Published in final edited form as:

J Am Geriatr Soc. 2006 February ; 54(2): 224–230.

Benzodiazepine Use and Physical Disability in Community-Dwelling Older Adults

Shelly L. Gray, PharmDMS^{*}, Andrea Z. LaCroix, PhD^{†,‡,§}, Joseph T. Hanlon, PharmDMS^{||,¶,♯}, Brenda W. J. H. Penninx, PhD^{**}, David K. Blough, PhD^{*}, Suzanne G. Leveille, PhD^{††}, Margaret B. Artz, PhD^{‡‡}, Jack M. Guralnik, MD, PhD^{§§}, and Dave M. Buchner, MD^{***}

^{*}School of Pharmacy, University of Washington, Seattle, Washington [†]Department of Epidemiology, University of Washington, Seattle, Washington [‡]Women's Health Initiative Clinical Coordinating Center, Fred Hutchinson Cancer Research Center, Seattle, Washington [§]Group Health Cooperative, Seattle, Washington ^{||}Department of Medicine, Division of Geriatric Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania [¶]Department of Pharmacy and Therapeutics, School of Pharmacy, University of Pittsburgh, Pittsburgh, Pennsylvania [♯]Center for Health Equity Research and Promotion, Veterans Administration Pittsburgh Health Care System, Pittsburgh, Pennsylvania ^{**}Department of Psychiatry, VU University Medical Center, Amsterdam, the Netherlands ^{††}Department of Medicine, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, Massachusetts ^{‡‡}College of Pharmacy, University of Minnesota, Minneapolis, Minnesota ^{§§}Epidemiology and Demography Section, Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, Bethesda, Maryland ^{***}Physical Activity and Health Branch, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia

Abstract

OBJECTIVES—To determine whether benzodiazepine use is associated with incident disability in mobility and activities of daily living (ADLs) in older individuals.

DESIGN—A prospective cohort study.

SETTING—Four sites of the Established Populations for Epidemiologic Studies of the Elderly.

PARTICIPANTS—This study included 9,093 subjects (aged ≥65) who were not disabled in mobility or ADLs at baseline.

MEASUREMENTS—Mobility disability was defined as inability to walk half a mile or climb one flight of stairs. ADL disability was defined as inability to perform one or more basic ADLs (bathing, eating, dressing, transferring from a bed to a chair, using the toilet, or walking across a small room). Trained interviewers assessed outcomes annually.

RESULTS—At baseline, 5.5% of subjects reported benzodiazepine use. In multivariable models, benzodiazepine users were 1.23 times as likely as nonusers (95% confidence interval (CI) = 1.09–1.39) to develop mobility disability and 1.28 times as likely (95% CI = 1.09–1.52) to develop ADL disability. Risk for incident mobility was increased with short- (hazard ratio (HR) = 1.27, 95% CI = 1.08–1.50) and long-acting benzodiazepines (HR = 1.20, 95% CI = 1.03–1.39) and no use. Risk for ADL disability was greater with short- (HR = 1.58, 95% CI = 1.25–2.01) but not long-acting (HR = 1.11, 95% CI = 0.89–1.39) agents than for no use.

CONCLUSION—Older adults taking benzodiazepines have a greater risk for incident mobility and ADL disability. Use of short-acting agents does not appear to confer any safety benefits over long-acting agents.

Keywords

benzodiazepines; activities of daily living; disability; adverse drug event

Benzodiazepines are often used to manage symptoms of anxiety and insomnia in older adults. Expert panels have urged clinicians to limit or avoid use of these medications in older adults given the prominent adverse effects on the central nervous system (CNS).^{1,2} These CNS effects may exhibit themselves in a wide range of adverse health effects, including increased risk for falls,³ hip fractures,^{4,5} depressed mood,⁶ impaired cognition,⁷ motor vehicle crashes,⁸ and urinary incontinence.⁹ Despite these health risks, benzodiazepines are still commonly used, with a prevalence of 10% to 12% in older adults residing in the community.^{10,11}

Of particular concern in older adults is the potential for benzodiazepine use to contribute to physical disability.^{11–16} In cross-sectional studies, benzodiazepine use was associated with impaired physical function.^{11–13} A large longitudinal study of older women suggested that benzodiazepine use increased risk of decline in basic activities,¹⁴ whereas a smaller study did not.^{15,16} In a more-recent analysis, community-dwelling women who used benzodiazepines had a greater decline over 4 years in timed physical performance tests than did nonusers.¹⁷

Determining whether benzodiazepine use contributes to disability is important, because the decision to prescribe this type of medication might be altered with knowledge of this adverse drug effect. To the authors' knowledge, no studies have evaluated the association between benzodiazepine use and self-reported mobility measures or standard activity of daily living (ADL) assessments in male and female community-dwelling older adults. The current study explored whether risk of disability may vary according to the benzodiazepine elimination half-life, because research in the area of hip fractures has yielded conflicting results. It was hypothesized that risk does not vary according to half-life. In this large population-based study of older adults without disability at baseline, the association between benzodiazepine use and incident mobility and ADL disability was examined over a 6-year follow-up.

METHODS

Study Population

Data for this study were collected from four communities of the Established Populations for Epidemiologic Studies of the Elderly (EPESE), a prospective cohort study of older persons (≥ 65) living in the community. The sampling and data collection procedures have been described in depth previously.^{18,19} The four cohorts were assembled from the entire population in East Boston, Massachusetts; two counties in rural Iowa; a random sample of the population in New Haven, Connecticut; and a random sample from those living in a five-county area surrounding Durham, North Carolina (Piedmont). Baseline interviews were conducted between 1981 and 1983 for Iowa, East Boston, and New Haven and between 1986 and 1987 for Piedmont.

A total of 14,456 individuals were interviewed at baseline. The sample for this analysis consisted of those who were not disabled at baseline in mobility²⁰ or basic ADLs.²¹ Individuals were excluded if they were impaired in mobility and ADLs ($n = 1,599$), impaired in ADLs ($n = 371$), impaired in mobility ($n = 2,490$), or had missing information for either disability outcome ($n = 426$). Of the remaining 9,570 participants, 26 had missing medication information, and 184 had proxy interviews, leaving a sample of 9,360 with complete baseline

information. Of these, 230 died before the next follow-up, and 37 were loss to follow-up, leaving the final sample of 9,093 (2,380 from East Boston, 2,468 from Iowa, 1,752 from New Haven, 2,493 from Piedmont).

Data Collection

Follow-up in-home interviews were conducted at Years 3 and 6, and phone follow-up interviews occurred at Years 1, 2, 4, and 5. Vital status of all participants during follow-up was ascertained through information collected at the annual interview, contacts with proxies, obituaries in local newspapers, and a linkage with the National Death Index.

Assessment of Benzodiazepine Exposure

Trained study personnel collected information about medication use during in-home interviews using structured questionnaires (baseline, follow-up Years 3 and 6). Participants were asked whether they had taken any medications prescribed by a doctor or obtained from a store during the previous 2 weeks. If they responded yes, they were asked to show the interviewer all prescription and nonprescription medications. The name of each medication was recorded at all sites. In addition, the strength and number of dosage forms taken in the previous day was recorded at Iowa and Piedmont. Medication information was entered into computerized files using an updated and modified version of the Drug Product Information Coding System, which assigns a five-digit code to each medication.^{22,23}

The primary exposure variable was any benzodiazepine use (yes = 1, no = 0). For secondary exposure variables, benzodiazepines were categorized according to half-life and dose. Benzodiazepines were classified as short acting (elimination half-life <24 hours) or long acting (elimination half-life ≥24 hours). Specifically, clonazepam, clorazepate, chlorthalidopoxide, diazepam, flurazepam, and prazepam were categorized as long-acting, with the remaining categorized as short-acting (temazepam, oxazepam, triazolam, lorazepam, alprazolam).²⁴ To evaluate the possibility of a dose–response relationship, the standardized daily dose (SDD) was estimated for each benzodiazepine.⁷ First, the daily dose was calculated by multiplying the number of dosage forms taken the previous day by the tablet/capsule strength. Second, this sum was standardized by dividing by the minimum effective dose per day according to standardized references: diazepam (4 mg), alprazolam (0.75 mg), clorazepate (15 mg), lorazepam (2 mg), flurazepam (15 mg), oxazepam (30 mg), temazepam (15 mg), triazolam (0.125 mg), clonazepam (0.5 mg), and chlorthalidopoxide (15 mg).²⁵ Dosage was defined operationally as minimum effective dose or less (≤1 SDD) and higher than minimum effective dose (>1.0 SDD).

Assessment of Mobility and ADL Disability

The two outcome measures were onset of mobility and ADL disability, which were measured at each annual follow-up visit.^{26,27} Mobility disability was defined as inability to walk half a mile or climb stairs without help.²⁰ ADL disability was defined as the inability to perform one or more of the following without help: bathe, eat, dress, transfer from a bed to a chair, use the toilet, and walk across a small room.²¹

Assessment of Covariates

Potential confounding variables that might influence the relationship between benzodiazepine use and disability measures were adjusted for.²⁸ Covariates were categorized into three domains: sociodemographic characteristics, health status, and health behaviors or characteristics. The sociodemographic characteristics included: age (65–69, 70–74, ≥75), sex, level of education (≤8 years, 9–12 years, >12 years), and annual household income (<\$5,000, \$5,000–9,999, ≥\$10,000). The presence of 10 self-reported chronic conditions or symptoms

(myocardial infarction (MI), high blood pressure, stroke, diabetes mellitus, cancer, dyspnea, angina pectoris,²⁹ exertional leg pain, hip fracture, and arthritis/joint pain (not assessed at Piedmont)) was assessed at baseline. Participants were also asked about select newly occurring conditions that were assessed at each follow-up interview (MI, stroke, cancer, diabetes mellitus, hip fracture). Subjects were asked whether they had vision or hearing problems. Individuals making four or more errors on the Short Portable Mental Status Questionnaire were considered to have impaired cognition.^{30,31}

To control for possible confounding by indication, items regarding sleep and depression were included in the models. Confounding by indication can occur when an observed association between a drug and an outcome is due to the underlying illness and not the use of the medication itself. Participants were asked about difficulty with falling asleep (never, sometimes, or most of the time). The presence of depressive symptoms was assessed using the Center for Epidemiologic Studies Depression Scale (CES-D).³² The standard 20-item version (4 response categories), with a score range of 0–60 was used in New Haven; abbreviated versions were used in East Boston (10 items), Iowa (11 items) and Piedmont (20 item version, 2 response categories). The scores from the abbreviated versions were transformed to make them compatible with the standard version using previously validated methods.³³ A cutoff score of 20 was used to identify participants with depressed mood, which has been found to increase the accuracy of the CES-D for identification of major depression in older adults.^{34,35} The health behaviors or characteristics included body mass index calculated from self-reported weight and height (weight (kg)/height (m²)), smoking (current, past, never), and alcohol use (none, ≤ 1 drink/d, >1 drink/d). Physical activity was measured using three items concerning the frequency of self-reported walking, gardening and vigorous exercise (not at Piedmont). The frequency of each activity was categorized and scored as follows: frequently (≥ 3 times/wk) = 2, sometimes (weekly or several times/month) = 1, and rarely or never = 0. A composite indicator of physical activity was created by summing the individual activities and grouping them into low (0), moderate (1–2), and high (3–6).²⁶

Statistical Analysis

Characteristics of benzodiazepine users and nonusers were compared using chi-square tests for categorical variables. For the multivariable analyses, multiple imputation techniques were used for independent variables with missing values ($<15\%$), which has been shown to appropriately account for the uncertainty in imputing missing data.³⁶ Estimates of standard errors are therefore valid in relevant tests of significance.

Subjects with no disability at baseline were followed for up to 6 years for evidence of new mobility or ADL disability. Separate multivariable Cox regression models for interval censored data were used to examine the relationship between benzodiazepine use and time to develop each disability outcome.³⁷ Exposure was modeled as a time-dependent factor, with status switching at Years 3 and 6, when new exposure information became available. For each outcome, Model 1 adjusted for age, sex, time, and site, whereas Model 2 included all potential confounding variables. Changes in status of five chronic conditions (MI, diabetes mellitus, stroke, cancer, hip fracture) during the follow-up were also modeled as time-dependent risk factors. The first report of disability at follow-up was considered as the event of incident disability, regardless of the functional status reported in subsequent follow-up interviews. Subjects who survived with no evidence of disability were censored at 6 years, those who died with no evidence of disability were censored at the time of their death, and those lost to follow-up were censored after their last interview. Secondary analyses were conducted for the exposure variable (dose available at two sites; $n = 4,961$) and potential confounders (physical activity, arthritis available at 3 sites; $n = 6,600$) that were not available for all sites.

For exposure variables with more than two categories, large-sample univariate z tests were used to examine pairwise comparisons of the exposure levels (e.g., the difference between short acting and long acting). Two-way interactions were examined between the primary exposure and sex, age, and site. Whether the baseline hazard varied by site was examined by including an interaction term with time and site in each model. The coefficient for the primary exposure did not change appreciably, therefore an interaction term was not included for time and site in the main models. SAS version 8.1 (SAS Institute Inc, Cary, NC) was used and parameter estimates are reported with 95% confidence intervals (CIs).

RESULTS

Of the 9,093 participants, 498 (5.5%) used a benzodiazepine at baseline, with similar percentage use at each follow-up visit. Of users at baseline, 50.4% were using higher-than-recommended minimal effective dose, and 79.1% were using long-acting benzodiazepines. The use of long-acting benzodiazepines declined over the study period, representing 56.3% of users at 3-year follow-up and 34.7% at 6-year follow-up. Of users at baseline, the most common long- and short-acting agents were diazepam (41.7%) and lorazepam (8.5%), respectively. Of those remaining in the analysis at 3-year follow-up ($n = 6,327$), 185 (2.9%) reported use at 3-year follow-up only, 151 (2.4%) reported use at baseline only, and 168 (2.7%) reported use at both interviews.

Baseline characteristics of participants according to benzodiazepine use are shown in Table 1. Benzodiazepine users were more likely to be female and have lower body mass index and were less likely to have cognitive impairment than nonusers. Several health conditions (MI, angina pectoris, dyspnea, exertional leg pain, high blood pressure, arthritis, depressive symptoms and more difficulty falling asleep) were more common in benzodiazepine users.

During the follow-up period, 4,279 participants experienced mobility disability, and 2,221 experienced ADL disability. The incidence rate for mobility and ADL disability was 112/1,000 person-years and 50.3/1,000 person-years, respectively.

Table 2 displays the relationship between benzodiazepine use and incident mobility and ADL disability adjusted for age, sex, time, and site (Model 1) and for all potential confounders (Model 2). In the fully adjusted model, benzodiazepine use was associated with a 23% greater risk for mobility disability (adjusted hazard ratio (HR) = 1.23, 95% confidence interval (CI) = 1.09–1.39). Risk for incident mobility disability was increased with short- and long-acting benzodiazepines. A 28% greater risk was also found for ADL disability (adjusted HR = 1.28, 95% CI = 1.09–1.52). Risk for ADL disability was greater with short-acting (adjusted HR = 1.58, 95% CI = 1.25–2.01) but not long-acting (adjusted HR = 1.11, 95% CI = 0.89–1.39; $P = .03$; z test comparing coefficients for half-life) agents.

The models were rerun without prevalent or incident hip fracture, because this may be one mechanism by which benzodiazepines may increase risk for disability, and the HRs were identical to the models that included these variables. Exploration of a dose–response effect was examined at two sites. Risk of mobility disability was greater irrespective of dose; thus, even those taking the recommended minimum effective dose or less had greater risk for mobility disability. For ADL disability, the risk was higher for those taking higher than the recommended minimum effective dose, but a post hoc comparison revealed that the coefficients for the dose levels was not significantly different ($P = .18$; z test comparing coefficients for dose).

The inclusion of physical activity and arthritis in the adjusted models for the three sites yielded no appreciable change in the point estimate of the relative hazard of benzodiazepine use for

each disability measure. No significant interactions were found between age, sex, or site and the primary exposure for each outcome.

DISCUSSION

The findings of this large population-based prospective cohort of community-dwelling older adults provide further evidence that benzodiazepine use contributes to disability. This is the first study to the authors' knowledge that has examined the effect of benzodiazepine use on measures of mobility. Benzodiazepine use increased risk for incident mobility disability 23% after adjusting for several health conditions and health behaviors and characteristics. This study extends prior work that suggested that benzodiazepine use was associated with decline in physical performance measures (e.g., chair stand, walking speed, and standing balance).¹⁷ Risk for incident mobility disability was found for short- and long-acting agents. Of particular concern, these results suggest that greater risk was evident even with the use of low doses of these medications.

A significantly greater risk of ADL disability was also observed in those who used benzodiazepines, which is consistent with one previous report¹⁴ but not another,¹⁶ although previous studies have used nonstandard assessments of ADLs, so results may not be directly comparable. The risk for ADL disability was greatest for those using short-acting agents. In a prior study (n = 1,516),¹⁶ benzodiazepine use was associated with becoming limited in one or more self-reported basic ADLs (bathing, toileting, feeding, and dressing) that were asked as a single question as part of the Medical Outcome Study (MOS) Physical Function Scale and loss of physical function as measured by a decline of two or more points on the MOS Physical Function Scale, with only the latter association reaching statistical significance. This study may have been limited in ability to find an association with ADLs because of the small sample, use of an abbreviated measure of ADLs, and a low incidence of decline in basic ADLs. In contrast, a large cohort of community-residing women (n = 6,632) reported that short- and long-acting benzodiazepines were associated with inability to complete without assistance one or more basic activities (getting in or out of bed, turning faucets on and off, getting in and out of a car, dressing, washing and drying entire body, bending to pick up clothing, preparing own meals, lifting a full cup to the mouth).¹⁴ The definition of basic activities used in this study included some activities that are traditionally classified as instrumental ADLs.

A question that continues to evade providers and researchers is what influence, if any, the elimination half-life has with regard to risk for adverse outcomes with benzodiazepine use. Early investigations suggested that long-acting agents were more likely to cause adverse events (e.g., hip fractures) than short-acting agents,^{4,38} but studies have emerged that also implicate greater risk with short-acting agents.^{5,39} In this study, risk was greater regardless of half-life for mobility disability but only with use of short-acting agents for ADL disability. Why was greater risk found only with short-acting benzodiazepines and ADL disability? One possibility is that those using short-acting agents were also more likely to take higher doses. A post hoc analysis was conducted that revealed that this was not the case. Users of short-acting benzodiazepines were not more likely to take a higher mean daily dose ($1.0 \text{ SDD} \pm 0.1$ vs $1.4 \text{ SDD} \pm 0.1$; Wilcoxon rank sum test; $P = .07$) than users of long-acting agents. Another possibility is the differential prescribing of short- and long-acting agents. Most of the data collection for three of the four sites predated the emergence of data suggesting risk of hip fracture with use of long-acting benzodiazepines,⁴ but it cannot be excluded that the results of the current study may be explained in part by clinicians preferentially prescribing short-acting agents to high-risk patients. This explanation would be more plausible if the same pattern of risk had been found with half-life and mobility disability.

The mechanism(s) by which benzodiazepine use may affect mobility and the ability to perform ADLs is not clear. Benzodiazepines produce sedation and impairment of psychomotor performance, memory, and neuromuscular processing.⁴⁰ Furthermore, use of benzodiazepines has been associated with falls, hip fractures, and depressed mood. It is certainly plausible that these adverse effects could have a cumulative negative effect on ADLs or measures of mobility. It is also likely that different mechanisms with different thresholds may mediate the development of each type of disability, which may explain why a dose-response relationship was noted with ADL but not mobility disability. A question that remains unanswered is whether benzodiazepine use results in inactivity, which may contribute to the onset of disability. In the secondary analyses, adjusting for activity level did not appreciably change the effect size for either outcome, suggesting that difference in baseline activity was not a confounder. Further research is needed to investigate whether benzodiazepine use is associated with future inactivity that may be in the causal pathway leading to disability.

Benzodiazepines were the most prevalent psychotropic medications used by the EPESE populations. The prevalence reported in the current study is lower than what has been reported previously (10–12%), in part because those with disability at baseline were excluded. In general, the prevalence of antidepressant (2.0–4.1%)⁴¹ and antipsychotic (1.5–2.6%)⁴² use was low in these populations, which precluded examination of these medications and risk for disability. Furthermore, antidepressants were not related to disability in a cross-sectional multivariate analysis of the four EPESE sites⁴¹ nor to decline in physical performance in a longitudinal analysis.⁴³

This study has a number of strengths, including the large representative sample of older adults and ability to control for several potential confounding variables, but a number of potential limitations should be considered when interpreting these results. First, residual confounding or confounding by indication could account for the small point estimates for greater risk with benzodiazepines. For example, for anxiety, a potential independent risk factor for disability and a common indication for benzodiazepine use, could not be controlled for, because the EPESE survey did not ask about this element. Nevertheless, sleep disturbances and depression, two other common conditions for which benzodiazepines may be prescribed, were controlled for. Future studies should consider adjusting for physical performance measures, if available, to further reduce residual confounding. A second limitation is that misclassification of benzodiazepine exposure may have occurred. Benzodiazepines used for sleep disorders are often used intermittently.¹⁰ Intermittent use would bias the findings toward the null; thus the findings are likely conservative estimates of risk. Another source of exposure misclassification is that duration of use was not known precisely, because medication information was collected at 3-year intervals. Thus, benzodiazepines used between interviews would not be detected. As this would be nondifferential exposure misclassification, the bias would be a reduction in the observed strength of any real association between benzodiazepine use and disability. In addition, these analyses did not take into account the duration of benzodiazepine exposure. Thus, these analyses may have underestimated the “true” risk of benzodiazepine use, because long-term exposure included those who “tolerated” benzodiazepines without adverse effects that could have lead to discontinuation.

Despite these potential limitations, the results from this study have important clinical implications for the care of older adults. Although benzodiazepines may be appropriate for many older adults, clinicians should continue to weigh heavily the risks and benefits of initiating a benzodiazepine. Other agents (e.g., selective serotonin reuptake inhibitors (SSRIs)) may be more-appropriate agents for managing anxiety disorders in older adults, although SSRIs have also been associated with falls and hip fractures in older adults. Evidence increasingly supports that short-acting agents are not safer than long-acting benzodiazepines. Use of the lowest effective dose is prudent, although greater risk may be present even in doses that are

recommended for use in older adults. Periodic assessment for possible reduction and discontinuation of therapy is warranted to minimize serious adverse effects.

Acknowledgements

We would like to thank Monte Carlow for his programming support.

Financial Disclosures: Shelly L. Gray, Joseph T. Hanlon, Brenda W. J. H. Penninx, David K. Blough, Suzanne G. Leveille, Jack M. Guralnik, and Dave M. Buchner: None. Andrea Z. LaCroix participates in a multicenter international trial of a new selective estrogen-receptor modulator sponsored by Pfizer, Inc. She serves as a consultant on the Pacific Northwest Regional Osteoporosis Board for Proctor and Gamble. In the past 12 months, Dr. LaCroix has received honoraria for speaking at national and regional meetings in continuing medical education symposia from Schering-Plough and Proctor and Gamble. Margaret B. Artz received \$3,500 from Pfizer for an unrestricted educational grant unrelated to the current study.

Author Contributions: All authors contributed to concept and design, analysis and interpretation of data, and preparation of manuscript. Drs. Gray, Penninx, Guralnik, and Hanlon also contributed to acquisition of subjects and/or data.

Sponsor's Role: The National Institute on Aging (NIA) had no role in the design, methods, analysis, or preparation of this manuscript. This study was a secondary analysis of data collection that was originally funded by the NIA.

Financial support was provided by Grant K08AG00808-01 from the National Institute on Aging (Dr. Gray) and from the VFW Endowed Chair in Pharmacotherapy for the Elderly, College of Pharmacy, University of Minnesota (Drs. Hanlon and Artz).

References

1. Fick DM, Cooper JW, Wade WE, et al. Updating the Beers criteria for potentially inappropriate medication use in older adults: Results of a U.S. consensus panel of experts. *Arch Intern Med* 2003;163:2716–2724. [PubMed: 14662625]
2. McLeod PJ, Huang AR, Tamblyn RM, et al. Defining inappropriate practices in prescribing for elderly people: A national consensus panel. *Can Med Assoc J* 1997;156:385–391. [PubMed: 9033421]
3. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people. A systematic review and meta-analysis. I Psychotropic drugs. *J Am Geriatr Soc* 1999;47:30–39. [PubMed: 9920227]
4. Ray WA, Griffin MR, Downey W. Benzodiazepines of long and short elimination half-life and the risk of hip fracture. *JAMA* 1989;262:3303–3307. [PubMed: 2573741]
5. Herings RM, Stricker BH, de Boer A, et al. Benzodiazepines and the risk of falling leading to femur fractures. Dosage more important than elimination half-life. *Arch Intern Med* 1995;155:1801–1807. [PubMed: 7654115]
6. Patten SB, Williams JV, Love EJ. Self-reported depressive symptoms following treatment with corticosteroids and sedative-hypnotics. *Int J Psychiatry Med* 1996;26:15–24. [PubMed: 8707452]
7. Hanlon JT, Horner RD, Schmader KE, et al. Benzodiazepine use and cognitive function among community-dwelling elderly. *Clin Pharmacol Ther* 1998;64:684–692. [PubMed: 9871433]
8. Hemmelgarn B, Suissa S, Huang A, et al. Benzodiazepine use and the risk of motor vehicle crash in the elderly. *JAMA* 1997;278:27–31. [PubMed: 9207334]
9. Landi F, Cesari M, Russo A, et al. Benzodiazepines and the risk of urinary incontinence in frail older persons living in the community. *Clin Pharmacol Ther* 2002;72:729–734. [PubMed: 12496754]
10. Gleason PP, Schulz R, Smith NL, et al. Correlates and prevalence of benzodiazepine use in community-dwelling elderly. *J Gen Intern Med* 1998;13:243–250. [PubMed: 9565387]
11. Blazer D, Hybels C, Simonsick E, et al. Sedative, hypnotic, and antianxiety medication use in an aging cohort over ten years: A racial comparison. *J Am Geriatr Soc* 2000;48:1073–1079. [PubMed: 10983906]
12. Ried LD, Johnson RE, Gettman DA. Benzodiazepine exposure and functional status in older people. *J Am Geriatr Soc* 1998;46:71–76. [PubMed: 9434668]
13. Ensrud KE, Nevitt MC, Yunis C, et al. Correlates of impaired function in older women. *J Am Geriatr Soc* 1994;42:481–489. [PubMed: 8176141]

14. Sarkisian CA, Liu H, Gutierrez PR, et al. Modifiable risk factors predict functional decline among older women: A prospectively validated clinical prediction tool. The Study of Osteoporotic Fractures Research Group. *J Am Geriatr Soc* 2000;48:170–178. [PubMed: 10682946]
15. Leveille S, LaCroix A, Hecht J. The cost of disability in older women and opportunities for prevention. *J Womens Health* 1992;1:53–61.
16. Gray SL, LaCroix AZ, Blough D, et al. Is the use of benzodiazepines associated with incident disability? *J Am Geriatr Soc* 2002;50:1012–1018. [PubMed: 12110059]
17. Gray SL, Penninx BW, Blough DK, et al. Benzodiazepine use and physical performance in community-dwelling older women. *J Am Geriatr Soc* 2003;51:1563–1570. [PubMed: 14687385]
18. Cornoni-Huntley J, Ostfeld AM, Taylor JO, et al. Established populations for epidemiologic studies of the elderly: Study design and methodology. *Aging (Milano)* 1993;5:27–37. [PubMed: 8481423]
19. Cornoni-Huntley, J.; Blazer, DG.; Lafferty, ME., editors. Resource Data Book. 2. Bethesda, MD: National Institute on Aging; 1990. Established Populations for Epidemiologic Studies of the Elderly.
20. Rosow I, Breslau N. A Guttman health scale for the aged. *J Gerontol* 1966;21:556–559. [PubMed: 5918309]
21. Katz S, Akpom CA. A measure of primary sociobiological functions. *Int J Health Serv* 1976;6:493–508. [PubMed: 133997]
22. Helling DK, Lemke JH, Semla TP, et al. Medication use characteristics in the elderly: The Iowa 65 + Rural Health Study. *J Am Geriatr Soc* 1987;35:4–12. [PubMed: 3794145]
23. Hanlon JT, Fillenbaum GG, Burchett B, et al. Drug-use patterns among black and nonblack community-dwelling elderly. *Ann Pharmacother* 1992;26:679–685. [PubMed: 1591430]
24. Greenblatt DJ. Pharmacology of benzodiazepine hypnotics. *J Clin Psychiatry* 1992;53(Suppl):7–13. [PubMed: 1319429]
25. Facts and Comparisons. St. Louis: Facts and Comparisons; 2000.
26. Penninx BW, Leveille S, Ferrucci L, et al. Exploring the effect of depression on physical disability: Longitudinal evidence from the established populations for epidemiologic studies of the elderly. *Am J Public Health* 1999;89:1346–1352. [PubMed: 10474551]
27. LaCroix AZ, Guralnik JM, Berkman LF, et al. Maintaining mobility in late life. II Smoking, alcohol consumption, physical activity, and body mass index. *Am J Epidemiol* 1993;137:858–869. [PubMed: 8484377]
28. Stuck AE, Walther JM, Nikolaus T, et al. Risk factors for functional status decline in community-living elderly people: A systematic literature review. *Soc Sci Med* 1999;48:445–469. [PubMed: 10075171]
29. Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull World Health Organ* 1962;27:645–658. [PubMed: 13974778]
30. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc* 1975;23:433–441. [PubMed: 1159263]
31. Taylor DH Jr, Schenkman M, Zhou J, et al. The relative effect of Alzheimer's disease and related dementias, disability, and comorbidities on cost of care for elderly persons. *J Gerontol B Psychol Sci Soc Sci* 2001;56B:S285–S293. [PubMed: 11522810]
32. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. *Appl Psychol Meas* 1977;1:385–401.
33. Kohout FJ, Berkman LF, Evans DA, et al. Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. *J Aging Health* 1993;5:179–193. [PubMed: 10125443]
34. Beekman AT, Deeg DJ, Van Limbeek J, et al. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): Results from a community-based sample of older subjects in the Netherlands. *Psychol Med* 1997;27:231–235. [PubMed: 9122304]
35. Lyness JM, Noel TK, Cox C, et al. Screening for depression in elderly primary care patients. A comparison of the Center for Epidemiologic Studies-Depression Scale and the Geriatric Depression Scale. *Arch Intern Med* 1997;157:449–454. [PubMed: 9046897]
36. Little, RJA.; Rubin, DB. Statistical Analysis with Missing Data. New York: John Wiley and Sons; 1987.

37. Collett, D. Modeling Survival Data in Medical Research. London: Chapman & Hall; 1994.
38. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Engl J Med* 1995;332:767–773. [PubMed: 7862179]
39. Wagner AK, Zhang F, Soumerai SB, et al. Benzodiazepine use and hip fractures in the elderly: Who is at greatest risk? *Arch Intern Med* 2004;164:1567–1572. [PubMed: 15277291]
40. Cutson TM, Gray SL, Hughes MA, et al. Effect of a single dose of diazepam on balance measures in older people. *J Am Geriatr Soc* 1997;45:435–440. [PubMed: 9100711]
41. Brown SL, Salive ME, Guralnik JM, et al. Antidepressant use in the elderly: Association with demographic characteristics, health-related factors, and health care utilization. *J Clin Epidemiol* 1995;48:445–453. [PubMed: 7897465]
42. Dealberto MJ, Seeman T, McAvay GJ, et al. Factors related to current and subsequent psychotropic drug use in an elderly cohort. *J Clin Epidemiol* 1997;50:357–364. [PubMed: 9120537]
43. Penninx BW, Guralnik JM, Ferrucci L, et al. Depressive symptoms and physical decline in community-dwelling older persons. *JAMA* 1998;279:1720–1726. [PubMed: 9624025]

Table 1

Baseline Characteristics According to Benzodiazepine Use: Established Populations for Epidemiologic Studies of the Elderly (N = 9,093)

	Benzodiazepine Users (n = 498)	Nonusers (n = 8,595)	
Characteristic	n (%)		P-value *
Demographic			
Age			
65–69	181 (36.4)	3,189 (37.1)	
70–74	160 (32.1)	2,584 (30.1)	.61
≥75	157 (31.5)	2,822 (32.8)	
Female	343 (68.9)	5,015 (58.4)	<.001
Education, years			
≤8	218 (44.1)	3,724 (43.7)	
9–12	194 (39.3)	3,492 (41.0)	.65
>12	82 (16.6)	1,305 (15.3)	
Income, \$			
≥10,000	156 (36.6)	2,454 (33.6)	
5,000–9,999	157 (36.9)	2,878 (39.4)	.40
<5,000	113 (26.5)	1,982 (27.1)	
Health-related factors			
Heart attack	68 (13.7)	775 (9.0)	<.001
Stroke	22 (4.4)	295 (3.4)	.25
Diabetes mellitus	71 (14.3)	1,030 (12.0)	.13
Cancer	72 (14.3)	1,043 (11.9)	.88
Hip fracture	10 (2.0)	188 (2.2)	.79
Angina pectoris	64 (13.0)	694 (8.3)	<.001
Dyspnea	175 (35.1)	2,160 (25.7)	<.001
Exertional leg pain	183 (36.8)	2,226 (26.4)	<.001
High blood pressure	281 (56.4)	3,618 (42.1)	<.001
Arthritis [†]	154 (54.2)	2,746 (45.0)	.002
Hearing problem	46 (9.3)	722 (8.5)	.51
Vision problem	42 (8.5)	786 (9.4)	.50
Depressed (Center for Epidemiologic Studies Depression Scale score ≥20)	101 (20.6)	626 (7.5)	<.001
Cognitive impairment (≥4 errors on Short Portable Mental Status Questionnaire)	26 (5.2)	736 (8.6)	.009
Difficulty falling asleep			<.001
Never	183 (36.8)	4,838 (57.6)	
Sometimes	177 (35.6)	2,424 (28.8)	
Most of the time	137 (27.6)	1,142 (13.6)	
Health behaviors and characteristics			
Cigarette smoking			
Never	262 (52.8)	4,812 (56.0)	
Past	136 (27.4)	2,332 (27.2)	.17
Current	98 (19.8)	1,432 (16.7)	
Alcohol intake, ounces/d			.008
0	315 (64.0)	4,883 (57.6)	
≤1	29 (5.9)	460 (5.4)	
>1	148 (30.1)	3,141 (37.0)	
Body mass index, kg/m ²			<.001
<18.5 (underweight)	19 (4.0)	226 (2.8)	
18.5–24.9 (normal)	220 (46.4)	3,216 (40.2)	
25.0–29.9 (overweight)	188 (39.7)	3,272 (40.9)	
≥30.0 (obese)	47 (9.9)	1,283 (16.0)	
Activity level [†]			
Low	34 (11.9)	684 (11.2)	.004
Moderate	180 (62.9)	3,303 (54.1)	
High	72 (25.2)	2,119 (34.7)	

Note: Denominators for all variables except age, sex, heart attack, stroke, diabetes mellitus, cancer, and hip fracture vary slightly from those shown.

* Chi-square test was used to evaluate differences in percentages.

[†] Data available from three of four sites. Denominator for arthritis = 6,393 and for activity level = 6,392.

Table 2
Adjusted Hazard Ratios Relating Benzodiazepine Use, Half-Life, and Dose to Incident Mobility and Activity of Daily Living (ADL) Disability

	Benzodiazepine Use, Half-Life, and Dose	Exposure n (%)	Mobility Disability		ADL Disability	
			Model 1*	Model 2†	Model 1*	Model 2‡
			Hazard Ratio (95% Confidence Interval)			
Any use		498 (5.5)	1.36 (1.21–1.53)	1.23 (1.09–1.39)	1.43 (1.22–1.67)	1.28 (1.09–1.52)
Half-life						
Short-acting		100 (1.1)	1.47 (1.21–1.79)	1.29 (1.06–1.58)	1.96 (1.57–2.44)	1.58 (1.25–2.01)‡
Long-acting		394 (4.3)	1.30 (1.13–1.50)	1.20 (1.03–1.39)	1.14 (0.93–1.42)	1.11 (0.89–1.39)
Dose (n = 4,961)						
>Minimum effective dose		115 (2.3)	1.41 (1.10–1.81)	1.33 (1.02–1.73)	1.54 (1.12–2.12)	1.50 (1.06–2.10)§
≤Minimum effective dose		113 (2.3)	1.45 (1.14–1.83)	1.29 (1.01–1.66)	1.21 (0.87–1.67)	1.08 (0.76–1.53)

* Adjusted for age, sex, time, and site.

† Adjusted for variables in Model 1 plus education, income, baseline health conditions (myocardial infarction, stroke, diabetes mellitus, cancer, hip fracture, angina pectoris, dyspnea, exertional leg pain, high blood pressure), hearing difficulties, vision difficulties, depressive symptoms, cognitive impairment, difficulty falling asleep, cigarette smoking, alcohol intake, and body mass index.

‡ $P = .03$, z test comparing coefficients for short half-life and long half-life.

§ $P = .18$, z test comparing coefficients for minimum effective dose or less and more than minimum effective dose.