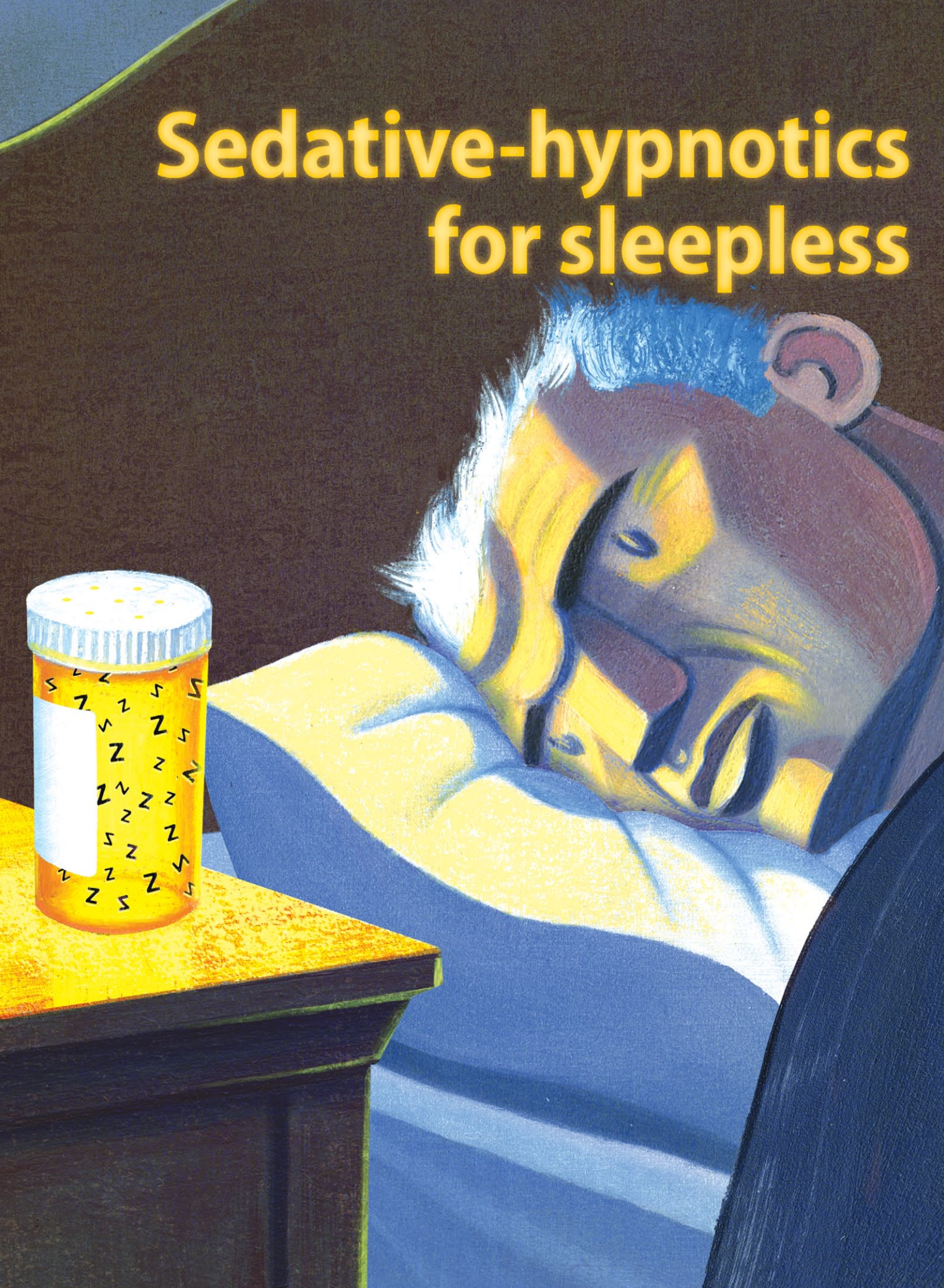
Sedative-hypnotics for sleepless



geriatric patients: Choose wisely

Age-related physiologic changes, risk of adverse effects guide your prescribing

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Mr. R, age 75, is having difficulty sleeping. When he goes to bed, he lies there for what seems like forever, unable to fall asleep. He feels "so tired" and ends up taking naps during the day, but he cannot break this cycle. He has tried using over-the-counter products with little relief.

Mr. R's primary care physician prescribes zaleplon, 10 mg/d, and asks him to call the clinic in 2 weeks to discuss his progress. He takes zaleplon as directed for several nights and begins to feel "sluggish" during the day, both mentally and physically, despite reporting an increase in the overall amount of sleep at night.

Sedative-hypnotic drugs are among the most commonly used medications in the United States. Use of these drugs, as well as anxiolytics, has increased from 2.8% between 1988 and 1994 to 4.7% between 2007 and 2010, according to the Department of Health and Human Services.[1] In 2011, drugs categorized as sedative-hypnotics or antipsychotics were involved in 6.1% of all human exposures identified in the American Association of Poison Control Centers' National Poison Data System.[2] Therefore, an understanding of clinical and pharmacological variables related to safe and effective use is important for clinicians prescribing and monitoring therapy with these agents.

Neuropsychiatric disorders are prevalent among geriatric patients and are associated with age-related physiologic changes in the CNS.[3] Such changes involve:

- neuroanatomy (brain atrophy, decreased neuronal density, increased plaque formation)
- neurotransmitters (reduced cholinergic transmission, decreased synthesis of dopamine and catecholamines), and

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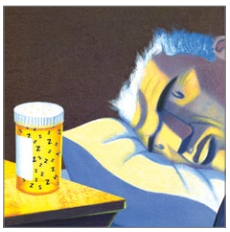

Sedative-hypnotics

Clinical Point

Although the process of drug absorption can change with age, the amount of drug absorbed might not be significantly affected

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- neurophysiology (reduced cerebral blood flow).

These physiologic processes manifest as alterations in mental status, reflexes, sensation, gait, balance, and sleep. Examples of sleep changes among geriatric patients include decreased sleep efficiency, more frequent awakenings, and more variable sleep duration.[3,4] Sleep disorders also may be related to mental disorders and other medical conditions.[5] For example, the prevalence of sleep-related respiratory disorders, such as obstructive sleep apnea and central sleep apnea, increases with age.[6]

Sleep disorders are common among geriatric patients. In a large epidemiologic study of sleep complaints in patients age ≥65, more than one-half of patients had at least 1 sleep complaint (ie, difficulty falling asleep, trouble waking up, early awakening, need for naps, and feeling ill-rested).[7] As many as 34% of patients reported symptoms of insomnia. In an analysis of National Ambulatory Medical Survey Data over 6 years, 24.8% to 27.9% of sleep-related medical office visits were attributed to patients age ≥65.[8]

Pharmacology in aging

Prescribing sedative-hypnotic drugs is not routinely recommended for older patients with a sleep disorder. Geriatric patients, compared with younger patients, are at higher risk of iatrogenic complications because of polypharmacy, comorbidities, relative renal and hepatic insufficiency, and other physiologic changes leading to alterations in drug exposure and metabolism (***Table 1***).[9-12]

Aging is associated with changes in body composition, including an increase in total body fat and decrease in lean body mass and total body water. These changes, as well as a prolonged GI transit time, decrease in active gut transporters, decreased blood perfusion, and decrease in plasma proteins such as albumin (because of reduced liver function or malnutrition), may lead to alteration in drug absorption patterns and may increase the volume of distribution for lipophilic drugs. Additionally, the elimination half-life of some drugs may increase with age because of larger volumes of distribution and reduction in hepatic or renal clearance.

The clinical significance of these changes is not well established. Although the process of drug absorption can change with age, the amount of drug absorbed might not be significantly affected. An increase in the volume of distribution and reduction in drug metabolism and clearance might lead to increasing amounts of circulating drug and duration of drug exposure, putting geriatric patients at an increased risk for adverse effects and drug toxicity.[9]

Among these mechanisms, Dolder et al[11] hypothesized that drug metabolism catalyzed by cytochrome P450 (CYP) enzymes and renal excretion may be of greatest concern. Although in vitro studies suggest that concentration of CYP enzymes does not decline with age, in vivo studies have demonstrated reduced CYP activity in geriatric patients.[11,12] Theoretically, a reduction in CYP activity would increase the bioavailability of drugs, especially those that are subject to extensive first-pass (ie, hepatic) metabolism, and may lead to a reduction in systemic clearance.

Independent of metabolic changes, geriatric patients are at risk of reduced renal clearance because of age-related changes in glomerular filtration rate. Pharmacodynamic changes might be observed in older patients and could be a concern even in the setting of unaltered pharmacokinetic factors.[9] These changes usually require administering smaller drug dosages.

Sedative-hypnotic medications

Sedative-hypnotic agents include several barbiturates, benzodiazepines (BZDs), non-BZD benzodiazepine-receptor agonists (BzRAs), a melatonin-receptor agonist (ie, ramelteon), and an orexin-receptor antagonist (ie, suvorexant).[13,14] ***Table 2*** (***page 46***)[14-29] summarizes selected sedative-hypnotic drugs. Additional drug classes used to treat insomnia include:

- sedating antidepressants (trazodone, amitriptyline, doxepin, mirtazapine)
- antiepileptic drugs (gabapentin, tiagabine)
- atypical antipsychotics (quetiapine, olanzapine).

Table 1

Effects of age-associated physiologic changes on pharmacokinetic parameters

Physiologic changes	Pharmacokinetic parameters	Clinical implications
↑ Total body fat ↓ Lean body mass ↓ Total body water ↓ GI motility ↓ Plasma protein Hypochlorhydria	Absorption • Unaffected for IV drugs • Extent of absorption may be complete, but T_{max} may be longer, C_{max} may be lower • Reduced for drugs requiring lower pH environment	May observe slight decrease in absorption; literature suggests that this rarely is clinically significant
	Distribution • Reduced for water-soluble drugs and drugs bound to muscle • Increased for lipid-soluble drugs	May require dosage reduction of hydrophilic drugs May observe prolonged time to elimination of lipophilic drugs Note: reduction in protein binding alone does not usually result in clinically significant change in volume of distribution
↓ Hepatic mass ↓ Hepatic blood flow	Metabolism • Reduced first-pass metabolism • Reduced Phase I metabolism	Potential increase in bioavailability of drugs subject to extensive hepatic metabolism and increased drug exposure
↓ Cardiac output ↓ Blood flow to kidneys and liver ↓ Renal mass ↓ Renal or hepatic clearance	Elimination • Reduced renal elimination • Increased elimination half-life	Increased plasma concentration of drug or metabolites and duration of drug action

C_{max}: maximum plasma concentration; T_{max}: time to maximum plasma concentration

Source: References 9-12

FDA-approved agents for treating insomnia include amobarbital, butabarbital, pentobarbital, phenobarbital, secobarbital, chloral hydrate, diphenhydramine, doxylamine, doxepin, estazolam, flurazepam, lorazepam, quazepam, temazepam, triazolam, eszopiclone, zaleplon, zolpidem, ramelteon, and suvorexant. Not all of these drugs are recommended for use in geriatric patients. Barbiturates, for example, should be avoided.[30]

Pharmacokinetic characteristics vary among drugs and drug classes. Choice of pharmacotherapy should account for patient and drug characteristics and the specific sleep complaint. Sleep disorders may be variously characterized as difficulty with sleep initiation, duration, consolidation, or quality.[13] Therefore, onset and duration of effect are important drug-related considerations. Sedative-hypnotic drugs with a short time-to-onset may be ideal for patients with sleep-onset insomnia.

The drugs' duration of effect (eg, presence of active metabolites, long elimination half-life) also must be reviewed. A long elimination half-life may lead to increased drug exposure and unwanted side effects such as residual daytime drowsiness. Despite this, sedative-hypnotic drugs with a longer duration of effect (eg, intermediate- or long-acting drugs) may be best for patients with insomnia defined by difficulty maintaining sleep.

Benzodiazepines vary in their time to onset of effect, rate of elimination, and metabolism.[15-21] BZDs that are FDA-

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Clinical Point

Prescribing sedative-hypnotic drugs is not routinely recommended for older patients with a sleep disorder

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Sedative-hypnotics

Clinical Point

Geriatric patients are at risk of reduced renal clearance because of age-related changes in glomerular filtration rate

Table 2

Characteristics of select oral sedative-hypnotic agents and recommended dosing in geriatric patients

Drug	Dosage form	Pharmacokinetic characteristics: Absorption (onset of effect, T_{max})[a]	Pharmacokinetic characteristics: Distribution (protein binding, Vd)[b]
Benzodiazepines			
Estazolam	1, 2 mg tablets	T_{max}: 2 hours	High protein binding Vd: large
Flurazepam[e]	15, 30 mg capsules	Onset of effect: 15 to 20 minutes T_{max}: 0.5 to 1 hour; T_{max} of major metabolite: 10.6 hours	High protein binding Vd: large
Quazepam[e]	15 mg tablets	T_{max}: 2 hours	High protein binding Vd: large
Temazepam	7.5, 15, 22.5, 30 mg capsules	T_{max}: 1.2 to 1.6 hour	High protein binding Vd: medium
Triazolam	0.125, 0.25 mg tablets	Onset of effect: 0.25 to 0.5 hour T_{max}: 2 hours	High protein binding Vd: medium
Benzodiazepine-receptor agonists			
Eszopiclone	1, 2, 3 mg tablets	T_{max}: 1 hour	Moderate protein binding Vd: medium
Zaleplon	5, 10 mg capsules	T_{max}: 1 hour	Moderate protein binding Vd: medium
Zolpidem	5, 10 mg tablets	Onset of effect: 0.5 hour T_{max}: 1.6 hour	High protein binding Vd: small
	6.25, 12.5 mg ER tablets	T_{max}: 1.5 hour	
	5, 10 mg sublingual tablets	T_{max}: 0.5 to 3 hour	
	1.75, 3.5 mg sublingual tablets	T_{max}: 0.5 to 1.25 hours	
	5 mg spray solution	T_{max}: 0.9 hour	
Melatonin-receptor agonist			
Ramelteon	8 mg tablets	Onset of effect: 0.5 hour T_{max}: 0.75 hour	Moderate protein binding Vd: medium
Orexin-receptor antagonist			
Suvorexant	5, 10, 15, 20 mg tablets	T_{max}: 2 hours	High protein binding Vd: small

[a]Time to maximum plasma concentration and/or onset of effect specified if available
[b]Extent of protein binding: high: >90%; moderate: ≤90% and ≥50%; low: <50%; Vd specified if available: large: >2 L/kg; medium: ≤2 and ≥1 L/kg; small: <1 L/kg
[c]Extent of metabolism: high: <10% excreted unchanged; moderate: ≤50% and >10% excreted unchanged; low: >50% excreted unchanged
[d]For half-lives reported as a range, a mean is specified if available
[e]Flurazepam and quazepam are not recommended in geriatric patients because of safety concerns

CR: controlled-release; CYP: cytochrome P450; ER: extended-release; NS: not specified; $T_{1/2}$: elimination half-life; T_{max}: time to maximum plasma concentration; Vd: volume of distribution

Source: References 14-29

	Pharmacokinetic characteristics		
	Metabolism[c]	Elimination[d]	Recommended adult dosing
	Hepatic; extent high Enzyme: CYP 3A4	$T_{1/2}$: 10 to 24 hours	Hypnotic: 1 or 2 mg at bedtime **Geriatric: 0.5 mg initially for small or debilitated patients; 1 mg if healthy**
	Hepatic; extent high Enzyme: CYP 3A4	$T_{1/2}$: 2.3 hours $T_{1/2}$ of major metabolite: 47 to 100 hours; mean 126 to 158 hours in geriatric patients	Hypnotic: 30 mg at bedtime **Geriatric: 15 mg**
	Hepatic; extent high Enzyme: CYP 3A4	$T_{1/2:}$ 39 hours $T_{1/2}$ of major metabolite: 73 hours	Hypnotic: 7.5 mg initially **Geriatric: NS**
	Hepatic; extent low Enzyme: CYP 2B6, 2C19, 2C9, 3A4 (all minor)	$T_{1/2}$: 3.5 to 18.4 hours, mean 8.8 hours	Hypnotic: 15 mg at bedtime **Geriatric: 7.5 mg initially**
	Hepatic; extent moderate Enzyme: CYP 3A4	$T_{1/2}$: 1.5 to 5.5 hours	Hypnotic: 0.25 mg at bedtime; 0.125 mg for patients with low body weight **Geriatric: 0.125 mg initially, 0.25 mg maximum**
	Hepatic; extent high Enzyme: CYP 3A4, 2E1	$T_{1/2}$: 6 hours	Hypnotic: 2 mg at bedtime **Geriatric: 1 mg initially, 2 mg maximum**
	Hepatic; extent high Enzyme: CYP 3A4	$T_{1/2}$: 1 hour	Hypnotic: 10 mg at bedtime **Geriatric: 5 mg initially, 10 mg maximum**
	Hepatic; extent high Enzyme: primarily CYP 3A4, minor 1A2, 2C19, 2C9, and 2D6	$T_{1/2}$: 2.5 to 2.6 hours	Hypnotic: 5 or 10 mg at bedtime **Geriatric: 5 mg**
		$T_{1/2}$: 2.8 hours	Hypnotic: 6.25 or 12 mg at bedtime **Geriatric: 6.25 mg**
		$T_{1/2}$: 2.65 to 2.85 hours	Hypnotic: 5 or 10 mg at bedtime **Geriatric: 5 mg**
		$T_{1/2}$: 2.5 hours	
		$T_{1/2}$: 3.0 hours	Hypnotic: 5 or 10 mg at bedtime **Geriatric: 5 mg**
	Hepatic; extent high Enzyme: primarily CYP 1A2, minor 2C and 3A4	$T_{1/2}$: 1 to 2.6 hours	Hypnotic: 8 mg at bedtime **Geriatric: NS**
	Hepatic; extent high Enzyme: primarily CYP 3A, minor 2C19	$T_{1/2}$: 12 hours	Hypnotic: 10 mg at bedtime, 20 mg maximum **Geriatric: NS**

Clinical Point

Sedative-hypnotic drugs with a longer duration of effect may be best for patients who have difficulty maintaining sleep

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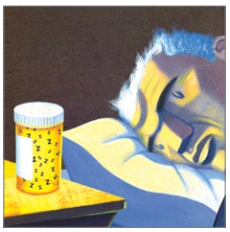


Sedative-hypnotics

Clinical Point

No dosage adjustments for ramelteon or suvorexant in geriatric patients have been specified

approved for use as sedative-hypnotics are listed in ***Table 2*** (***page 46***).[14-29] These BZDs have different onsets of effect as evidenced by time to achieve maximum plasma concentration (T_{max}), ranging from 0.5 hours (flurazepam) to 2 hours (estazolam, quazepam, triazolam). The elimination half-life varies widely among these medications, from 1.5 hours (triazolam) to >100 hours (flurazepam). Flurazepam's long half-life is attributable to its active major metabolite. Although most BZDs are metabolized hepatically, temazepam is subject to minimal hepatic metabolism.

Benzodiazepine-receptor agonists. There is substantial variation in the pharmacokinetic characteristics of BzRAs.[15,16,22-28] There also are differences among the zolpidem dosage forms; sublingual formulations have the shortest onset of effect. Eszopiclone and zaleplon have low protein binding compared with zolpidem. Elimination half-lives vary among drugs with the shortest attributed to zaleplon (1 hour) and longest to eszopiclone (6 hours). All BzRAs are subject to extensive hepatic metabolism.

Ramelteon. Singular in its class, ramelteon is a treatment option for insomnia.[29] This drug has a short onset of effect, moderate protein binding, and extensive hepatic metabolism. Ramelteon is primarily excreted in the urine as its metabolites, and the drug half-life is relatively short.

Suvorexant is the latest addition to the sedative-hypnotic armamentarium, approved by the FDA in August 2014 for difficulty with sleep onset and/or sleep maintenance.[14] As an orexin-receptor antagonist, suvorexant represents a novel pharmacologic class. Suvorexant exhibits moderately rapid absorption with time to peak concentration ranging from 30 minutes to 6 hours in fasting conditions; absorption is delayed when taken with or soon after a meal. The drug is highly protein bound and extensively metabolized, primarily through CYP3A. The manufacturer recommends dose reduction (5 mg at bedtime) in patients taking moderate CYP3A inhibitors and avoiding suvorexant in patients taking strong CYP3A inhibitors. Suvorexant is primarily excreted through feces and the mean half-life is relatively long.

Considering these characteristics and age-related physiologic changes, the practitioner should be concerned about drugs that undergo extensive hepatic metabolism. Age-related reductions in CYP activity may lead to an increase in drug bioavailability and a decrease in the systemic clearance,[11] which might be associated with an increase in elimination half-life and duration of action. Dosage adjustments are recommended for several BZDs (lower initial and maximum dosages for most agents) and BzRAs.[17-28] No dosage adjustments for ramelteon or suvorexant in geriatric patients have been specified[14,29]; the manufacturers for both products assert that no differences in safety and efficacy have been observed between older and younger adult patients.

Alternative and complementary medications

Several non-prescription products, including over-the-counter drugs (eg, diphenhydramine, doxylamine) and herbal therapies (eg, melatonin, valerian), are used for their sedative-hypnotic properties. There is a lack of evidence supporting using diphenhydramine in patients with chronic insomnia, and tolerance to its hypnotic effect has been reported with repeated use.[31] Concerns about anticholinergic toxicity and CNS depression limit its use in geriatric patients. Among herbal therapies, melatonin may have the strongest evidence for its ability to alleviate sleep disorders in geriatric patients[32]; however, meta-analyses have demonstrated small effects of melatonin on sleep latency and minimal differences in wake time after sleep onset and total sleep time.[13]

Clinical practice guidelines

Non-pharmacotherapeutic interventions, such as behavioral (eg, sleep hygiene measures) and psychological therapy, are recommended for initial management of sleep disorders in geriatric patients.[13,33] In conjunction, the American Medical Directors Association (AMDA) recommends address-

ing underlying causes and exacerbating factors (eg, medical condition or medication).[33] The AMDA recommends avoiding long-term pharmacotherapy and advises caution with BZD-hypnotic drugs, tricyclic antidepressants, and antihistamines. The American Academy of Sleep Medicine (AASM) recommends an initial treatment period of 2 to 4 weeks, followed by re-evaluation of continued need for treatment.[13] The AASM recommends short- or intermediate-acting BzRAs or ramelteon for initial pharmacologic management of primary insomnias and insomnias comorbid with other conditions. The AASM also recommends specific dosages of BzRAs and BZDs for geriatric patients, which coincide with manufacturer-recommended dosages (***Table 2, page 46***).[14-29]

Barbiturates, chloral hydrate, and non-barbiturate, non-BZD drugs such as meprobamate are not recommended because of potential significant adverse effects and tolerance/dependence, and low therapeutic index. The AASM advises caution when using prescription drugs off-label for insomnia (eg, antidepressants, antiepileptics, antipsychotics) and recommends avoiding them, if possible, because of limited evidence supporting their use.[13]

Safety concerns

Two commonly used references contain recommendations for sedative-hypnotic medication use in geriatric patients.[30,34] According to Gallagher et al's[34] Screening Tool of Older Person's Prescriptions (STOPP), long-term (>1 month) use of long-acting BZDs (eg, flurazepam, diazepam) and prolonged use (>1 week) of first-generation antihistamines (eg, diphenhydramine, doxylamine) should be avoided in patients age ≥65 because of the risk of sedation, confusion, and anticholinergic side effects. STOPP recognizes that any use of BZDs, neuroleptics, or first-generation antihistamines may contribute to postural imbalance; therefore these agents are not recommended in older patients at risk for falls.

In the 2012 American Geriatrics Society (AGS) Beers Criteria, the AGS recommends avoiding barbiturates in older adults because of the high rate of physical dependence, tolerance to sleep effects, and overdose risk at low dosages.[30] The AGS also recommends avoiding BZDs, stating that older adults have increased sensitivity to these agents and are at an increased risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents when taking these drugs. Non-BZD BzRAs also should not be prescribed to patients with a history of falls or fractures, unless safer alternatives are not available.

The FDA has issued several advisory reports regarding sedative-hypnotic drugs. In 2007, all manufacturers of sedative-hypnotic drugs were required to modify their product labeling to include stronger language about potential risks.[35] Among these changes, warnings for anaphylaxis and complex sleep-related behaviors were added. Also, the FDA requested that manufacturers of sedative-hypnotic drugs develop and provide patient medication guides, advising consumers on the potential risks and precautions associated with these drugs. More recently, the FDA announced changes to dosing recommendations for zolpidem-containing products because of the risk of impaired mental alertness[36]; manufacturers were required to lower the recommended dosages for each product.

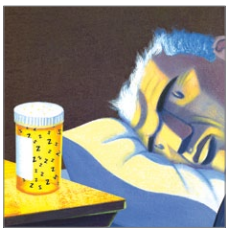
Manufacturers of FDA-approved sedative-hypnotic drugs urge caution when prescribing these medications for geriatric patients, citing the potential for increased sensitivity, manifesting as marked excitement, depression, or confusion (eg, barbiturates), and greater risk for dosage-related adverse effects (eg, oversedation, dizziness, confusion, impaired psychomotor performance, ataxia).[17-29]

Use in clinical practice

Several variables should be considered when evaluating appropriateness of pharmacotherapy, including characteristics of the drug and the patient. Geriatric patients may be prone to comorbidities resulting from age-related physiologic changes. These diseases may be confounding (ie, contributing to sleep disorders); examples include medical illnesses, such

Clinical Point

Non-drug interventions are recommended for initial management of sleep disorders in geriatric patients



Sedative-hypnotics

Clinical Point

Recently, FDA changed dosing recommendations for zolpidem-containing products because of the risk of impaired mental alertness

Practice Points

- Review the patient's medical history for conditions that may be related to sleep disorders.
- Initiate non-pharmacotherapeutic management, such as sleep hygiene measures.
- If a sleep disorder persists, determine the need for an agent with a short onset of effect or long duration, or both.
- Assess renal and hepatic function.
- Evaluate the metabolic profile for drugs subject to extensive hepatic metabolism and identify those with active metabolites; such drugs may be associated with increased exposure/effect.
- Once an agent is selected, start with a low dosage and monitor for improvement within 2 weeks.
- Use the lowest effective dosage and limit the treatment period, if possible.
- Watch for drug-related adverse effects, such as residual drowsiness and confusion, and address the risk of falls.
- Monitor for changes in drug therapy; recognize and avoid potentially inappropriate medications.

as hyperthyroidism and arthritis, and psychiatric illnesses, such as depression and anxiety.[37] Other conditions, such as renal and hepatic dysfunction, may lead to alteration in drug exposure. These conditions should be assessed through routine renal function tests (eg, serum creatinine and glomerular filtration rate) and liver function tests (eg, serum albumin and liver transaminases).

Multiple comorbidities suggest a higher likelihood of polypharmacy, leading to other drug-related issues (eg, drug-drug interactions). Although these issues may guide therapy by restricting medication options, their potential contribution to the underlying sleep complaints should be considered.[37] Several drugs commonly used by geriatric patients may affect wakefulness (eg, analgesics, antidepressants, and antihypertensives [sedating], and thyroid hormones, corticosteroids, and CNS stimulants [alerting]).

CASE CONTINUED

In Mr. R's case, zaleplon was initiated at 10 mg/d. Because of his age and the nature of his sleep disorder, the choice of sedative-hypnotic was suitable; however, the prescribed dosage was inappropriate. The sluggishness Mr. R experienced likely was a manifestation of increased exposure to the drug. According to manufacturer and AASM recommendations, a more appropriate dosage is 5 mg/d.[13,23] Mr. R's medical history and current medications, and his hepatic and renal function, should be assessed. If Mr. R continues to have issues with sleep initiation, zaleplon, 5 mg at bedtime, should be considered.

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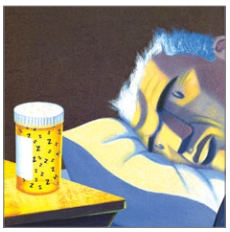

Sedative-hypnotics

Clinical Point

Geriatric patients may be prone to comorbidities resulting from age-related physiologic changes that may be confounding

Related Resources

- Institute for Safe Medication Practices. www.ismp.org.
- MedWatch: The FDA Safety Information and Adverse Event Reporting Program. www.fda.gov/Safety/MedWatch/default.htm.

Drug Brand Names

Amitriptyline • Elavil
Amobarbital • Amytal
Butabarbital • Butisol
Chloral hydrate • Somnote
Diazepam • Valium
Diphenhydramine • Benadryl, others
Doxepin • Silenor
Doxylamine • Unisom, others
Estazolam • ProSom
Eszopiclone • Lunesta
Flurazepam • Dalmane
Gabapentin • Neurontin, Gralise, Horizant
Lorazepam • Ativan
Meprobamate • Equanil
Mirtazapine • Remeron
Olanzapine • Zyprexa
Pentobarbital • Nembutal
Phenobarbital • Luminal
Quazepam • Doral
Quetiapine • Seroquel
Ramelteon • Rozerem
Secobarbital • Seconal
Suvorexant • Belsomra
Temazepam • Restoril
Tiagabine • Gabitril
Trazodone • Desyrel
Triazolam • Halcion
Zaleplon • Sonata
Zolpidem • Ambien, Edluar, Intermezzo, Zolpimist

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