychiatric (eg, depression, anxiety) and medical disorders (eg, pain, chronic obstructive pulmonary disease, gastroesophageal reflux disease).<sup>2,3</sup> Because insomnia is increasingly prevalent with age, the daytime consequences that elderly patients experience (eg, daytime sleepiness, fatigue, reduced concentration and motivation) can impair their functioning and affect quality of life.<sup>4</sup>

Numerous pharmacological treatment options are available for the management of insomnia. Commonly used hypnotic drug classes include the benzodiazepine receptor agonists (eg, temazepam, triazolam), non-benzodiazepine gamma-aminobutyric acid, type A (GABA<sub>A</sub>) receptor agonists (eg, zolpidem, zaleplon, zopiclone, eszopiclone), melatonin receptor agonists (ie, ramelteon), sedating antidepressants (eg, doxepin, amitriptyline, mirtazapine, trazodone), and antihistamines (eg, diphenhydramine, doxylamine). The use of hypnotics in the elderly population is limited secondary to

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increased sensitivity to adverse drug effects and an overall paucity of trials to support the safety and efficacy of hypnotic agents. The use of long-acting benzodiazepine hypnotics (eg, flurazepam, quazepam) has been associated with hypotension, confusion, dizziness, disorientation, and falls in the elderly population.<sup>5,6</sup> Tricyclic antidepressants (ie, amitriptyline, doxepin) can cause anticholinergic side effects and use is not recommended in elderly patients.<sup>6</sup> Low doses of trazodone in the elderly on concomitant antihypertensives may be associated with orthostatic hypotension.<sup>7</sup> Over-the-counter antihistamines should not be used as hypnotics in the elderly because of an increased risk of confusion and anticholinergic side effects.<sup>6</sup>

The non-benzodiazepine GABA<sub>A</sub> receptor agonist hypnotics are alternatives to the benzodiazepines for the treatment of insomnia in the elderly. Eszopiclone received approval in the United States in 2004 for the treatment of insomnia and sleep maintenance. Approval was based on efficacy studies in adult patients with chronic insomnia (6-week and 6-month trials)<sup>8,9</sup> and elderly patients (2-week trials).<sup>10,11</sup> Clinical efficacy was also demonstrated in a 12-week trial in older adults, in patients with transient insomnia, and in a 6-month open-label trial extension after 6 months of controlled use.<sup>12–14</sup> The use of eszopiclone 3 mg in adults was well-tolerated for 12 months with no evidence of the development of tolerance or adverse events typically associated with withdrawal on discontinuation.<sup>14</sup> In a polysomnographic comparison between eszopiclone (1 mg, 2 mg, 2.5 mg, or 3 mg), zolpidem 10 mg and placebo, both hypnotics were found to be more effective than placebo in adults.<sup>15</sup> The purpose of this article is to review the current information on the pharmacology, safety and efficacy, and use of eszopiclone in the elderly population.

## Pharmacology

Eszopiclone is a non-benzodiazepine cyclopyrrolone hypnotic agent.<sup>16</sup> It is the *S*-enantiomer of racemic (*R,S*)-zopiclone, a hypnotic available in Europe since the early 1990s.<sup>17</sup> Its specific hypnotic mechanism of action is unknown, but it is thought to interact with the GABA<sub>A</sub> complex.<sup>16</sup> Eszopiclone has affinity for the  $\alpha 1$ ,  $\alpha 2$ ,  $\alpha 3$ , and  $\alpha 5$  subunits of the GABA<sub>A</sub> complex with varying potency at these sites.<sup>18</sup> It is postulated that eszopiclone acts primarily through  $\alpha 2$  and  $\alpha 3$  receptors and, to a lesser extent, the  $\alpha 1$  receptor.<sup>18</sup>

Eszopiclone is rapidly absorbed after oral administration and reaches peak concentrations ( $C_{max}$ ) within 1 hour after oral administration. Plasma protein binding ranges from 52% to 59%.<sup>16</sup> Eszopiclone is metabolized through oxidation and demethylation by the cytochrome P450 isoenzymes

CYP3A4 and CYP2E1 to two principal metabolites – (*S*)-zopiclone-*N*-oxide and (*S*)-*N*-desmethylzopiclone. The desmethyl metabolite is active and binds to the GABA receptor but at lower potency than the parent compound.<sup>16</sup> In a multiple-dose pharmacokinetic comparison between eszopiclone 3.5 mg and zopiclone 7.5 mg, the area under the plasma concentration curve ( $AUC_{0-\infty}$ ) was lower and the half-life ( $t_{1/2}$ ) was shorter for the desmethyl metabolite after eszopiclone dosing compared with zopiclone dosing.<sup>19</sup> Next-day driving impairment was reported to occur 9–11 hours after zopiclone 7.5 mg.<sup>20</sup> The lower concentrations of the desmethyl metabolite may explain the lack of effect on next-day functioning outcomes reported after eszopiclone dosing.<sup>19,21</sup>

Eszopiclone does not inhibit other cytochrome P450 isoenzymes. The average  $t_{1/2}$  of eszopiclone is 6 hours with less than 10% excreted unchanged in the urine. In elderly subjects there was an increase in the AUC (41%) and the  $t_{1/2}$  was increased to 9 hours.<sup>16</sup>

## Efficacy trials

The efficacy of eszopiclone in the elderly (aged 64–86 years), was established in two 2-week, randomized, double-blind, placebo-controlled trials, and one 12-week trial.<sup>10–12</sup> A summary of the results of these trials appears in Table 1. Scharf et al<sup>10</sup> examined the use of eszopiclone in 231 community dwelling elderly patients (mean age 72.3 years) diagnosed with primary insomnia (using *the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*). To be included in the study, participants had to report sleeping less than 6.5 hours per night and taking greater than 30 minutes to fall asleep each night for a minimum of 1 month. Participants were randomized to receive eszopiclone 1 mg ( $n = 72$ ), eszopiclone 2 mg ( $n = 79$ ), or placebo ( $n = 80$ ). Patients were directed to take one tablet each night at bedtime. The primary endpoints of this study were subjective and assessed using an interactive voice response system (IVRS) every morning and every evening. The morning questionnaire evaluated the efficacy variables of sleep latency, total sleep time (TST), wake time after sleep onset (WASO), number of awakenings, morning sleepiness, quality of sleep, and depth of sleep. The evening questionnaire measured ratings of daytime alertness, ability to function, sense of physical well-being, number of naps taken, and length of naps.<sup>10</sup>

All 231 patients completed the study and were included in the analysis. Both eszopiclone 1 mg and 2 mg had significantly shorter sleep latency compared with placebo ( $P = 0.12$  and  $P = 0.0034$ , respectively). Only eszopiclone 2 mg had significantly longer TST compared with placebo ( $P = 0.0003$ ). On secondary endpoints, eszopiclone 2 mg

**Table 1** Clinical trials of eszopiclone in the elderly

Citation	Design	Population mean age diagnosis	Treatment [n]	Results	Conclusions
Scharf 2005 <sup>10</sup>	2-week RDBPC	72.3 yrs Primary insomnia	EZ 1 mg [n = 72] EZ 2 mg [n = 79] PBO [n = 80]	Mean parameter (min) DB avg: SL 53.6 <sup>a</sup> TST 345.8 WASO 72.6 Number of naps (total over all patients) 223	SL statistically significant for EZ1 and EZ2, TST only for EZ2. EZ2 had significance over PBO on many secondary outcomes PBO 85.5 EZ2 50.0 <sup>a</sup> EZO 328.2 EZO 74.1 P-value 0.0034 0.0003 0.0423 ≤0.05
McCall 2006 <sup>11</sup>	2-week RDBPC	EZ2 = 71.5 yrs PBO = 70.7 yrs Primary insomnia	EZ 2 mg [n = 136] PBO [n = 128]	Mean parameter (min) by PSG over DB avg: LPS 19.3 <sup>a</sup> TST 332.6 <sup>a</sup> SE (%) 79.4 <sup>a</sup> WASO 83.6 Median number of naps (per patient) 2	ESZ2 significant improvement in LPS, SE and TST by PSG PBO 40.8 EZ2 361.9 EZO 73.4 EZO 93.9 P-value <0.001 <0.001 <0.001 0.013 3 0.03
Ancoli-Israel 2010 <sup>12</sup>	12-week RDBPC	EZ2 = 71.6 yrs PBO = 72.4 yrs Insomnia	EZ 2 mg [n = 194] PBO [n = 194]	Only baseline measurements provided; statistical improvements in TST, SL, WASO were seen within the first week and maintained throughout the 12 weeks Focus on next day functioning DB avg: mean change from baseline	EZ2 significantly improved TST, SL, and WASO from baseline Improvement occurred at week 1 and was sustained for the remainder of weekly assessments for 12 weeks Improvements were seen in daytime alertness, ability to concentrate and function and overall physical well-being with EZ treatment PBO 0.6 EZ2 1.0 P-value <0.001 0.5 <0.001 0.9 <0.001 0.5 <0.001

<sup>a</sup>Statistically significant.

**Abbreviations:** RDBPC, randomized, double-blind, placebo-controlled; EZ, eszopiclone 1 mg; EZ2, eszopiclone 2 mg; PBO, placebo; DB avg, double-blind period average; SL, sleep latency; TST, total sleep time; WASO, wake time after sleep onset; PSG, polysomnography; LPS, latency to persistent sleep; SE, sleep efficiency measured in %.

had significantly higher quality and better depth of sleep ( $P = 0.0006$  and  $P = 0.0015$ , respectively), and significantly less WASO ( $P \leq 0.05$ ) compared with placebo, but did not differ in the number of awakenings per night. On the secondary sleep endpoints, eszopiclone 1 mg did not differ from placebo for WASO, number of awakenings, sleep quality or sleep depth. For daytime functioning variables, compared with placebo, the eszopiclone 2 mg group had significantly higher reports of daytime alertness ( $P \leq 0.05$ ) and sense of physical well-being ( $P \leq 0.05$ ). On the change from baseline for daytime variables, eszopiclone 2 mg significantly decreased morning sleepiness ( $P = 0.0058$ ), and increased daytime alertness ( $P = 0.0107$ ), ability to function ( $P = 0.0098$ ), and sense of physical well-being ( $P = 0.0142$ ). No significant differences on daytime variables were detected between the eszopiclone 1 mg group and placebo. Patients receiving eszopiclone 1 mg and 2 mg took 223 and 220 naps, respectively, versus 325 naps in patients receiving placebo. Eszopiclone-treated patient naps were significantly shorter in duration (1 mg [ $P = 0.05$ ] and 2 mg [ $P = 0.0005$ ] versus placebo).<sup>10</sup>

A second 2-week study, conducted by McCall et al,<sup>11</sup> included 264 patients (mean age 70.7 years for placebo, and 71.5 years for eszopiclone). Similar to the previous study, to be included participants were diagnosed with primary insomnia (using the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*), and reported sleeping less than 6.5 hours per night and taking greater than 30 minutes to fall asleep each night for a minimum of 1 month. Additional inclusion criteria of mean WASO of at least 20 minutes with no night less than 15 minutes, and a mean latency to persistent sleep of 20 minutes or longer with no night less than 15 minutes were established on a 2-night screening completed by polysomnography (PSG). Patients were randomized to receive either eszopiclone 2 mg ( $n = 136$ ) or placebo ( $n = 128$ ). Efficacy was evaluated objectively with PSG on nights 1, 2, 13, and 14, and subjectively using daily patient morning and evening questionnaires via IVRS. On evenings 3 through 12 patients slept at home. Additionally the Insomnia Severity Index (ISI) was completed at baseline and after 14 days of study medication. The primary efficacy endpoints evaluated by PSG were sleep latency to persistent sleep (LPS, defined as time from lights out to the beginning of 10 minutes of uninterrupted sleep) and sleep efficiency (SE, defined as the ratio of TST to total time in bed). Secondary PSG endpoints included WASO, number of awakenings, wake time before persistent sleep, wake time during sleep, and cumulative wake time. The endpoints assessed on the

patient questionnaire were similar to those discussed above for the Scharf et al<sup>10</sup> trial.<sup>11</sup>

Of the 264 patients randomized, 255 completed the study. Patients receiving eszopiclone 2 mg showed significant improvement in LPS, SE and TST ( $P < 0.001$ ) by PSG compared with placebo. On PSG, it was noted that patients treated with eszopiclone 2 mg did not exhibit clinically significant changes in sleep architecture from baseline. Non-rapid eye movement (non-REM) stage 2 sleep was significantly increased by 2.3% in the eszopiclone group, versus a 0.1% decline in the placebo group. Mean time spent in rapid eye movement (REM) sleep increased in both groups (eszopiclone 7.7 minutes, and placebo 9.1 minutes,  $P = 0.97$ ). On the patient-reported endpoints, eszopiclone 2 mg significantly improved sleep latency, TST and ISI score ( $P < 0.001$ ) compared with placebo and to baseline. Sleep quality and depth of sleep were also significantly better in the eszopiclone group over placebo. Fifty percent of patients reported taking at least one nap during the study time period. Similar to the Scharf et al<sup>10</sup> study, eszopiclone use was associated with fewer naps, and shorter duration of naps. Variables of daytime functioning (eg, ability to function, daytime alertness, sense of well-being) were not significantly different between groups.<sup>11</sup>

Ancoli-Israel et al<sup>12</sup> compared the efficacy and safety of eszopiclone 2 mg over 12 weeks in a multicenter, randomized, double-blind, placebo-controlled trial. A follow-up period of 4 weeks to assess discontinuation effects consisted of 2 weeks of single-blinded placebo and 2 weeks of no drug. The study included 388 patients (65–85 years of age) who met the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* criteria for insomnia. Subjects were required to have a TST less than or equal to 6 hours/per night for greater than or equal to 3 nights per week, and a WASO equal to or exceeding 45 minutes per night for at least 3 nights weekly for a month. It was necessary that all subjects retire to bed between 9 pm and 12 midnight. Subjects with stable Axis I diagnoses were included in the study and concurrent use of selective serotonin reuptake inhibitors was allowed if the patient had been maintained on a steady dose for the past 2 months. Excluded from the trial were subjects with another sleep disorder, or the presence of a medical or psychiatric condition or ingestion of substances that could interfere with sleep. Data were collected each morning and evening from electronic sleep/wake diaries maintained by the subjects (ie, sleep latency, TST, WASO, number of awakenings, quality of sleep, and depth of sleep). Subject-reported change from baseline in TST was the primary efficacy endpoint of this study. Secondary endpoints were the change from baseline

in subject-reported SL and WASO averaged over the 12 weeks. The ISI was used to assess the severity and impact of insomnia symptoms. To evaluate the emergence of withdrawal symptoms subjects completed the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) at weeks 12 and 14.

Of the 194 patients in each of the eszopiclone 2 mg and placebo groups, 74% of patients completed the trial. There was significant improvement on the average TST, sleep latency and WASO from baseline after treatment with eszopiclone 2 mg ( $P < 0.001$ ) compared with placebo. The improvement occurred at week 1 and was sustained for the remainder of weekly assessments for 12 weeks. Patient reports of number of awakenings ( $P < 0.01$ ), sleep quality ( $P < 0.001$ ), and depth of sleep ( $P < 0.001$ ) showed significant improvement at all time points. There was a decrease in naps per week after the initial three weeks of eszopiclone treatment compared with placebo ( $P = 0.006$ ) which was not maintained on assessments at weeks 6, 9, or 12. Results for total nap time were similar to that of naps per week. There was a significant improvement in ISI total scores with eszopiclone compared with placebo at all assessments ( $P < 0.001$ ). Eszopiclone-treated patients had significant increases in daytime alertness, ability to function, ability to concentrate, and sense of physical well-being compared with placebo at all assessment points ( $P < 0.001$ ) and for the double-blind average ( $P < 0.001$ ).

## Safety

Scharf et al<sup>10</sup> measured safety parameters through clinical laboratory values (ie, hematology, serum chemistry, urinalysis), 12-lead electrocardiograms, vital signs, physical and brief neurologic examination, and collection of adverse events. More elderly patients discontinued treatment secondary to adverse events in the placebo group (6.3%), than the eszopiclone 1 mg (2.5%) or eszopiclone 2 mg (1.4%) groups. Adverse events leading to discontinuation were not discussed. One of the most common adverse events seen in the adult population, unpleasant taste, occurred in 8.3% and 11.4% of elderly patients treated with eszopiclone 1 mg and 2 mg, respectively. In this 2-week trial, no adverse events related to falls, amnesia, or hallucinations were reported. No significant abnormalities on clinical laboratory values, vital signs, or physical exam were identified across all three treatment groups.<sup>10</sup>

In the McCall et al<sup>11</sup> study, two elderly patients (1.5%) discontinued treatment in the eszopiclone group secondary to adverse events. The first patient experienced hypertonia, pruritis, and diarrhea that were considered possibly related to study medication. The second patient experienced dizziness, which was considered probably related to study medication. In the 136 patients treated

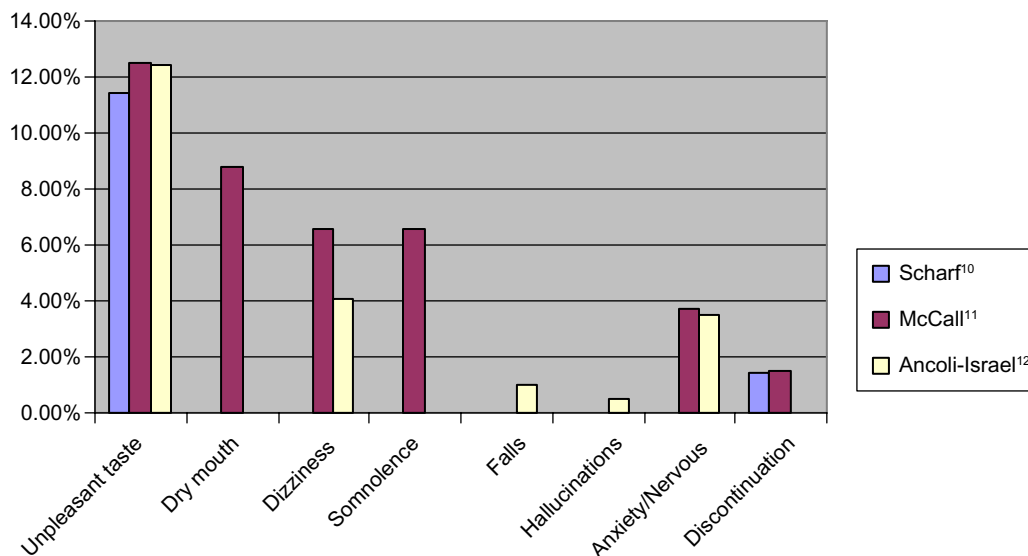
with eszopiclone 2 mg adverse effects occurring in greater than or equal to 3% of patients were unpleasant taste (12.5%), dry mouth (8.8%), dizziness (6.6%), somnolence (6.6%), pain (5.9%), rash (3.7%), and nervousness (3.7%). Accidental injury was reported by 1.6% of placebo-treated patients versus 2.9% of eszopiclone-treated patients. The investigators did not consider these injuries to be related to study medications. One patient reported an accidental injury from a fall that occurred 2 days after termination of eszopiclone treatment. No significant abnormalities on clinical laboratory values, vital signs, electrocardiogram, or physical exam were identified in either treatment groups.<sup>11</sup>

Long-term safety of eszopiclone was assessed over 12 weeks in the Ancoli-Israel et al trial.<sup>12</sup> Similar to the 2-week trials, unpleasant taste was reported in 12.4% of eszopiclone-treated patients. Of interest to the elderly population, dizziness (4.1%), anxiety (2%), nervousness (1.5%), falls (1%), memory impairment (1%), hallucinations (0.5%), and attention disturbance (0.5%) were reported more frequently than placebo (ranges 0–1.5%). The side effects that worsened in severity or frequency during the continuation phase included headache, dizziness, agitation, and restlessness (3.4%, 2.1%, 0.7%, and 0.7%, respectively). After 12 weeks of treatment, rebound insomnia was not evident after eszopiclone discontinuation.<sup>12</sup>

The adverse events of eszopiclone 2 mg are summarized in Figure 1.

## Drug interactions

Eszopiclone is metabolized through the cytochrome P450 CYP3A4 isoenzyme. The concurrent administration of ketoconazole 400 mg (a potent CYP3A4 inhibitor) and eszopiclone 3 mg resulted in a 2.2-fold increase in eszopiclone plasma concentrations. Thus, coadministration of eszopiclone with other CYP3A4 enzyme inhibitors (eg, itraconazole, nefazodone, nelfinavir, ritonavir, clarithromycin) would be expected to increase the AUC,  $C_{max}$ , and  $t_{1/2}$  of eszopiclone. It is recommended to use a starting dose of eszopiclone 1 mg and maximum dose of 2 mg if concurrent administration is required with a potent CYP3A4 inhibitor.<sup>16,22,23</sup> Data from the combined use of rifampicin (a CYP3A4 inducer) and racemic zopiclone revealed an 80% reduction in zopiclone exposure. An analogous effect would be predicted with concurrent administration of rifampicin and eszopiclone.<sup>16</sup> In separate studies of the combined use of eszopiclone with digoxin, warfarin, or paroxetine there were no alterations in pharmacokinetic parameters.<sup>23–25</sup> There were no pharmacodynamic interactions between eszopiclone and warfarin or paroxetine.<sup>25,26</sup> In a study of the effect of ethanol on eszopiclone, there was an additive effect on psychomotor performance for up to four hours after administration of alcohol



**Figure 1** Incidence of adverse drug events of eszopiclone 2 mg.

with eszopiclone.<sup>16,22</sup> Combined administration of eszopiclone 3 mg and lorazepam 2 mg reduced the maximum concentration of each drug and there were no pharmacodynamic effects.<sup>16,22</sup> The concurrent use of eszopiclone 3 mg and olanzapine 10 mg resulted in a reduction in Digit Symbol Substitution Test scores but no pharmacokinetic interaction occurred.<sup>16</sup>

## Dosing and administration

For elderly patients, the suggested dose for persons having difficulty sleeping is 1 mg immediately before bedtime. It can be increased to 2 mg if indicated. If an individual is having difficulty staying asleep, the recommended dose in the elderly is 2 mg before bedtime.<sup>15</sup> Eszopiclone is available in a 3 mg strength, however this dosage was not studied in the above three trials, and should not be used in elderly adults.<sup>27</sup>

## Patient-focused outcomes

The clinical efficacy trials of eszopiclone in elderly patients with insomnia measured quality of life using validated scales. The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) was used in the Scharf et al trial.<sup>10</sup> On the Q-LES-Q, when compared with placebo, patients receiving eszopiclone 2 mg had a significantly higher quality of life on 5 of 16 domains (ie, mood, physical health, household activities, medication, and leisure activities;  $P < 0.05$ ); no significant differences were detected in the eszopiclone 1 mg group. Erman et al<sup>28</sup> reported improvement in the SF-36 (Short-Form Health Survey) domains of physical functioning ( $P = 0.045$ ) and vitality ( $P = 0.056$ ) in elderly patients with chronic insomnia receiving eszopiclone 2 mg nightly for 2 weeks. After 12 weeks of nightly eszopiclone 2 mg, patients

reported significant improvements compared with placebo on the SF-36 scales of vitality at week 6 ( $P = 0.04$ ) and at week 12 ( $P = 0.008$ ), and general health at week 12 ( $P = 0.009$ ).<sup>12</sup> On the Sheehan Disability Scale, there was significant improvement reported in eszopiclone-treated patients compared with placebo on measures of social life and family life/home responsibilities ( $P \leq 0.03$ ) at week 6 only.<sup>12</sup>

## Discussion

The management of insomnia in elderly patients includes nonpharmacological and pharmacological treatment options. Dzierzewski et al<sup>29</sup> recently reviewed the evidence supporting the use of sleep hygiene and stimulus control methods, relaxation exercises, sleep restriction, cognitive behavioral therapy (CBT), and combination therapies.

This article focuses on the safety and efficacy of eszopiclone for the treatment of insomnia in the elderly population. It is important to note, that all three eszopiclone trials discussed above were supported by Sepracor, the manufacturer of eszopiclone. Across all three studies, the majority of patients were Caucasian (range 89.4%–96.5%), with African-Americans being the second most represented population (range 2.0%–7.2%), which may limit its applicability to all geriatric populations. Furthermore, other non-benzodiazepine hypnotic options in addition to eszopiclone are available. Before eszopiclone's approval zopiclone (the racemic mixture) was available in Europe for over 15 years.<sup>17</sup> Additional non-benzodiazepine hypnotics include zaleplon, zolpidem (immediate and controlled-release formulations), and indiplon, all of which have small trials in the geriatric population to support use, and may be viable options.

Zopiclone was evaluated in older adults and was compared to CBT, temazepam, flunitrazepam, triazolam, nitrazepam, and flurazepam.<sup>30–35</sup> In the elderly, zopiclone doses of 3.75, 5, 7.5, and 10 mg were studied. Sivertsen et al<sup>30</sup> found that CBT (n = 18) was superior to zopiclone 7.5 mg (n = 16) for both short-term and long-term management of insomnia in older adults (mean age 60.8 years). In an elderly population (mean age 73.2 years), both zopiclone 7.5 mg and nitrazepam 5 mg were efficacious for the treatment of insomnia.<sup>34</sup> A comparison of triazolam (0.125 or 0.25 mg) and zopiclone (5 or 7.5 mg) found that hypnotic activity was most pronounced with zopiclone 7.5 mg and triazolam 0.25 mg after 3 weeks of administration. Rebound effects persisted longer with triazolam than zopiclone upon withdrawal of the hypnotics.<sup>33</sup>

Zaleplon, which has a shorter half-life than eszopiclone, was studied in a 2-week, randomized, double-blind, placebo-controlled trial in 437 patients  $\geq$  65 years (mean age 72.5 years) with primary insomnia. Both zaleplon 5 mg and 10 mg were found to be safe and effective options to treat insomnia in the elderly by decreasing sleep latency.<sup>36</sup>

Zolpidem controlled-release was evaluated in a 3-week, randomized, double-blind, placebo-controlled trial in 205 elderly patients (mean age 70.2 years) with primary insomnia. Zolpidem controlled-release 6.25 mg was effective for sleep maintenance and sleep induction in the geriatric population.<sup>37</sup> Multiple studies assessing use of zolpidem immediate release (dosage range 5 mg to 20 mg per night) were conducted in the elderly, further supporting its use (preferred doses  $\leq$  10 mg) to treat insomnia.<sup>38–40</sup>

Regarding safety, when zopiclone 7.5 mg was compared with nitrazepam 5 mg, significantly more patients treated with nitrazepam (n = 24) failed the Romberg test than those treated with zopiclone (n = 16).<sup>34</sup> In a double-blind, 3-way crossover design, highway driving was assessed after treatment with temazepam 20 mg, zopiclone 7.5 mg, and placebo in patients with a mean age of 64.3 years.<sup>31</sup> Temazepam was determined unlikely to impair driving 10 hours or more after bedtime, and did not differ from placebo. Whereas zopiclone 7.5 mg moderately impaired driving at least up to 11 hours post ingestion, and driving performance was considered significantly impaired when compared to temazepam or placebo ( $P \leq 0.002$ ).<sup>31</sup> Like eszopiclone, bitter taste has been reported with zopiclone.<sup>34</sup>

Indiplon, which has a similar time to  $C_{max}$  as eszopiclone but a shorter  $t_{1/2}$ , was studied in 36 elderly patients in a placebo-controlled, active comparator crossover trial (mean age 68.6 years) to assess next day residual effects.<sup>41</sup> Indiplon 5 mg and

10 mg were compared to placebo, and zopiclone 3.75 mg was included as the control. Indiplon 5 mg was not significantly different than placebo on simple cognitive and motor tasks 4 hours post-ingestion. However impairment was noted with indiplon 10 mg.<sup>41</sup> Headaches were the only noted treatment emergent adverse event in this trial.<sup>41</sup>

The most commonly reported adverse effects of zaleplon included headache, dizziness, and pain.<sup>36</sup> Some patients who received 10 mg of zaleplon experienced mild rebound insomnia on the first night of discontinuation.<sup>36</sup> The most commonly reported side effects with zolpidem controlled-release were headache, dizziness, somnolence, and nasopharyngitis; no falls were reported.<sup>37</sup> Adverse effects were more common with zolpidem immediate-release 20 mg, therefore 10 mg is preferred in the elderly.<sup>38</sup> Except for the incidence of unpleasant taste, side effects are similar across the agents available in the non-benzodiazepine class when compared to eszopiclone in the geriatric population.

## Conclusions

Many agents are available to treat insomnia in the geriatric population. Eszopiclone is a non-benzodiazepine hypnotic agent effective for the management of chronic insomnia in elderly patients as demonstrated in three controlled trials. Eszopiclone doses of 2 mg were needed to increase sleep maintenance. Both eszopiclone 1 mg and 2 mg reduced latency to sleep and the number of daytime naps and decreased nap duration. Eszopiclone improved several domains of quality of life and physical well-being in elderly patients in both 2-week and 12-week trials. Eszopiclone was well-tolerated for up to 12 weeks of continuous use by elderly patients. Tolerance to the hypnotic effect of eszopiclone 2 mg for 12 weeks did not develop. Rebound insomnia was not evident after discontinuation of eszopiclone.

## Disclosure

No conflicts of interest were declared in relation to this paper.

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