

## Insomnia

## Safe and effective therapy for sleep problems in the older patient

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Insomnia is a problem in all stages of life but is particularly common after age 65. A number of factors—including advanced age, psychosocial influences, medical illness, and the use of medications and alcohol—may disturb sleep architecture. Evaluation of insomnia in the older patient requires a careful history and physical examination, supplemented by a sleep diary. Treatment of underlying conditions and nonpharmacologic improvements in sleep hygiene are first-line therapy, but pharmacologic agents such as benzodiazepines, nonbenzodiazepine hypnotics, or antidepressants may be needed. Nonbenzodiazepines with rapid elimination may offer a lower side-effect profile than other hypnotic agents when used for insomnia in the older population.

Schneider DL. Insomnia: Safe and effective therapy for sleep problems in the older patient. *Geriatrics* 2002; 57(May):24-35.

**S**leep-related complaints and use of sedative-hypnotics are more common in the older population than in younger patients.<sup>1</sup> In a National Institute of Aging evaluation of late-life sleep complaints, more than 80% of 9,000 persons age 65 and older reported having experienced sleep disturbance, and more than one-half reported the frequent occurrence of:

- trouble falling asleep
- difficulty waking or waking too early

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The author received an honorarium and editorial assistance in the preparation of this article through an unrestricted educational grant from Wyeth-Ayerst, manufacturer of the sedative-hypnotic agent zaleplon.

- needing to nap
- not feeling rested.<sup>2</sup>

The desire to get a good night's sleep often leads older patients to self-medicate with over-the-counter products containing antihistamines or alcohol. When these experiments fail or cause adverse effects, patients may turn to their physicians for help. This article discusses the factors that affect sleep, the primary care work-up of the older patient with complaints of insomnia, nonpharmacologic therapy, and the safe and effective use of sedative-hypnotic agents when indicated.

### Definitions

Insomnia can be defined by the patient's perception of inadequate sleep. The disorder may be divided into three types:

- sleep-onset insomnia, which occurs at bedtime
- sleep-maintenance insomnia, characterized by awakening during the night

- and nonrestorative sleep, or awakening without feeling refreshed.<sup>3</sup>

Temporally, insomnia may be classified as transient, short-term, or chronic.<sup>3</sup> Transient insomnia may be related to temporary stress, jet travel, or other schedule changes and usually resolves within several days. Short-term insomnia often accompanies acute illness or stress and continues for several days to weeks. Chronic insomnia, which persists for months to years, is often a manifestation of a primary sleep disorder, chronic medical disorder, or medication effect.

The frequency, duration, and severity of sleeplessness in a patient with chronic insomnia can vary despite a relatively stable underlying cause. Although occasional episodes of disturbed sleep are common and without long-term effects, chronic insomnia may impair quality of life and daytime functioning, cause cognitive difficulties or mood disturbances, and increase the risk of accidents. Daytime sleepiness can adversely affect social life and increases the risk of a motor vehicle or other accident.<sup>4</sup> Independent-living older persons with insomnia are four times more likely to suffer a fall resulting in major injury than those who sleep normally.<sup>5</sup>

### Factors affecting sleep

In the older population, sleep disorders tend to occur secondary to comorbidities such as respiratory problems, physical disabilities, use of nonpre-

scription medications, symptoms of depression, and poorer self-perceived health.<sup>2</sup>

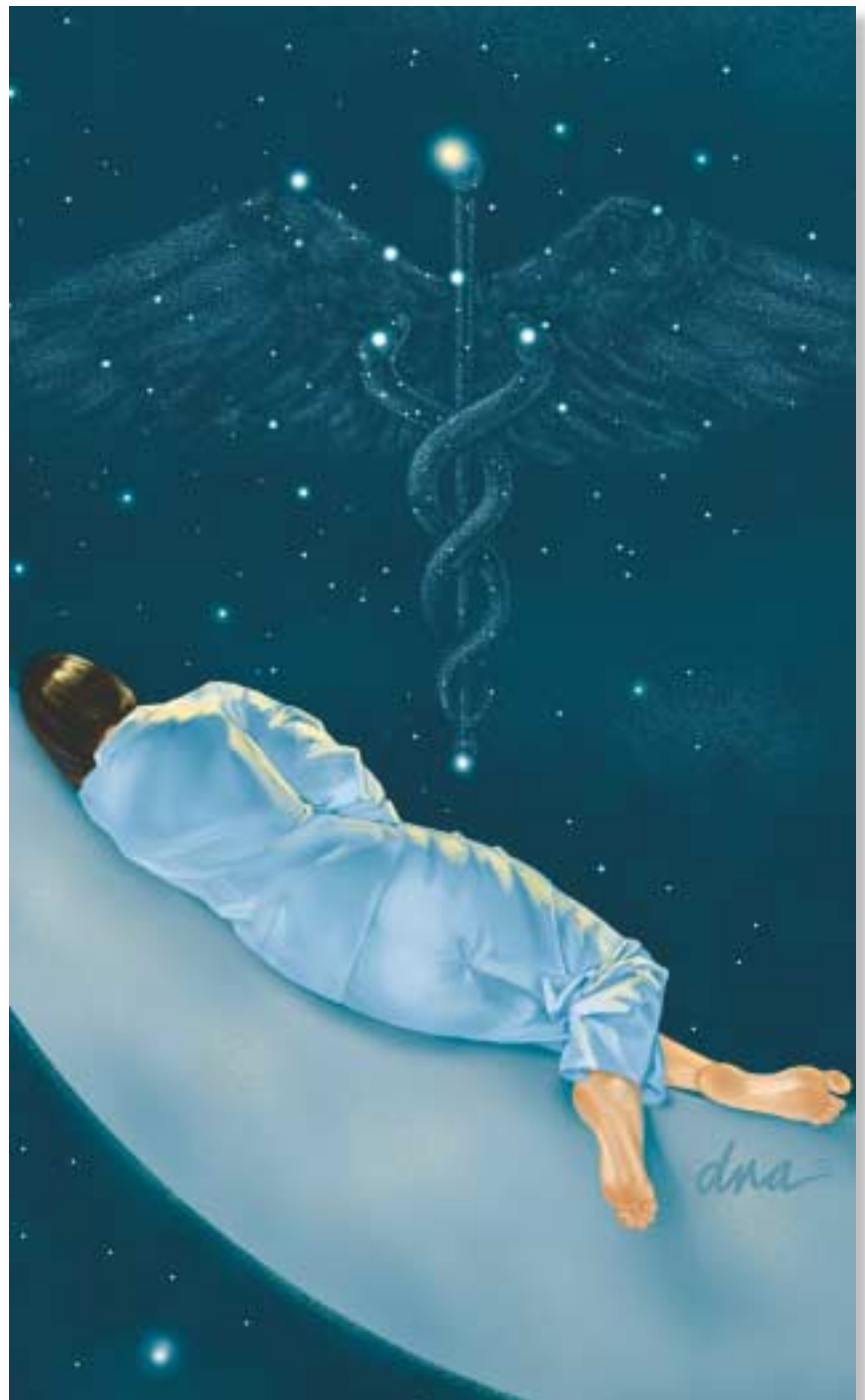
**Advanced age.** Age-related sleep deterioration is most likely to occur after age 75,<sup>6</sup> when both quantity and quality of sleep decrease. Although the time it takes to get to sleep (sleep latency) does not change, the duration of the deep sleep phase decreases and the number of awakenings increases.

The San Marino Epidemiologic Study of sleep disorders<sup>7</sup> asked 5,713 men and women up to age 94, "Do you sleep well without using sleeping pills?" Responses revealed that 13.4% of the sample were poor sleepers. Reports of insomnia increased with advancing age. This pattern may be related to the presence of somatic and psychiatric diseases, unfavorable sleep habits, and lifestyle factors. The two main causes given for insomnia were worries (43.3%) and physical discomfort (22.5%).

**Psychosocial factors.** In the San Marino study,<sup>7</sup> insomnia was related to both work and domestic problems but not to professional status. In the National Institute of Mental Health Epidemiologic Catchment Area study of 7,954 respondents,<sup>8</sup> insomnia increased after age 65 in conjunction with psychiatric disorders in 40% of respondents with insomnia.

Alterations in work status and finances after retirement may cause anxiety and depression with resultant insomnia. Other significant factors are the death of a partner or loved ones, hospitalization, a change in residence to a nursing home or child's home, or extended travel. The San Marino study found an association between unremitting insomnia and new cases of major depression and anxiety disorders that had not been previously identified.<sup>7</sup>

**Medical diseases.** With aging, the increase in sleep disturbances is paralleled by increases in medical problems. Cardiovascular disease can cause alterations in normal breathing patterns, blood oxygenation, and cardiac rate fluctuations that can awaken a patient



Occasional episodes of disturbed sleep are common in later life and without long-term effects, but chronic insomnia may impair quality of life and daytime functioning, cause cognitive difficulties or mood disturbances, and increase the risk of accidents.

Illustration for Geriatrics by Alexandra Baker

with chest pain. Episodes of sleep apnea may precipitate cardiac ischemia. Paroxysmal nocturnal dyspnea in patients with congestive heart failure can produce awakening.<sup>9</sup>

Pain and disorders affecting respiratory, endocrine, neurologic, and

renal function can all disturb sleep. Patients with diabetes appear to have an increased incidence of sleep apnea,<sup>10</sup> possibly because of autonomic neuropathy, obesity, or metabolic alterations involving insulin and glucose regulation. Diabetic neuropathy can

cause sensory disturbances that interfere with sleep.

Disordered sleep may be a feature of hyperthyroidism or hypothyroidism.<sup>9</sup> Stroke, dementia, and other neurologic disorders can produce insomnia.<sup>9</sup> Alzheimer's disease and other progressive dementias can be accompanied by reversal of normal diurnal rhythms, sleep fragmentation, poor sleep quality, and shallow sleep.<sup>9</sup>

**Psychiatric illnesses.** Depression often is accompanied by sleep disturbances.<sup>6</sup> Although early-morning awakenings are the most common manifestation, depression may also produce sleep-onset or sleep-maintenance insomnia. Accumulating evidence indicates that there is a direct relationship between sleep disturbances and depression and that early treatment of the sleep difficulty may prevent depression.<sup>8</sup> Insomnia can also accompany other psychiatric conditions, including anxiety, panic disorder, and adjustment disorders.<sup>11</sup>

**Medications.** Evaluation of a sleep disorder should include a medication review. Sleep onset may be delayed and depth of sleep reduced by thyroid hormone, theophylline, cimetidine, phenytoin, and levodopa. Medications prescribed for cardiac disorders may also disturb sleep. Lipid-soluble beta blockers that cross the blood-brain barrier and quinidine can produce nightmares. Nocturnal diuresis resulting from diuretics administered late in the day can disrupt sleep with the urge to urinate.<sup>6</sup>

## Patient work-up

Older patients presenting with insomnia should receive a full medical and psychiatric examination plus a medication history that includes over-the-counter (OTC) and herbal products.<sup>6</sup> The patient's bed partner should be included in the interview to provide important clues and supportive history.<sup>12</sup> During the initial interview, the insomnia can usually be classified as transient, short-term, or chronic.

**Sleep diary.** Patients with insomnia

should be encouraged to keep a sleep diary over a period of 2 weeks or longer. The diary should include the schedule of bedtime and awakening, quality of sleep, daytime alertness, number and timing of naps, food amounts and scheduling, and use of medications.<sup>12,13</sup> These diaries can help the physician determine the dimensions of the problem and provide a baseline to measure the efficacy of interventions. Furthermore, the diary promotes patients' cooperation in the treatment process.

## Alcohol use in the evening initially promotes sleep, but ultimately disrupts and fragments sleep

**Self-medication.** Clinicians should review remedies already used by patients, as many adults with sleeping difficulties may have tried nonprescription compounds or alcohol. A review by Reynolds et al<sup>12</sup> reported that 11% of Americans ages 65 to 79 use OTC products to help them sleep. Although the OTC availability of these sleep aids implies safety and efficacy, they can cause daytime sedation and anticholinergic effects (eg, constipation, urinary retention), especially in older persons. These agents may induce cognitive impairment or worsen preexisting cognitive loss.<sup>12</sup> The American Society of Consultant Pharmacists recommends avoiding the use of agents with anticholinergic side effects (eg, antihistamines as hypnotics) in older patients.<sup>14</sup>

The effect of alcohol as a soporific may be less helpful than many older patients imagine. A glass of wine taken with dinner may cause initial drowsiness but wakefulness later in the night. Older people who abuse alcohol may experience impaired sleep with or without alcohol.<sup>12</sup> Although low to moderate intake of alcohol ini-

tially promotes sleep, it ultimately disrupts and fragments sleep.<sup>11</sup> This may result from partial tolerance to the effects of ethanol withdrawal during the night. Alternatively, wakefulness may be due to somatic effects of alcohol, such as gastric distress or headache.

## Treatment

Treatment of chronic insomnia should be based on the documented history of the sleep problem, the sleep diary, and the physical examination. The primary therapy is treatment of any medical problems and depression or other psychiatric disorders. After identifying the underlying cause, direct treatment of insomnia is indicated.

**Nonpharmacologic therapy.** Measures such as sleep hygiene and relaxation techniques can be used to improve sleep.<sup>12</sup> Because body clocks govern the sleep/wake cycle, regular bedtimes, rising times, and mealtimes help synchronize internal timing. Excess time spent in bed trying to sleep may worsen overall sleep quality, so in-bed time should be restricted to that necessary for adequate rest.

The number of naps tends to increase with advancing age, and this may impair the regular sleep/wake cycle. In the patient with insomnia, substitution of mental or physical activity for an after-lunch or midafternoon nap may improve nocturnal sleep and should be recommended.

A convenient and regular exercise program will also improve sleep quality. Warm baths and relaxation techniques may ease the transition from evening activity to sleep. A regular evening routine, including restriction of bed activities to sleep and sex, as well as avoidance of caffeine, nicotine, and other stimulants before bedtime, may also be helpful.<sup>12</sup>

## Goals of pharmacologic therapy

The goal of pharmacotherapy for insomnia in the older patient is to restore a normal sleep pattern with minimal adverse effects. Age-related changes in pharmacokinetic parameters and phar-

macodynamic effects that can affect the safety and efficacy of drugs used to treat insomnia must be considered.<sup>6,12</sup>

Total body fat increases during the aging process. Consequently, fat-soluble drugs (eg, benzodiazepines such as diazepam and flurazepam) have an increased volume of distribution and decreased clearance. In addition, drug metabolism can be altered in older persons through impaired oxidation, reduction, and hydroxylation. Drug excretion can also decrease markedly as the result of age-related declines in hepatic blood flow and glomerular filtration.

Age-related pharmacodynamic alterations are reflected in increased sensitivity to CNS depressant effects.<sup>6</sup> Recommended qualities of sedative-hypnotic agents for management of insomnia in the older patient are listed in table 1.

**Hypnotic agents**

**Benzodiazepines.** In the past, when therapeutic options for effective treatment of insomnia were limited, benzodiazepines were the agents of choice. Benzodiazepines can be categorized by their half-lives, which correlate with effects:

- long-acting, such as quazepam and flurazepam

**Table 1 Recommended qualities of a sedative-hypnotic agent for management of insomnia in the older patient**

**Efficacy**

- Should consolidate fragmented sleep (ie, reduce nighttime awakenings)
- Can be administered at different times in the sleep cycle (ie, whether insomnia occurs at bedtime or in the middle of the night)
- No impairment of next-day functioning
- No effect on memory
- Equally effective in transient and chronic types of insomnia

**Safety**

- No pharmacokinetic differences between younger and older age groups
- Minimal adverse events
- Rapid elimination, as indicated by short half-life
- No withdrawal symptoms with abrupt discontinuation
- No tolerance after extended use

Source: Prepared for Geriatrics by Diane L. Schneider, MD, MSc

- intermediate-acting, such as estazolam and temazepam (table 2)

- and short-acting, such as triazolam.<sup>13</sup>

In older patients, adverse effects related to the use of benzodiazepines—especially the long-acting agents—include memory impairment, motor inhibition, falls and fractures, and extended drowsiness.<sup>12</sup> Evidence of the

increased risk of falls in older patients treated with benzodiazepines has been reported.<sup>15</sup> Long-term use of diazepam or flurazepam to treat insomnia in persons over age 75 can lead to confusion, apathy, and psychomotor retardation.<sup>16</sup> The effects of long-term treatment of insomnia with certain benzodiazepines can mimic dementia.<sup>16</sup>

Triazolam is often prescribed for in-

**Table 2 Selected sedative-hypnotics for treatment of insomnia in the older patient\***

Drug	Usual adult therapeutic dose (mg/d)		Time until onset of action (min)	Half-life (hr) <sup>†</sup>	Active metabolites
	Age <65	Age ≥65			
<b>Benzodiazepines</b>					
<b>Estazolam</b> (ProSom)	1 to 2	0.5 to 1	15 to 30	8 to 24 (intermediate-acting)	No
<b>Temazepam</b> (Restoril)	15 to 30	7.5 to 15	45 to 60	3 to 25 (intermediate-acting)	No
<b>Nonbenzodiazepines</b>					
<b>Zaleplon</b> (Sonata)	10	5	30	1	No
<b>Zolpidem</b> (Ambien)	10	5	30	1.5 to 4.5	No

\* Adverse effects related to the use of benzodiazepines in older patients include memory impairment, motor inhibition, falls and fractures, and extended drowsiness

<sup>†</sup> Terminal elimination half-life

Source: Prepared for Geriatrics by Diane L. Schneider, MD, MSc.

somnia because of its short half-life and lack of accumulation. However, possibly because of its high receptor-binding affinity and other properties, triazolam has a unique adverse event profile that is troublesome in older patients.<sup>17</sup> Side effects include confusion, agitation, and impaired psychomotor performance as well as amnesia, especially in patients with cognitive impairment. In addition, triazolam may produce daytime anxiety during treatment and rebound insomnia following discontinuation. Therefore, triazolam is not the ideal agent for treatment of insomnia in the older patient.<sup>17</sup>

**Nonbenzodiazepines.** To address concerns that limit the usefulness of benzodiazepines, newer hypnotics such as zolpidem (Ambien) and zaleplon (Sonata) were developed to treat insomnia (table 2). Although they are not benzodiazepines, these agents have selective affinity for the benzodiazepine receptor subtype 1, and they are eliminated rapidly. Compared with conventional hypnotics, these nonbenzodiazepines have a low risk for producing muscle hypotonia, retrograde amnesia, and behavioral disturbances. They also are not normally associated with tolerance.

Zolpidem, an imidazopyridine, has a half-life of approximately 2.5 hours, shorter than that of most benzodiazepines. Its short half-life makes zolpidem appropriate for use in sleep-onset insomnia, but patients taking the drug in the middle of the night may experience morning sleepiness or decreased mental alertness. An increased risk of falls has been reported in older patients who use zolpidem.<sup>15</sup> In older patients, the half-life may increase by 50% compared with that in younger adults, so the use of one-half the usual dosage (ie, 5 mg) is recommended.<sup>18</sup> The elimination of zolpidem is slower in patients with hepatic insufficiency.<sup>18</sup> Zolpidem is generally well tolerated. Adverse effects include dizziness or lightheadedness, somnolence, headache, GI upset, and pain.

Zaleplon, a pyrazolopyrimidine with an elimination half-life of approxi-

mately 1 hour, has been shown to be effective for the treatment of both transient and chronic insomnia in older patients.<sup>19,20</sup> Recommended initial dose of zaleplon for older patients is 5 mg.<sup>21</sup> Rapid elimination allows the drug to be taken for sleep-onset insomnia or during a mid-sleep awakening, without residual daytime effects.<sup>13</sup> Zaleplon has shown no effects on memory, learning, or psychomotor skills associated with vigilance in adults,<sup>22,23</sup> although data are limited to patients under age 45.

Zaleplon is known to have clinically significant pharmacokinetic interactions with rifampin, which reduces zaleplon levels, and cimetidine, which increases zaleplon blood levels.<sup>21</sup> Neither withdrawal syndrome nor rebound insomnia develop after discontinuation.<sup>20,24</sup> In clinical studies, adverse events reported at doses of 5 and 10 mg were infrequent, mild, and generally equivalent to placebo; the most common adverse event in older patients was headache.<sup>19,20</sup> Zaleplon showed no pharmacokinetic differences between young and older adults.<sup>24</sup>

**Antidepressants.** Antidepressants with sedative activity are frequently used to treat chronic insomnia in older patients, despite the lack of well-controlled, double-blind studies showing their efficacy.<sup>3,11,12</sup> Although antidepressants offer the benefit of addressing comorbid depression, they can cause significant side effects.

Tricyclic agents such as trimipramine, amitriptyline, and doxepin can produce orthostatic hypotension, cardiac arrhythmias, and bothersome anticholinergic side effects. Amitriptyline can impair memory. Other antidepressants such as low-dose trazodone HCl (Desyrel) and nefazodone HCl (Serzone) have a lower incidence of side effects than the tricyclics. An increased risk of orthostatic hypotension with the use of trazodone requires blood pressure monitoring.

When antidepressants are used for insomnia in the absence of comorbid depression, reduced doses are recommended.<sup>3</sup> For example, the recom-

mended dose of trazodone for insomnia is 25 to 100 mg at bedtime, compared with 150 to 400 mg/d for depression. Antidepressants may be the appropriate choice only for the depressed older patient with insomnia.<sup>6</sup> Because the onset of action of antidepressants is usually measured in weeks, concomitant use of a rapidly eliminated hypnotic (eg, zaleplon, 5 mg, or zolpidem, 5 mg) may be beneficial to bridge the therapeutic gap for the patient with depression and insomnia.

### Instruction and follow-up


Many patients find that medication assists them in coping with insomnia as they await the benefits from nonpharmacologic interventions, such as cutting back on daytime napping. Instruct patients to use a hypnotic only when insomnia occurs, as this gives them a sense of control over the sleep problem without forcing reliance on the medication. Use of sedative-hypnotic compounds is not recommended to extend beyond a few weeks.

If the patient is likely to need a hypnotic later than bedtime, consider residual effects and choose an agent with the shortest half-life. Whatever treatment is chosen, encourage the patient to keep a sleep diary and report the results of therapy within several weeks, especially if sleep difficulties do not resolve. Most important, assess treatment in an ongoing manner to provide continuing support and to tailor therapy to individual needs.

### Conclusion

Insomnia is common among all age groups but particularly in persons over age 65. Life alterations and comorbidities accompanying advanced age increase the occurrence of insomnia. Before undertaking treatment, physicians should make a careful examination, paying particular attention to conditions and medications that may be disrupting a patient's sleep.

Treatment should begin with attention to proper sleep hygiene. When

pharmacologic agents are needed, they should be prescribed with attention to pharmacokinetic and pharmacodynamic considerations specific to the older population. Compared with benzodiazepines, the newer nonbenzodiazepine hypnotics offer advantages in safety and efficacy. 

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