Benzodiazepines for Insomnia in Community-Dwelling Elderly: A Review of Benefit and Risk

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To critically assess and summarize the beneficial effects of benzodiazepine therapy for insomnia in community-dwelling elders, a systematic search was undertaken to review all published clinical trials and sleep laboratory studies. The risk of injury for benzodiazepine users was also reviewed.

Ten studies met inclusion criteria for assessing benefit. There are no studies regarding the long-term effectiveness of benzodiazepines for the treatment of sleep disorders in the elderly. In the sleep laboratory setting, triazolam 0.125 mg, flurazepam 15 mg, and estazolam 1 mg improved sleep latency by 27 to 30 minutes and increased total sleep time by 47 to 81 minutes for the first 2 to 3 nights of treatment, compared with baseline measurements taken while the patients were receiving placebo. In contrast to these modest short-term benefits, there is an association between the use of benzodiazepines with a long half-life, eg, flurazepam, diazepam, and chlordiazepoxide, and an increased risk of hip fracture in the elderly. Triazolam can cause rebound insomnia as well as anterograde amnesia.

Clinicians should discontinue their prescribing of long-acting benzodiazepines for elderly patients with insomnia. More research is needed on the effects of nondrug interventions as well as on short- and intermediate-acting benzodiazepines, such as oxazepam and temazepam, to treat insomnia in community-dwelling elderly.

Key words. Insomnia; aged; benzodiazepines; anti-anxiety agents, benzodiazepine; ambulatory care.
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A recent analysis of drug prescribing for the elderly in the province of Quebec revealed that benzodiazepines were prescribed for an estimated 30.8% of this population for more than 30 consecutive days in 1990.[1] The average duration of exposure to benzodiazepines in this study was estimated at 119 days, and 13% of prescriptions were for long-acting benzodiazepines. Although the specific indications for benzodiazepine use were not described in this epidemiologic study, it is possible that many elderly were taking these drugs for the treatment of insomnia.[2,3]

Fairly high levels of hypnotic drug use were also reported in a recent British survey of community-dwelling elders.[4] Given the relatively high prevalence of benzodiazepine use in the elderly, the objective of this study was to systematically review evidence regarding the benefit of benzodiazepine therapy for insomnia. In reporting the outcome of treatment for the subjective symptom of insomnia, an attempt was made to standardize the measurement of benefit by applying a set of four criteria to the evaluation of clinical trials and sleep laboratory studies. Because clinicians and patients need to know about risk as well as benefit, observational studies on the hazards of benzodiazepine use in the elderly were also reviewed.

Methods

Two separate computer searches were conducted for English-language articles from 1966 to July 1994 using the MEDLINE database and the following key words: *insomnia* and *aged* and *benzodiazepine tranquilizers* or *benzodiazepines*. This was followed by a careful review of

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Table 1. Sample Size, Patient Age, Sex, and Outcomes Reported for Sleep Laboratory Studies of Outpatient Benzodiazepine Therapy of Insomnia

Study	Year	No. of Subjects	Age, y*	Women, %	Duration, d	Outcomes Measured
Frost and DeLucchi[15]	1979	6	67–82	100	15	Nocturnal sleep,† sleep stages
Carskadon et al[16]	1982	13	64–79	69	6	Daytime sleepiness, nocturnal sleep,† sleep apnea, psychomotor performance and mood
Roehrs et al[17]	1985	22	69.4±4.8, women 67.2±6.6, men	41	4	Daytime sleepiness, nocturnal sleep,† sleep apnea, and periodic leg movements
Mouret et al[18]	1990	10	72.7±13.8‡ 64.0±6.1§	NR	35	Nocturnal sleep,† sleep stages, subjective evaluation of sleep quality
Vogel and Morris[19]	1992	11	61–70	55	56	Nocturnal sleep,† psychomotor performance¶

**Age is given as a range or as a mean±standard deviation, depending on information available.*
†Includes sleep latency, total sleep time, number of awakenings.
‡Subjects receiving zopiclone.
§Subjects receiving triazolam.
¶Includes daytime performance and memory tests.
NR denotes not reported.

all bibliographic hints in the articles generated from the computer search. A textbook of geriatric medicine and a local expert were also consulted for further references.[5] Only articles involving elderly outpatients were reviewed, as family physicians see most patients for complaints of insomnia in the outpatient setting and because the treatment of institutionalized patients with insomnia may differ from that of outpatients.[6]

Four outcome measures were chosen to assess the benefit of benzodiazepine treatment: (1) Did patients fall asleep more quickly? (sleep latency); (2) Did patients awaken less frequently? (number of awakenings per night); (3) Did patients sleep longer? (total sleep time); and (4) Did patients awaken well rested or was there a feeling of sleepiness on awakening? These measures were first suggested by Dement[7] to assist clinicians in determining whether their patients had benefited from benzodiazepine therapy of insomnia. It seemed appropriate to use these same measures to assess the magnitude of benefit ascribed to such therapy from the original research literature as they would provide for a standard measure of effect across articles reviewed. Criteria for critical appraisal of the literature were also used to assess the articles on the benefits[8] and risks[9] of benzodiazepines.

Results

One hundred five citations were identified in the search for articles on benefit. Ten met the criteria for inclusion.[10–19] Although one study involved subjects as young as 55 years old,[11] it was included because it was the only trial to report results on subjects up to 90 years of age. Articles were excluded if they included nonelderly subjects (n=41) or inpatients (n=25), or were reviews or reports of adverse effects (n=21). Eight articles were excluded for miscellaneous reasons, eg, some were studies of nonbenzodiazepine hypnotics.

Women comprised the majority of patients in seven trials, but the response to benzodiazepine therapy was not reported by sex. One study did not report whether investigators or subjects were blinded to treatment,[17] eight studies were double-blind, and one was single-blind.[15] Five acknowledged funding by the pharmaceutical industry.[11–15] Triazolam 0.125 and 0.25 mg and flurazepam 15 mg were studied four times, and quazepam 15 mg was studied twice; nitrazepam 5 mg, estazolam 1 mg, and brotizolam 0.25 mg were each studied once. This search did not locate any studies of temazepam, lorazepam, or oxazepam for the treatment of insomnia in community-dwelling elderly.

Studies of benzodiazepine therapy of insomnia can be divided along methodological lines into two groups: sleep laboratory studies based on polysomnography (Table 1) and clinical trials based on data derived from patient reports (Table 2). Subjects in the five clinical trials were randomized to receive either active treatment or placebo. The sleep laboratory studies all used a crossover design, and the application of the four criteria to assess the benefit of benzodiazepine therapy was most successful for these studies, as they reported quantitative data from standardized measures of sleep.

Results from the Sleep Laboratory

All sleep laboratory studies started with baseline measurements of sleep while subjects were taking placebo. Triazolam, flurazepam, and estazolam all improved sleep latency by 27 to 30 minutes for the first 2 to 3 nights of

Table 2. Sample Size, Patient Age and Sex, and Outcomes Reported for Clinical Trials of Outpatient Benzodiazepine Therapy of Insomnia

Study	Year	No. of Subjects	Age, y*	Women, %	Duration, d	Outcome Measures†
Reeves[10]	1977	41	61+	66	28	Nocturnal sleep‡ and feeling of restfulness in morning measured by 9-item questionnaire
Martinez and Serna[11]	1982	60	54–90	80	8	Sleep quantity and sleep quality indices derived from 9-item questionnaire; physicians' global evaluation of treatment response
Caldwell[12]	1982	57	60–81	74	8	Sleep quantity and sleep quality indices derived from 9-item questionnaire; physicians' global evaluation of treatment response
Klimm et al[13]	1987	71	73.2±1.5	80	14	Nocturnal sleep‡ and feeling of restfulness in morning derived from visual analogue scales and Spiegel Sleep Questionnaire
Mamelak et al[14]	1989	36	60–72	NR	19	Nocturnal sleep‡ derived from post-sleep questionnaires; psychomotor performance§ and daytime sleepiness; memory

**Age is given as a range or as a mean±standard deviation, depending on information available.*
†Based on patient self-report.
‡Includes sleep latency, total sleep time, number of awakenings.
§Includes daytime performance and memory tests.
NR denotes not reported.

treatment compared with baseline measurements while subjects were receiving placebo. These three drugs also increased total sleep time by 47 to 81 minutes (Table 3).

In 1979, Frost and DeLucchi[15] showed that flurazepam 15 mg was efficacious in the treatment of primary insomnia. Two of four measures of drug efficacy—sleep latency and total sleep time—showed statistically significant and clinically important improvements with drug treatment. Daytime sleepiness due to carry-over drug effect was not measured. In 1982, Carskadon and colleagues[16] found that compared with baseline measurements, the number of awakenings was significantly reduced with triazolam (5.0±3.0 vs 6.4±3.1) but not flurazepam. Triazolam 0.25 mg and flurazepam 15 mg also increased total sleep time by 55 to 62 minutes. An objective measure of daytime sleepiness, the Multiple Sleep Latency Test,[20] revealed that flurazepam increased whereas triazolam reduced daytime sleepiness. A psychological test, the Profile of Mood States,[21] was conducted on mornings after drug therapy. Patients treated with flurazepam showed statistically significant improvement on five of six measures (fatigue, depression, anger, tension and confusion, $P<.05$), while no improvement in these measures was found in patients treated with triazolam.

Roehrs and associates[17] found that compared with placebo, triazolam 0.125 mg improved sleep latency by 27 minutes (18.1±11.2 vs 45.1±39.8 minutes, $P<.01$). Total sleep time also increased by 47 minutes (399.3±42.4 vs 352.1±71.6 minutes, $P<.01$). The number of awakenings was reduced (6.6±2.6 vs 8.2±3.8, $P<.05$), and triazolam did not increase daytime sleepiness. Memory was not tested following triazolam treatment, and anterograde amnesia was later reported.[22]

Mouret and co-workers[18] studied two groups of five patients randomized to receive either zopiclone 7.5 mg or

Table 3. Change in Mean Outcome Measures after Short-term Benzodiazepine Treatment

Study	Year	Drug, mg	Sleep Latency, min	Total Sleep Time, min	Awakenings, per night
Frost and DeLucchi[15]	1979	Flurazepam 15	−30*	81†	−4
Carskadon et al[16]	1982	Flurazepam 15	−4	55†	−1
		Triazolam 0.25	−26	62†	−1.4†
Roehrs et al[17]	1985	Triazolam 0.125	−27*	47*	−1.6†
Mouret et al[18]	1990	Triazolam 0.25	−20	69	Not measured
		Zopiclone 7.5	−40	110*	
Vogel and Morris[19]	1992	Estazolam 1.0	−28‡	62‡	−1.7

**Mean change from baseline significant at .01 level.*
†Mean change from baseline significant at .05 level.
‡Mean change from baseline significant at .001 level.
NOTE: A negative change indicates a reduction in the nocturnal sleep measure from placebo baseline.

triazolam 0.25 mg following measurements taken during an 8-day placebo baseline period. Triazolam increased total sleep time by an average of 69 minutes for the first 3 nights of treatment, falling to 33 minutes during the last 3 nights. The reduction in sleep latency was not statistically significant, possibly because of the small number of subjects. No difference between groups was found on ratings of subjective effects, eg, how patients felt on awakening in the morning.

Vogel and Morris[19] studied the effects of estazolam, a benzodiazepine of intermediate half-life, during a 4-week period bounded by two 2-week periods of placebo treatment. Sleep latency was reduced by 28 minutes, and total sleep time increased by 62 minutes on average. These improvements were sustained over the entire 4-week period of drug treatment. On the first night of drug withdrawal, rebound insomnia was noted, as total sleep time was reduced by a mean of 48 minutes.

Results of Clinical Trials Based on Patient Reports

The five studies conducted outside the sleep laboratory also reported a modest benefit from benzodiazepine treatment for insomnia in the elderly. In these studies, data collection was based on patient reports using sleep diaries, various sleep questionnaires, or both. As such, the magnitude of benefit resulting from treatment was not expressed quantitatively as time in minutes, but rather as mean scores on rating scales completed by study participants.

In 1977, Reeves[10] reported that triazolam 0.25 mg was better than placebo for all four sleep measures ($P<.001$) based on analysis of a nine-item sleep questionnaire. Flurazepam 15 mg was better than placebo for sleep latency only ($P<.05$). A three-point scale was used to assess "feeling in the morning." Patients treated with either triazolam or flurazepam felt "more rested than usual" at the end of 28 days of treatment.

Two identical studies compared quazepam, a long-acting benzodiazepine, with placebo in the short-term treatment of insomnia in older patients.[11,12] The evaluation of treatment efficacy was derived from daily responses to a post-sleep nine-item instrument that was different from that used by Reeves.[10] Item scores were summed to generate two categories: a "hypnotic activity index," which measured how much sleep the patients believed they had obtained, and a "sleep quality index." Mean scores on the two indices obtained during treatment were compared with baseline scores. Both studies found statistically significant improvement in scores of sleep quantity and quality as compared with the placebo period ($P<.01$).

Klimm and colleagues[13] reported statistically significant improvements for all four criteria in elderly subjects with chronic insomnia treated with zopiclone and nitrazepam. Results were derived from a seven-item questionnaire and visual analogue scales. Unfortunately, the magnitude of benefit from treatment, expressed as a reduction in number of awakenings or a gain in total sleep time in minutes, was not reported.

On the first night of treatment with brotizolam and flurazepam, Mamelak and associates[14] found statistically significant improvements in reported estimates of total sleep time and number of awakenings as compared with placebo. Brotizolam also improved sleep latency by 42 minutes, which represented a decline from 1.1 to 0.3 hours. Placebo treatment was also effective over time; after 12 nights, there were no significant differences between the placebo and the two drug treatment groups. Rebound insomnia was noted on brotizolam withdrawal. At the end of this 19-night study, only the placebo group was sleeping significantly longer than at baseline. Both drugs in this study increased daytime sleepiness. Psychomotor performance was also impaired with benzodiazepine treatment, although these effects waned after 2 weeks of treatment with brotizolam.

Assessing the Evidence on Excess Risk: What Are the Specific Risks of Injury for Elderly Benzodiazepine Users?

It is difficult to view the benefits of benzodiazepines in isolation, since decisions to prescribe are usually considered in relation to the risks and alternatives. In this regard, the studies of benefit reviewed above did not have adequate power to detect relatively infrequent but clinically important side effects, such as falls and hip fractures. For example, to detect an adverse event occurring at the rate of 1 in 100 exposed subjects, when the spontaneous background incidence in the absence of the drug is also 1 in 100, a study would have to include a minimum of 2000 subjects taking the drug.[23] A number of observational studies, however, have demonstrated an association between benzodiazepines and adverse events in the elderly, such as falls, hip fracture, cognitive impairment, and auto accidents.[24–33] Table 4 provides a summary of the key features of each of these studies.

As part of the Boston Collaborative Drug Surveillance Program, Greenblatt and co-workers[24] reported on the toxicity of flurazepam in the elderly. Patients in this study were at high risk for adverse reactions, given that 43% were receiving concurrent daytime therapy with an antianxiety drug, such as chlordiazepoxide, diazepam, or phenobarbital, in the context of a hospital setting. An impressive increase in the rate of adverse effects, eg,

Table 4. Observational Studies on the Relationship Between Benzodiazepines and Adverse Events in the Elderly

Study	Year	No. of Subjects	Study Design	Confounder Adjustment	Adverse Event	Drug	Adverse Event Risk Estimate (95% Confidence Interval)
Greenblatt et al[22]	1977	2542 (46%≥60 y)	Case series		Drowsiness, confusion, ataxia	Flurazepam	*
Tinetti et al[25]	1988	336	Prospective cohort	Multiple risk factors for falls	Falls	SHDs	3.1 (2.0, 4.9)
						(BZDs, TCAs, phenothiazines)	28.3† (3.4, 239.0)
Sorock and Shimkin[26]	1988	169	Prospective cohort	Age, sex, mental status, position sense, TCAs and antipsychotics	Falls	BZDs	1.8 (0.9, 3.6)
Ray et al[27]	1987	1021 cases 5605 controls	Nested case-control	Age, sex, race, location	Hip fracture	LABZDs	1.8 (1.3, 2.4)
						TCAs	1.9 (1.3, 2.8)
						Antipsychotics	2.0 (1.6, 2.6)
						SA hypnotics	1.1 (0.8, 1.6)
Ray et al[28]	1989	4501 cases 24,041 controls	Nested case-control	Sex, age, index date, prescribed drugs	Hip fracture	LABZDs	1.7 (1.5, 2.0)
						SABZDs	1.1 (0.9, 1.3)
Taggart[29]	1988	282 cases 145 controls	Case-control		Hip fracture	SHDs	1.1‡
						NSAIDs	0.3§
Cumming and Klineberg[30]	1993	209 cases 207 controls	Case-control	Age, sex, type of residence	Hip fracture	BZDs	1.6 (0.95, 2.5)
						Temazepam	3.8 (1.6, 8.9)
						Diazepam	0.6 (0.2, 1.6)
						Oxazepam	0.8 (0.3, 1.9)
						Antidepressants	1.3 (0.7, 2.8)
						Antipsychotics	1.3 (0.6, 2.6)
Cummings et al[31]	1995	9516	Prospective cohort	Age, bone density, history of fractures	Hip fracture	LABZDs,	1.6 (1.1, 2.4)
						Anticonvulsants	2.0 (0.8, 4.9)
						Caffeine (per 190 mg/d)	1.2 (1.0, 1.5)
Larson et al[32]	1987	62 cases 273 controls	Case-control	Age, duration of cognitive impairment, no. of drugs	Global cognitive impairment	SHDs	5.9 (2.3, 15.0)
						Antihypertensives	4.3 (1.6, 11.1)
Ray et al[33]	1992	16,262 Medicaid	Retrospective cohort	Age, sex, race, health care use, other drugs, year	Injurious car crash	BZDs	1.5 (1.2, 1.9)
						Diazepam ≤4 mg	1.1 (0.5, 2.2)
						Diazepam ≥20 mg	2.4 (1.3, 4.4)
						TCAs	2.2 (1.3, 3.5)

**For patients age ≤60 years, 1.9% risk of adverse drug reaction; for patients age ≥80years, 7.1% risk of adverse drug reaction; for patients age ≥70 years taking ≥30 mg/day, 39% risk of adverse drug reaction.*
†Adjusted odds ratio.
‡Not significant.
§P<.001.
SHD denotes sedative hypnotic drug; BZD, benzodiazepine; TCA, tricyclic antidepressant; LABZD, long-acting benzodiazepine; SA, short-acting; SABZD, short-acting benzodiazepine; NSAID, nonsteroidal anti-inflammatory drug.

drowsiness, confusion, and ataxia, among subjects ≥70 years of age as a function of dose was noted; the frequency of adverse reactions to flurazepam jumped from 7.8% at average daily doses of 15 to 29.99 mg to 39% at 30 mg or more per day.

An association between falls and sedative-hypnotic drugs, eg, benzodiazepines, antidepressants, and phenothiazines, was reported in two prospective cohort studies. Tinetti and colleagues[25] sought to minimize recall bias in measuring the frequency of falls during a 1-year period by telephoning subjects bimonthly to ascertain whether any falls had occurred. A diary for recording falls was also provided. In a multivariate analysis, the use of sedative-hypnotic drugs was found to be the strongest risk factor for falls. The number of patients taking sedative hypnotic drugs in this study was too small to explore dose–response relationships or the effects of individual drugs. Sorock and Shimkin[26] ascertained sedative-hypnotic drug use by interview in patients' homes. Each subject was asked to show the interviewer all medications in current use, and a specific question was asked regarding the use of medication for sleep or "nerves." Although the adjusted relative risk of falls was increased for benzodiazepine users as compared with that of nonusers, an adjust-

ment for confounding by indication was impossible, as data on the specific reasons for benzodiazepine use were not obtained.

Ray and associates[27,28] conducted two large database case-control studies on the risk of hip fracture among elderly users of psychotropic drugs. In both studies, drug exposure (drug and dose) was determined from computerized pharmacy records. Controls were selected from computerized files to provide a stratified random sample of patients without hip fracture. In the second study, the authors randomly reviewed the hospital records of 194 cases to check the validity of data for the diagnosis of hip fracture and to obtain information on potential confounders. There was no significant difference in the distribution of potential confounders, such as dementia, use of a cane or walker, and need for assistance with activities of daily living, with regard to type of benzodiazepine (long vs short half-life). In each study, hip fracture subjects were entirely comparable to control subjects in terms of age, sex, and index year.

In contrast to shorter-acting benzodiazepines and other sedative hypnotic drugs, such as chloral hydrate and hydroxyzine, long-acting benzodiazepines were associated with an increased risk of hip fracture. A dose–response gradient was noted: the risk of hip fracture increased in relation to the daily dose of long-acting benzodiazepine. No similar dose–response gradient was found for the shorter-acting benzodiazepines. In describing the association between long-acting benzodiazepines and hip fracture, the use of computerized databases avoided both interviewer and recall bias. As a result, the clinician should have more confidence in their findings of a nearly twofold increase in the risk of hip fracture in users of long-acting benzodiazepines.

Taggart[29] conducted a small case-control study to examine the relationship between sedative hypnotic drug use (hypnotics and neuroleptics) and hip fracture in elderly women and found no association. Two hundred eighty-two hip fracture subjects from one city hospital were compared with 145 control subjects selected from one general practice. Drug use was subject to interviewer and recall bias, which could have underestimated sedative hypnotic drug use, leading to nonrandom misclassification of benzodiazepine use. Selection bias may have been present as well. A larger and perhaps more representative sample of control subjects could have been randomly gathered from several general practices.

Cumming and Klineberg[30] also sought to measure the association between sedative hypnotic drug use and hip fracture risk. Drug use was again subject to interviewer and recall bias in this study. Temazepam, a benzodiazepine of intermediate half-life, was associated with a fourfold increase in the risk of hip fracture, whereas the risk seen with diazepam and oxazepam was not significantly increased. Confounding due to comorbidity may have contributed to a spurious elevation of risk if temazepam was preferentially prescribed for the frail elderly, but health status was not objectively assessed in this Australian study. Given the relatively small number of subjects involved, this study may have lacked the statistical power to detect a significant risk associated with the many individual drugs considered.

Cummings and colleagues[31] followed a large cohort of community-dwelling women 65 years of age and older to determine their frequency of hip fracture. During an average 4.1 years of follow-up, 16 independent risk factors for hip fracture were identified. After adjusting for a history of fractures and bone density, it was found that current use of long-acting benzodiazepines increased the risk of hip fracture.

To determine the clinical features associated with adverse drug reactions, Larson and associates[32] studied cognitively impaired elderly outpatients with and without adverse drug reactions. Sedative hypnotic drugs—principally diazepam and flurazepam—were the drugs most commonly associated with global cognitive impairment. A possible association between the degree of cognitive impairment and sedative-hypnotic drug dose was not studied; however, the association found should serve to alert clinicians to the potential for sedative-hypnotic drug-related adverse reactions in the cognitively impaired elderly.

Ray and co-workers[33] examined the risk of injurious car crash in elderly drivers using psychoactive drugs, eg, benzodiazepines and tricyclic antidepressants. By examining Tennessee Medicaid files, they identified sedative-hypnotic drug use among 16,262 drivers 65 to 84 years old. These findings were then linked with records for car crashes reported to the Tennessee Department of Safety. Two thirds of benzodiazepines used in this sample were long-acting benzodiazepines, and benzodiazepine use was found to be associated with an increased risk of injurious accident. The magnitude of the risk of car crash for elderly users of tricyclic antidepressants was slightly greater than that reported for benzodiazepines. A similar relationship was seen in an earlier study of psychotropic drugs and the risk of hip fracture.[27] Alcohol use was not a confounding variable: the rate of reported alcohol use was equal for both current users and nonusers of sedative hypnotic drugs.

Discussion

According to the authors of a 1990 consensus conference, there are no studies demonstrating the long-term effectiveness of benzodiazepines for the treatment of sleep disorders in the elderly.[34] Similarly, this review found that

published studies are of short duration only (56 nights or less including nights of placebo treatment) and small sample size (72 subjects or less). Thus, relative to the widespread use of benzodiazepines in this age group, benzodiazepine therapy of insomnia in community-dwelling elderly has received remarkably little testing in controlled trials.

While the trials of benzodiazepine therapy in this review all reported a modest beneficial effect of treatment on nocturnal sleep measures, only the quantitative results from sleep laboratory studies permit a comparison of the magnitude of benefit seen across studies. Given the similarity of findings across studies in both direction and magnitude of treatment effect, it did not seem helpful to pool the results of individual studies to derive an "average" effect as reported in a meta-analysis. The five clinical trials based on patient self-report used different instruments, making any comparison of study results somewhat tenuous.

How well do patients sleep in a sleep laboratory? Although sleep laboratory studies provide the most objective data, the artificial environment in which subjects are evaluated may actually produce results that differ from those obtained in a more "natural" setting, such as the home. The "first night effect" results from sleeping in an unfamiliar environment,[35] and if this effect increased the likelihood that subjects had a worse-than-usual first night's sleep in the laboratory, this bias could have acted to spuriously increase the magnitude of benefit seen from treatment.

The goal of insomnia therapy should be not only improved sleep but also improved daytime functioning. To assess daytime sleepiness, which is one of the common side effects of intermediate and long-acting benzodiazepines, the American Sleep Disorders Association Task Force recommends the Multiple Sleep Latency Test.[20] This test is a polysomnographic procedure that measures the time it takes to fall asleep in a sleep-inducing environment at five time points over the course of a single day. Flurazepam and brotizolam were found to increase daytime sleepiness[14,16]; however, in one half of the articles appraised, the problem of drug-induced daytime sleepiness was not objectively studied.

Other methodological problems were noted. In Reeves's study,[10] six patients dropped out during treatment and were not included in the evaluation of efficacy. Although side effects were reported in all groups, they were not tabulated by treatment group. For example, the most frequent side effect was drowsiness, yet it was not possible to tell whether this was more common with flurazepam or placebo. In two other studies,[11,12] the frequency of side effects was reported to be equal in both groups, but it is not clear what process was used to search for adverse effects. It is possible that side effects were underreported.

In all studies except one,[17] the process used to recruit subjects was not well defined. Were these patients similar to those seen in primary care practice? The likely presence of referral filter bias and volunteer bias limits the generalizability of these studies to the primary care setting.[36] In two studies, subjects were defined as "volunteers" with chronic insomnia, and the duration of symptoms was not specified.[16,17] Insomnia was defined in all studies, in that subjects had to meet two of the following criteria at least 3 to 4 times per week: (1) sleep latency of 30 minutes or more; (2) total sleep time of less than 6 hours; and (3) two or more awakenings per night. Two studies[13,18] required a longer period (at least 60 minutes) of sleep latency for eligibility. Only one study[14] used the definition of primary insomnia found in the *Diagnostic and Statistical Manual of Mental Disorders-III-R* [37] for subject selection. Roehrs and associates[17] selected subjects for study specifically because they suffered from excessive daytime sleepiness.

Exposing elderly patients to the potential complications of benzodiazepine therapy is justified only if the benefits of such treatment clearly outweigh the risks. This issue is largely a matter of judgment, as there is no standard method for measuring and contrasting benefit and risk.[38] With regard to the risk of hip fracture among elderly benzodiazepine users, how strong are the studies that demonstrated harm? Given the limitations of observational research, there will always be some doubt about the extent to which unknown confounders contributed to the findings.

Based on the large database studies, the association between hip fracture and the use of long-acting benzodiazepines, as compared with that of the shorter-acting benzodiazepines and sedative hypnotic drugs, is statistically significant but weak in magnitude (risk estimate, 1.6 to 1.8). Unfortunately, large database studies assessing risk reported neither the specific indications for drug prescribing nor at what time of the day subjects took the drugs. Therefore, it is impossible to specifically assess from these studies what proportion of elderly benzodiazepine users had insomnia or what was the relationship between bedtime dosing and adverse outcomes, such as hip fracture or car crash. It is interesting to note that the positive findings of the large, well-controlled studies[27,28,31] conflict with the negative results of studies with much smaller samples.[29,30] It seems that the observed heterogeneity of results across studies is related to interstudy differences in sample size and control over confounding variables, with higher quality studies showing statistically significant and clinically important associations between long-acting benzodiazepine use and the risk of hip fracture.

From a public health perspective, the implication of

this risk estimate for hip fracture is substantial. In the United States, 217,000 persons aged 65 years and older sustained hip fractures in 1987, and in a Medicaid population, as many as 14% of these fractures may be attributable to psychotropic drug use.[39] If this estimate is correct and can be generalized to elderly individuals not receiving Medicaid, it can be concluded that the use of psychotropic drugs by persons aged 65 years and older potentially results in 30,000 excess hip fractures each year in the United States.

Conclusions

Although the average duration of benzodiazepine use by the elderly was estimated in a recent epidemiological study to be 119 days, there are no long-term studies involving the elderly to document sustained benefit for insomnia beyond 1 month. In this review, an attempt was made to standardize the measurement of benefit from benzodiazepine therapy by using predetermined criteria. However, because the results of the clinical trials were not reported in a standard manner, it was impossible to conduct an analysis of benefit for all studies in this review using the four criteria. Nevertheless, based on data from sleep laboratory studies, it is possible to report on the magnitude of short-term benefit experienced by select elderly patients taking a benzodiazepine for insomnia. Although efficacy has been demonstrated in the sleep laboratory setting, the effectiveness of treatment in the elderly recruited from primary care practice remains to be determined.

Results from several large observational studies suggest that long-acting benzodiazepines, eg, diazepam, chlordiazepoxide, and flurazepam, are associated with a significantly increased risk of hip fracture in the elderly. Clinicians should curtail their prescribing of these drugs, which do not confer any special advantage in the treatment of insomnia in the elderly. Benzodiazepines with a short half-life are not necessarily safer. Triazolam was removed from the market in the United Kingdom in 1991 following reports regarding rebound insomnia, amnesia, and other psychiatric disturbances.[40] When benzodiazepines are used in the elderly, dosage should be reduced because equivalent effects can be achieved in elderly patients at one half the dose normally given to young subjects.[22,41]

It is hoped that further research will increase the body of knowledge about the effectiveness of nondrug treatments for insomnia in the elderly, such as sleep hygiene techniques and stimulus control instructions. To address a possible bias resulting from the "first night effect" and to increase the generalizability of results, subjects should be recruited from primary care and polysomnographic studies conducted in the home. For more chronic forms of insomnia, careful attention to underlying factors and nondrug treatments could potentially supplant the need for long-term benzodiazepine therapy. Clinicians and their elderly patients should consider the current evidence on the risks and benefits of benzodiazepine therapy for insomnia before choosing this therapeutic route.

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