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REVIEW

Eszopiclone in the Management of Insomnia Among Elderly Patients

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Abstract: Insomnia is an increasingly common disorder in the elderly and can have a profound, negative impact on both health and quality of life. Effective management can mitigate the adverse effects on morbidity and mortality. When possible, treatment of insomnia in the elderly should focus on conservative, non-pharmaceutical strategies and control of any potential co-morbid medical or psychiatric conditions. When needed, pharmacologic agents can be both safe and effective. Several classes are available for the treatment of insomnia. However, given their efficacy, relative safety and tolerability, non-benzodiazepines such as eszopiclone should be considered the mainstay of therapy. Eszopiclone can be a safe and effective agent for the long-term treatment of insomnia in the elderly.

Keywords: insomnia, elderly, safety, non-benzodiazepine, eszopiclone

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Introduction

Insomnia is a common disorder that has adverse effects on both health and quality of life. The American Academy of Sleep Medicine (AASM) defines insomnia as difficulty initiating and/or maintaining sleep resulting in daytime somnolence or decreased executive function.[1] Similarly, the American Psychiatric Association's (APA) Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) states that insomnia is characterized by difficulty initiating or maintaining sleep, or experiencing non-restorative sleep, for at least 1 month. These sleep disturbances result in an associated impairment in social, occupational or other important areas of functioning. The APA also states that the diagnosis cannot be made if there are conditions that would better explain the sleep disruptions, such as concomitant drug use, sleep disorder or mental/psychiatric condition.[2]

Insomnia is exceedingly common. In most industrialized nations, 10%–15% of adults experience insomnia at any given time and at least 30% will have insomnia over the course of their adult life.[3,4] Clinically significant insomnia is more common in patints with underlying concomitant or co-morbid medical and psychological conditions. In fact, nearly 80% of all cases of insomnia are the result of some underlying, predisposing factor or disease process.[5] Insomnia is frequently associated with concomitant behavioral health disorders, such as generalized anxiety and depression.[6] It is also more common in patients with underlying cardiopulmonary disease. The incidence of insomnia increases with increasing age and is two to three times more prevalent in persons over the age of 65.[4,7] A recent community based, longitudinal study found that 27% of those over the age of 65 reported difficulty initiating or maintaining sleep at least 3 nights per week.[8] During the two year observation period, 40% of these individuals reported continued difficulty maintaining sleep.[8]

Elderly patients are particularly vulnerable to sleep disruptions. Both subjective and objective measures of sleep quality progressively decline with increasing age. The diminished sleep quality in this population is largely the result of age-related changes in sleep quality as well as sleep fragmentation resulting from underlying medical conditions. Changes in sleep architecture are a normal phenomenon in the aging process. In a recent meta-analysis of quantitative sleep parameters, elderly patients were noted to have a progressive decrease in total sleep time (TST), sleep efficiency (SE), percentage of slow wave sleep (SWS) and percentage of Rapid Eye Movement (REM) sleep.[9] Similarly, there was significantly more sleep fragmentation and wake after sleep onset (WASO).

While age related impairments in both sleep architecture and continuity contribute to the poor sleep quality experienced by the elderly, this does not, in and of itself, account for the high prevalence of symptomatic insomnia in this population. Most insomnia in the elderly is secondary to co-morbid conditions. The increased incidence of chronic diseases in this population is clearly associated with an increased risk of insomnia.[10] When adjusted for co-morbidities the prevalence of insomnia in the elderly is similar to the general population, supporting the theory that insomnia is more likely to result from underlying medical problems that than age related effects on sleep quality alone.[10–12] In fact, the Established Populations for Epidemiologic Studies of the Elderly (EPESE) trial showed that only 7% of insomnia among the elderly occurred in the absence of co-morbid factors.[10] Sleep disruptions are frequently the consequence of underlying medical conditions and treatments that can impair both sleep onset and continuity. Numerous conditions can fragment sleep and subsequently lead to symptoms of insomnia. Many of which are more common among the elderly, such as arthritis, chronic pain, gastroesophageal reflux disease, chronic rhinitis, and depression. Cardiopulmonary disorders are frequently associated with sleep disturbances and insomnia. Prolonged latency to sleep, nocturnal awakenings, disrupted sleep architecture and sleep disordered breathing are common among patients with heart failure.[13,14] Fifty to seventy percent of patients with chronic obstructed pulmonary disease (COPD) report difficulty initiating or maintaining sleep. Regardless of severity, patients with COPD experience a decrease in total sleep time and increase in wake after sleep onset. This is largely the result of alterations in ventilation-perfusion matching and a diminished ability to clear secretions. Both mucociliary clearance and the cough reflex are diminished during sleep, which can lead to frequent arousals and awakenings, especially in those with COPD who experience an overproduction of and pre-existing inability to clear mucous secretions.

Airway patency and function are reduced during sleep and there is a normal amount of bronchoconstriction during the night. Patients with airflow obstruction, such as asthma and COPD, frequently develop profound bronchoconstriction, particularly in the early morning hours. This circadian influence on airway function can result in or contribute to sleep maintenance insomnia. Not only can numerous disease states fragment sleep, but many of the medications used to treat them also adversely affect sleep quality and continuity. For example, antidepressants and antipsychotics diminish SWS, diuretics can cause nocturnal awakenings, bronchodilators can lead to initiation insomnia and sleep fragmentation and analgesics may increase the risk of sleep disordered breathing. In fact, numerous classes of medications can exert a negative impact on sleep continuity and architecture. As such, polypharmacy, common with the elderly, can significantly contribute to the high prevalence of insomnia in this population.

Consequences of Insomnia in the Elderly

Chronic sleep disorders in the elderly, especially insomnia, are associated with significant morbidity and mortality. They are also associated with increased utilization of health care resources among persons 65 years and older.[10,11]

Insomnia can cause or contribute to neurocognitive impairment and behavioral health disorders. Several studies investigating the impact of insomnia on the elderly have shown a two-way reciprocal relationship between insomnia and both mental and physical health.[8] Sleep disorders, particularly insomnia, have been shown to be directly related to a decreased perception of health, a diminish quality of life, and decreased general sense of well-being.[10,11,15] Similarly, insomnia is frequently associated with depression and both a cause and effect relationship exists.[15] This is particularly more likely to occur in elderly patients. Insomnia has also been shown to cause or contribute to progressive declines in cognition and executive function. This is particularly true among the elderly who are more susceptible to these changes or potentially have pre-existing causes of cognitive impairment.[16–18] The need for long-term care or nursing home placement is also more common among those with chronic insomnia.[19]

Compared to those without insomnia, elderly patients with chronic insomnia are at an increased risk of accidental falls and traumatic fractures.[19–23] Elderly patients with symptoms of difficulty falling asleep and awakenings during the night are respectively 1.53 and 1.91 times more likely to fall than those without sleep disturbances.[22] In addition, symptoms of insomnia in the elderly such as increased sleep latency (greater than 30 minutes) and decreased sleep efficiency (less than 80%) were found to be associated with a 2.14 ($P = 0.005$) and 1.93 ($P = 0.014$) times greater risk of death[17] and is associated with an increase in mortality.[24]

Treatment of Insomnia in the Elderly

Given the high prevalence and adverse outcomes associated with insomnia among the elderly, clinicians must remain vigilant and proactive towards recognizing and effectively treating sleep disturbances in this population. The goal of insomnia treatment is to promote restorative sleep and mitigate daytime impairments by improving both sleep onset and continuity.

Safe and effective therapy can have a profound impact on health and well being. However, the benefits of therapy must be weighed against the potential for toxicity. This is especially true among the elderly who are more prone to the adverse side effects of pharmacotherapy. Treatment in this population remains challenging as the impact of poly-pharmacy, drug-drug interactions, diminished drug clearance, excessive responses to medical agents and the potential for exacerbating underlying medical and psychiatric co-morbid conditions is more likely to occur in the elderly. Given this, the long-term management of insomnia should be based on conservative, non-pharmacologic interventions.

Conservative therapy can be effective in most individuals. Patients should be counseled and educated regarding stimulus control and sleep hygiene. Maintaining a regimented sleep-wake cycle, avoidance of naps when possible and an active lifestyle that incorporates exercise can promote both sleep onset and continuity. Stimulants, such as nicotine and caffeine, should be avoided, particularly in the evening. When possible, better control of underlying medical conditions or adjustments in the timing, dosage or selection of other medications should be

accomplished as these can have significant impacts on both sleep onset and quality. These interventions can easily be initiated and should be performed in all patients with insomnia. Cognitive-behavioral therapy can be effective for those who continue to experience sleep disruption despite more conservative behavioral modifications. A meta-analysis assessing the impact of behavioral interventions for insomnia in the elderly showed significant improvements in sleep latency ($ES_m = -0.51$, $P \leq 0.001$), sleep efficiency ($ES_m = 0.38$, $P = 0.005$) and WASO ($ES_m = -0.73$, $P \leq 0.001$).[25] In this meta-analysis, there was little difference in efficacy noted between cognitive-behavioral therapy, relaxation therapy and behavioral modifications. While pharmacotherapy is clearly easier and has been shown to be as effective as cognitive-behavioral therapy, it is associated with the inherent risks of chronic sedative-hypnotic therapy. To minimize this risk, pharmacotherapy should be considered for treatment failures or to augment the effects of more conservative measures.

Clinicians should distinguish the difference between insomnia and advanced sleep phase syndrome. Advanced sleep phase syndrome is characterized by an advancement in the timing of sleep which results in a chronic inability to stay awake in the evening and early morning awakenings.[26] This can be confused for terminal insomnia, which also causes early morning awakenings. Advanced sleep phase syndrome is an uncommon circadian rhythm disorder in young adults, but is more frequent with advanced age. This is an important distinction when managing sleep complaints in the elderly as the treatment for advanced sleep phase syndrome is different than for insomnia. Failure to differentiate the two disorders may subject patients to inappropriate therapies. This advancement of the circadian rhythm may be a normal effect of aging. As such, advanced sleep phase syndrome should only be treated if the timing of sleep is interfering with social or occupational commitments. There are no AASM recommended treatments for advanced sleep phase syndrome. However, evening light exposure can produce subjective improvements.[26]

When needed, pharmacotherapy, using appropriate dose adjustments and monitoring, can be both safe and effective in the elderly. Medical therapy should be considered when conservative approaches have not produced an adequate resolution of symptoms or as a bridge to effective, non-drug therapy. The AASM outlines many evidenced based approaches to the treatment of insomnia in their 2008 clinical guideline.[27] After optimizing treatment for underlying co-morbid conditions, the AASM recommends behavioral/psychological therapy initially, followed by a stepwise addition of pharmacologic agents. Numerous classes of sedating medications are used for the treatment of insomnia, each of which is associated with varying degrees of efficacy and safety. Consideration of drug-drug interactions and side effect profiles should be considered when choosing pharmacotherapy for insomnia. This is especially important in the elderly due to polypharmacy and the increased prevalence of co-morbid conditions.

Benzodiazepines are effective for both initiation and maintenance of sleep. However, while effective, they are associated with several adverse consequences. In fact when compared to non-benzodiazepine sedative hypnotics they are associated with a more than doubled risk of harm.[28] The long elimination half-life of many of these agents and their adverse effect on sleep architecture commonly produce residual daytime somnolence. They can also exacerbate underlying co-morbid conditions, especially heart failure and sleep disordered breathing. In addition, these medications are associated with an increased risk of confusion, delirium, falls, and hip or femur fracture in the elderly.[29–31] Given these risks, and the potential for dependence, tolerance and abuse, benzodiazepines are not recommended for the treatment of chronic insomnia.

Antipsychotic medications are frequently used to treat elderly patients with insomnia. Unfortunately, like benzodiazepines, these agents alter normal sleep architecture and are commonly associated with daytime somnolence. Antipsychotics even in low doses have been associated with depressed cardiac function, abnormal limb movements, and hyperglycemia.[32] Because of these sometimes irreversible effects, antipsychotic agents should be avoided unless otherwise indicated.

Sedating antidepressants can be effective for the treatment of insomnia. However, side effects are common, including orthostatic hypotension, xerostomia, cognitive impairment, exacerbation of heart failure, urinary retention and cardiac conduction abnormalities.[32] These adverse effects are often dose

related and these agents can be both safe and effective. In a recent study, low doses of doxepin improved both subjective and objective sleep measures and adverse effects were similar to placebo.[33] However, given the numerous potential toxicities and adverse effect on sleep architecture, these agents should be used with caution, particularly among the elderly.

Ramelteon is a selective melatonin receptor agonist approved for the treatment of insomnia. In a 5 week randomized, double blind placebo controlled trial of elderly patients, ramelteon was shown to improve sleep latency by 16%–35% without a significant increase in adverse events when compared to placebo.[34] Ramelteon may offer a reasonable treatment for insomnia in the elderly. However, there are no long term studies in this population and the improvements in sleep onset may wane over time. In addition, data regarding ramelteon's effect on sleep maintenance is inconsistent. Despite some concerns over efficacy, this agent appears to be relatively safe and well tolerated.

Non-benzodiazepine sedative hypnotics, or benzodiazepine receptor agonists, offer an effective and generally well-tolerated option for the treatment of both acute and chronic insomnia. Given their likelihood of success and favorable side-effect profile, these agents have become the cornerstone treatment for insomnia. Commonly utilized medications in this class include zolpidem, zaleplon, and the newer agent eszopiclone.

Non-Benzodiazepine Sedative Hypnotics: Targets of Therapy and Mechanism of Action

Sleep is an intricate balance between numerous neurotransmitters in the central nervous system. To understand the therapeutic interventions for insomnia a fundamental understanding of wakefulness and sleep is critical. Schwartz and Roth examined the neurophysiology of sleep in their 2008 article describing two complex pathways that control the balance between cortical arousal and suppression.[35] These mutually inhibitory systems act by inducing one state while suppressing the other. In short, sleep requires the active promotion of sleep and a concomitant inhibition of wake. Likewise, wake requires the promotion of wakefulness and the suppression of sleep.

The primary neurotransmitter responsible for sleep onset and continuity is GABA.[35] GABA exerts its effects through GABA receptors. While there are numerous different GABA receptors throughout the central nervous system, the GABA-Aα 1, 2 and 3 subunit receptors appear to be primarily responsible for sleep onset and maintenance. Given that the treatment of insomnia should focus on both the initiation and maintenance of sleep, it seems that stimulation of all three of these subunits is required to induce and maintain continuous sleep. Subsequently, these subunit receptors are the target of many of the new saprophytic agents. Non-benzodiazepine sedative hypnotics bind to the GABA-Aα receptor to augment the initiation and maintenance of sleep. All non-benzodiazepines bind to the GABA-Aα 1 subunit receptor, which is thought to be responsible for sleep initiation. The older agents only bind to this receptor subunit and, as such, are less effective for sleep continuity and maintenance. In contrast, the newer agent, eszopiclone, binds to all three GABA-Aα subunit receptors and is effective for both the sleep onset and maintenance. While eszopiclone's precise mechanism of action is unknown, its effect is thought to result from its interaction with these GABA receptors in the central nervous system.

Eszopiclone is a non-benzodiazepine sedative-hypnotic which is FDA approved for both short and long term treatment of sleep initiation and maintenance insomnia. Eszopiclone is hepatically metabolized by CYP3A4 and CYP2E1 and is excreted in the urine. Eszopiclone is rapidly absorbed and reaches a maximum serum concentration within one hour. The elimination half life is six hours and the duration of clinical effect is seven hours for most people. The recommended dose for most healthy adults is 3 mg. Elderly patients and those with hepatic dysfunction may experience a prolonged clearance of eszopiclone. For these individuals, the recommended dose is 1–2 mg.[36] Renal disease does not alter drug metabolism or clearance.[36] As with most medications, the dose should be titrate to obtain the desired effect while minimizing the potential risk for toxicity. Eszopiclone has not been found to have an effect on the pharmacokinetics of warfarin or digoxin. Co-administration of eszopiclone with ethanol has been shown to have an additive effect on psychomotor performance.[36] Like other sedating agents, eszopiclone should not be used concomitantly with other CNS depressants.

Safety and Efficacy of Eszopiclone in the Elderly

There have been several clinical trials establishing the safety and efficacy of eszopiclone in the elderly. In a 14-day, randomized, double-blind, placebo-controlled, multi-center trial, Scharf et al found that both eszopiclone 1 mg and 2 mg significantly improved subjective sleep onset compared with placebo in a cohort of elderly patients with insomnia.[37] Eszopiclone 2 mg also showed significant improvements in wake after sleep onset (WASO), total sleep time and subjective sleep quality. Both doses were well tolerated and no decrement in next day function was noted using the Digit Symbol Substitution Task.[37] While common, adverse events did not differ between placebo or either dose of eszopiclone. Overall, adverse events were reported in 40%, 43%, and 40% of those receiving eszopiclone 1 mg, 2 mg or placebo respectively. The most common adverse effect noted with eszopiclone was unpleasant taste. There was no difference in the incidence of headache or dyspepsia and there were no reported adverse effects related to falls, hallucinations or amnesia noted for any of the treatment groups. Interestingly, next day somnolence was less common among those receiving eszopiclone than placebo, likely reflecting improvements in sleep quality and continuity. Somnolence was reported in 6.9% of those receiving eszopiclone 1 mg, 3.8% with eszopiclone 2 mg and 8.8% with placebo. More subjects discontinued treatment in the placebo group (6.3%) than the 1 mg (1.4%) or 2 mg (2.4%) eszopiclone groups.

In a randomized, double blind, placebo-controlled polysomnographic trial, McCall and colleagues assessed the effects of eszopiclone on subjects aged 64–86 years meeting DSM-IV diagnostic criteria for insomnia. Participants were randomized to eszopiclone 2 mg or placebo for 14 consecutive nights. Polysomnography was conducted on nights 1, 2, 13, and 14. Those receiving eszopiclone experienced significant improvements in latency to persistent sleep (14.8 vs. 30.4 minutes, $P < 0.0001$), sleep efficiency (80.4% vs. 74.6% $P < 0.0001$), total sleep time (385 vs. 358 minutes, $P < 0.01$), and WASO (91.2 vs. 81.7 minutes, $P = 0.036$). Subjective sleep quality and the frequency of daytime napping were also improved compared to placebo.[38] Similar to the prior study, both safety and tolerability were similar between eszopiclone and placebo. Overall, reported adverse events did not differ between the two groups and were reported in 46.3% of the eszopiclone group and 43.8% of the placebo group. Only unpleasant taste and dizziness were more common compared with placebo. There was a lower incidence of study discontinuation in the eszopiclone group (1.5%) than the placebo group (2.3%).

In a recent study examining the efficacy and safety of eszopiclone in the elderly, Ancoli-Israel and co-workers performed a 12-week randomized, double-blind, placebo controlled trial of patients aged 65–85 years old meeting DSM-IV-TR criteria for insomnia.[39] Participants were randomized to 12 continuous weeks of eszopiclone 2 mg or placebo followed by a 2-week single blind placebo run-out period. Compared to placebo, the authors demonstrated significant improvements in subjective measures of total sleep time, sleep latency and wake after sleep onset in those receiving eszopiclone. These effects were evident by the first week of therapy and improvements were maintained throughout the treatment period. The authors further demonstrated significant improvements in insomnia severity index (ISI) scores at all measured time intervals. Self reports of daytime alertness, ability to function, ability to concentrate, and physical well-being were significantly greater with eszopiclone than placebo. Similar to previous reports, the overall incidence of adverse events was similar for eszopiclone (59.3%) and placebo (50.5%). Only unpleasant taste differed significantly from placebo. The authors further explored the risk of side effects concerning to an elderly population. There were no differences in reports of dizziness (4.1% vs. 1.5%), falls (1.0% vs. 0.5%), hallucinations (0.5% vs. 0.0%), memory impairment (1.0% vs. 0.0%), attention disturbances (0.5% vs. 0.0%), or anxiety (2.1% vs. 1.0%) in those receiving eszopiclone or placebo, respectively. No evidence of rebound insomnia was noted following discontinuation of therapy.[39]

Of note the three trials detailed are the only studies to date which have examined the use of eszopiclone for the treatment of insomnia in the elderly. All three were industry sponsored. In addition, the study populations in these trials were predominantly Caucasian women with primary insomnia, which may limit the applicability to those with comorbid, or secondary insomnia. To date,

there are no large studies examining the safety and efficacy of eszopiclone in the treatment of the elderly with insomnia secondary to co-morbid conditions.

Conclusions

Insomnia is a common condition which can have a profound, negative impact on both health and quality of life. Like other sleep disorders, insomnia is significantly more common with advancing age. Unfortunately, sleep complaints are often under recognized and undertreated older persons. The elderly are not only more likely to have insomnia, but they are significantly more susceptible to insomnia related morbidity.

Elderly patients should be routinely screened for sleep disturbances. Once the symptoms are recognized, confounding factors should be identified and treatment of co-morbid conditions should be optimized. If symptoms persist, conservative, non-pharmaceutical management is always preferred, especially in the elderly. However, when needed, medical therapy can be both effective and safe. When used, agents should be selected that minimize the potential for adverse effects, appropriately dosed and used for a limited duration to minimize the potential for toxicity. Among elderly patients, pharmacotherapy should be initiated with careful consideration to factors unique to this population, including, cognition, falls risk, drug-drug interactions and adverse drug reactions. While there are numerous agents and classes of medications used for the treatment of insomnia, their utility should be weighed against their potential for toxicity and side effects in this population. Given their efficacy and relative safety and tolerability, non-benzodiazepines should be considered the mainstay of therapy. Eszopiclone is a safe and effective medication for the long term treatment of insomnia in the elderly.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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