The Long-Term Use of Eszopiclone in the Elderly

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Learning Objectives

1. Discuss background information and physiology of insomnia
2. Discuss treatment options of insomnia in the elderly
3. Evaluate long-term use of eszopiclone through literature review
4. Provide future recommendations regarding the use of eszopiclone in the elderly
1. **Introduction**
   - Insomnia is the most prevalent sleep disorder within the general population and is commonly encountered in medical practice.
   - Within the aging population it is estimated that 57% of older adults complain of significant sleep disruption:
     - 29% experience insomnia
     - 19% have complaints of early morning awakening
   - The American Academy of Sleep Medicine (AASM) warrants the use of benzodiazepine drugs or non-benzodiazepine hypnotics after failure of psychological and behavioral intervention.
   - Beers Criteria recently recommended avoiding long-term use of nonbenzodiazepine hypnotics in older adults:
     - Also recommended avoiding use of all benzodiazepines in patients older than 65.

2. **Epidemiology**
   - Insomnia is estimated to affect approximately 50 million people in the United States.
   - Annual direct and indirect costs associated with the treatment of insomnia in the US have been estimated to be approximately $13.9 billion and $77-92 billion.
   - An estimate of over 50% of the elderly population living at home and up two-thirds of those institutionalized report sleep disturbance.
   - Insomnia is one of the most common sleep complaints of the elderly, prevalence with age can result in daytime consequences that impair functioning and quality of life.

3. **Definition**
   - Insomnia is defined as a subjective report of difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity for sleep, and that results in some form of daytime impairment:
     - Insomnia symptoms occur in approximately 33% to 50% of adults.
     - Insomnia symptoms with distress or impairment occur in 10% to 15% of adults.
     - Specific insomnia disorders occur in 5% to 10% of the population.

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Patients with insomnia may complain of difficulty falling asleep, frequent awakenings, difficulty returning to sleep, awakening too early in the morning, or sleep that does not feel restful, refreshing, or restorative.

Insomnia should primarily be diagnosed by clinical evaluation through a thorough sleep history and detailed medical, substance, and psychiatric history.

Figure 1. **Insomnia in the General Population**

4. **Risk Factors**
   - Increasing age
   - Female sex
   - Comorbid disorders
   - Psychiatric illness
   - Lower socioeconomic status
   - Shift Work
   - Impaired social relationships

5. **Types and Causes of Insomnia** (Table 2)

<table>
<thead>
<tr>
<th>Type</th>
<th>Acute Insomnia (&lt; 30 days)</th>
<th>Chronic Insomnia (≥ 30 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>• Situational Stress</td>
<td>• Medical disorders</td>
</tr>
<tr>
<td></td>
<td>• Environmental Stressors</td>
<td>• Psychiatric disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Medications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Primary Sleep disorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sleep-wake schedule disorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Substance abuse</td>
</tr>
</tbody>
</table>
6. **Pathophysiology**

- Insomnia is thought to be a disorder of hyper-arousal experienced throughout the day exhibited by difficulty initiating and maintaining sleep at night
  - Explained by cognitive and physiological models of insomnia
- Cognitive model suggests arousal results from life stressors disrupting sleep and creating acute episodes of insomnia
  - Particularly in initiating sleep and returning to sleep after awakening
Physiological model suggests arousal is primarily due to physiologic or neurophysiologic factors:
- Increased whole body metabolic rate
- Heart rate variability
- Corticotropin releasing factor hyperactivity
- Increased cerebral glucose metabolism

7. Sleep Architecture\textsuperscript{10,11}
- Sleep is composed of two states: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep
- NREM is further broken down into stages 1, 2, 3 and 4. Stage 1 sleep is the lightest level of sleep, and each subsequent stage gets progressively deeper
  - Deepest stages 3 and 4 are referred to as slow wave sleep or deep sleep
- Changes in sleep architecture occur with age, the amount of deep sleep is reduced and majority of the night is spent in lighter stage 2 sleep

Figure 3. Comparison of Sleep Cycles in Young Adults and the Elderly\textsuperscript{11}

8. Circadian Rhythm Changes\textsuperscript{10-12}
- Circadian rhythms such as endogenous hormone secretions, core body temperature, and the sleep-wake cycle are controlled by the internal pacemaker in the suprachiasmatic nucleus
  - These rhythms are synchronized to the 24-hr day by external cues (zeitgebers) and internal rhythms
- The sleep-wake cycle is synchronized by: core body temperature, endogenous melatonin, the light-dark cycle, activity and meals (external)
- With aging, synchronization of the sleep-wake cycle is reduced and internal circadian rhythms become weaker, resulting in less consistent periods of sleep-wake
The sleep-wake cycle also shifts or advances in the older adult, causing advanced sleep phase syndrome (ASPS)

- Attributed to changes in core body temperature cycle, decreased light exposure, and environmental factors
- Most common complaints of ASPS are feeling sleepy early in the evening and waking up too early in the morning

ASPS is a common and expected development in older age, and appropriate treatment approach can reduce unnecessary use of sedative-hypnotic drugs

- Bright light exposure later in the day delays sleep-wake circadian rhythm
- Exogenous melatonin has been shown to be effective in synchronizing sleep-wake

Figure 4. Standard phase of sleep vs. advanced phase of sleep

9. Diagnosis

- Insomnia is primarily diagnosed by clinical evaluation through sleep history and detailed medical, substance, and psychiatric history

- Diagnostic tools:
  - International Classification of Sleep Disorders (ICSD-2)
  - Diagnostic and Statistical Manual of Mental Disorders, text revision, 4th edition (DSM-IV-TR)
    - DSM-V (2013) places further emphasis on co-existing medical conditions in relation to sleep disorders
Table 3.10

<table>
<thead>
<tr>
<th>DSM-IV Criteria for Primary Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. The predominant complaint is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month</td>
</tr>
<tr>
<td>B. The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning</td>
</tr>
<tr>
<td>C. The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia</td>
</tr>
<tr>
<td>D. The disturbance does not occur exclusively during the course of another mental disorder (e.g., major depressive disorder, generalized anxiety disorder, a delirium)</td>
</tr>
<tr>
<td>E. The disturbance is not due to the direct effects of a substance (e.g., a drug of abuse) or a general medical condition</td>
</tr>
</tbody>
</table>

- AASM guidelines recommend that at minimum the patient completes:
  - General medical/psychiatric/medication questionnaire
  - Sleepiness assessment such as The Epworth Sleepiness Scale
  - Two week sleep log to identify general patterns, sleep-wake times, and day to day variability

10. Insomnia in the Elderly7-10,13

- Subjective and objective measurements suggest older adults:
  - take longer to fall asleep
  - have lower sleep efficiency
  - more nighttime awakenings
  - wake up earlier in the morning than preferred
  - require more naps

- The most common complaints of insomnia in the elderly are associated with sleep maintenance and early morning awakenings

Figure 6. Subjective Reports and Objective Findings of Sleep in the Elderly16

<table>
<thead>
<tr>
<th>Subjective reports</th>
<th>Objective findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spend too much time in bed</td>
<td>Decrease in deep sleep (stages 3 and 4)</td>
</tr>
<tr>
<td>Spend less time asleep</td>
<td>Decrease in REM sleep</td>
</tr>
<tr>
<td>Increased number of awakenings</td>
<td>Significant increase in awakenings</td>
</tr>
<tr>
<td>Increased time to fall asleep</td>
<td>Increased frequency of sleep disorders</td>
</tr>
<tr>
<td>Less satisfied with sleep</td>
<td>Reduced sleep efficiency</td>
</tr>
<tr>
<td>More tired during the day</td>
<td>Increased daytime sleepiness</td>
</tr>
<tr>
<td>Longer and more frequent naps</td>
<td>Increased number of naps</td>
</tr>
</tbody>
</table>
Chronic insomnia is prevalent in older adults

- The National Sleep Foundation conducted telephone interviews of 1000 randomly selected adults chronic insomnia was highest in those aged 65 and older
- Occasional insomnia did not change with age
- The National Sleep Foundation found that adults age 65 or older who had more medical conditions reported significantly more sleep complaints

Comorbid conditions associated with insomnia in the elderly:
- Depression
- Chronic pain
- Cancer
- COPD
- Cardiovascular disease

Figure 7. Prevalence of One or More Sleep Problems by Number of Medical Conditions in Elderly

11. Consequences of Insomnia in the Elderly
- Decreased quality of life
- Mood changes
- Cognitive and functional impairment
- Reduced independence
- Increased risk of falls
- Potential impact on morbidity and mortality

12. Treatment of Insomnia
- Goals of therapy
  - Improve sleep quantity and quality
  - Improve insomnia related daytime impairments
  - Minimal or no adverse drug effects
- Treatment Options
  - Lifestyle and sleep habit changes may be enough to relieve mild or situational sleep disorders, optimizing sleep hygiene should also be used as part of treatment regimens
- Cognitive behavior therapy (CBT) may be sufficient alone or effective in combination with pharmacological therapy to prevent long-term use
  - Sivertsen et al. suggested that CBT intervention produced better results when compared to treatment with a BzRA for both short-term and long-term treatment of insomnia in the elderly
- Bright Light Therapy
- Pharmacologic treatment
- Nonprescription agents
  - Guideline Recommendations

Table 4.

<table>
<thead>
<tr>
<th>Summary of Guideline Treatment Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults (AASM)</td>
</tr>
<tr>
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</tbody>
</table>

BZD = benzodiazepine, BzRA = benzodiazepine receptor agonist
Table 5. FDA Indicated Treatment for Insomnia

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Dose (mg)</th>
<th>Mechanism of action</th>
<th>T max (h)</th>
<th>T ½ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flurazepam</td>
<td>Dalmene</td>
<td>15, 30</td>
<td>BzRA</td>
<td>0.5-1.0</td>
<td>47-100a</td>
</tr>
<tr>
<td>Triazolam</td>
<td>Halcion</td>
<td>0.125, 0.25</td>
<td>BzRA</td>
<td>2</td>
<td>1.5-5.5</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Restoril</td>
<td>7.5, 15, 30</td>
<td>BzRA</td>
<td>1.2-1.6</td>
<td>3.5-18.4</td>
</tr>
<tr>
<td>Estazolam</td>
<td>ProSom</td>
<td>1, 2</td>
<td>BzRA</td>
<td>0.5-6</td>
<td>10-24</td>
</tr>
<tr>
<td>Quazepam</td>
<td>Doral</td>
<td>7.5, 30</td>
<td>BzRA</td>
<td>2</td>
<td>39-73*</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Ambien</td>
<td>5, 10</td>
<td>BzRA</td>
<td>1.6</td>
<td>1.4-4.5</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Sonata</td>
<td>5, 10, 20</td>
<td>BzRA</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>Lunesta</td>
<td>1, 2, 3</td>
<td>BzRA</td>
<td>1.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Zolpidem CR</td>
<td>Ambien CR</td>
<td>6.25, 12.5</td>
<td>BzRA</td>
<td>1.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Zolpidem sublingual</td>
<td>Intermezzo</td>
<td>1.75, 3.5</td>
<td>BzRA</td>
<td>0.5-0.75</td>
<td>1.4-3.6</td>
</tr>
<tr>
<td>Ramelton</td>
<td>Rozerem</td>
<td>8</td>
<td>MtRA</td>
<td>0.75</td>
<td>1.0-2.6</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Silenor</td>
<td>3, 6</td>
<td>H₁Ant</td>
<td>3.5</td>
<td>15.3-31†</td>
</tr>
</tbody>
</table>

BzRA = benzodiazapine receptor agonist; FDA = Food and Drug Administration; H₁Anti-histamine 1 receptor antagonist; MtRA = melatonin receptor agonist, *Half-life for active metabolites*

13. Pharmacotherapy considerations in the elderly

- Beers Criteria
  - Tool to improve care by decreasing exposure to potentially inappropriate medication unique to the elderly
  - In 2012 The American Geriatric Society updated The Beers Criteria using a panel of healthcare and pharmacy experts
    - Noteworthy additional recommendations of “drugs-to-avoid“:
      - Short-acting benzodiazepines regardless of dose
      - Ongoing use of nonbenzodiazepine hypnotics (≥ over 90 days)
    - Normal and disease-associated physiological changes impacting pharmacokinetic and pharmacodynamic parameters in the elderly
Table 6. **Recommended Pharmacotherapy for Insomnia in the Elderly**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Geriatric Dose (mg)</th>
<th>Half-life (h)</th>
<th>Adverse Effects</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolpidem IR*</td>
<td>5</td>
<td>1.5-3.0</td>
<td>Abdominal pain, dizziness, headache, rebound insomnia, somnolence, memory loss</td>
<td>Sleep onset</td>
<td>Low risk of tolerance, dependency, or hangover; CYP3A4 inhibitors ↑ t½; contraindicated in SRBD/respiratory depression, advanced liver disease</td>
</tr>
<tr>
<td>Zolpidem ER*</td>
<td>6.25</td>
<td>2.0-7.5</td>
<td>Abdominal pain, dizziness, headache, rebound insomnia, somnolence, memory loss</td>
<td>Sleep onset</td>
<td>Low risk of tolerance, dependency, or hangover; CYP3A4 inhibitors ↑ t½; contraindicated in SRBD/respiratory depression, advanced liver disease</td>
</tr>
<tr>
<td>Zaleplon*</td>
<td>5</td>
<td>1</td>
<td>Color vision; nausea, myalgias</td>
<td>Sleep onset and sleep maintenance</td>
<td>CYP3A4 inhibitors ↑ t½; no tolerance, hangover or rebound Reduced number and duration of naps; less memory or psychomotor impairment</td>
</tr>
<tr>
<td>Eszopiclone*</td>
<td>1-2</td>
<td>9</td>
<td>Headache, bitter taste, dry mouth, somnolence, amnesia</td>
<td>Sleep onset and sleep maintenance (includes 1st insomnia)</td>
<td>CYP3A4 inhibitors ↑ t½; no tolerance, hangover or rebound Reduced number and duration of naps; less memory or psychomotor impairment</td>
</tr>
<tr>
<td>Ramelteon†</td>
<td>8</td>
<td>1.0-2.6</td>
<td>Headache, fatigue, somnolence, dizziness</td>
<td>Sleep-onset latency and total sleep time in chronic insomnia</td>
<td>Contraindicated with fluvoxamine and liver failure; least psychomotor or cognitive impairment</td>
</tr>
</tbody>
</table>

SRBD, Sleep-related breathing disorder, *Non-benzodiazepine, Melatonin receptor agonist†

14. Eszopiclone (Lunesta)⁷¹⁹
   - Non-benzodiazepine sedative hypnotic approved for short and long term treatment of sleep initiation and maintenance insomnia
   - Binds to all 3 GABA-Aα subunit receptors to augment initiation and maintenance of sleep
     - Benzodiazepines bind only to GABA-Aα 1 subunit and are less effective for sleep continuity and maintenance

![GABA receptor diagram](image)

Figure 7.

- Several clinical trials have established the safety and efficacy of eszopiclone in the elderly
### 12-week, randomized, double-blind, placebo-controlled study evaluating the effect of eszopiclone 2 mg on sleep/wake function in older adults with primary and comorbid insomnia.  
Ancoli-Israel et al. (2010)

<table>
<thead>
<tr>
<th>Design</th>
<th>12-week randomized, double-blind, placebo-controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>To evaluate the efficacy and safety of 12 weeks of nightly treatment with eszopiclone in elderly outpatients with insomnia</td>
</tr>
</tbody>
</table>
| **Method** | • Conducted at 82 private practice clinics and research sites in the United States  
• Participants (65-85 years) met DSM-IV-TR criteria for insomnia with Total Sleep Times (TST) ≤ 6h, and Wake time After Sleep Onset (WASO) ≥ 45min  
• Prior to enrollment patient adherence was assessed through utilization of sleep/wake diaries  
• Participants were randomized to 12 weeks of eszopiclone (ESZ) 2 mg (n=194) or placebo (PCB) (n=194) followed by a 2-week single-blind placebo run out and 2 week withdrawal period  
• Subject reported measures were assessed for:  
  o Sleep: TST, WASO, Sleep Latency (SL)  
  o Daytime function: alertness, concentration, well-being, ability to function  
• Severity and impact of insomnia symptoms, quality of life, and symptoms were also assessed  
• Adverse Effects (AEs) were monitored |
| **Selection Criteria** | **Inclusion** |  
• 65-85 years of age  
• Met DSM-IV-TR criteria for primary insomnia  
• TST ≤ 6 h per night for ≥ 3 nights per week  
• WASO ≥ 45 min per night for ≥3 nights per week  
• Mini-Mental State Examination ≥28  
• Eligible participants could have a psychiatric disorder diagnosed w/in 6 mo. of screening with good symptomatic control |
| | **Exclusion** |  
• Primary or secondary sleep disorder (other than primary insomnia)  
• Acute medical or psychiatric condition that could affect sleep  
• Unstable medical abnormality or chronic disease  
• Clinically significant ECG abnormalities  
• Condition that could interfere with drug metabolism  
• Previously enrolled in zopiclone or eszopiclone trial  
• History of drug or alcohol abuse or dependence w/in past 6 months  
• Use of substances affecting sleep |
| Results | |

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• Measured mean sleep variables of ESZ vs. PCB over double-blind period
  o TST 360.08 min vs. 297.86 min (P < 0.0001)
  o SL 24.62 min vs. 19.92 min (P = 0.0014)
  o WASO 36.4 min vs. 14.8 min (P < 0.0001)

• Most common AEs (≥ 5%) ESZ vs. PCB
  o Headache 13.9% vs. 12.4%
  o Unpleasant taste 12.4% vs. 1.5% (P < 0.001)
  o Nasopharyngitis 5.7% vs. 6.2%

• Insomnia Severity Index (ISI) in ESZ vs. PCB improved on average over 12 weeks (P < 0.001)
  o Decline in improvement occurred in ESZ group in week 14 – 16

• Daytime function in ESZ vs. PCB improved on average over 12 weeks (P < 0.001)

• General health and vitality significantly improved in ESZ vs. over 12 weeks
  (P = 0.008, P = 0.009)

• There were no statistically significant differences in eszopiclone treated participants on withdrawal measures from week 12 to week 14

• Number of naps per week significantly decreased in the first 3 weeks in ESZ vs. PCB but not at remaining follow up weeks

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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Eszopiclone 2 mg (N = 194)</th>
<th>Placebo (N = 194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>N = 194</td>
<td>N = 194</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>71.6 (5.0)</td>
<td>72.4 (5.2)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>70 (38.1%)</td>
<td>75 (38.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>124 (53.9%)</td>
<td>119 (61.3%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>178 (91.8%)</td>
<td>181 (93.3%)</td>
</tr>
</tbody>
</table>

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Authors’ Conclusions: Eszopiclone significantly improved and maintained patient-reported sleep and daytime function for 3 months in comparison to placebo, with no evidence of rebound insomnia occurring after discontinuation.

Comments:
- Industry sponsored
- Study design ensured patient adherence
- Patient demographics
- Inclusion of comorbid and psychiatric conditions
- All data was based on subjective reporting
- Withdrawal reporting incomplete
### Effects of eszopiclone on safety, subjective measures of efficacy, and quality of life in elderly and nonelderly Japanese patients with chronic insomnia, both with and without comorbid psychiatric disorders: a 24-week, randomized, double-blind study

Uchimura, N et al. (2012)

<table>
<thead>
<tr>
<th>Design</th>
<th>2 year multicenter, randomized, double-blind, parallel group study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To evaluate long-term safety (24-week) and short-term efficacy (4-week) of eszopiclone (ESZ) in elderly and nonelderly Japanese patients with chronic insomnia</td>
</tr>
</tbody>
</table>

| Method | • Conducted at 46 sites in Japan with outpatients seeking evaluation and treatment for sleep difficulties  
• Patients (20-84 years) with or without psychiatric comorbidities were randomized to receive ESZ:  
  ○ low-dose (1mg, elderly; 2mg, nonelderly)  
  ○ high-dose (2mg, elderly; 3mg nonelderly)  
• Safety evaluated by ADE, vital signs, lab parameters, ECG and questionnaire of drug dependence  
• Efficacy assessed w/ reports of SL, TST, WASO, NA, quality of sleep, depth of sleep, daytime ability to function and Short-form36 Health Survey |

<table>
<thead>
<tr>
<th>Selection Criteria</th>
<th>Inclusion</th>
</tr>
</thead>
</table>
| • Presence of primary insomnia diagnosed by DSM-IV-TR  
• Insomnia associated w/ physical or psychiatric disorder  
• Reported symptoms w/ SL > 30 minutes on 3 or more nights  
• TST < 390 minutes on 3 or more nights |

| Exclusion | • Risk of suicide, manic episode, PTSD, antisocial personality disorder  
• Alcohol abuse, history of drug dependence  
• Anorexia nervosa, bulimia nervosa  
• Drug-induced insomnia, primary sleep disorders (other than primary insomnia)  
• Severely disturbed sleep by medical conditions  
• Organic psychiatric disorder  
• Suicide ideation or attempt in past 5 years  
• Sever dysfunction of liver, kidney, cardiovascular or hematologic system  
• Presence of malignant tumor  
• Pregnancy or breast-feeding |

| Results | • Study consisted of 10 visits and 4 periods: screening period, 1st treatment (weeks 1 to 4), 2nd treatment (weeks 5 to 24), and follow up (week 25)  
• After 1st treatment period patients whose insomnia did not improve could increase dose (placebo given for patients on max dose)  
• Adverse events were recorded at all visits except baseline:  

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Dose of ESZ</th>
<th>Percentage that reported at least 1 ADE</th>
</tr>
</thead>
</table>
| Elderly (n=164) | 1 mg | 81.5 %  
| | 2 mg | 79.5 %  
| Nonelderly (n=161) | 2 mg | 82.1 %  
| | 3 mg | 87.0 % |
Median values of sleep latency in all subgroups (baseline – week 4)

- Median values for SL at baseline and week 1 – week 4
- Elderly: 1mg (A), 2mg (B); Nonelderly: 2mg (C), 3mg (D)
- P<0.0001 vs. baseline for all treatment groups

**Efficacy in the Elderly**

<table>
<thead>
<tr>
<th>Sleep Variable</th>
<th>Time Frame: Base vs. Week 4 (P- Value)</th>
<th>Time Frame: Base vs. week 24 (P- Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency</td>
<td>↓ &lt;0.001</td>
<td>↓ &lt;0.001</td>
</tr>
<tr>
<td>Total Sleep Time</td>
<td>↑ &lt;0.05</td>
<td>↑ &lt;0.001</td>
</tr>
<tr>
<td>Wake After Sleep Onset</td>
<td>↑ &lt;0.05</td>
<td>↑ &lt;0.01</td>
</tr>
<tr>
<td>Night Awakenings</td>
<td>↓ &lt;0.05</td>
<td>↓ &lt;0.01</td>
</tr>
<tr>
<td>Daytime Sleepiness and Function</td>
<td>↓, ↑ &lt;0.01</td>
<td>↓, ↑ &lt; 0.05</td>
</tr>
<tr>
<td>Quality and Depth of Sleep</td>
<td>↑ &lt;0.05</td>
<td>↑ &lt;0.01</td>
</tr>
</tbody>
</table>

- There was no apparent evidence of rebound insomnia after discontinuation of treatment in any treatment subgroups

**Short-Form 36:**
- ESZ did not significantly change physical component summary scores from baseline in all subgroups
- ESZ did significantly improve mental component summary scores at final visit in elderly and nonelderly with psychiatric disorders (4.6 to 3.6, P < 0.01)
- In patients elderly and nonelderly patients without psychiatric disorder mental component summary score improved slightly or remained the same
### Authors’ Conclusions
- Regardless of age treatment with ESZ over 24 weeks in patients with chronic insomnia was shown to be safe and well tolerated with no evidence of rebound insomnia or dependency after discontinuation

### Comments
- Varied age range and insomnia subtype
- Significance of statistics
- Inclusion of patients with psychiatric disorders
- Specific population
- Subjective measures largely used

## An evaluation of the efficacy and safety of eszopiclone over 12 months in patients with chronic primary insomnia

*T. Roth et al., Sleep Medicine (2005)*

<table>
<thead>
<tr>
<th>Design</th>
<th>6 month open-label extension of a prior 6 month double-blind, placebo-controlled eszopiclone study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To further assess the efficacy and safety of eszopiclone in adults with primary insomnia in up to a year of continuous nightly treatment</td>
</tr>
</tbody>
</table>
| Method          | • Conducted amongst adults (21-64) with primary insomnia who reported sleep duration < 6.5h/night or sleep latency > 30 min/night  
• Patients previously completed a 6 month double-blind, placebo-controlled eszopiclone study  
• Patient-reported data collected assessed  
  o Sleep: SL, WASO, TST, number of nightly awakenings, number of nights awakened/week, daytime ability to function, daytime alertness, and sense of physical well being  
• Safety and compliance were assessed at monthly clinic visits  
• The final double blind month was used as the baseline for efficacy analyses of the open-label period |
| Selection Criteria | Inclusion  
• 21-64 years of age  
• DSM-IV diagnosis of primary insomnia  
• Sleeping <6.5 h per night or having sleep latency >30 min per night for at least 1 month prior to screening  
**Exclusion**  
• More than 2 alcoholic beverages per day  
• Use of any medication known to affect sleep |
| Results         | • Baseline for comparisons was considered to be the 6th month of the double-blind, placebo-controlled eszopiclone trial  
• Eszopiclone-eszopiclone (ESZ-ESZ, n=296), placebo-eszopiclone (PCB-ESZ, n=86)  
ESZ-ESZ treatment vs. baseline:  
• Decreased sleep latency (P < 0.05)  
• Decreased WASO (P < 0.05)  
• Increase in TST (P < 0.02)  
• Decrease in nighttime awakenings (P < 0.05)  
• Improved daytime alertness |
- Improved ability to function
- Improved sense of physical well-being
- Incidence of ADEs 27.5%

PCB-ESZ treatment vs. baseline:
- Decreased sleep latency ($P < 0.0001$)
- Decreased WASO ($P < 0.000$)
- Increase in TST ($P < 0.0001$)
- Decreased number of nighttime awakenings ($P < 0.0001$)
- Improved daytime alertness
- Improved ability to function
- Improved sense of physical well-being
- Incidence of ADEs 31.4%

<table>
<thead>
<tr>
<th>Authors’ Conclusions</th>
<th>Use of eszopiclone led to continually improved sleep time, these improvements appear to result in improved daytime function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comments</td>
<td>Varied age range, unusual treatment dose&lt;br&gt;Subjective patient reports of sleep variables&lt;br&gt;Design similar to clinical practice&lt;br&gt;Failed to address issues related with long-term therapy</td>
</tr>
</tbody>
</table>

**Recommendation**

- Treatment of insomnia in the elderly should address the primary sleep problem and aim to improve daytime functioning
- Any contributing factors to insomnia should be identified and treatment of co-morbid conditions optimized if appropriate
- Non-pharmacological management is preferred and pharmaceutical therapy should be initiated only when necessary
- Beers Criteria recommendation for the use of non-benzodiazepine hypnotics <90 days in the elderly should be upheld until further studies prove otherwise
- Further studies with the long-term use of eszopiclone in the elderly are warranted, treatment should be used during the suggested time frame and tapered appropriately while integrating non-pharmacological management.
References

Appendix

Appendix A:

Sleep Hygiene Education for Patients

1. Do not spend too much time in bed
2. Maintain a consistent sleep/wake time
3. Get out of bed if unable to fall asleep
4. Restrict naps to 30 min in the late morning or early afternoon
5. Exercise regularly
6. Spend more time outside, without sunglasses, especially late in the day
7. Increase overall light exposure
8. Eat a light snack (i.e. milk, bread) before bed
9. Avoid caffeine, tobacco and alcohol after lunch
10. Limit liquids in the evening

Appendix B:

Sleepiness Assessments

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>ESS is an 8-item self report questionnaire used to assess subjective sleepiness (score range: 0-24; normal &lt;10).</td>
</tr>
<tr>
<td>Insomnia Severity Index</td>
<td>ISI is a 7-item rating used to assess the patient’s perception of insomnia.</td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index</td>
<td>PSQI is a 24-item self report measure of sleep quality (poor sleep: global score &gt;5).</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>BDI (or BDI-II) is a 21-item self report inventory used to measure depression (minimal or no depression: BDI &lt;10; moderate to severe: BDI &gt;18).</td>
</tr>
<tr>
<td>State-Trait Anxiety Inventory Form Y Trait Scale</td>
<td>STAI is a 20-item self report inventory used to measure anxiety (score range: 20-80; minimum anxiety: T-score &lt;50; significant anxiety: T score &gt;70).</td>
</tr>
<tr>
<td>Fatigue Severity Scale</td>
<td>FSS is a 9-item patient rating of daytime fatigue.</td>
</tr>
<tr>
<td>Short Form Health Survey (SF-36)</td>
<td>SF-36 is a 36-item self report inventory that generically measures quality of life for any disorder (range from 0 (poorest) to 100 (well-being).</td>
</tr>
<tr>
<td>Dysfunctional Beliefs and Attitudes about Sleep Questionnaire</td>
<td>DBAS is a self-rating of 28 statements that is used to assess negative cognitions about sleep.</td>
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</table>