# Sleep in the Elderly: Burden, Diagnosis, and Treatment

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Insomnia is commonly seen in elderly populations and is associated with numerous individual and socioeconomic consequences. Elderly patients are more likely to suffer from chronic insomnia characterized by difficulty maintaining sleep than difficulty initiating sleep. Management of insomnia in these patients requires very careful evaluation and exclusion of an underlying medical or psychiatric condition. Nonpharmacologic interventions in elderly patients, especially use of behavioral therapy, have demonstrated some success. Commonly prescribed medications have also been effective, though they have limitations. Newer agents currently under investigation for insomnia hold promise for good efficacy and safety in the elderly population. The following review presents clinical studies, survey results, and guidelines retrieved from peer-reviewed journals in the PubMed database using the search terms *elderly*, *temazepam*, *trazodone*, *zolpidem*, *zaleplon*, *insomnia*, and *prevalence* and the dates 1980 to 2003. In addition, newer research with emerging agents has been included for completeness.

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Insomnia is a condition that is underrecognized, underdiagnosed, and undertreated in the general population.[1] Despite being a common complaint among elderly people (aged 65 years and older), sleep disorders are rarely systematically diagnosed and treated, even by geriatric specialists.[2] Insomnia is a serious problem among older individuals because of its widespread prevalence and because poor sleep can have detrimental consequences for many of the aspects of vitality and resilience required for successful aging.[3] Sleep disturbances among the elderly are associated with significant morbidity and mortality and increase the risk for nursing home placement.[4,5] Insomnia is also correlated with risk for falls.[6] Sleep maintenance, rather than sleep initiation, is the most commonly reported problem among older people with sleep disturbance[2,7,8] and can have serious consequences.[8,9] However, while a range of treatment options exists, there is currently a lack of pharmacologic agents that provide an optimum combination of therapeutic benefits. Ideal pharmacologic outcomes would include improved sleep initiation, sleep maintenance without next-day residual effects, and, ideally, improved next-day functioning.

## EPIDEMIOLOGY OF INSOMNIA IN THE ELDERLY

In 1982, the National Institute on Aging conducted a multicenter, epidemiologic study to assess the prevalence of sleep complaints among more than 9000 noninstitutionalized elderly persons aged 65 years and older. Over half (57%) of these elderly people reported some form of chronic disruption of sleep, while only 12% reported no sleep complaints.[7] Among all participants (N = 9282; mean age = 74 years), the prevalence of chronic sleep complaints included difficulty in initiating or maintaining sleep (43%), nocturnal waking (30%), insomnia (29%), daytime napping (25%), trouble falling asleep (19%), waking too early (19%), and waking not rested (13%).[7] A 3-year follow-up study reported an annual incidence rate of approximately 5%, with roughly 15% of elderly insomniacs resolving their symptoms each year.[10] Chronic insomnia is also more common in this population. A 1991 National Sleep Foundation poll of a representative sample of 1000 Americans aged 18 years or older, who were divided by age into 6 groups (18–24, 25–34, 35–44, 45–54, 55–64, and ≥ 65), found that 9% of the sample reported chronic insomnia, while 20% in the group ≥ 65 years reported chronic insomnia, the highest among all age groups.[11]

## BURDEN OF INSOMNIA IN THE ELDERLY

Insomnia incurs a significant direct and indirect burden on society. Direct economic costs of insomnia were calculated to be $13.9 billion in 1995,[12] and a 1996 review indicated that total direct, indirect, and related costs may run as high as $30 to $35 billion annually.[13]

While the overall economic costs of insomnia specifically in the elderly population have not been assessed to date, several studies[14,15] have provided data on segmented direct and indirect costs and on adverse effects on quality-of-life parameters in the elderly. Insomnia may precipitate injuries, such as falls, and aggravate existing health conditions. In a survey of 1526 community-dwelling older adults aged 64 to 99 years, difficulties with "falling asleep at night," "waking during the night," and "waking up in the morning" were significantly related to the number of reported falls.[6] Subsequent fall-related injuries are an important factor for nursing home placement.[4] Estimates indicate that of the $158 billion of lifetime economic costs of injury in the United States, fall-related injuries will contribute a total of $10 billion.[6]

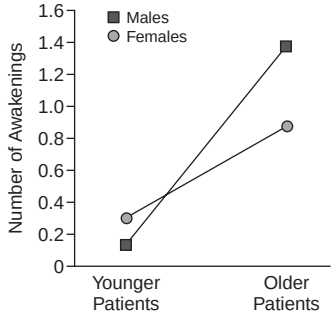
A 1995 assessment of health care service costs found that nursing home care related to insomnia in the elderly amounted to $10.9 billion (91% of all health care services related to insomnia, across all age groups).[12] Sleep disturbances in the elderly, and the subsequent disruption of caregivers' sleep, exact a toll on family support. Insomnia has been cited as a primary factor in caregivers' decisions to institutionalize an elder, with 20.4%[12] and 52%[16] of admissions to long-term care directly attributable to elderly sleep disturbances. A survey of 1855 elderly urban residents found that insomnia was the strongest predictor among males for both mortality and nursing home placement.[5] Insomnia may also contribute to cognitive decline,[17] and insomnia-induced cognitive impairments can confound accurate dementia diagnoses and lead to suboptimal and delayed treatment.[4]

## FOCUS ON SLEEP MAINTENANCE

Insomnia is associated with difficulty in *initiating* sleep (i.e., is a problem of sleep onset), *maintaining* sleep, or *obtaining restorative* sleep[18]; however, the elderly spend more time awake after initially falling asleep than their younger counterparts < 65 years, and sleep maintenance problems are therefore the primary symptoms in this age group.[2,8,19] Foley et al.[7] reported that 49% of elderly patients experienced sleep maintenance symptoms (30% complained of waking during the night; 19% complained of waking too early), compared with only 19% who experienced the sleep-onset symptom—difficulty falling asleep.

These findings have been confirmed in a study that utilized objective measures. Webb[2] compared electroencephalograph measures of 80 healthy older adults (aged 50–60 years) and a control group of 32 younger adults (aged 20–30 years). Sleep in the older group was characterized by more frequent and prolonged awakenings (Figure 1). Among older men, wake after sleep onset, a robust measure of poor sleep maintenance, defined in this study as time (in minutes) awake after sleep onset/time asleep and expressed as a percentage, was increased approximately 8-fold over that of younger men (8.1 vs. 1.2, respectively; $p < .01$). Number of awakenings lasting 5 minutes or longer were more frequent and of longer duration in the older groups (1.4 in men and 0.9 in women, aged 50–60 years; 0.1 in men and 0.3 in women, aged 20–30 years; $p < .01$ for comparison among older and younger groups in both genders).[2]

**Figure 1. Number of Awakenings in Men and Women as a Function of Age[a]**




[a]Reprinted with permission from Webb.[2]

Sleep maintenance dysfunction contributes to the daytime fatigue and napping common among elderly people and can have negative repercussions on next-day functioning.[8,9] Therefore, there is a special need for agents that target both sleep initiation and sleep maintenance without residual next-day effects. An improvement in next-day functioning could have a substantial positive impact on patients and their caregivers.

## ASSESSMENT AND DIAGNOSIS OF INSOMNIA IN ELDERLY PATIENTS

There are currently no guidelines that indicate how much sleep is normal for elderly people; however, changes that occur and progress gradually as we age are well documented. Healthy elderly people are prone to spending more time in bed, with no additional time spent asleep.[20] They are also more likely to spend more time in stage 1 (light) sleep and less time in deep or slow-wave sleep.[20] Abnormal breathing events[21] and leg movements[22] are also more common in the elderly (≥ 65 years) than in younger adults.

Appropriate recognition of insomnia in elderly patients is vital, as evidenced by the high use of nonprescription remedies in this population. A recent survey administered to ambulatory elderly subjects found that 48% had used one or more therapies for sleep within the past year; 50% of those therapies were nonprescription products. Of the 27% of subjects who used such products, 19% used acetaminophen, 15% used diphenhydramine, and 13% used alcohol.[23]

**Table 1. Questions to Include When Taking a Sleep History in Elderly Patients[a]**

| |
|---|
| How much do you sleep during the day? |
| At what times of day do you tend to sleep? |
| What is the effect of your sleeping patterns on your daytime ability to function? |
| What time do you go to bed at night? |
| How long does it take you to fall asleep? |
| Do you snore? |
| Do you have leg discomfort at bedtime? |
| How often do you wake during the night, and when you do, how long does it take you to fall back asleep? |
| What time in the morning do you wake up? |
| What time do you get up for the day? |

[a]Adapted with permission from Martin et al.[9]

A few probing questions should be sufficient to detect insomnia (Table 1), followed by queries into the chronicity and causality of the insomnia complaint. Transient insomnia is defined by problems lasting just a few nights, while chronic insomnia is defined as persistent problems lasting at least 1 month.[18]

Because sleep complaints are fairly common in this population, it is important for the physician to consider 2 major factors: the real nature of the complaint and the presence of underlying medical or psychiatric causes. Some patients attain adequate amounts of total sleep, but they do so by napping during the day or at other unconventional times. Such patients may have advanced or delayed sleep phase syndrome,[8] rather than insomnia, and in order to establish a complete picture of a patient's sleep complaint, a thorough sleep history should be taken[24] (examples of important questions are listed in Table 1). If there is no or minimal impairment in daytime functioning (such as impaired memory, sudden unplanned napping, mood changes, sleepiness, or falling asleep while driving), patients may simply need to be reassured that their symptoms are part of normal aging. It is often useful to ask that the patient maintain a 2-week sleep diary so that an accurate account of sleeping habits can be recorded.[8] Bed partners are useful sources of information and can often shed light on diagnoses that would otherwise not be elicited and give more detailed and reliable accounts of sleep and waking habits. A careful review of medical/sleep history and medication records should also be conducted to ensure proper diagnosis and treatment and to exclude non-insomnia sleep disorders such as sleep apnea, restless legs syndrome, or periodic leg movements. Sleep histories should always include specific questions about illnesses if they are suspected; for example, asking about snoring may elicit a sleep apnea diagnosis and questions regarding leg discomfort should help elicit the diagnosis of restless legs syndrome.

Referral and consultation should be considered in cases of suspected primary sleep conditions and sleep apnea, which could be better managed by a sleep disorder expert. Surprisingly, many persons with insomnia deny

**Table 2. Example of the Epworth Sleepiness Scale[a]**

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

| Situation | Chance of Dozing (0–3)[b,c] |
|---|---|
| Sitting and reading | _____ |
| Watching television | _____ |
| Sitting inactive in a public place, for example, a theatre or meeting | _____ |
| As a passenger in a car for an hour without a break | _____ |
| Lying down to rest in the afternoon | _____ |
| Sitting and talking to someone | _____ |
| Sitting quietly after lunch (when you've had no alcohol) | _____ |
| In a car, while stopped in traffic | _____ |

[a]Adapted with permission from Johns.[25]
[b]0 = would never doze, 1 = slight chance of dozing, 2 = moderate chance of dozing, 3 = high chance of dozing.
[c]A total score > 10 is considered abnormal.

daytime sleepiness. A complaint of daytime sleepiness, coupled with other symptoms, should trigger consideration of a primary sleep disorder such as sleep apnea. The Epworth Sleepiness Scale[25] is a well-validated, self-administered test for excessive sleepiness that the patient can complete in the office in less than 2 minutes. A score above 10 indicates excessive sleepiness and warrants further investigation, such as referral to a sleep specialist (Table 2).

As sleep disturbances among the elderly are often secondary to existing chronic disease, overall poor physical health, and psychosocial morbidity, it is important for practitioners to assess if insomnia is a primary or secondary condition.[9] The principal medical or psychiatric condition, as well as medications used to treat it (e.g., cardiovascular medication), may cause sleep disruption and contribute to daytime sleepiness.[4,10,26,27] Common causes of insomnia in the elderly are listed in Table 3.

Longitudinal data have consistently established depression as one of the strongest correlates of insomnia,[10,28,29] and while the causal relationship between insomnia and depression remains unclear, it is important to exclude the possibility of a depressive episode in an elderly patient who presents with symptoms of insomnia. The Beck Depression Inventory[30] is one of many useful, well-validated, self-administered scales to detect depression symptoms. A score above 10 suggests clinical depression might be present and warrants a more thorough investigation of whether it is, in fact, depression (Table 4).

Due to the high prevalence of comorbidities and use of concomitant prescription medication in the elderly population, it is imperative that the primary treatment goal be to identify and address any underlying condition,

Table 3. Common Causes of Insomnia[a]

| |
|---|
| Medical causes |
| Nonprescription drugs |
| Caffeine |
| "Diet pills" (eg, those including pseudoephedrine, ephedrine, phenylpropanolamine) |
| Nicotine |
| Prescription drugs |
| β-Blockers |
| Theophylline |
| Albuterol |
| Quinidine |
| Stimulants: pemoline, dextroamphetamine, methylphenidate |
| Decongestants: pseudoephedrine, phenylephrine, phenylpropanolamine |
| Thyroid preparations |
| Corticosteroids |
| Selective serotonin reuptake inhibitors |
| Monoamine oxidase inhibitors |
| Methyldopa |
| Phenytoin |
| Chemotherapy |
| Benzodiazepines |
| Medical conditions |
| Primary sleep disorders (sleep apnea, periodic limb movement disorder, nocturnal myoclonus, restless legs syndrome, circadian rhythm sleep disorder, rapid eye movement behavior disorder) |
| Pain from any source or cause |
| Drug or alcohol intoxication or withdrawal |
| Thyrotoxicosis |
| Dyspnea from any cause |
| Neurologic disease (Parkinson's, Alzheimer's) |
| Acute and chronic medical illnesses (arthritis, cardiovascular disease, gastrointestinal disease, asthma, chronic obstructive pulmonary disease) |
| Psychological causes |
| Depression |
| Anxiety |
| Life stressors |
| Bedtime worrying |
| Conditioning (associating the bed with wakefulness) |
| Mania or hypomania |
| Environmental causes |
| Bedroom too hot or too cold |
| Noise |
| Eating, exercise, or caffeine or alcohol use before bedtime |
| Jet lag |
| Shift work |
| Daytime napping |

[a]Reprinted with permission from Doghramji.[24]

as well as the potential for drug-drug interaction with the patient's existing medication regimen. Although limited research demonstrates that treating the insomnia symptom improves the primary condition, renewed interest exists in this area, with some indication that addressing secondary insomnia may have adjunctive benefits in treating depression[31] and may improve quality of life in dementia disorders and Parkinson's disease.[32]

## MANAGEMENT OF INSOMNIA

### Nonpharmacologic Therapies

Most treatment guidelines recommend that nonpharmacologic approaches to insomnia control, including sleep hygiene and behavioral methods, be used as supportive therapies.[3,4,33,34] Sleep hygiene rules are listed in Table 5.[3,4,35,36,37] Behavioral therapy techniques, such as cognitive-behavioral therapy, may be used either alone or in combination with pharmacotherapy and may aid in long-term management of insomnia following medication discontinuation.[33] Stimulus control, progressive muscle relaxation, and paradoxical intention meet American Academy of Sleep Medicine criteria for empirically supported psychological treatments for insomnia; sleep restriction, biofeedback, and multifaceted cognitive-behavioral therapy were the treatments considered most likely to be efficacious.[38] There are very few data regarding behavioral therapy in primary care.[33,39] The effectiveness and extent of use of this treatment in the primary care setting has yet to be determined.

### Pharmacologic Therapies

Pharmacologic therapy should take into consideration the pharmacokinetic and pharmacodynamic changes in drug metabolism that typically accompany the aging process. Caution should be exercised in selecting appropriate medication and medication dosages for treatment of insomnia in elderly patients.[35] Medications that impair cognitive and psychomotor function can have serious consequences for elderly patients who are institutionalized and for those living in the community.

Use of benzodiazepines has been correlated with an increased risk of falling,[40–43] and a higher serum concentration of benzodiazepines has been noted in those who fall compared with those who do not fall.[44] Falls appear to be associated with the use of both short- and long-term benzodiazepines.[45] Cumming and Klineberg[46] found that use of the relatively short-acting temazepam, the most commonly used of all the benzodiazepines for insomnia treatment,[47] increased risk of falls compared with nonusers.[46] Diazepam was also found to be a risk factor for multiple falls in one study (odds ratio = 3.7, 95% CI = 1.5 to 9.3).[41]

More recent studies have indicated that excessive benzodiazepine dosage may be a more salient factor than drug half-life.[48] According to Beers' 1997 criteria for determining potentially inappropriate medication use in the elderly, short- to intermediate-acting benzodiazepines (e.g., temazepam) and zolpidem are to be considered inappropriate if maximum recommended doses are exceeded.[49] Although very little research has been conducted to evaluate the use of agents like temazepam and zolpidem in the naturalistic setting, a recent review[50] of the pharmacy profiles of 2193 homebound people older than age 60 years was conducted. Of these people, 285 patients were prescribed excessive doses of temazepam and zolpidem. It was determined that 28% of short- to intermediate-acting benzodiazepine prescriptions and 60% of zolpidem prescriptions exceeded recommended dosing limitations,[50] which suggests that excessive dosing does indeed occur.

**Table 4. The 21-Item Beck Depression Inventory**[a,b,c]

| | | |
|---|---|---|
| 1 | 0 | I do not feel sad. |
| | 1 | I feel sad. |
| | 2 | I am sad all the time and I can't snap out of it. |
| | 3 | I am so sad or unhappy that I can't stand it. |
| 2 | 0 | I am not particularly discouraged about the future. |
| | 1 | I feel discouraged about the future. |
| | 2 | I feel I have nothing to look forward to. |
| | 3 | I feel that the future is hopeless and that things cannot improve. |
| 3 | 0 | I do not feel like a failure. |
| | 1 | I feel I have failed more than the average person. |
| | 2 | As I look back on my life, all I can see is a lot of failure. |
| | 3 | I feel I am a complete failure as a person. |
| 4 | 0 | I get as much satisfaction out of things as I used to. |
| | 1 | I don't enjoy things the way I used to. |
| | 2 | I don't get any real satisfaction out of anything anymore. |
| | 3 | I am dissatisfied or bored with everything. |
| 5 | 0 | I don't feel particularly guilty. |
| | 1 | I feel guilty a good part of the time. |
| | 2 | I feel quite guilty most of the time. |
| | 3 | I feel guilty all of the time. |
| 6 | 0 | I don't feel I am being punished. |
| | 1 | I feel I may be punished. |
| | 2 | I expect to be punished. |
| | 3 | I feel I am being punished. |
| 7 | 0 | I don't feel disappointed in myself. |
| | 1 | I am disappointed in myself. |
| | 2 | I am disgusted with myself. |
| | 3 | I hate myself. |
| 8 | 0 | I don't feel I am any worse than anybody else. |
| | 1 | I am critical of myself for my weaknesses or mistakes. |
| | 2 | I blame myself all the time for my faults. |
| | 3 | I blame myself for everything bad that happens. |
| 9 | 0 | I don't have any thoughts of killing myself. |
| | 1 | I have thoughts of killing myself, but I would not carry them out. |
| | 2 | I would like to kill myself. |
| | 3 | I would kill myself if I had the chance. |
| 10 | 0 | I don't cry any more than usual. |
| | 1 | I cry more now than I used to. |
| | 2 | I cry all the time now. |
| | 3 | I used to be able to cry, but now I can't cry even though I want to. |
| 11 | 0 | I am no more irritated by things than I ever am. |
| | 1 | I am slightly more irritated now than usual. |
| | 2 | I am quite annoyed or irritated a good deal of the time. |
| | 3 | I feel irritated all the time now. |
| 12 | 0 | I have not lost interest in other people. |
| | 1 | I am less interested in other people than I used to be. |
| | 2 | I have lost most of my interest in other people. |
| | 3 | I have lost all of my interest in other people. |
| 13 | 0 | I make decisions about as well as I ever could. |
| | 1 | I put off making decisions more than I used to. |
| | 2 | I have greater difficulty in making decisions than before. |
| | 3 | I can't make decisions at all anymore. |
| 14 | 0 | I don't feel that I look any worse than I used to. |
| | 1 | I am worried that I am looking old or unattractive. |
| | 2 | I feel that there are permanent changes in my appearance that make me look unattractive. |
| | 3 | I believe that I look ugly. |
| 15 | 0 | I can work about as well as before. |
| | 1 | It takes an extra effort to get started at doing something. |
| | 2 | I have to push myself very hard to do anything. |
| | 3 | I can't do any work at all. |
| 16 | 0 | I can sleep as well as usual. |
| | 1 | I don't sleep as well as I used to. |
| | 2 | I wake up 1–2 hours earlier than usual and find it hard to get back to sleep. |
| | 3 | I wake up several hours earlier than I used to and cannot get back to sleep. |
| 17 | 0 | I don't get more tired than usual. |
| | 1 | I get tired more easily than I used to. |
| | 2 | I get tired from doing almost anything. |
| | 3 | I am too tired to do anything. |
| 18 | 0 | My appetite is no worse than usual. |
| | 1 | My appetite is not as good as it used to be. |
| | 2 | My appetite is much worse now. |
| | 3 | I have no appetite at all anymore. |
| 19 | 0 | I haven't lost much weight, if any, lately. |
| | 1 | I have lost more than 5 pounds. |
| | 2 | I have lost more than 10 pounds. |
| | 3 | I have lost more than 15 pounds. (Score 0 if you have been purposely trying to lose weight.) |
| 20 | 0 | I am no more worried about my health than usual. |
| | 1 | I am worried about physical problems such as aches and pains, or upset stomach, or constipation. |
| | 2 | I am very worried about physical problems, and it's hard to think of much else. |
| | 3 | I am so worried about my physical problems that I cannot think about anything else. |
| 21 | 0 | I have not noticed any recent change in my interest in sex. |
| | 1 | I am less interested in sex than I used to be. |
| | 2 | I am much less interested in sex now. |
| | 3 | I have lost interest in sex completely. |

[a]Adapted with permission from Beck et al.[30]
[b]0 = minimal; 3 = severe.
[c]1–10: these ups and downs are considered normal; 11–16: mild mood disturbance; 17–20: borderline clinical depression; 21–30: moderate depression; 31–40: severe depression; over 40: extreme depression.

Despite the increased risk for falls, benzodiazepines and generic antidepressants (such as trazodone) are among the most popular classes of medications prescribed for elderly patients.[47,51] Benzodiazepines were second only to cardiac medications in frequency of prescription, and there was a high prevalence of antidepressant drugs.[50] An analysis of inappropriate (risk > benefit) psychotropic prescribing, using data from the 1996 National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey, determined that antidepressant agents, antianxiety drugs, and sedative-hypnotics were the drug classes most frequently prescribed to ambulatory elderly patients.[52]

Consensus guidelines regarding the treatment of insomnia established in 1984[53] and now considered obsolete by the National Institutes of Health (NIH) appear to have influenced the U.S. Food and Drug Administration's (FDA) decision to restrict prescription of hypnotic medications to a maximum of 1 month.[54] This restriction may have contributed to increased utilization of antidepressants for treating insomnia among physicians, as there is evidence that chronic insomnia frequently persists far beyond 1 month, especially in elderly patients.[55] These guidelines were formulated, in part, on the basis of the dearth of research exploring longer-term safety and efficacy of these agents. Recently, however, longer-term

Table 5. Sleep Hygiene Rules[a]

| |
|---|
| Reduce time spent in bed when not sleeping—particularly if feeling frustrated or worried about difficulty falling asleep. |
| Leave the bed if there is difficulty falling asleep and engage in a relaxing, distractive activity—such as reading or watching TV. |
| Establish and maintain a regular sleep/wake schedule. Avoid daytime naps. |
| Moderate exercise daily, but not right before bed. |
| Establish a calm, quiet bedroom setting. Remove the bedroom clock from view at night. |
| Ensure comfortable bedroom temperature. |
| Have a light snack before bed, but avoid excessive fluid intake. |
| Limit consumption of nicotine, caffeine, and alcohol, particularly before bed. |
| Use sleep aids only occasionally. |

[a]Adapted with permission from Zarcone[36] and Stepanski.[37]

double-blind[56] and open-label[57,58] studies have demonstrated the safety of nonbenzodiazepine agents in adults and elderly patients with chronic insomnia. In the future, such findings may contribute to increased confidence for longer-term usage of these medications. So, in the absence of widely accepted algorithms for the use of hypnotics, common sense dictates that hypnotics are justified for short-term, symptomatic relief of transient insomnia, and for short-term relief of chronic insomnia in patients who are frantic and in crisis about their condition. Anxious patients may not be willing to wait for the delayed onset of behavioral therapy for primary insomnia or the delayed onset of treatments for secondary insomnia (i.e., antidepressant treatment of major depression). Hypnotics may be avoided, at least initially, in patients with chronic insomnia who are not anxious and are willing to wait a few weeks to see if alternative treatments work. Hypnotics could be judiciously added later if the initial approach is not fruitful.

In terms of overall trends in insomnia treatment, a 10-year analysis of pharmaceutical data from the National Disease and Therapeutic Index (NDTI) indicated a dramatic decrease in overall pharmacologic treatment of insomnia from 1987 to 1996.[51] The NDTI provides descriptive information on disease and treatment patterns in U.S. private medical practices and includes 2790 office-based physicians drawn from 24 medical specialties. Hypnotic drug mentions decreased 53.7%, while antidepressant mentions for insomnia treatment increased 146%. There was a substantial shift away from the use of benzodiazepines and toward the prescribing of antidepressants and nonbenzodiazepine hypnotics. In 1996, NDTI data indicated that trazodone and zolpidem were the 2 drugs prescribed most frequently for treatment of insomnia.[51] Temazepam is the most commonly prescribed benzodiazepine for insomnia.[47] Therefore, based on current utilization patterns, the following section will review pertinent data on temazepam, trazodone, zolpidem, and the newest nonbenzodiazepine—zaleplon—for the treatment of insomnia in elderly patients.

**Temazepam**

Temazepam is currently the most commonly prescribed benzodiazepine hypnotic for insomnia.[47] As a short-acting benzodiazepine, with an elimination half-life of approximately 8 hours, it carries less danger of dependence than ultra–short-acting benzodiazepines.[59,60] Temazepam use has, however, been associated with the development of tolerance over time,[61] and long-term use exceeding 4 to 5 weeks is not recommended.[59] For the elderly, the standard dose of 30 mg/day is reduced to 15 mg; as noted previously, prescribing patterns commonly exceed dosage recommendations and too-high dosage levels may increase the risk for falls.[48,50]

In adult studies, temazepam has not objectively demonstrated efficacy in maintaining sleep.[62–64] Data are limited for benzodiazepine efficacy in the elderly population.[59] One large-scale study[65] of 335 elderly insomniacs found that temazepam significantly decreased subjective sleep latency at weeks 1, 3, and 4 versus placebo and only significantly increased subjective sleep duration during week 1. Temazepam use produced a significantly higher incidence of daytime drowsiness (temazepam, 11.9% vs. placebo, 3.6%) and fatigue (temazepam, 6% vs. placebo, 1.2%) than placebo.[65] Overall, despite its wide prescription usage, temazepam has not been as extensively studied as other benzodiazepines, and conclusions on the basis of the majority of existing studies are hampered by small sample sizes (18–78 subjects).[33,66,67] Although it may be unclear how much of the general benzodiazepine data can be extrapolated specifically to temazepam, benzodiazepines as a pharmaceutical class confer a serious risk of adverse effects, including next-day sedation,[68] impaired delayed and immediate recall,[69–71] cognitive impairment,[72–75] and risk for abuse and dependence.[62,76] For the elderly, benzodiazepines have been reported to be a major, independent risk factor for falls leading to femur fractures.[48] In one population case-controlled study of 416 elderly subjects, temazepam was associated with a nearly 4-fold increase in risk of hip fracture.[46] Due to the high risks and consequences faced by this vulnerable population, many researchers warn that caution should be exercised in prescribing benzodiazepines for elderly patients.[43,46,48]

**Trazodone**

Trazodone is a triazolopyridine derivative, chemically and pharmacologically distinct from other antidepressants.[77] Trazodone's precise mechanisms of action are unclear. Due to its sedating qualities, trazodone has increasingly been prescribed off-label at subtherapeutic antidepressant doses of 100 mg or less for the treatment of insomnia.[4,52] Trazodone prescription for antidepressant purposes has decreased, while its use as an agent for insomnia has substantially increased.[51] The recommended maximum tolerated doses of trazodone for elderly pa-

tients for the treatment of depression are 300 to 400 mg/day.[77,78] The pharmacokinetics of trazodone have been shown to be dependent on age, primarily due to decreased oxidative metabolism in older patients.[78,79] The half-life of trazodone is significantly longer in patients older than 69 years compared with younger adults (mean age, 24 years) (11.6 vs. 6.4 hours, respectively),[78] and clearance rates are also significantly decreased.[78] This difference is most likely influenced by the increased presence of chronic illness and debility in elderly patients.

Despite trazodone's wide clinical use, there is a paucity of clinical trials assessing its effectiveness in the treatment of insomnia and, specifically, in the geriatric population. Most studies have examined trazodone's antidepressant efficacy in this population. In one study[80] that evaluated the efficacy of trazodone treatment of primary insomnia in adult patients aged 50 to 70 years (mean age, 61 years), 9 patients received trazodone, 150 mg/night, for 3 weeks. There was no control group. Compared with baseline, trazodone improved subjective sleep quality during weeks 1 and 2 (visual analog scale; $p < .001$), but not during week 3. There was no improvement with trazodone use on objective polysomnographic measures of sleep-onset latency or total sleep time, in spite of reduced wake after sleep onset ($p < .05$). Rebound insomnia was significant after trazodone discontinuation on the second withdrawal night ($p < .05$).[80] Other studies have consistently shown that trazodone has negative subjective residual effects, including next-day sedation and worsening of feelings on or after awakening.[81] Given the pharmacokinetic implications of trazodone use in the elderly, it is conceivable that elderly patients are more likely to suffer from these effects than are younger patients.[82,83]

Trazodone is associated with a number of side effects and drug-drug interactions, which may have important implications for elderly patients. Commonly reported adverse effects of trazodone based on pooled data in adult populations include gastrointestinal disorders, such as constipation (13.6%), nausea and vomiting (15.7%), headache (10.4%), blurred vision (8.3%), dry mouth (17.7%), and hypotension (10.1%).[84] Dizziness and sedation occur in as many as 21.9% of patients.[84] Other central nervous system adverse events are also common, such as anxiety and fatigue. Priapism, which is reported to occur at rates between 1 in 10,000 and 1 in 1000, has been documented even at doses of 50 to 100 mg/day.[77,85]

Several sleep experts, on the basis of this problematic evidence, have expressed reservations about trazodone's widespread usage. In a clinical review, Ancoli-Israel suggests: "The safety and efficacy of antihistamines and trazodone for use as hypnotics in the elderly have not been adequately evaluated and are not recommended for the treatment of insomnia in the elderly."[4(p.S27)] Walsh and Schweitzer comment, "The observation that trazodone is used more often than any other prescription medication [for insomnia] is startling given the dearth of hypnotic efficacy data."[51(p.374)] In addition, a 1990 NIH Consensus Panel statement concluded that the safety and efficacy of trazodone for use as a hypnotic in the elderly have not been evaluated, and it is not recommended for this population.[86] There are no more recent guidelines available.

### Nonbenzodiazepine Hypnotics

Because of their shorter half-lives, the nonbenzodiazepine hypnotics zolpidem and zaleplon are effective agents for improving sleep onset, but not sleep maintenance. Shorter half-life may contribute to the reduced evidence of subjective and objective next-day residual effects associated with zolpidem in adult subjects[87–89] as compared with benzodiazepines. There is also some experiential evidence that the nonbenzodiazepine hypnotics may be safer than the benzodiazepines in certain patient populations, for example, those at risk for respiratory depression[90]; more research is needed to confirm this. In addition, given that elderly patients frequently take numerous medications, it is important to consider the risk of drug-drug interactions when treating insomnia. There appears to be a lower risk of drug-drug interactions associated with zaleplon and zolpidem use,[91] possibly related to the differences in xenobiotic metabolism.

***Zolpidem.*** Zolpidem is a nonbenzodiazepine hypnotic agent approved by the FDA in 1992 for the short-term treatment of insomnia. It is thought to exhibit a more selective binding action than benzodiazepines and may thus avoid some of the side effects associated with benzodiazepine agents.[92,93] Zolpidem, in its standard-release form, has a short half-life (2.4 hours in adults; 2.9 hours in the elderly) with no active metabolite, and it does not accumulate during repeated dosing.[93] Due to age-associated decreased clearance rates and volumes of distribution, the recommended dosing for elderly patients is reduced from 10 mg/day to 5 mg/day, with an increase to 10 mg/day in more severe cases of insomnia.[92,93] In practice, however, most elderly patients are prescribed a dose above the 5-mg daily limit.[50] Golden et al.[50] found that 75 (60%) of the 125 elderly patients whose medication profiles they reviewed were prescribed zolpidem at doses above 5 mg/night.

As shown in Table 6, many of the zolpidem studies in the elderly population have been conducted with doses that are 2- to 4-fold higher than the recommended doses, which may make these studies less informative from a clinical perspective and may promote higher than recommended dosing in elderly patients.

In addition, use of higher doses of zolpidem increases the potential for adverse events, as demonstrated here. While efficacy at the 5-mg dosage has been demonstrated for sleep-onset measures, there is less convincing evidence (either objective or subjective) of improvement in sleep-maintenance measures or absence of next-day

**Table 6. Clinical Trials of Zolpidem in the Elderly**

| Reference | Study Population | Drug Arms and Dosages | Study Design and Active Treatment Duration | Efficacy/Improvements |
|---|---|---|---|---|
| Fairweather et al[96] (N = 24) | Elderly, healthy (noninsomniac) volunteers | ZOL, 5 mg/d<br>ZOL, 10 mg/d<br>PBO | Double-blind, PBO-controlled, crossover study<br>SBJ<br>7 days | Both doses (equally vs PBO):<br>Sleep onset latency<br>Sleep quality<br>More restful sleep<br>Less waking (ZOL, 10 mg/d only)<br>No impairment (improvement not assessed) in next-day waking from sleep or SBJ/OBJ psychomotor impairment; no residual sedation or ↑ daytime drowsiness |
| Roger et al[97] (N = 218) | Elderly inpatients with chronic insomnia | ZOL, 5 mg/d<br>ZOL, 10 mg/d<br>TRI, 0.25 mg/d<br>Note: 5 dropouts in 5-mg group due to lack of efficacy | Randomized, double-blind, multicenter study<br>SBJ<br>21 days | TST (ZOL, 5 mg/d +1.5 h; ZOL, 10 mg/d +2 h, TRI +2 h)<br>Sleep quality (both doses ZOL, TRI)<br>Nocturnal awakenings (both doses ZOL)<br>Morning awakening (delayed by 1 h; both doses ZOL)<br>Well rested in morning (both doses ZOL); daytime residual effects (sedation, falls) reported as uncommon<br>Measures remained improved 7 days after drug cessation |
| Scharf et al[94] (N = 30) | Elderly, healthy (noninsomniac) volunteers | Group A<br>ZOL, 5 mg/d<br>ZOL, 15 mg/d<br>PBO<br>Group B<br>ZOL, 10 mg/d<br>ZOL, 20 mg/d<br>PBO | Randomized, PBO-controlled, crossover study<br>PSG<br>SBJ<br>2 days | TST (SBJ)<br>Sleep quality (SBJ)<br>Sleep latency (PSG and SBJ) (all doses ZOL)<br>Sleep efficiency (PSG) (↑ with higher dose—both groups)<br>No effect on nocturnal waking<br>% REM sleep (PSG) (↓ with ZOL, 10 and 20 mg/d, but not with ZOL, 5 and 15 mg/d)<br>No ↑ in daytime sleepiness/psychomotor impairment |
| Shaw et al[95] (N = 119) | Elderly psychiatric inpatients with chronic insomnia | ZOL, 10 mg/d<br>ZOL, 20 mg/d<br>PBO | Double-blind, parallel-group, PBO-controlled study<br>SBJ<br>21 days | TST (ZOL, 10 and 20 mg/d)<br>Sleep latency (ZOL, 10 and 20 mg/d), NS<br>Nocturnal awakenings (ZOL, 10 mg/d)<br>Total time awake (ZOL, 10 mg/d)<br>Sleep quality (ZOL, 10 mg/d)<br>Daytime sedation reported in 3 patients (ZOL, 20 mg/d) and 1 patient (ZOL, 10 mg/d) |
| Schlich et al[121] (N = 107) | Middle-aged and elderly outpatients with chronic insomnia | ZOL, 20 mg/d (flexible; by day 20, 18 patients took 10 mg/d and 3 patients took > 20 mg/d) | Single-blind, flexible-dose, multicenter study<br>SBJ<br>172 days | TST<br>Sleep latency<br>Nocturnal awakenings<br>Sleep quality<br>ZOL, 10 mg/d, most effective dose<br>Significant improvement in SBJ "feeling well in the morning"<br>Reduced diurnal napping (duration and incidence) |
| Kummer et al[58] (N = 14) | Elderly psychiatric patients | ZOL, 20 mg/d | Open study<br>PSG<br>179 days | TST (↓ with time)<br>Sleep efficiency (↓ with time)<br>% REM sleep<br>Slow-wave sleep (after 90 days) (reversed over time)<br>Time awake (↑ with time)<br>No impairment of psychomotor function (CFF and reaction time)<br>Next-day improvement not assessed |

Abbreviations: CFF = critical flicker fusion, NS = nonsignificant, OBJ = objective measures, PBO = placebo, PSG = polysomnographic, REM = rapid eye movement, SBJ = subjective measures, TRI = triazolam, TST = total sleep time, ZOL = zolpidem. Symbols: ↑ = increase, ↓ = decrease.

impairment. Four studies, which included a total of 391 patients, were identified in a MEDLINE search, using the terms *randomized controlled trial*, *zolpidem*, and *elderly*, as randomized, controlled trials that focused on sleep effects of zolpidem in the elderly (Table 6).[94–97] In the 1 randomized, controlled (and short-term [2-night]) crossover study that included objective measures, polysomnographic recordings showed dose-response effects for sleep latency and sleep efficiency with greater improvement at higher dosages (15 or 20 mg) than lower dosages (5 or 10 mg).[94] However, zolpidem showed no objective effect on the number of nocturnal awakenings, a measure of sleep maintenance.[94] Two studies conducted in adult patients that included objective measures have borne out that zolpidem does not appear to be effective in sleep maintenance measures (number of nocturnal awakenings and wake after sleep).[89,98]

In their review of zolpidem literature, Langtry and Benfield[99] note that while zolpidem at a 5-mg dose or higher reduced sleep latency, dosages of 7.5 mg or higher were required to increase total sleep time.[99,100] Other studies have failed to find a significant increase in total sleep time with zolpidem, 5 mg.[101] Roger et al.[97] reported in their subjective measure trial of 221 elderly patients that estimated total sleep time was more improved with zolpidem 10 mg and triazolam 0.25 mg (+2 hours) than with zolpidem 5 mg (+1.5 hours). In addition, 5 patients dropped out of the zolpidem 5-mg group (N = 70) due to a lack of efficacy, compared with 1 each in the zolpidem 10-mg (N = 74) and triazolam 0.25-mg (N = 77) groups.

Zolpidem has a desirable safety profile at recommended doses, with no significant rebound insomnia, withdrawal effects, pharmacologic tolerance, or drug interactions.[92,93,99] However, higher doses (≥ 15 mg) of zolpidem increase the risk of adverse events, with overall incidence rates of adverse drug reactions increasing from 13.2% in elderly patients administered less than 15 mg daily compared with 20.3% in those receiving 15 mg or more.[99] Postmarketing data from Europe found adverse events in the elderly occurring at a starting dose of 10 mg.[93,102] Most adverse events have been reported at doses of 20 mg or higher, although studies in the elderly utilizing such doses are rare. Scharf et al.[94] noted adverse events at 20 mg to be primarily associated with central nervous system symptoms (drowsiness, headache, lightheadedness, vertigo) and gastrointestinal symptoms (nausea, vomiting). A case of zolpidem-induced psychosis in a 74-year-old woman administered 20 mg has also been reported,[103] and effects have been observed on anterograde memory.[104]

Mental confusion and cognitive impairment are associated with increased risk for falls, and there is some evidence that hip fractures may be a specific risk associated with zolpidem use. Several literature reviews have indicated that higher zolpidem dosage and user age correlate with a significantly increased fall rate.[77,101] Although dosing strata were not reported, a recent large-scale study of 1222 cases of hip fracture in elderly patients and 4888 age- and gender-matched controls observed a 90% increased risk of hip fracture in older (≥ 65 years) users of zolpidem.[92]

***Zaleplon.*** Zaleplon is a short-acting nonbenzodiazepine hypnotic, with an estimated half-life of 1 hour. Adult studies have demonstrated sleep onset, but not sleep maintenance, efficacy at the recommended 10-mg dose.[105,106] It was noted, however, that improvements in total sleep time were not achieved below the 20-mg dose in either study.[105,106] The 1 identified randomized, controlled trial of zaleplon in elderly insomniacs was of 2 weeks' duration, and results were based on subjective patient reports.[107] Total sleep time and number of awakenings were improved with zaleplon 10 mg at week 1 only, while zaleplon 5 mg had no effect on total sleep time or number of awakenings.[107]

### Over-the-Counter Remedies: Antihistamines

Antihistamines, particularly diphenhydramine, appear to be used frequently among elderly patients,[4] especially in nursing home settings.[67,108] Beers et al.[109] studied medication use among 850 elderly residents of 12 representative intermediate-care facilities. Twenty-eight percent of patients were receiving sedating agents, and 26% of those patients were taking diphenhydramine. In another study of 2193 "homebound older adults" over age 60 years,[50] approximately 10% of subjects were taking first-generation antihistamines. This use was despite a 1990 NIH Consensus Development Panel statement that concluded that the safety and efficacy of antihistamines for use as hypnotics in the elderly have not been evaluated, and the practice is not recommended.[86] Since that time, little research has been conducted to advance the understanding of the use of such agents in elderly patients.

Cognitive side effects associated with antihistamine use are well documented and include next-day sedation[110,111] and impaired psychomotor and cognitive function.[111–114] Diphenhydramine, the most commonly used antihistamine for insomnia, is associated with toxicity and numerous drug-drug interactions.[115] Other side effects include urinary retention and blurred vision,[116] orthostatic hypotension, dizziness, and palpitations.[110,116]

## CONCLUSIONS AND FUTURE DIRECTIONS

The elderly population in the United States is growing. The 2000 U.S. Census counted 35 million people over age 65 years, a 12% increase since 1990.[117] As the elderly population grows, more attention is being placed on ensuring that quality of life is maintained during the aging process. Insomnia is a condition that disproportionately affects the elderly, as seen by high prevalence (57%) and

incidence (5%) rates, and it carries a substantial personal, caregiver, and societal burden. Appropriate recognition and diagnosis of insomnia are thus extremely important. Office consultation should include questions regarding sleep history, and adequate attempts should be made to exclude other primary sleep conditions and underlying medical and psychiatric conditions so that these may be adequately treated.

The goal of insomnia treatment in the elderly is to improve sleep onset and maintenance, ideally with next-day benefits rather than residual effects, with attention to the risk of drug-drug interactions and safety profiles. Currently, commonly used available agents are associated with advantages and limitations, and much work needs to be done in order to understand the problems of elderly insomnia and the utility of various agents for insomnia in this population. Efficacy for sleep maintenance should be considered, along with safety and next-day performance effects. Clinical pharmacotherapy guidelines for geriatric patients recommend using the lowest effective dose, agents with shorter elimination half-lives, short-term treatment (3–4 weeks), gradual discontinuation, and monitoring for rebound insomnia.[3,9]

At present, there are no clear guidelines that direct the choice and utilization of pharmacologic and nonpharmacologic therapies, and trial and error is often used to determine the proper course of action. There is a clear need for prospective, controlled, randomized data of the safety and efficacy of anti-insomnia agents assessed specifically in elderly populations. Fortunately, 2 investigational agents in development have been prospectively assessed in this setting. Indiplon, a nonbenzodiazepine, has been assessed in 2 trials in the elderly. One 60-patient trial demonstrated sleep onset and maintenance over 2 nights of treatment, as determined by polysomnography.[118] The other indiplon trial evaluated 42 patients and demonstrated sleep-onset efficacy and improved total sleep time over 2 nights of treatment, as determined by polysomnography. Wake after sleep onset was not reported.[119] Eszopiclone, also a nonbenzodiazepine sedative hypnotic, has been assessed in a prospective, controlled trial of 231 elderly patients treated for 2 weeks.[120] This study demonstrated improvements in patient-reported sleep onset, maintenance, total sleep time, sleep quality and depth, measures of next-day function, and several quality-of-life parameters. Eszopiclone also showed statistically significant decreases in the number and duration of naps. A similar 2-week prospective, randomized, placebo-controlled trial evaluating polysomnographic endpoints in 264 elderly patients receiving eszopiclone has completed enrollment. To date, data on both of these agents have been reported only at medical meetings and must be considered preliminary. As these trials represent some of the largest controlled data in this setting, they will add important clinical perspective on the treatment of insomnia in the elderly.

*Drug names:* acetaminophen (Phrenilin and others), albuterol (Ventolin), dextroamphetamine (Dexedrine and others), diazepam (Diastat and Valium), diphenhydramine (Ambenyl and others), ephedrine (Semprex-D, Trinalin, and others), methyldopa (Aldumet and others), methylphenidate (Ritalin, Concerta, and others), pemoline (Cylert), phenylephrine (Cyclomydril, Prometh VC, and others), phenytoin (Dilantin and others), quinidine (CinQuin and others), temazepam (Restoril), theophylline (Aerolate, Theolair SR, and others), trazodone (Desyrel), triazolam (Halcion), zaleplon (Sonata), zolpidem (Ambien).

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