Review Article

Review of Safety and Efficacy of Sleep Medicines in Older Adults

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ABSTRACT

Purpose: Insomnia is problematic for older adults. After behavioral modifications fail to show adequate response, pharmacologic options are used. The pharmacokinetics of agents used to treat insomnia may be altered. This review focuses on the safety and efficacy of medications used to treat insomnia.

Methods: A literature search of Medline, PubMed, and Embase was conducted (January 1966–June 2016). It included systematic reviews, randomized controlled trials, observational studies, and case series that had an emphasis on insomnia in an older population. Search terms included medications approved by the US Food and Drug Administration for insomnia: benzodiazepines (triazolam, estazolam, temazepam, flurazepam, and quazepam), nonbenzodiazepine receptor agonists (non-BzRAs; zaleplon, zolpidem, and eszopiclone), suvorexant, ramelteon, doxepin and trazodone. Off-label drugs such as other antidepressants, antihistamines, antipsychotics, gabapentin, pramipexole, tiagabine, valerian, and melatonin were also included.

Findings: Cognitive behavioral therapy and sleep hygiene are considered initial therapy for insomnia. Benzodiazepines are discouraged in the geriatric population, especially for long-term use. Although non-BzRAs have improved safety profiles compared with benzodiazepines, their side effects include dementia, serious injury, and fractures, which should limit their use. Ramelteon has a minimal adverse effect profile and is effective for sleep-onset latency and increased total sleep time, making it a valuable first-line option. Although the data on suvorexant are limited, this drug improves sleep maintenance and has mild adverse effects, including somnolence; residual daytime sedation has been reported, however. Sedating low-dose antidepressants should only be used for insomnia when the patient has comorbid depression. Antipsychotic agents, pramipexole, and tiagabine have all been used for insomnia, but none has been extensively studied in an older population, and all have considerable adverse effects. Gabapentin may be useful in patients with restless leg syndrome or chronic neuropathic pain and insomnia. Diphenhydramine should be avoided in the elderly. Valerian and melatonin are unregulated products that have a small impact on sleep latency and can produce residual sedation.

Implications: An ideal treatment for insomnia should help to improve sleep latency and sleep duration with limited awakenings and be without significant adverse effects such as daytime somnolence or decreased alertness. Cognitive behavioral therapy should always be first line treatment. Clinical inertia regarding previous prominent use of benzodiazepines and non-BzRAs will be a significant challenge for patients accustomed to their issuance. The future direction of insomnia treatment should have an emphasis on nonpharmacologic interventions, treating comorbid conditions, and focusing therapy on using benzodiazepines and non-BzRAs

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Key words: aged, benzodiazepines, hypnotics and sedatives, ramelteon, sleep initiation and maintenance disorder, suvorexant.

INTRODUCTION

Insomnia is a prevalent sleep disorder that adversely affects older adults at a rate higher than the adult population.[1] One third of adults will subjectively describe problems falling asleep, remaining asleep, or awakening too early.[2] The elderly population will be the largest segment of the population in the next 20 years.[3] Thus, the assessment, diagnosis, and treatment of insomnia is paramount in this age group, who are often more vulnerable to the adverse effects of treatment.[1]

Despite the common misconception, insomnia is not consistent with the normal aging process.[4] The progression of sleep throughout the night, referred to commonly as sleep architecture, is composed of 3 segments as described by using EEG and electromyographic criteria.[5] The first segment consists of stages 1 and 2 and is characterized by light sleep. The second segment consists of stages 3 and 4 and is characterized by deep sleep or delta sleep. Stages 3 and 4 are believed to be the most restorative stages of sleep. Collectively, stages 1 through 4 constitute non–rapid eye movement (non-REM). The third segment of sleep, REM sleep, occurs during the second half of sleep, while stages 3 and 4 occur during the first half of the sleep period. REM sleep is also commonly referred to as "dream sleep," and most people will cycle through the 4 stages of sleep 4 to 5 times per night.[6] Nocturnal arousals defined according to EEG activity are also very common during sleep. An older healthy adult with no sleep complaints will have an average of 27 arousals per hour compared with 10 to 20 arousals per hour of younger age groups.[7]

There are several important physiologic processes that occur to create age-related changes in sleep that span a lifetime. As a person ages, the average amount of sleep time decreases to ~5 to 7 hours of sleep per night.[8] This finding highlights the fact that the maximal sleep capacity, as indicated by total sleep time (TST), will also decrease with age. Younger patients will have a maximal sleep capacity of 8.9 hours versus 7.4 hours in older subjects.[9] Other components of sleep architecture will also change with age advancement. There are increases in wakefulness after sleep onset (WASO), less time spent in the restorative stages of sleep, and increased time spent awake at night.[8] The increase in WASO may be explained by the increases in nocturnal arousals as demonstrated by EEG. Physiologic changes in circadian rhythm will also influence the elderly to retire to bed earlier and ultimately wake up earlier. This scenario directly decreases both the quality and duration of sleep.[10] Ironically, sleep latency is decreased in the elderly, possibly explaining why the elderly may be more somnolent than the younger population.[11] Comprehension of these physiologic changes that occur in sleep architecture will assist older adults in adjusting expectations of sleep in context with a reduction in sleep need.

Cognitive behavioral therapy for insomnia (CBTI) is a critical approach to address behaviors and preconceived notions of sleep that will perpetuate insomnia in the elderly. CBTI is considered a first-line therapy approach for all forms of insomnia. It consists of several first-line interventions that may have significant positive effects on time to sleep onset and time awake after sleep onset.[12,13] The critical components of CBTI are based on elements of sleep hygiene and maladaptive behavior modifications. Specifically, there are goals to control the environment, restrict the amount of time in bed, reduce outside stimulus, promote relaxation through mediation and mindfulness, limit caffeine and alcohol, and avoid daytime napping and exercise close to bedtime. The benefits of CBTI are generally not immediately realized, but in a trial comparing it versus benzodiazepines, there were no significant differences in time to sleep onset or TST at 4 to 8 weeks.[14] Despite the impact not being immediate, CBTI was superior when assessed 6 to 12 months after discontinuation.[15] Sleep hygiene, which is a critical component of CBTI, is not overtly effective as the sole intervention to treat insomnia, but its components are part of an overall behavior modification program.[16]

There are barriers to appropriate implementation of CBTI, which has the potential for a provider to rely on prescribing a sleep agent with possible adverse effects. Inherently, changing the course of poor sleeping habits is a tedious process that can be met with opposition, especially because efficacy may not be realized early in therapy. Implementation is not only time-consuming, but the process required to initiate CBTI is not always possible given the numerous responsibilities of the providers. Using effective strategies for CBTI often takes several sessions to restructure behavior; these strategies may be met with patient indifference due to the

immediate impact of perceived sleep deprivation. Despite the long-term efficacy, these collective challenges may severely limit the effective use of CBTI, but this should not belie CBTI as a proven first-line or complimentary treatment program for insomnia.

Unfortunately, despite guidelines that stress the efficacy of sleep hygiene and cognitive behavioral therapy, insomnia in the elderly will routinely be treated with medication. The goals of pharmacologic treatment include improving sleep quality and quantity, enhancing associated daytime function, reducing sleep latency and WASO, and increasing TST. Pharmacologic therapy for insomnia in the United States includes many different classes of medications. Medications approved by the US Food and Drug Administration (FDA) for insomnia include nonbenzodiazepine receptor agonists (non-BzRAs; zaleplon, zolpidem, and eszopiclone), benzodiazepines (triazolam, estazolam, temazepam, flurazepam, and quazepam), the orexin receptor antagonist suvorexant, the melatonin receptor agonist ramelteon, the antidepressants doxepin and trazodone, and off-label drugs such as other antidepressants, antihistamines, antipsychotic agents, gabapentin, pramipexole, tiagabine, valerian, and melatonin.[17]

The older adult population is at an increased risk for experiencing adverse events due to alterations of pharmacokinetic properties. The absorption of drugs is not affected by aging due to passive absorption; however, due to the increase in body fat, decrease in total body water, and reduction in plasma proteins, a resulting increase in drug elimination $t_{½}$ is observed.[5,18,19] Alteration in phase I metabolism in the elderly consists of the potential for reduction in the cytochrome P450 (CYP) system. Hypnotic agents, which are cleared through this system, include, but are not limited to, diphenhydramine, eszopiclone, flurazepam, ramelteon, and zolpidem. Agents such as temazepam and zaleplon that are cleared by phase II metabolism (consisting of glucuronidation, acetylation, or sulfation) are not affected by aging.[18] We review the pharmacokinetic properties of each agent, with an emphasis on the changes that occur in aging.

The presence of insomnia increases the risk for falls.[1,20] Insomnia has also been linked with daytime dysfunction, decreased quality of life, development of psychiatric disorders, and an increase in morbidity and mortality.[21–23] It has also been linked with loss of productivity and increase in accidents.[1,24]

The purpose of the present review was therefore to identify pharmacologic agents and their effect on sleep-onset latency (SOL), sleep duration, sleep maintenance, and residual sedation. This article highlights a history of each agent, as well as its efficacy and safety, with emphasis in the aged population and pharmacokinetic alterations (Table I).

MATERIALS AND METHODS

Definitions

The following definitions were used throughout the article[25,26]: sleep-onset latency (SOL), the length of time that it takes to accomplish the transition from full wakefulness to sleep; rapid eye movement (REM) sleep, a recurrent period of sleep characterized by REMs that has been associated with vivid dreams; sleep maintenance, which may be considered the ability to stay asleep, measured by using total sleep time (TST); TST, the total time asleep after sleep onset; nocturnal awakening, which is characterized by having difficulty returning to sleep after waking up during the night or very early in the morning; and wake after sleep onset (WASO), the sum of wake times from sleep onset to the final awakening.

Literature Search Strategy

The articles included in this review were chosen after a search of the published English-language medical literature. A secondary search was performed via review of the references found from the initial search. Non-English abstracts were included from the secondary search if an abstract was available in English. The search was conducted by using MEDLINE via Ovid (1966–June 2016), PubMed, and EMBASE (1980–June 2016) and included systematic reviews, randomized controlled trials, observational studies, case series, and case reports that involved neurologic effects, specifically sleep initiation and maintenance disorders in the geriatric patient population. Search terms included medications approved by the US Food and Drug Administration for insomnia: benzodiazepines (triazolam, estazolam, temazepam, flurazepam, and quazepam), non-BzRAs (zaleplon, zolpidem, and eszopiclone), the orexin receptor antagonist suvorexant, the melatonin receptor agonist ramelteon, and the antidepressants doxepin and trazodone. Off-label drugs such as other antidepressants, antihistamines, antipsychotics, gabapentin, pramipexole, tiagabine, valerian, and melatonin were also included.

Table I. Dosage, indications, metabolism, and adverse effects for commonly used insomnia medications in older adults.

Drug	Bedtime Dosage for Older Adults	Effects on Sleep	Metabolism/ Clearance	Adverse Effects	Comments
Nonbenzodiazepine receptor agonists					
Eszopiclone[1–5,*]	1 mg (sleep-onset latency)	Sleep-onset latency	Oxidation and demethylation	Headache, unpleasant taste, somnolence, dyspepsia, dry mouth, dizziness	Absorption may be reduced if taken with high-fat/heavy meal
	2 mg (sleep maintenance)	Sleep maintenance			
Zolpidem[1,6,7,*]	2.5 mg	Sleep-onset latency	Oxidation and hydroxylation	Headache, dizziness, drowsiness, nausea, vomiting, anterograde amnesia, hallucinations, delirium, unusual nighttime behaviors	Absorption may be delayed if given with or immediately after a meal
	MDD, 5 mg				Use caution in patients with hepatic impairment, COPD, sleep apnea, or depression
Zolpidem (controlled release)[1,6,7,*]	6.25 mg	Sleep-onset latency Sleep maintenance			Swallow whole
Zolpidem (oral mist)[*]	5 mg/spray	Sleep-onset latency			Spray directly into mouth over tongue
Zolpidem sublingual tablet[*]	1.75 mg	Nighttime awakening			Place under tongue and allow it to disintegrate Do not swallow whole
Zaleplon[1,6,8–13,*]	5 mg	Sleep-onset latency	Aldehyde oxidase	Headache, nausea, dizziness, somnolence, rhinitis, asthenia, abdominal pain	Avoid administration with or immediately after a high-fat meal

(continued)

Table I. (continued).

Drug	Bedtime Dosage for Older Adults	Effects on Sleep	Metabolism/ Clearance	Adverse Effects	Comments
	MDD, 10 mg				Avoid use in patients with severe hepatic impairment Contraindicated in patients with sleep apnea, myasthenia gravis, severe respiratory dysfunction, or allergy to tartrazine dye May be taken middle of the night as long as 4 h available for sleep
Benzodiazepines					
Estazolam[1,14–20,*]	0.5 mg	Sleep maintenance	Oxidation	Daytime drowsiness, dizziness, lightheadedness, dementia, fall risk, hip fractures, mobility problems	Short- to intermediate-acting
					Caution in patients with seizure disorder, respiratory depression, severe hepatic disease, or renal impairment
Temazepam[1,6,14–20,*]	7.5 mg	Sleep maintenance	Glucuronidation	Drowsiness, dizziness, dementia, fall risk-hip fractures, mobility problems	Short- to intermediate-acting
	MDD, 15 mg				Caution in patients with seizure disorder, respiratory depression, severe hepatic disease, or renal impairment

(continued)

Table I. (continued).

Drug	Bedtime Dosage for Older Adults	Effects on Sleep	Metabolism/ Clearance	Adverse Effects	Comments
Triazolam[1,6,14–18,20–23,*]	0.125 mg	Sleep-onset latency	Oxidation	Rebound insomnia, anterograde amnesia, psychological dependence, anxiety	Short-acting
	MDD, 0.25 mg				Caution in patients with seizure disorder, respiratory depression, severe hepatic disease, or renal impairment
Flurazepam[1,14–20,*]	15 mg	Sleep maintenance	Oxidation	Residual daytime sedation, confusion, dizziness, impaired motor coordination, fall risk, motor vehicle accidents	Long-acting
					Caution in patients with seizure disorder, respiratory depression, severe hepatic disease, or renal impairment
Melatonin receptor agonist					
Ramelteon[1,24–36]	8 mg	Sleep-onset latency	Oxidation	Headache, somnolence, nasopharyngitis	Does not cause CNS depression Avoid administration around a high-fat meal Minimal abuse potential Minimal withdrawal effects
Orexin antagonist					
Suvorexant[6,37–39]	5 mg	Sleep induction	Oxidation	Somnolence, fatigue, headache, dry mouth, residual	Administration 30 min before bedtime

(continued)

Table I. (continued).

Drug	Bedtime Dosage for Older Adults	Effects on Sleep	Metabolism/ Clearance	Adverse Effects	Comments
				daytime sedation, sleep paralysis, fall risk	
	MDD, 20 mg	Sleep maintenance			Require minimum sleep period of 7 h
Antidepressants					
Trazodone[6,40,41]	25 mg	Sleep maintenance	Oxidation	Residual daytime sedation, orthostasis, headache, nausea, vomiting, xerostomia	Lacks anticholinergic activity
	MDD, 100 mg				Indicated for insomnia secondary to depression, alcohol dependence, substance abuse
Mirtazapine[6,42–46,*]	7.5 mg	Sleep-onset latency	Oxidation, demethylation, hydroxylation	Residual daytime sedation, anticholinergic effects, weight gain	Beneficial in patients with comorbid depression
	MDD, 30 mg	Nighttime awakening			
Doxepin[6,47,*]	3 mg	Sleep maintenance	Oxidation	Headache, somnolence, sedation, mild anticholinergic effects	Brand name product only
	MDD, 6 mg				Administration 30 min before bedtime Separate with food for at least 3 h
Miscellaneous					
Gabapentin[6,48–51]	100 mg	Sleep maintenance	Renal clearance	Drowsiness, somnolence	Beneficial in patients with comorbid restless leg

(continued)

Table I. (continued).

Drug	Bedtime Dosage for Older Adults	Effects on Sleep	Metabolism/ Clearance	Adverse Effects	Comments
					syndrome or chronic neuropathic pain
	MDD, 900 mg				Dose adjustment in renal impairment
Pramipexole[52]	0.125 mg	Sleep maintenance	Renal clearance	Insomnia, hallucinations	Use should be limited to patients with rapid eye movement sleep behavioral disorder
	MDD, 0.5 mg				Administration 2–3 h before bedtime
Tiagabine[53]	2 mg	Sleep maintenance	Oxidation	Drowsiness	8-mg dose associated with residual effects and reduced alertness
	MDD, 8 mg				
Over-the-counter					
Diphenhydramine[54–56,*]	12.5 mg	Sleep-onset latency	Oxidation	Residual daytime sedation, anticholinergic effects,	Tolerance development
	MDD, 50 mg	Sleep maintenance			
Herbal					
Valerian[57–60]	300 mg	Sleep-onset latency	Not well established	Drowsiness, headache, depression	Inconsistent results
	MDD: 600 mg				
Melatonin[61–64]	1 mg	Sleep-onset latency	Not well established	Residual daytime sedation	Administer within 1 h of sleep
	MDD, 2 mg				

CNS = central nervous system; COPD = chronic obstructive pulmonary disease; MDD = maximum daily dose.
*Medication appears in the Beer's criteria. Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults in 2015.

Table II. Pharmacokinetics of benzodiazepines approved for use in insomnia.

Generic Name	T_{max}, h	$t_{½}$, h*	Dose in Elderly, mg	Metabolic Pathway	Clinically Significant Metabolites
Estazolam	2	12–15	0.5	Oxidation	—
Flurazepam	1	8	Avoid	Oxidation	Hydroxyethylflurazepam, flurazepam aldehyde
Quazepam	2	39	Avoid	Oxidation, *N*-dealkylation	2-Oxo-quazepam, *N*-desalkylflurazepam
Temazepam	1.5	10–15	7.5	Glucuronidation	—
Triazolam	1	2	0.125	Oxidation	—

*The $t_{½}$ of the parent drug.

RESULTS

Benzodiazepines

First synthesized in the mid-1950s, benzodiazepines offered sedative/hypnotic, anxiolytic, anticonvulsant, and muscle-relaxing properties without the toxicity and overt lack of dependence common with barbiturates.[27] The perceived benefits of benzodiazepines coupled with the alleged lack of adverse effects led to these agents becoming the most commonly prescribed drugs worldwide by the late 1970s.[28] Ironically, during this same time period, it was noted that patients were developing dependence on benzodiazepines after chronic use, and withdrawal symptoms occurred when these medications were discontinued.[29] As time progressed, benzodiazepine use was associated with numerous class effects, including daytime sedation, delirium, ataxia, anterograde memory disturbance, fractures, falls, motor vehicle accidents, and rebound insomnia.[5,30,31]

The benzodiazepine class of medications remains frequently used in the treatment of sleep disorders in the elderly, despite well-documented dangers. Its use is ~3 times more frequent in older adults.[32] Nearly one third of older adults prescribed benzodiazepines were using them on a long-term basis, which corresponds with greater risk of fractures, cognitive decline, and dependence.[32–36]

Benzodiazepines approved by the FDA for the treatment of short-term insomnia include triazolam, estazolam, temazepam, flurazepam, and quazepam.[37–41] This class of medications improves insomnia by reducing time to REM sleep, shortening SOL, and decreasing nocturnal awakenings.[5,19] These agents bind to the γ-aminobutyric acid (GABA) receptors in the central nervous system (CNS), resulting in the inhibition of neuronal excitation.[42,43] GABA receptors are present throughout the brain, including the ventral lateral preoptic area that controls sleep.[44] Older adults experience changes in the GABA neurotransmitter system, which results in an increased sensitivity to benzodiazepines and predisposes these patients to ataxia, sedation, and cognitive impairment.[18,45,46]

Older patients are more susceptible to the potential adverse effects of benzodiazepines because of altered pharmacokinetics and pharmacodynamics.[47] Triazolam is absorbed rapidly after oral administration and has an onset of action within 0.5 hour, whereas temazepam is less lipophilic and has a slower onset of action (~1 hour).[1,43] Onset of action for estazolam, flurazepam, and quazepam occurs 1 to 2 hours after ingestion (Table II).

Medication duration of action and adverse effect profile may be attributed to elimination $t_{½}$ and active metabolites.[1,48] Metabolism occurs primarily through the liver via oxidation, nitroreduction, and glucuronidation. Temazepam is metabolized exclusively via glucuronidation, whereas the other benzodiazepine hypnotic agents are metabolized by hepatic microsomal oxidation followed by glucuronide conjugation.[43] Oxidative capacity is reduced with aging, resulting in a prolonged elimination $t_{½}$; glucuronidation is not affected by aging. Therefore, with the exception of temazepam, the benzodiazepine hypnotic agents have a prolonged elimination $t_{½}$ in aged subjects.[1,44,48,49] This Phase I metabolism of oxidation and reduction through the CYP enzyme system creates a potential for altered pharmacokinetics related to age. Changes in drug metabolism will also potentiate drug–drug interactions due to competing CYP inducers, inhibitors, and substrates.[1,18] Alternatively, triazolam,

which is metabolized by the CYP3A4 isoenzyme, is contraindicated with concurrent use of CYP3A4 inhibitors such as ketoconazole, itraconazole, nefazodone, ritonavir, indinavir, nelfinavir, saquinavir, or lopinavir.[37,45,50] Triazolam, estazolam, and temazepam lack clinically significant metabolites. Flurazepam and quazepam have a long elimination $t_{½}$ and active metabolites that have the potential to accumulate with repeated dosing.[43] Renal excretion of benzodiazepines is minor.[19]

Benzodiazepine indication for use is based on the specific medication's pharmacokinetic parameters and safety profile. The benzodiazepines' elimination $t_{½}$ ranges from very short to extended.[1,43] With a very short $t_{½}$ and quick onset, triazolam is indicated for sleep-onset insomnia. Flurazepam, quazepam, estazolam, and temazepam, with their intermediate to long $t_{½}$ findings and slower onset of action, are indicated for sleep maintenance insomnia.[50,51] Triazolam would seem to be the benzodiazepine of choice with its quick onset and short $t_{½}$; however, it is well documented that triazolam causes rebound insomnia, anterograde amnesia, psychological dependence, and anxiety.[37,51,52] Triazolam is therefore not considered a first-line agent.[12] Flurazepam and quazepam should be avoided in the elderly due to the long $t_{½}$ findings and active metabolites of these agents.[19,50] These long-acting agents are associated with significant daytime hangover effect, confusion, dizziness, impaired motor coordination, increased risk of falls resulting in fractures, and increased risk of motor vehicle accidents.[53–58] Concomitant administration with alcohol or other CNS depressants can potentiate the CNS effects and should be avoided.[51,59] Benzodiazepines must also be used with caution in patients with seizure disorders, respiratory depression, severe hepatic disease, or renal impairment.[51]

Benzodiazepines have been commonly studied for short duration of use. Glass et al[60] reviewed 24 randomized controlled trials of any pharmacologic treatment for insomnia for at least 5 consecutive nights in people aged >60 years with insomnia. Significant results included improvement in sleep quality, TST (mean, 34 minutes), and decreased nighttime awakenings with benzodiazepine use compared with placebo. Adverse events with benzodiazepines were more common, including cognitive events and adverse psychomotor events, and were statistically significant; the effect size was small, however, and the clinical benefits were modest at best. In individuals aged >60 years, the benefits of benzodiazepines may not justify the increased risk of adverse events.

A large meta-analysis reviewing the use of benzodiazepines in the treatment of insomnia illustrated the lack of well-controlled studies regarding the efficacy of long-term exposure to these medications in patients with chronic insomnia. Holbrook et al[61] performed a meta-analysis of 45 randomized controlled trials of benzodiazepine use in insomnia in subjects of all ages. Only 15 of these studies included patients aged >65 years. Compared with placebo, benzodiazepines nonsignificantly decreased SOL by 4.2 minutes and significantly increased total sleep duration by 61.8 minutes (95% CI, 37.4–86.2). As expected, daytime drowsiness, dizziness, and decline in cognitive function were reported in the active treatment arm, leaving the question of risk versus benefit. No benzodiazepine has been evaluated in randomized controlled trials exceeding 12 weeks, making long-term safety and efficacy of benzodiazepines in chronic insomnia difficult to be determined.[58]

Temazepam is the most commonly used benzodiazepine for insomnia.[62] In a small study of older adults, temazepam 7.5 mg was evaluated in a sleep laboratory using a 14-night protocol (4 placebo baseline nights, 7 drug nights, and 3 placebo withdrawal nights). Short-term use of temazepam was effective in producing a significant improvement in TST from baseline with no major CNS and behavioral adverse effects. This study also reported no significant increase in rebound insomnia.[63]

The evidence of harms associated with benzodiazepines from the 2016 American College of Physicians (ACP) guidelines from randomized controlled trials focused mostly on withdrawal phenomena. However, there were observational studies that linked benzodiazepines to daytime drowsiness, dizziness or lightheadedness, dementia, increased risk for falls, hip fractures, mobility problems, and an increased incidence of cancer.[17,64,65] Similarly, the American Geriatrics Society published the Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults in 2015 and strongly recommends avoiding benzodiazepines in elderly patients due to increased risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes.[66] The role of benzodiazepines in clinical practice for insomnia is clearly diminishing. The 2014 Clinical Guideline for the Treatment of Primary Insomnia in Middle-Aged and Older Adults from the Agency for Healthcare Research and Quality recommends against the use of benzodiazepines in primary insomnia.[67]

Benzodiazepine use, even for only a few days, has the potential to cause physical dependence.[27,47] Abrupt discontinuation of benzodiazepines may result in withdrawal symptoms. Typical symptoms include agitation, anxiety, dysphoria, rebound insomnia, tachycardia, diarrhea, increased awareness of sensory stimuli, perceptual disturbances, depersonalization, confusion, delirium, and seizures.[47,68] After long-term use, the benzodiazepine dosage should have a gradual tapering of 5% to 10% every 1 to 2 weeks to discontinue.[28] Elderly patients had better outcomes and demonstrated less severe withdrawal symptoms during a gradual tapering off of benzodiazepines.[69]

In summary, benzodiazepine use is discouraged in the elderly and should be avoided. If a benzodiazepine medication is used, then the lowest dose for the shortest duration is preferred. Regular reassessment of the benefits and risks is recommended, with follow-up visits scheduled at least every 6 months to monitor for efficacy, side effects, tolerance, and appropriate medication use.[12,30] Gradual dose tapering, as opposed to abrupt discontinuation, is safer and less likely to lead to withdrawal symptoms.[70]

Nonbenzodiazepine Receptor Agonists

Non-BzRAs, sometimes referred to as nonbenzodiazepine sedative-hypnotics, were first developed in the 1980s with the intent of overcoming the deleterious aspects of benzodiazepine therapy. These medications are commonly referred to as the "Z drugs" and include zolpidem, zopiclone, eszopiclone, and zaleplon.

Because of the known adverse events associated with benzodiazepines, the trend in the past decade has been to use non-BzRAs.[71–73] With proven efficacy, as well as the reduced possibility of dependence and withdrawal, non-BzRAs are now the most commonly prescribed hypnotic agents worldwide.[74–76] The percentage of office visits by patients aged ≥65 years during which a non-BzRA was prescribed increased almost 1200% from 1999 (0.2%) to 2010 (2.5%).[77] Analysis of data from the National Ambulatory Medical Care Survey over a 15-year period (1993–2007) showed that prescriptions for non-BzRAs grew 21 more times rapidly than sleeplessness complaints and 5 times more rapidly than diagnoses for insomnia, indicating non-BzRAs are being prescribed without documented patient complaint or diagnosis.[75]

The 2014 guidelines of the Agency for Healthcare Research and Quality and the 2016 ACP guidelines recommend that all adult patients receive CBTI as the initial treatment for chronic insomnia.[17,67] ACP cautiously recommends adding pharmacologic therapy when CBTI is unsuccessful.[17] If a pharmacologic agent is to be used, low-quality evidence showed that eszopiclone improved global and sleep outcomes and zolpidem decreased SOL.[17]

Non-BzRAs are not benign agents. Evidence of harm according to observational studies has linked these medications with infrequent but serious adverse effects, including dementia, delirium, sleepwalking, serious injury, fractures, and increased cancer risk (zolpidem).[17,64,65,78–80] Use is associated with an increase in hospitalizations and motor vehicle accidents, which can limit future independence and functionality.[66] There is insufficient evidence to evaluate the balance of benefits and harms associated with long-term use of pharmacologic treatment in adults with chronic insomnia, and the ACP guidelines mirror FDA approvals that these pharmacologic agents should be for short-term use of 4 to 5 weeks only.[17] The FDA also recommends lower doses for elderly patients and that patients with insomnia that does not resolve after 7 to 10 days be further evaluated.[17,81] The American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults strongly recommends avoiding non-BzRAs in elderly patients without consideration for duration of use due to their minimal efficacy in treating insomnia but significant risk for possible adverse effects.

Similar to benzodiazepines, non-BzRAs bind to the GABA receptor complex. The GABA receptor is a multicomponent transmembrane protein complex with multiple ligand binding sites, with GABA receptors classified based on pharmacologic binding studies.[82] $GABA_B$ receptors are coupled to calcium and potassium channels. Functioning as an ion channel that alters chloride ion conduction across the cell membrane, the $GABA_A$ complex is the major inhibitory receptor in the CNS. $GABA_A$ receptors are composed of 5 subunits that form a central ion channel with at least 19 different receptor subunits, each deriving from 1 of 7 distinct gene families: α_{1-6}, β_{1-3}, γ_{1-3}, δ, ε, π, and θ.[73,82–85] These $GABA_A$ receptors and subunit compositions are what mediate the physiologic effects associated with sedative-hypnotic agents, including sedation, anxiolysis, muscle

relaxation, amnesia, and other cognitive effects. It has been hypothesized and tested in animal models that this binding to the individual subunit is responsible for producing an agent's unique pharmacologic response.[86] The α_1-receptors selectively mediate sedation and hypnotic effects, whereas the α_2-, α_3- and α_5-receptors mediate anxiolytic pathways.[73,83] Anticonvulsant, ataxic, and muscle-relaxing effects are controlled by a number of different receptors.[73,85] Benzodiazepines bind nonselectively to the $GABA_A$ receptor α subunits, resulting in the sedative, hypnotic, anticonvulsant, muscle relaxant, and anxiolytic properties and corresponding adverse effects. The non-BzRAs are chemically distinct from the benzodiazepines and bind more selectively to the $GABA_A$ receptor α_1 subunits, resulting in more therapeutic sedative and hypnotic effects with less risk of negative consequences.

All of the non-BzRAs are Schedule IV controlled substances, which brings an inherent concern for potential abuse. Initial clinical trials reported no evidence of abuse or dependence potential with zolpidem.[87]A postmarketing surveillance report involving a literature review of case reports from 1996 to 2002 found similar rates of zolpidem abuse in men and women from all age groups, with most cases involving individuals with drug and alcohol abuse problems and/or psychiatric illness.[72] The French study performed by Victorri-Vigneau et al[88] concluded that zolpidem has potential for abuse and dependence and should be used with caution in patients who have a history of substance abuse. The 2014 Drug Abuse Warning Network Report highlighted the increased emergency department visits attributed to overmedication with zolpidem, showing that 11% of these visits involved patients ≥65 years old.[89]

Zolpidem

Zolpidem is a short-acting α_1-selective i*midazopyridine* with intermediate potency at the α_2 and α_3 receptors that is available as an immediate-release tablet, controlled-release (CR) tablet, a sublingual tablet, and an oral spray mist formulation.[83,84,90] The immediate-release zolpidem formulations are FDA indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation, whereas the CR tablet is approved for difficulty of sleep onset and/or sleep maintenance. The sublingual tablet is indicated for as-needed, middle-of-the-night awakening. Recommended dosing for elderly patients is 5 mg for the immediate-release tablet and spray, 6.25 mg for the CR formulation, and 1.75 mg for the sublingual middle-of-the-night tablet.[90,91] Administration of zolpidem with or immediately after a meal may delay absorption; thus, it should be taken on an empty stomach.

Zolpidem is rapidly absorbed, with an absolute oral bioavailability of ~70%.[92] The onset of effect is rapid, usually within ~30 minutes to 1 hour depending on formulation. Peak plasma concentrations are achieved within 1.2 to 2.5 hours.[73,84,90,91] In elderly patients, both C_{max} and AUC were significantly increased compared with younger people, explaining why dose reduction to 5 mg nightly in the elderly is recommended.[82] Zolpidem undergoes extensive hepatic metabolism via CYP isoenzymes, primarily CYP3A4 and to a lesser degree CYP1A2 and CYP2C9, to 3 inactive metabolites. Oxidation and hydroxylation are the major routes of metabolism, with up to 96% of the administered dose eliminated as metabolites in the urine, feces, or bile.[82,92,93] Elimination $t_{½}$ varies depending on route of administration and ranges from ~2.5 to 3 hours.[90,91] Zolpidem is highly protein bound in plasma (92%); however, the unbound fraction increases in patients with renal or hepatic failure.[93,94] Large increases in elimination $t_{½}$ along with C_{max} and AUC were seen in patients with cirrhosis, resulting in recommendations regarding dose reductions.[94] Although not specifically recommended in package labeling, patients with renal insufficiency or those undergoing dialysis had slower elimination rates and increased AUC, which may necessitate dose reductions.[90,91,93,94] Combining alcohol or other CNS depressant medications (antipsychotics, antidepressants, hypnotics, anxiolytics/sedatives, narcotic analgesics, anticonvulsants, anesthetics, and sedating antihistamines) may enhance the CNS depressant effects of zolpidem.[92] With zolpidem being metabolized via CYP isoenzymes, coadministration with inhibitors or inducers of CYP3A4 isoenzymes can result in significant drug interactions. When zolpidem is combined with multiple doses of a CYP3A4 inducer such as rifampicin, significant decreases in the AUC, C_{max}, and elimination $t_{½}$ and pharmacodynamic effects can be seen. Conversely, CYP3A4 inhibitors have the potential to increase AUC and elimination $t_{½}$ and decrease the oral clearance of zolpidem. Ketoconazole has been linked to zolpidem-related impairment of psychomotor function.[87]

Zolpidem has proven efficacy for decreasing SOL and improving TST in the elderly.[95] In a double-blind, placebo-controlled trial performed by Leppik et al,[96] 335 elderly patients ages 60 to 85 years were randomized to receive 28 days of double-blind treatment with zolpidem 5 mg, triazolam 0.125 mg, temazepam 15 mg, or placebo followed by a 4-day single-blind, placebo withdrawal period. Over the 4-week treatment period assessed by using patient questionnaires, zolpidem and temazepam (but not triazolam) produced significantly shorter SOL. Sleep duration was increased above baseline levels in all groups, and no tolerance or rebound insomnia above baseline was noted in any of the treatment groups. Patients taking temazepam experienced a significantly higher incidence of drowsiness and fatigue compared with zolpidem and placebo. Triazolam produced a significantly higher incidence of nervousness compared with zolpidem. The most common adverse effects associated with zolpidem included headache, myalgia, nausea, and upper respiratory tract infection.

Zolpidem's adverse effects seem to be dose related. When dosed at 5 mg daily, zolpidem is generally well tolerated in elderly patients with insomnia.[94] The most frequent adverse events documented in postmarketing studies are headache, dizziness, drowsiness, nausea, and vomiting.[92] As long-term experience with zolpidem accumulated, more adverse effects were identified. There have been case reports of anterograde amnesia, hallucinations, and delirium, along with unusual nighttime behaviors such as sleep-eating, sleep-sex, and sleep-driving.[44,92] These unusual nighttime behaviors associated with zolpidem gained much media attention, prompting the FDA in December 2006 to request that the labeling of all medications approved for the treatment of sleep disorders include a warning about rare and potentially serious adverse effects. Labeling now includes warnings for anaphylaxis and angioedema along with an increased risk for hazardous sleep-related activities such as sleep-driving, preparing and eating food, making telephone calls, or having sex while asleep.[97,98] Other potentially serious adverse effects associated with zolpidem in the older adult include balance impairment, memory impairment, driving impairment/motor vehicle crashes, increased risk of fracture, and higher risk of major injury requiring hospitalization[17,66,79,80,99–101]

The incidence of rebound insomnia with zolpidem is minimal, except for the zolpidem CR formulation.[92] This formulation consists of a bilayer tablet that immediately releases a portion of zolpidem, followed by a slower release of the remaining medication during the middle portion of the night (3–6 hours after dosing).[102] This process enables therapeutic plasma concentrations to be maintained. In a clinical study performed by Walsh et al, zolpidem CR demonstrated improvements in both SOL and sleep duration in elderly patients with primary insomnia during a 3-week period.[102,103] Compared with placebo, zolpidem CR exhibited no next morning residual effects, and the overall incidence and nature of adverse effects were comparable between the 2 groups. Abrupt discontinuation of zolpidem CR has the potential to produce a single night of rebound insomnia.[95,97]

Zaleplon

Zaleplon is a pyrazolopyrimidine that also binds selectively to the $GABA_A$ α_1-receptor subunit but to a lesser degree than zolpidem.[83,84] Zaleplon is FDA approved for the treatment of short-term treatment of chronic insomnia. Of all the "Z drugs," zaleplon is the shortest acting. With a rapid onset of action ($\sim$30 minutes) and a short duration of action (2–4 hours), zaleplon is an ideal option for patients who exhibit problems with sleep latency.[68] Zaleplon also has the advantage of being used for nighttime wakening as long as the patient has $>$4 hours of sleep time remaining before wakening.[81,91]

A review of pharmacokinetic parameters shows that zaleplon undergoes significant first-pass hepatic metabolism with only $\sim$30% available systemically.[82] It is metabolized via aldehyde oxidase along with minor metabolism from the CYP system, mainly by the CYP3A4 isoenzyme to inactive metabolites.[82,104,105] Because CYP metabolism is not the primary means of activation, zaleplon may be less susceptible to drug interactions related to the induction or inhibition of the CYP system.[83] Even with the minor CYP activity, when administered concurrently with strong CYP3A4 inducers including rifampin, phenytoin, carbamazepine, and phenobarbital, zaleplon's C_{max} and AUC may be significantly decreased.[105] Cimetidine inhibits both aldehyde oxidase and CYP3A4 and has been shown to cause an 85% increase in the mean C_{max} and AUC of zaleplon; the zaleplon dose should be reduced if prescribed along with cimetidine or should be avoided altogether. Potent CYP3A4 inhibitors including ketoconazole, itraconazole, and erythromycin may

increase the C_{max} of zaleplon, yielding a prolonged effect.[83,91,105] Combining alcohol or other CNS depressant medications (antipsychotics, antidepressants, hypnotics, anxiolytics/sedatives, narcotic analgesics, anticonvulsants, anesthetics, and sedating antihistamines) can result in increased CNS depressant effects.[91,104] C_{max} is ~1 hour, and the elimination $t_{½}$ is ~1 hour. Age has not been found to significantly affect the pharmacokinetics of zaleplon, although further study is need in this area.[83]

Ancoli-Israel et al[106] performed a randomized, placebo-controlled outpatient study to determine the efficacy and safety of zaleplon in elderly patients. Using patient questionnaires, sleep was assessed in 549 patients aged ≥65 years. Outcomes concluded that zaleplon effectively reduced sleep latency with no clinically significant rebound insomnia after treatment discontinuation. A multicenter, double-blind, randomized, placebo-controlled, 2-week outpatient study was performed in Europe by Hedner et al[107] with the objective of reviewing the safety and efficacy of zaleplon in patients ≥65 years old. Study results concluded that zaleplon significantly reduced sleep latency and improved sleep quality in elderly patients with no significant difference in adverse events. Rebound insomnia was not seen with the 5-mg dose in the study, but there was a weak indication for rebound insomnia noted the first night after the 10-mg dose was discontinued. These 2 studies showed that the tolerability profile of zaleplon was similar for both elderly and nonelderly patients, with the overall incidence of adverse events being similar to placebo.[104,106,107] Ancoli-Israel et al[108] examined the results of long-term use of zaleplon in older adults after 1 year in a single-blind, open-label multicenter (United States and Europe) study, which was an extension phase of 2 randomized, double-blind trials. The investigators concluded that long-term therapy with zaleplon is safe and effective for community-dwelling older adults with primary insomnia. Although double-blind, placebo-controlled studies would be needed to confirm these results, the open-label study provides evidence that zaleplon is not associated with rebound in time to sleep onset, sleep duration, or number of middle of the night awakenings.

During double-blind, placebo-controlled trials in >2000 patients, the most common treatment-emergent study adverse events were headache (28%), nausea (7%), dizziness (7%), somnolence (5%), rhinitis (5%), asthenia (5%), and abdominal pain (5%).[109] These adverse events were reported with a frequency comparable to that of placebo that did not increase with patient age.

Zaleplon is available in 5- and 10-mg tablets. Recommended dosing for elderly patients is 5 mg immediately before bedtime, with a maximum daily dose of 10 mg.[91] Although a dosage reduction is not recommended in patients with impaired renal function, this medication has not been extensively studied in patients with severe renal impairment. Zaleplon should be avoided in patients with severe hepatic impairment and is contraindicated in patients with sleep apnea syndrome, myasthenia gravis, severe respiratory dysfunction, or an allergy to tartrazine dye.[81,91,104] Administration of zaleplon with or immediately after a high-fat meal may delay onset of action and is therefore not recommended.[81,91]

Eszopiclone

First synthesized by researchers in the 1970s, racemic zopiclone has been available for use outside of the United States for decades.[110,111] Eszopiclone is the S (+)-enantiomer of zopiclone, which was reported in preclinical studies to be more active than the racemic zopiclone, although there is insufficient evidence to prove significant clinical benefit.[84,110] With no structural similarity to zolpidem, zaleplon, or the benzodiazepines, eszopiclone is a pyrrolopyrazine derivative of the cyclopyrrolone class.[112] Unlike zolpidem and zaleplon, eszopiclone demonstrates little or no selectivity for the $GABA_A$ receptors, with binding profiles similar to benzodiazepines but with more intense agonist activity with certain $GABA_A$ receptor subtypes.[82] It is specifically indicated for patients with difficulty falling asleep as well as for patients who have trouble with sleep maintenance.[91,113,114]

The majority of pharmacokinetic data published for eszopiclone is based on zopiclone.[112,115] After oral administration, eszopiclone is rapidly absorbed and extensively distributed to body tissues, with peak concentrations occurring within 1 hour.[111,113] Plasma protein binding ranges from 52% to 59%, and disposition is not affected by protein binding–related drug–drug interactions.[112,114] Eszopiclone is metabolized primarily in the liver through oxidation and demethylation via CYP isoenzymes CYP3A4 and CYP2E1 to 2 principal metabolites, (S)-zopiclone-N-oxide and (S)-N-desmethylzopiclone. The desmethyl metabolite is

active and binds to the GABA receptor, which contributes to the sleep-inducing and maintenance effects of the parent drug.[111,113,116] Eszopiclone is primarily excreted through the urine with <10% excreted as parent drug. The $t_{½}$ of eszopiclone is ~6 hours in healthy adults, but clearance is reduced in patients ≥65 years old, resulting in an increased AUC (41%) and $t_{½}$ of ~9 hours. Absorption of eszopiclone may be reduced if a high-fat/heavy meal is consumed at dosing time.[114] Combining alcohol or other CNS depressant medications (antipsychotics, antidepressants, hypnotics, anxiolytics/sedatives, narcotic analgesics, anticonvulsants, anesthetics, and sedating antihistamines) with eszopiclone can result in increased CNS depressant effects.[113,114,116] With metabolism through CYP isoenzyme CYP3A4, concurrent administration of a potent CYP3A4 inhibitor (ketoconazole, itraconazole, nefazodone, nelfinavir, ritonavir, and clarithromycin) may increase the AUC, C_{max}, and $t_{½}$ of eszopiclone. If these inhibitors are going to be taken concurrently, the dose of eszopiclone should be reduced to 1 mg nightly with a maximum dose of 2 mg. When combined with the CYP3A4 inducer rifampicin, the exposure and effects of eszopiclone are significantly decreased.[114]

The efficacy of eszopiclone in older adults (aged 64–86 years) was documented in 2 short-term use (2 weeks) trials and one 12-week trial.[111,117–119] Scharf et al[118] performed a randomized, double-blind, placebo-controlled, multicenter outpatient study to evaluate the efficacy of eszopiclone in elderly patients with primary insomnia. This study comprised 231 patients aged 65 to 85 years who received either placebo, eszopiclone 1 mg, or eszopiclone 2 mg nightly for 2 weeks. Eszopiclone 1 mg nightly was effective at inducing sleep, whereas eszopiclone 2 mg nightly was effective in reducing SOL and WASO. Compared with placebo, eszopiclone 2 mg nightly improved sleep quality and depth, daytime alertness, and quality of life. In a 2-week, multicenter, randomized, double-blind, placebo-controlled study, McCall et al[119] included 255 patients who received either eszopiclone 2 mg or placebo nightly. Results revealed that eszopiclone was associated with significantly shorter SOL, less WASO, higher sleep efficiency, more TST, and greater patient-reported quality and depth of sleep scores than placebo ($P < 0.05$ for all) with a trend in patient-reported morning sleepiness ($P = 0.07$). Although the aforementioned studies illustrate the safety and efficacy of eszopiclone for short-term use, there is a lack of pharmacologic studies examining long-term use. In a 12-week, multicenter, randomized, double-blind, placebo-controlled trial with a 4-week follow-up, Ancoli-Israel et al[108] evaluated the safety and efficacy of eszopiclone in patients aged 65 to 85 years of age with insomnia. There was significant improvement in the TST, SOL, and WASO from baseline compared with placebo.

Eszopiclone clearance is not altered in mild, moderate, or severe renal insufficiency, and no dose reduction is recommended for patients with renal failure.[91,111,112,114] Dose reduction is not recommended in mild to moderate hepatic impairment; however, severe hepatic impairment will double systemic exposure and requires a dose reduction to 1 mg, with a maximum dose of 2 mg. There is no specific patient population in whom eszopiclone use is contraindicated, but it should be used in caution in patients with depression, hepatic impairment, and respiratory dysfunction.[91,114] The most common adverse effects associated with eszopiclone were headache, unpleasant taste, somnolence, and dyspepsia.[118,119]

Ramelteon

The significant individual, social, and economic effects of insomnia, as well as the expected adverse reactions of many other current treatments, have set the stage for novel treatment approaches to insomnia. The role of melatonin, once thought to be a potential panacea for insomnia treatment, has fueled interest in the development of ramelteon, a novel melatonin agonist.

Melatonin innervates the suprachiasmatic nucleus via the G protein–coupled receptors (MT_1/MT_2). Both receptors are highly expressed in the suprachiasmatic nucleus, which helps to regulate the primary mammalian circadian rhythm. The biological mechanism led to the development of receptor agonist targets for MT_1 and MT_2 receptors, and ramelteon became the first novel MT_1/MT_2 melatonin receptor agonist.[120]

From a pharmacodynamic standpoint, ramelteon exhibits 6- and 4-fold higher binding affinity for MT_1 and MT_2 receptors, respectively, compared with melatonin.[121] It has low affinity for the MT_3-binding site, which is considered negligible in its importance to the sleep–wake cycle. Interestingly, ramelteon has great selectivity for melatonergic receptors, limiting adverse effects.[122] This finding is especially important in elderly patients who may be more vulnerable to adverse reactions. Ramelteon is distinguishable from

other common competitors in the insomnia market in that it does not cause general CNS sedation.[122–124] In contrast, ramelteon functions to positively alter the sleep–wake cycle to improve sleep latency.

Ramelteon is rapidly absorbed after oral administration. Despite this action, it has a relatively low bioavailability due to a high first-pass metabolism and probable tissue uptake.[120,125] It is more lipophilic than melatonin and has a longer $t_{½}$.[126] The longer $t_{½}$ may partially explain why ramelteon has greater efficacy in improving sleep maintenance compared with melatonin. Administration of ramelteon with food showed a decrease in C_{max} and a delay in T_{max} compared with the fasting state.[120] Administration should therefore be avoided around a high-fat meal. Ramelteon undergoes extensive oxidative metabolism, leading to 4 oxidative metabolites (MI–MIV).[127] Metabolite II has the highest plasma concentrations and longer $t_{½}$ compared with the other metabolites. This could be the major contributor of the pharmacologic effects of ramelteon.[128] CYP1A2 is the enzyme predominantly involved in ramelteon biotransformation. CYP2C subfamily enzymes and CYP3A4 seem to play a minor role.[120] It is mostly eliminated in the urine ($\geq$84%) and feces (4%).

Elderly patients will have differences in systemic exposure of ramelteon compared with younger counterparts. A small study completed by Greenblatt et al[129] found that elderly subjects given a 16-mg dose of ramelteon had a longer $t_{½}$, greater C_{max}, and reduced clearance. A potential explanation for these findings may stem from reduced phase I metabolism in the elderly, which is in part dependent on CYP metabolism. Despite the higher mean AUC, there were no significant pharmacodynamic effects. This is critical because no dose adjustments from the approved 8-mg dose are recommended based on age. Thus, the pharmacokinetic properties are relatively insignificant based on age alone; therefore, the metabolism of this medication is not a deterrent for use in vulnerable populations.

Drug interactions of ramelteon revolve around CYP1A2. Fluvoxamine is a potent CYP1A2 inhibitor, and its combination with ramelteon should be avoided. It is also recommended to avoid use with other CYP1A2 inhibitors such as zileuton, ciprofloxacin, and mexiletine.[130]

Ramelteon has consistently proved to be efficacious in the literature. Several studies have compared ramelteon versus placebo to illustrate its effect on subjective sleep latency. In each study, the ramelteon groups exhibited statistical improvement in SOL.[131–133] Mixed efficacy data were found for TST, and no differences in sleep maintenance were demonstrated.[134] In addition, Roth et al[135] conducted a randomized, double-blind, placebo-controlled, 35-night trial with weekly clinic visits at multiple centers. In this study, older adult (aged $\geq$65 years old) patients with chronic insomnia reported reductions in SOL and increases in TST during a 5-week nightly treatment with ramelteon. Compared with the baseline measurements, ramelteon produced $\sim$13- to 29-minute reductions in sleep latency. Patient-reported increases in TST were also evident at both doses of ramelteon compared with placebo at weeks 1 and 3. It should be noted, however, that at week 4, there were no statistical differences in patient-reported TST between the placebo and the ramelteon groups (4 and 8 mg). This finding may be explained by improved sleep hygiene, which is typically evident in sleep studies.

Other studies have shown that ramelteon reduced latency to persistent sleep and increased TST as measured by using overnight polysomnography (PSG) readings.[136,137] In a PSG study of 100 elderly adults with chronic insomnia, ramelteon (4 and 8 mg) also resulted in statistically significant reductions in latency to persistent sleep, as well as statistically significant increases in TST and sleep efficiency.[137]

Mini et al[138] evaluated patients with severe sleep-onset difficulty (subjective sleep latency >60 minutes) who had received ramelteon 8 mg or placebo from a previously published multicenter outpatient trial of 829 adults ($\geq$65 years old) with primary, chronic insomnia. Patients received single-blind placebo for 7 days before receiving double-blind ramelteon 8 mg or placebo nightly for 35 nights. A 7-day, single-blind placebo washout period followed. This subjective subset analysis of older adults with severe baseline sleep-onset difficulties found that ramelteon 8 mg significantly and persistently reduced subjective reports of time to sleep onset during 5 weeks of nightly treatment.

Review of the literature shows ramelteon to be a favorable option in terms of safety and reported adverse reactions. Although much of the literature focuses on short-term usage, the adverse reaction profile seems to be more promising than benzodiazepine and non-BzRA ("Z" drugs) options. The most

common adverse effects of ramelteon are comparative to placebo and include headache, somnolence, and nasopharingitis.[127,131,133,135,137,139] Of equal importance is the lack of withdrawal effects and rebound insomnia displayed versus placebo in all studied doses.[131–133,139] Ramelteon also lacks abuse potential.[128] Ramelteon is therefore an attractive option because it has a favorable side effect profile, limited concern for abuse potential, and no significant rebound or withdrawal effects.

Ramelteon reduces sleep latency, which has been demonstrated across all age groups. Dose adjustments are not recommended based on age, sex, declining metabolism, and elimination functions. It is pharmacodynamically consistent across all age groups. Despite the benefit for sleep onset, ramelteon is not as effective for sleep maintenance and TST.

Further research is needed to compare ramelteon versus other treatment options such as the benzodiazepines and non-BzRAs. More information is also needed on the long-term safety data, but short-term safety data are very favorable. It should be considered as an early pharmaceutical option for an elderly patient after sleep hygiene has failed. Patients with chronic insomnia may not transition well from a benzodiazepine or non-BzRA to ramelteon due to lack of abuse potential and sleep maintenance efficacy concerns. Thus, the place in therapy is likely before the benzodiazepines or non-BzRAs.

Orexin Antagonist

Suvorexant is an orexin receptor antagonist that was FDA approved for insomnia in 2014.[140] Orexin antagonists are neuropeptides secreted from the hypothalamus neurons and play a large role in the sleep cycle, specifically in the promotion and maintenance of wakefulness.[140–142] Suvorexant is a reversible antagonist to orexin receptors A and B and inhibits the activation of the arousal system, resulting in improved sleep induction and maintenance.[140,142]

Suvorexant has rapid absorption once administered orally, with a median time of 2 hours to reach peak concentrations.[143] Administration with a high-fat meal can delay time to peak concentrations by 90 minutes; it is therefore recommended that suvorexant not be taken with food or shortly after food consumption for faster sleep onset. Suvorexant is metabolized by the CYP3A4 pathway (major) and the CYP2C19 enzyme pathway (minor). Oxidative metabolism is reduced in the elderly, which can result in decreased metabolism and prolonged $t_{½}$.[7] The metabolite is not pharmacologically active and is eliminated primarily through the feces and urine. The $t_{½}$ is ~12 hours.[142,144]

Drug interactions include those most likely to interfere with the major metabolizing pathway, CYP3A4. A reduced dose of 5 to 10 mg is recommended with co-administration of moderate CYP3A4 inhibitors including but not limited to diltiazem, fluconazole, grapefruit juice, and verapamil; use is not recommended with co-administration of strong CYP3A4 inhibitors such as ketoconazole, clarithromycin, and ritonavir. There are no dose adjustments with co-administration of CYP3A4 inducers (phenytoin, carbamazepine, and rifampin) but may lead to decreased efficacy of suvorexant.[142]

A multicenter trial conducted by Michelson et al[145] sought to determine the safety and efficacy as defined by patient-reported TST and time to sleep onset of suvorexant. Older adults receiving 30-mg doses were found to have significant improvements in both measures after 1 month of treatment. Suvorexant resulted in an increased mean subjective TST of 39 minutes compared with 16 minutes for placebo and a decreased mean subjective time to sleep onset of 18 minutes compared with 8 minutes for placebo. Additional studies have shown suvorexant, at doses ranging from 10 to 80 mg, to be effective for the treatment of insomnia ranging in duration from 4 weeks to 3 months of treatment.[146,147] Patients taking suvorexant reported improved sleep efficacy (defined as increased TST, improved WASO, and decreased time to sleep onset) compared with placebo. Despite reduced doses of 15 to 30 mg, older adults had effective results similar to adults receiving high doses.[145,147] Rebound or withdrawal symptoms were not observed with the discontinuation of suvorexant.[147]

Suvorexant was well tolerated in clinical trials with some mild adverse effects, including somnolence, fatigue, headache, and dry mouth.[144–148] Few serious adverse effects were reported but included excessive daytime sleepiness, driving impairment, sleep paralysis, falls, and complex sleep-related behaviors.[145] All adverse effects were more common in women versus men and appeared to be dose dependent.[144]

The FDA-approved dosing range of suvorexant is 5 to 20 mg daily.[144,149] The trials discussed previously included doses ranging from 10 to 80 mg daily; however, the FDA concluded that suvorexant was

effective at doses ≤20 mg with minimal safety concerns. Higher doses were associated with a larger incidence and/or severity of adverse events.[144] Of the 2 studies including elderly patients, doses of suvorexant were 15 to 30 mg daily.[145,147] The recommended starting dose of suvorexant is 10 mg taken within 30 minutes of going to bed, and the maximum recommended dose is 20 mg. Suvorexant should be taken only if the patient can guarantee a minimum of 7 hours of sleep.[144]

Overall, suvorexant has shown to have effective impact on sleep induction and maintenance compared with placebo. Providers may wish to use caution with this medication in the elderly (due to its adverse effect profile) as well as strict administration requirements.

Sedating Low-dose Antidepressants

Sedating low-dose antidepressants can be used in the treatment of insomnia when a patient has comorbid depression or in cases of treatment failure. Trazodone, doxepin, mirtazapine, and amitriptyline are included in this class. There is, however, a paucity of data from randomized trials to support the use of sedating antidepressants for the treatment of primary insomnia, with the exception of doxepin.[1,150] Antihistaminergic, anticholinergic, serotonergic, and adrenergic antagonistic activities are mechanisms responsible for the sedating effects of these antidepressants.

Trazodone

Trazodone is an oral psychoactive agent that is FDA indicated for the treatment of depression.[151] The sedating effects of trazodone may be produced by the α-adrenergic and histamine blockade. Trazodone prolongs slow-wave sleep that includes stages III and IV.[152,153] REM latency was prolonged without affecting the proportion of REM sleep.[153–155]

Trazodone is highly protein bound with extensive distribution, and animal studies show that it crosses the blood–brain barrier.[156] Trazodone is metabolized by the liver into pharmacologically inactive metabolites. Trazodone is a substrate of CYP2D6 and CYP3A4, creating a high potential for possible drug interactions. Due to its relatively short $t_{½}$, trazodone can be uptitrated every 3 to 4 days to achieve desired response. There was no significant difference in the maximal plasma concentration between older and younger patients who received a single 100-mg dose of trazodone, but the terminal $t_{½}$ doubled with significant prolongation in elderly patients (4.6–8.3 hours to 6.0–16.2 hours; $P < 0.05$), indicating an age-related hepatic drug-metabolizing change.[157]

Insomnia is commonly associated with depression and is also a well-documented side effect of selective serotonin reuptake inhibitors.[158] For this reason, there are several studies demonstrating the efficacy of trazodone for secondary insomnia due to depression, but there is less literature assessing its use for primary insomnia.[158–164] Treatment of insomnia with trazodone showed a reduction in scores on the Hamilton Depression Rating Scale in a group of middle-aged women (20–50 years old) who were receiving long-term selective serotonin reuptake inhibitor therapy for depression.[158] Trazodone has also been shown to significantly improve multiple sleep parameters, including TST, sleep–wake sleep, sleep efficiency index, sleep continuity index, and number of awakenings.

Limited published data regarding trazodone use in the elderly population are available. In Alzheimer's patients, trazodone 50 mg at bedtime improved TST and nighttime percentage of sleep compared with placebo.[163] Despite imperfect data, trazodone is considered a favorable option compared with other sleep aids such as hypnotics, benzodiazepines, and tricyclic antidepressants, which have unfavorable side effect profiles.

The most common side effects of trazodone are relatively mild and include dizziness, drowsiness, fatigue, headache, xerostomia, nausea, and vomiting.[157] Rarely, it can cause priapism.[30] It lacks anticholinergic activity and cardiotoxicity, making it particularly attractive for elderly patients who are at high risk of adverse drug reactions.[157] Trazodone had less potential for abuse compared with benzodiazepines. It was compared specifically with triazolam, based on the Addiction Research Center Inventory test.[165] Individuals with a history of alcohol dependence reported a significant improvement in sleep after 4 weeks of treatment with trazodone (dose range, 50–300 mg at bedtime).[159]

Dosing of trazodone for major depression typically ranges from 150 to 600 mg per day.[12] Symptoms of insomnia have been shown to improve at lower trazodone doses, typically starting at 25 mg and titrating up to 100 mg daily at bedtime as needed for effect. Sleep symptoms improved in a group of depressed patients after 2 weeks of receiving trazodone 50 to 100 mg at bedtime, and improved further at 4 and 6 weeks.[161] Of note, if trazodone is

being used to co-manage depression and insomnia, the dosing appropriate for depression should be used.

There are no double-blind, randomized controlled trials examining the efficacy of trazodone for insomnia in the elderly population. Still, the limited data that are available support the safety and efficacy of trazodone for insomnia, especially in patients with depression, Alzheimer's disease, and history of alcohol or substance abuse. The lack of anticholinergic activity and favorable side effect profile make it a promising therapy in older adults experiencing insomnia.

Mirtazapine

Mirtazapine is a noradrenergic and specific serotonergic antidepressant with the latter specifically involving 5-HT_1, 5-HT_2, and 5-HT_3 receptors.[166] It has sedating properties and may benefit patients with a comorbid diagnosis of depression. It has been found to improve sleep architecture and efficiency by shortening sleep latency and reducing nighttime awakenings. It has also been found to improve sleep maintenance and SOL in patients with depression and insomnia.[166–168] Mechanisms believed to be involved in its sleep-promoting effect include mirtazapine's high affinity for histamine$_1$ receptors and its inhibition of 5-HT_2 receptors. In addition, the enhancement of noradrenergic neurotransmission increases the synthesis of melatonin.[169,170]

Mirtazapine exhibits rapid oral absorption, with a peak plasma concentration within 2 hours of administration. Steady state is achieved after ~5 days of treatment. Mirtazapine is extensively metabolized to both pharmacodynamically active (desmethyl-mirtazapine) and inactive compounds. It is also a substrate and very weak competitive inhibitor of CYP3A4, CYP2D6, and CYP1A2. The drug is eliminated via the urine (70%–80%) and feces. Drug clearance is reduced by 30% to 50% in patients with renal failure and up to 30% in patients with hepatic failure. Compared with young adults, in older adults the clearance of mirtazapine is reduced by 10% to 40%, leading to higher plasma concentrations.[171,172] Caution should be exercised when prescribing to older adults secondary to reduced clearance.

Mirtazapine is approved for the treatment of depression, with evidence supporting its efficacy in older adults.[169,173,174] There is no indication for its use in the treatment of primary insomnia; however, it may be beneficial in patients with comorbid depression. Acute effects of mirtazapine on sleep were studied in a small set of patients with depression, based on the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria; their ages ranged from 18 to 65 years. Sleep parameters after 1 week of mirtazapine 15 mg and 1 week of mirtazapine 30 mg were compared with baseline sleep parameters. Mirtazapine significantly increased TST from 360 minutes to 420 minutes, increased sleep efficiency from 83% to 93%, and decreased sleep latency from 14 minutes to 5 minutes. Thirty milligrams of mirtazapine did not significantly improve parameters compared with 15 mg.[175] Similar results were seen in a study comparing the use of mirtazapine and fluoxetine in 19 patients ranging in age from 18 to 75 years old. Patients were initiated on mirtazapine 15 mg with titration up to 45 mg over the initial 2-week period. Significant improvements were again seen in sleep latency and TST. Although sleep efficiency trended toward improvement, it failed to show significance. These improvements were seen as early as 2 weeks after the initiation of mirtazapine.[166,168,175]

Mirtazapine is generally well tolerated. Compared with placebo, the most common adverse effects include drowsiness, excessive sedation, increased appetite, weight gain, and dry mouth.[166,176] Ironically, lower doses cause more sedation. This pattern of side effects in older adults was similar to that in the overall population.[166,173,177,178] Regardless of the cause, weight loss is an independent predictor of increased disability and mortality in older adults.[179–182] Raji and Brady[169] describe 3 case reports in which patients with Alzheimer's disease experienced response to mirtazapine, including complete remission of poor appetite, weight loss, sleep disturbances, and anxiety.

Doxepin

Doxepin, a tricyclic antidepressant, is commonly known for its use in the treatment of depression. At smaller doses (3–6 mg), doxepin has high selectivity for histamine receptors and primarily acts as a histamine antagonist that produces a sedative effect.[62,183] Doxepin is FDA approved for primary insomnia at doses of 3 and 6 mg.[183] At low doses, doxepin has high selectivity for histamine receptors and little to no effect on serotonin and adrenergic receptors, thus avoiding the anticholinergic adverse effects associated with higher doses.[184] The Beers criteria by the American Geriatric Society recommend caution against use of doxepin in doses >6 mg daily in the elderly population.[66]

Doxepin has rapid absorption once administered orally, with a median time of 3.5 hours to reach peak concentrations.[185] Administration with a high-fat meal can delay time to peak concentrations by 3 hours; it should not be taken within 3 hours of food consumption. Doxepin should be taken 30 minutes before bedtime.[186] Doxepin undergoes oxidative metabolism, mainly through the CYP2D6 and 2C19 enzyme pathways.[185] Oxidative metabolism is reduced in the elderly, which can result in decreased metabolism and prolonged $t_{1/2}$.[18] It is mainly eliminated in the urine and has an approximate $t_{1/2}$ of 15 hours.[185]

Due to its metabolism with the CYP enzyme pathways, increased systemic concentrations of doxepin can result if it is administered with inhibitors of either CYP enzyme. These include but are not limited to proton pump inhibitors such as omeprazole and pantoprazole, cimetidine, ketoconazole, paroxetine, bupropion, cinacalcet, and amiodarone. Drug–drug interactions should be reviewed before recommending doxepin.[185,186]

Doxepin has been shown to improve sleep maintenance.[150,187] Three published trials have studied doxepin in older adults. Lankford et al[150] conducted a 4-week trial of doxepin 6 mg versus placebo nightly in older adults. Doxepin resulted in significant increased subjective TST of 335 minutes versus 316 minutes for placebo at week 1 and 346 minutes versus 336 minutes for placebo at week 4. Doxepin resulted in significant improved subjective wake after sleep onset of 79 minutes versus 97 minutes for placebo at week 1 and 66 minutes versus 79 minutes for placebo at week 4. Patients taking doxepin were additionally found to have improvements in the Clinical Global Impression scale and Insomnia Severity Index score.[150] Results from the additional studies showed that doxepin at doses of 1 to 6 mg produced increased TST and improved WASO versus placebo. Outcomes were measured by using both subjective and objective assessments.[187,188]

The most commonly experienced adverse effects in all studies were comparable in frequency to placebo and included headache and somnolence/sedation. There were few reported events of anticholinergic effects and next-day residual sedation.[150,187,188] Additional studies of doxepin versus placebo were conducted in adults aged 18 to 64 years old and produced similar results and adverse events.[189–191]

Doxepin is available in 3- and 6-mg doses only as a brand name product, which could be a financial burden to older adults. Studies in the older adult population have shown promising results; however, all of the studies included placebo as the comparator group. There have been no published studies with doxepin versus another FDA-approved insomnia medication, resulting in doxepin being a second-line treatment recommendation for insomnia.[183,186]

Amitriptyline

Amitriptyline is a tricyclic antidepressant that carries an off-label indication of insomnia. Due to the availability of newer agents and medications with more favorable side effect profiles, the use of amitriptyline for insomnia is no longer recommended.[1,192] Amitriptyline is a lipophilic medication and reportedly has an increased $t_{1/2}$ as well as reduced clearance in elderly patients, leading to increased risk of adverse effects.[193] The American Geriatric Society strongly discourages the use of amitriptyline in the elderly population.[66] It has many anticholinergic effects, including dry mouth, urinary retention, constipation, and drowsiness, in addition to impaired cognition, increased risk of delirium, and drug–drug interactions.[1,193] There are limited studies of the efficacy of amitriptyline in patients with insomnia, especially in the elderly population, which makes it extremely difficult to recommend its use given the known side effect profile.

Miscellaneous Sleep Products

There are a number of medications whose adverse effects have been capitalized upon for sleep. These agents include antipsychotics, gabapentin, pramipexole, and tiagabine. In general, these medications have not been studied in the elderly population to evaluate the safety and efficacy of the medication for the treatment of insomnia. The limited data available are mostly from studies conducted in a small number of younger individuals and not in controlled randomized studies. These agents may only be appropriate in patients with comorbid psychiatric diagnoses who benefit from the primary action as well as the sedating side effect.[12] Off-label use of these agents should be avoided due to the lack of data to support their efficacy for primary insomnia along with their potential for adverse reactions.

Antipsychotic Agents

Antipsychotic agents are often used in elderly patients who are unable to sleep and also have behavioral disturbances or major depression disorder.[194] As a class, antipsychotic agents carry a black box warning for increased risk of death in patients with dementia (1.6–1.7 times that of placebo), and they are included in the 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults from the American Geriatrics Society.[195] Atypical antipsychotic agents cause less sedation than conventional antipsychotic agents such as haloperidol.[196] Olanzapine and quetiapine are the most sedating of the atypical antipsychotics, and sedation is less common with risperidone and ziprasidone. It is believed that the sedating effect of the antipsychotic agents is related to the affinity for the histamine H_1 and serotonin type 2A receptors in the CNS, which varies for each agent.[196,197]

In elderly patients with major depression disorder, quetiapine CR significantly reduced the Montgomery-Åesberg Depression Rating Scale total score ($P < 0.001$) and the Pittsburgh Sleep Quality index ($P < 0.001$) compared with placebo at week 9 of treatment.[194] Unfortunately, adverse events were reported in 80.7% of patients and led to discontinuation of therapy in 9.6% of patients.

Maher et al[198] conducted a literature review of the off-label use of antipsychotic agents in adults. The majority of the articles contained indications for psychosis, agitation, and global behavioral symptoms in dementia; generalized anxiety disorder; and obsessive-compulsive disorder. Only 1 trial evaluated the use of atypical antipsychotic agents for insomnia, and it was found to be inconclusive. In elderly patients with dementia, a number of adverse reactions were reported: increased risk of death (odds ratio, 1.54), cardiovascular symptoms, edema, vasodilation, increased appetite and weight, central and peripheral anticholinergic effects, sedation and fatigue, extrapyramidal symptoms, urinary tract symptoms, and cognitive decline.

There are limited data evaluating the use of antipsychotic agents in patients with insomnia in the absence of psychiatric conditions, and no trials are available comparing their safety and efficacy versus those of another active agent for insomnia such as zolpidem.[197] Considering the lack of robust data for efficacy and their adverse event profiles, the benefit of antipsychotic agents for the treatment of insomnia does not outweigh the risks associated with therapy.

Gabapentin

Gabapentin has been used for insomnia, especially in patients with restless leg syndrome or chronic neuropathic pain.[30,199] Gabapentin is a structural analogue of GABA that interacts with α_2-δ_1 subunits of voltage-gated calcium channels, resulting in the release of excitatory neurotransmitters. One of the associated adverse effects is drowsiness, which may be responsible for its effectiveness for insomnia.[200]

Gabapentin has fast absorption once administered orally, with a median time of 2 to 3 hours to reach peak concentrations.[201] Bioavailability decreases as a daily dose of gabapentin increases, ranging from 60% bioavailability with 900 mg daily to 27% bioavailability with 4800 mg daily.[201,202] Administration with food has little to no effect on absorption. Gabapentin is not metabolized and undergoes elimination as unchanged drug through the urine; the $t_{½}$ is ~5 to 7 hours. Gabapentin is highly lipid soluble, and it therefore readily distributes into the CNS, contributing to its common side effect of drowsiness.[201]

A trial conducted by Rosenberg et al[203] analyzed the effects of a single dose of gabapentin 250 mg and 500 mg on both subjective patient-reported sleep measures and PSG sleep measures in adults aged ≥18 years. Both doses of gabapentin (250 and 500 mg) resulted in a significantly improved PSG measure of WASO of 101 minutes and 73 minutes, respectively, compared with 135 minutes for placebo. Significantly increased PSG TST was found with both gabapentin 250 mg (356 minutes) and 500 mg (379 minutes) compared with placebo (311 minutes). The only significant patient-reported sleep measure was seen in TST with the gabapentin 500-mg dose only. An additional study assessed the 28-day treatment efficacy of gabapentin 250 mg on both subjective patient-reported sleep measures and PSG sleep measures in adults aged ≥18 years.[200] Gabapentin was associated with significant improvement in the PSG measure of WASO at both day 1 and day 28 of treatment. The use of gabapentin additionally resulted in a significant PSG increase in TST and self-reported measures, including improvement in WASO, increases in TST, and higher rates of sleep quality.

Adverse effects associated with gabapentin included headache, somnolence, dizziness, and GI disturbances. No residual daytime sedation was associated with this drug.[200,203] Although gabapentin has been shown to be efficacious, limited data are available that focus on older adults. Additional concerns include renal dose adjustment with kidney dysfunction, as well as adverse effects including dizziness and somnolence. Gabapentin may be a second-line recommendation for insomnia unless the patient has comorbidities of restless leg syndrome or chronic neuropathic pain.

Pramipexole

REM sleep behavior disorder (RBD) is traditionally treated with clonazepam as a first-line choice, but pramipexole has been theorized to be beneficial due to underlying pathophysiology involving dopaminergic deficiency.[204] Pramipexole is a dopamine agonist with specificity for the D_2 and D_3 receptors. In a small study of 9 elderly patients (mean age, 72 years), 89% of patients had moderate reduction or complete resolution in frequency of RBD symptoms. One patient experienced vivid hallucinations and withdrew from the study, indicating that pramipexole may be inappropriate for patients with history of psychiatric disorders or hallucinations. Interestingly, insomnia has been reported as a side effect in up to 27% of patients.[205] Considering the limited data available at this time and the high incidence of insomnia, pramipexole should be used cautiously and be limited to those with REM sleep behavioral disorder.

Tiagabine

Tiagabine inhibits the uptake of GABA by binding to recognition sites and is approved for the treatment of partial seizures. CNS effects are common with tiagabine use, and drowsiness has been reported in up to 21% of patients.[206] Currently, tiagabine does not have a labeled indication for insomnia.

Treatment with tiagabine 4 to 8 mg significantly increased slow-wave sleep and decreased stage 1 sleep compared with placebo in elderly patients (aged 65–87 years) with a *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) diagnosis of primary insomnia.[207] There was no significant change in wake after sleep onset, latency to persistent sleep, TST, or subjective sleep ratings. Tiagabine was well tolerated at 2 to 6 mg compared with placebo, but dosing at 8 mg was associated with residual effects and reduced alertness.

Summary

Antipsychotic agents, gabapentin, pramipexole, and tiagabine have all been used off-label for insomnia, but none has been studied extensively in the elderly population. Because other pharmacologic agents are available that have been studied extensively and have better side effect profiles, the current recommendation is to reserve these agents for individuals who have a comorbid condition that is a primary indication for use.

Over-the-Counter Drugs

Over-the-counter (OTC) or nonprescription medications such as antihistamines are frequently used for sleep. They are inexpensive and readily available options; however, they have limited data on safety and efficacy when used for insomnia. Diphenhydramine is the most commonly used OTC pharmacologic agent. OTC sleep aids should be utilized in short durations because tolerance can develop.[5]

Diphenhydramine is a first generation histamine$_1$-receptor antagonist that was discovered in the 1940s.[208,209] Histamine is a neurotransmitter that activates receptors leading to bronchoconstriction, acid secretion, contraction of the gut, and, in the CNS, controls vigilance during the waking state. First-generation histamine$_1$-receptor antagonists competitively block histamine from binding to its receptors. They readily penetrate the blood–brain barrier.[209] In the CNS, first generation histamine$_1$-receptor antagonists also have affinity for muscarinic, adrenergic, serotonergic, and dopaminergic receptors.[208,209] Diphenhydramine only has affinity for histamine$_1$, muscarinic, and adrenergic receptors.[183] Due to its receptor activity in the CNS, diphenhydramine is used as an OTC sedative, but there is much variability in efficacy and safety between patients. Older adults, especially in those with renal and hepatic impairment, tend to be more prone to the adverse effects of diphenhydramine. Anticholinergic agents are currently listed as inappropriate for use in older adults based on the updated Beer's criteria.[66]

Older studies comparing diphenhydramine versus placebo reported improvements in overall sleep parameters (TST, number of awakenings, sleep latency, sleep efficacy, and quality of sleep).[210,211] The designs of the studies lack the ability to show significant

clinical improvement in sleep for older adults because the studies have small sample sizes, have short study durations, and have a younger average patient age (40 to 60 years old). More recent studies comparing diphenhydramine versus placebo have only found moderate improvement in sleep efficiency (4.6% improvement vs 2.5% with placebo) or number of awakenings (1.7 awakenings vs 2.0 with placebo).[212,213] These more recent studies still consist of short treatment durations (2-week increments) and small sample sizes (20–65 patients), which brings to question the significance of clinical benefit. Even when differences in diphenhydramine dose are assessed, there is little added benefit with higher doses.[211] Furthermore, tolerance develops after 1 to 2 weeks of uninterrupted use of the antihistamines, which would render it an ineffective therapy.[1]

Adverse effects, both systemic and in the CNS, are important limitations of histamine$_1$-receptor antagonists and diphenhydramine. As mentioned, these medications tend to accumulate in patients with hepatic and renal impairment. Common adverse effects of diphenhydramine are dry mouth, blurred vision, urinary retention, constipation, orthostatic hypotension, and tachycardia.[62,214] Adverse effects are dose dependent and increase in occurrence with higher doses of diphenhydramine.[211] It is not just anticholinergic side effects that are of concern, however; cognitive effects of diphenhydramine, especially in older adults, play a role in appropriateness of use. Grogginess, drowsiness, confusion, and memory loss have been well described with use of diphenhydramine.[210,212,213] Community-dwelling older adults were shown to have reduced alertness, diminished memory task performance, and impaired episodic memory with diphenhydramine.[215] Diphenhydramine can place hospitalized older adults at increased risk of delirium and altered consciousness, as well as result in increased length of hospital stay.[214]

Although diphenhydramine is an inexpensive and easily obtained OTC option for insomnia and sleep disturbances, its impact on sleep is modest and nonsustained. In addition, diphenhydramine is used in many OTC products marketed to aid in sleep. Patients and providers need to be aware and cautious of all ingredients in OTC products to prevent unintentional use or overuse of diphenhydramine. Ultimately, the risks of residual daytime sedation and anticholinergic side effects outweigh the benefits of this agent.[30,212]

Herbal Supplements

Dietary supplements endorsed for the treatment of insomnia carry no FDA approval nor does their production undergo the scrutiny of FDA monitoring. Quality studies are limited with dietary supplements and often offer conflicting results. Use of dietary supplements is often not reported to practitioners. This scenario has the potential to lead to otherwise avoidable, drug interactions. The following section discusses the use of valerian and melatonin for sleep disorders.

Valerian

Valerian is extracted from the plant species *Valeriana officinalis* and *Valeriana edulis* and is available in many different dosage forms.[216,217] Unfortunately, the FDA does not regulate their production, and the various formulations contain different amounts of valerian.[216,218] Although the exact mechanism of valerian for insomnia is unknown, it is believed to have important interactions with the neurotransmitter GABA and its receptors. Valerian is thought to inhibit the uptake of GABA and also stimulate its release.[219] More recently, it has been shown to be a partial agonist at the adenosine and serotonin receptors.[220,221]

Studies of valerian on sleep have often shown mild effects and limited statistical significance, with conflicting results between different studies. Subjective improvement in sleep did not differ between valerian and placebo treatments.[212,222] Contradictory results have also been shown with changes in sleep latency; some studies exhibited improvement, whereas others have shown a decline in sleep latency.[212,223–225] Overall, valerian showed small improvement in sleep efficiency.[212] Regrettably, many of these studies were conducted in younger populations for short durations of time. In those studies that included older adults, comparisons between valerian and placebo were difficult to make because of differences in baseline characteristics between the groups or because testing was conducted over too short of a duration to appropriately assess outcomes.[223,226]

Adverse effects from valerian are usually mild and do not differ from those seen with placebo.[212] Residual and rebound drowsiness is not usually seen with valerian and is similar in frequency to that reported with placebo. Due to valerian's action on the GABA receptors, there may be potential for effects on the CNS. However, few studies have shown

differences in cognitive effects and residual daytime sedation when valerian was compared with placebo.[212,227] Although valerian does not have more documented adverse effects than placebo, its prolonged use has not been well documented and there is no robust documentation of use in the elderly population.

Melatonin

Melatonin, although a dietary supplement, is also a hormone produced by the pineal gland. Melatonin is released at night and binds to its receptors (MT_1 and MT_2) in the suprachiasmatic nucleus and results in suppression of neuronal activity.[228] Melatonin production is controlled by light; thus, during the evening hours, melatonin levels rise while during the day melatonin levels stay low.[229] Levels are decreased in elderly patients, which puts them at risk for more conditions related to circadian rhythms such as sleep disorders, cognitive impairment, and delirium.[229,230] The administration of melatonin as a dietary supplement can mimic the function of endogenous melatonin. However, it is important to note that different administration times can impact the effect melatonin has on circadian rhythms. Morning administration can delay the circadian rhythm and delay onset of evening fatigue.[231] However, when administered in the evening, melatonin can advance the circadian rhythm and induce sleep onset.[232]

The effects of melatonin on sleep have been widely studied in the literature. Similar to other studies of OTC and dietary supplements, the results are not consistent between trials. Some earlier studies indicated improvement in sleep latency and cognitive impairment.[233,234] More recent data from larger study populations have shown no improvement in objective measures even though subjective improvements were reported by caregivers.[235] Although some data suggest that melatonin can improve sleep latency, findings of significant overall improvement in sleep are lacking.[236] The potential for daytime drowsiness with the use of melatonin may, however, be of concern. Residual daytime sedation, tiredness at rising, and increased sleep disruption have been documented.[237,238] Some evidence also suggests that the sedative effects of melatonin can last for up to 7 hours even in younger patients.[239]

Compared with other dietary supplements used for sleep disturbances, melatonin's mechanism is the most closely linked to physiologic processes and is generally well tolerated.[236,240] There is still some uncertainty regarding the efficacy of melatonin; it may have a small effect on sleep latency but little effect on waking after sleep.[30,241] Some safety concerns, especially in the elderly, include the potential for residual daytime sedation and prolonged duration of action. However, melatonin could potentially be used to spare the use of prescription hypnotic agents. When choosing a melatonin supplement for use in older adults, controlled-release products should be avoided because they can result in prolonged melatonin levels. It is recommended that immediate-release formulations be used; a maximum of 1 to 2 mg should be administered 1 hour before bedtime.[229]

CONCLUSIONS

An ideal treatment for insomnia should help to improve sleep latency and sleep duration, with limited awakenings, and be without significant detrimental adverse reactions. Factors causing insomnia or sleep interruption should be ruled out before initiating therapy. Worsening of chronic medical conditions such as heart failure, pulmonary diseases, urinary incontinence, and nighttime pain must be considered and addressed to prevent addition of medications. Current medication regimens can be reviewed for drugs that may cause or contribute to insomnia (including specific drugs and timing of doses), noncompliance with necessary medications, and use of medications or supplements previously unreported that should be evaluated. CBTI and sleep hygiene should always be the initial therapy for insomnia and should continue throughout treatment. Ramelteon is a potentially desirable pharmaceutical option for an older patient after sleep hygiene has failed. Ramelteon's low adverse effect profile combined with reduced SOL and increase TST makes it a valuable first-line consideration. In addition, suvorexant decreases the time to sleep onset and increases TST. Adverse effects with suvorexant are mild and include somnolence, but residual daytime sedation has been reported. There is, however, limited clinical experience with suvorexant.

Complicating a potential new avenue of treatment for insomnia is a suspected clinical inertia faced with clinicians. For decades, benzodiazepines and non-BzRAs were the most commonly used options for

insomnia treatment. Although these agents are efficacious, as time progressed, their deleterious adverse effects have made these agents somewhat prohibitive. The challenge for clinicians is how to overcome the issue of inaction in patients who are dependent on the continued use of these agents.

Benzodiazepines should be avoided in the geriatric population, especially for long-term use. Non-BzRAs have improved safety profiles compared with benzodiazepines, but side effects such as dementia, serious injury, and fractures should also limit their use in the elderly.

Sedating low-dose antidepressants are an attractive option for insomnia when the patient has comorbid depression. Trazodone seems to be the safest because it lacks anticholinergic activity. Mirtazapine may be beneficial for the treatment of insomnia in the elderly when the patient is experiencing frailty syndrome, due to its side effect of appetite stimulation.

Antipsychotic agents, pramipexole, and tiagabine have all been used for insomnia, but none has been extensively studied in an older population. All have considerable adverse effects, once again limiting their use with insomnia and a corresponding comorbid condition. Gabapentin may be useful in patients with restless leg syndrome or chronic neuropathic pain and insomnia.

Diphenhydramine is unsuitable for the elderly due to its potent anticholinergic effects. Valerian and melatonin are unregulated products. Although the data on melatonin are inconsistent, it can be considered an option due to its comparatively favorable side effect profile.

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CONFLICTS OF INTEREST

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