APPROPRIATE USE OF HYPNOTICS IN THE ELDERLY

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"Take a trional powder when you retire and you will not be troubled with insomnia." This is a too common advice given to the laity and patients when either time or lack of interest prevents a thorough examination for the cause of insomnia. Before falling into the rut of routine hypnotics, it is well to take more time to study every case of insomnia and ferret out the cause, remove it if possible, and little sleep-giving medicine will be needed.
- W. Blair Stewart, A.M., M.D. (JAMA 1904)1

Sleep disorders are commonplace in the elderly and can have a multitude of causes. Table 1 lists common causes of impaired sleep in the elderly. Insomnia, defined as the inability to commence or sustain sleep resulting in next-day consequences, is the most commonly reported sleep complaint in patients over the age of 60. This is manifested in roughly 40% of elderly patients being dissatisfied with their quality of sleep, with 25% showing signs of chronic insomnia. In addition, despite the substantial impact on the elderly population, and the negative effects on activities of daily living, less than 15% of these patients receive treatment.[2, 3]

Sleep has been described as an elaborate balance of variable stages that are subdivided into NREM (non-rapid eye movement) and REM (rapid eye movement) sleep. NREM consists of 4 progressively deepening stages of sleep. Stages 3 and 4 of NREM, or delta sleep, have been associated with the perception of sleep quality. Stage 5, or REM sleep, is distinguished by dreaming and is considered to be necessary for learning and temperament.[4]

There are a variety of sleep cycle alterations that occur in the elderly that can contribute to the development of insomnia. Older patients tend to spend more time in stages 1 and 2 of NREM sleep, while spending less time in delta sleep. Additionally, the elderly spend less time in REM sleep.[3] These changes may explain why the elderly report spending more time in bed yet less time sleeping. They also report waking more frequently during the night, taking longer naps, and having more issues with getting to sleep than younger people.[5]

The proper management of insomnia caused by situational, medical, or psychiatric causes should focus first on the alleviation of the primary disease state. However if a primary sleep disorder is expected, then a thorough clinical history and physical exam should be performed to properly establish diagnosis. Additionally, nocturnal polysomnographic recordings may be warranted to establish causality in previously difficult to treat cases of insomnia. Once the diagnosis of insomnia has been established, a variety of nonpharmacologic management techniques should be attempted prior to initiating drug therapy. Nondrug treatments have been well established and are often underutilized in the management of insomnia in the elderly. Table 2 lists potential nonpharmacologic treatments in the management of insomnia.[6]

Since elderly patients often see multiple practitioners for their care, it is important to evaluate polypharmacy as a potential root cause of insomnia. Therefore, subsequent to the use of nondrug treatments for insomnia, it is important for the practitioner to evaluate all current medications for their insomnia-causing potential. The classes of medications most commonly associated with insomnia include anticonvulsants, antidepressants, antihypertensives, decongestants, and pulmonary medications. If possible, all sedating medications should be given prior to bedtime, while stimulating medications and diuretics should be given earlier in the day. Table 3 lists medications commonly associated with insomnia.[3, 5]

Once a clinician has attempted nonpharmacologic treatments *and* the removal of insomnia-inducing medications without improvement in sleep quality or next-day consequences, then a sedative hypnotic would be indicated. These agents produce sedation and calming by depressing the central nervous system, which in turn leads to improvements in sleep latency and maintenance. The ideal agent would have a rapid onset to reduce sleep latency, prevent nocturnal awakenings, not alter sleep architecture, cause no daytime sedation, and would have little abuse potential. The current FDA-approved sedative hypnotic medications for insomnia are classified as benzodiazepines, nonbenzodiazepines, and a melatonin-receptor agonist.[4]

Benzodiazepines

There are currently five benzodiazepines approved by the FDA for the treatment of insomnia. They are flurazepam, quazepam, estazolam, temazepam, and triazolam. These drugs potentiate sedation by nonselectively binding various $GABA_A$-receptor subtypes. This in turn leads to decreased sleep latency, increased stage 2 sleep, slightly decreased delta and REM sleep, and increased total sleep time.[3, 4] Table 4 lists some characteristics of the FDA-approved benzodiazepines.

Although benzodiazepines as a group can decrease sleep latency, and improve total sleep time, most of these agents should be avoided in the elderly due to risks for complications. Both flurazepam and quazepam have long half-lives and produce active metabolites, which will lead to daytime sedation in the elderly. This led Dr. Mark Beers and colleagues in their 2002 update of "Inappropriate Medication Use in Older Adults" to give these medications a high severity rating, meaning that they should be avoided, due to their risk of sedation-induced falls and fractures.[7] Estazolam also is converted to a metabolite. However, this metabolite has minimal activity and therefore low potential for complications. The primary issue with estazolam, as with all the benzodiazepines discussed in this article except temazepam, is that it is metabolized via an oxidation reaction. As people age, the enzymes that mediate oxidation reactions become less abundant, leading to drug accumulation and the risk for greater daytime sedation. Triazolam would appear to be a good agent due to its quick onset and short half-life. However, this agent should also be avoided due to its risk of rebound insomnia and anterograde amnesia. Therefore, if the use of a benzodiazepine is the only option in this population, then temazepam may be a viable choice. It has an intermediate duration of action, avoiding the daytime sedation of the long-acting agents and the amnesia of the shorter-acting agents. Also, it is metabolized via a conjugation reaction meaning that its actions will be more predictable in the elderly. The bottom line is that benzodiazepines are only approved for short-term use (< 2 weeks), can cause respiratory suppression, have abuse potential, and can cause rebound insomnia with discontinuation. Therefore, the use of these agents should be limited or avoided in the elderly.

Nonbenzodiazepine Hypnotics

The nonbenzodiazepine compounds were originally developed to offer clinicians alternative therapies to benzodiazepines in the treatment of insomnia. Zolpidem, zaleplon, and eszopiclone also promote sleep through the GABA receptor, but differ from benzodiazepines in their selectivity for the alpha$_1$-subunit, leading to fewer adverse effects. Table 5 lists the FDA-approved nonbenzodiazepine hypnotics.

The characteristics that distinguish the nonbenzodiazepine hypnotics from one another are their onset, duration, and approval for chronic insomnia. Of these agents, zaleplon has the shortest onset (around 20 minutes) and the shortest duration of action (roughly 4 hours). This makes zaleplon an ideal agent in patients that have issues with sleep latency or in patients who cannot dedicate 8 hours to sleep after taking the agent. However, this may not be the best sleep maintenance medication because of its short duration of action, unless patients wait to take it until they wake in the middle of the night. Absorption of this agent can be slowed or decreased by a high fat meal so it is best for patients to take it on an empty stomach. Also, zaleplon is FDA approved for short-term use only. Zolpidem also has a quick onset and short duration of action, and is available in both standard and controlled release (CR) formulations. Therefore, the standard release formulation would be ideal in patients with sleep latency issues, while the CR formulation could be used in cases of combined sleep latency and maintenance insomnia. Additionally, the CR formulation is not limited to short-term use in the management of insomnia. Absorption of this agent can be slowed or decreased by food, so it is best for patients to take it on an empty stomach. It is important to note that abrupt discontinuation of this agent has been linked to withdrawal symptoms and 1st night rebound insomnia.[3, 4] Eszopiclone is an agent with an intermediate duration of action approved for the treatment of both sleep latency and maintenance. The recommended dosage in the elderly for sleep latency is 1mg, but for sleep maintenance is 2 mg. Absorption of this agent can be slowed or decreased by a high fat meal so it is best for patients to take it on an empty stomach. Although eszopiclone is approved for use in both short-term and chronic insomnia, the longest trials to date in the elderly were only for 2 weeks. Therefore the long-term effects of this agent in the elderly are unknown. [8, 9] Overall, the nonbenzodiazepine hypnotics have proven to be well tolerated in the elderly provided that the lowest effective doses are used for the least amount of time possible.

Melantonin-Receptor Agonist

Ramelteon is a highly selective melatonin receptor agonist approved for use in the treatment of insomnia characterized by difficulty falling asleep. It works by selectively targeting MT_1 and MT_2 receptors. These receptors are postulated to be key mediators in the maintenance of circadian rhythm, thus encouraging sleep. Table 6 lists the characteristics of ramelteon.

Ramelteon is approved for both short-term and chronic use in the treatment of insomnia. In clinical trials, it has shown no potential for abuse, which may explain why it is the only FDA approved hypnotic that is not a controlled substance. Additionally, it has been characterized as having a benign side effect profile and no hangover effects. Similar to the nonbenzodiazepines, the absorption of ramelteon can be decreased or delayed when taken with food. Overall, ramelteon appears to be well tolerated in the management of insomnia marked by difficulty falling asleep. However, there are no comparative trials at this time with other classes of agents.[10]

In conclusion, the management of insomnia in the elderly continues to be a great challenge. Often patients are quickly started, or continued, on potentially harmful medications without discerning the underlying cause of their sleeplessness. However, this can be overcome through a process of eliminating insomnia-causing medications, initiating nonpharmacological management strategies and, if necessary, choosing the safest most effective agent for the shortest duration of time possible.

Table 1
Causes of Insomnia in the Elderly

Situational	Medical	Psychiatric
Stress	**CV** (angina, arrhythmias, HF) **Respiratory** (COPD, sleep apnea) **Endocrine** (diabetes, hyperthyroidism) **GI** (GERD, PUD) **Neurological** (delirium, Parkinson's) **Urologic** (BPH) **Chronic pain**	**Depression** **Anxiety** **Substance abuse**

Adapted from reference 3

Table 2
Nonpharmacologic Treatments in the Management of Insomnia

Relaxation	Progressive muscle relaxation Autogenic training Pleasant imagery
Stimulus Control	Reserve bedroom for sleeping Only go to bed if sleepy Only sleep in the bedroom Get out of bed if awake and return only when sleepy Avoid daytime napping
Sleep Restriction	A 2 week sleep log is kept to determine average sleep time An allowed sleep time of > 5 hours is subjectively chosen The time allowed in bed is adjusted in 15 minute increments
Cognitive Behavioral Therapy (CBT)	Addresses the patient's perceptions of insomnia Attempts to break the "vicious-cycle" of insomnia
Sleep Hygiene	Avoid excessive amounts of caffeine Avoid eating late meals Avoid exercise late in the evening Maintain the same sleep schedule 7 days per week Do not watch television in bed Make sure that the bedroom is properly cooled and low lit
Light Therapy	Morning light exposure is used to resynchronize circadian rhythm

Adapted from reference 6

Table 3 Medications Commonly Associated with Insomnia	
Anticonvulsants	Phenytoin
Antidepressants	SSRIs Venlafaxine Nortriptyline
Antihypertensives	ß-blockers Diuretics
Decongestants	Pseudoephedrine
Pulmonary Medications	ß-agonists Corticosteroids Theophylline
Other	Alcohol Caffeine Cimetidine Nicotine Thyroid preparations
Adapted from references 3 and 5	

Table 4
Benzodiazepines FDA-Approved for Use in Insomnia

Drug	Elderly Daily Dose	Onset (mins)	$t_{1/2}$ (hrs)	Duration	Metabolic Pathway
Flurazepam (Dalmane®)	15 - 30 mg	60 - 120	47 - 100 (metabolites)	Long	Oxidation
Quazepam (Doral®)	7.5 mg	20 - 45	24 - 41 (metabolites)	Long	Oxidation
Estazolam (ProSom®)	0.5 - 1 mg	15 - 30	8 - 24 (metabolites)	Intermediate	Oxidation
Temazepam (Restoril®)	7.5 - 15 mg	45 - 60	10 - 20	Intermediate	Conjugation
Triazolam (Halcion®)	0.125 mg	15 - 30	1.6 - 5.4	Short	Oxidation

Adapted from references 3 and 4

Table 5
Nonbenzodiazepines FDA Approved For Use In Insomnia

Drug	Elderly Dose	Onset (mins)	$t_{1/2}$ (hrs)	Duration	Common Side Effects
Zaleplon (Sonata®)	5 mg	20	0.5 - 1	Very short	Headache, dizziness
Zolpidem (Ambien®, Ambien CR®)	5mg 6.25mg (CR)	30	2.5 2.8 (CR)	Short	Residual drowsiness, dizziness, diarrhea, headache
Eszopiclone (Lunesta®)	1 - 2 mg	30	6	Intermediate	Unpleasant taste, headache, dizziness

Adapted from references 3, 4, and 8

Table 6
Melatonin-receptor agonist FDA Approved For Use In Insomnia

Drug	Elderly Dose	Onset (mins)	$t_{1/2}$ (hrs)	Duration	Common side effects
Ramelteon (Rozerem®)	8 mg	30	1 - 2.6	Short	Headache, somnolence, dizziness

Adapted from references 4 and 10

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