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Is the Use of Benzodiazepines Associated with Incident Disability?

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Abstract

OBJECTIVES—This study examined the association between benzodiazepine use and incident disability with an emphasis on elucidating whether the underlying health conditions that result in benzodiazepine use (confounding factors) or intrinsic adverse effects of benzodiazepine use were responsible for functional decline.

DESIGN—Cohort study with follow-up of 4 to 5 years.

SETTING—A health maintenance organization (HMO) in western Washington.

PARTICIPANTS—Individuals aged 65 and older from a random sample of HMO enrollees who participated in a health promotion intervention trial (n = 1,519).

MEASUREMENTS—Benzodiazepine use was ascertained from computerized pharmacy records. Self-reported functional status was assessed using a six-item physical function scale ranging from vigorous activity to self-care activities of daily living (ADLs). Two outcomes were examined: decline in overall physical function and limitations in self-care ADLs. Multivariate models were examined that included demographic characteristics, health status, and health behaviors that were likely to be confounders. Several analyses were conducted to examine whether benzodiazepine use or confounding factors were responsible for functional decline.

RESULTS—Benzodiazepine use was significantly associated with incident loss of physical function (hazard ratio (HR) = 1.51, 95% confidence interval (CI) = 1.02–2.24) in the fully adjusted model. Although use of benzodiazepines was associated with limitations in ADLs, it was not significant when adjusting for other factors (HR = 1.71, 95% CI = 0.87–3.34). Several of our findings suggest that the health conditions leading to benzodiazepine use may partly or fully explain these associations: (1) use of anxiolytic benzodiazepines (HR = 1.95, 95% CI = 1.24–3.07), but not hypnotic agents (HR = 1.21, 95% CI = 0.73–2.00), was associated with functional decline; (2) adjustment for health status variables minimized these associations; and (3) there was little evidence of dose response.

CONCLUSIONS—A modestly increased risk for decline in physical function was associated with benzodiazepine use, especially of anxiolytic agents. The health conditions that result in benzodiazepine use may be more important in the pathogenesis of disability than benzodiazepine use itself. Although there are many reasons for avoiding benzodiazepines in older adults, it is still unclear whether use contributes independently to functional decline.

Keywords

benzodiazepines; activities of daily living; disability; adverse event

Benzodiazepines are one of the most common types of psychotropic medication classes used by community-dwelling older people, with a prevalence of approximately 10% to 12%.^{1,2} Use of benzodiazepines has been associated with several negative health consequences, including falls,³ hip fractures,^{4,5} depressed mood,⁶ and impaired cognition.⁷ Long-term use of benzodiazepines is more common in older than in younger individuals,⁸ despite recommendations to avoid prolonged use in older people.

An important question is whether benzodiazepine use contributes to functional decline in older people. Several cross-sectional studies have demonstrated that older individuals using benzodiazepines have impaired physical function when compared with nonusers.^{2,9,10} Only two longitudinal studies have examined the association between benzodiazepine use and functional decline and have reported conflicting results.^{11,12} This issue deserves further attention, particularly because benzodiazepine use is a potentially modifiable risk factor for disability and other treatment options may be available.

One problem encountered when attempting to examine the effect of benzodiazepine use on functional decline is determining whether it is the drug itself or the medical condition for which the drug is prescribed that is contributing to the decline (e.g., confounding by indication). In general, users of benzodiazepines have poorer health status than nonusers, as indicated by poor self-rated health,^{1,2,13} higher healthcare utilization,² and presence of many chronic conditions including cardiac disease^{1,13} and emotional/mental health conditions.^{1,2,13,14} A limitation of prior research is that consideration of potential confounders was limited.^{11,12} It is still unclear whether benzodiazepine use independently increases risk of decline beyond the health conditions these agents are used to treat. The objective of this study was to evaluate the association between benzodiazepine use and incident disability, with an emphasis on elucidating whether it was the underlying health

conditions that result in benzodiazepine use (confounding factors) or the intrinsic adverse effects of benzodiazepine use itself that were responsible for functional decline.

METHODS

Study Population

This was a secondary analysis of data from a disability and falls prevention trial targeting multiple risk factors in nondisabled community-residing older people conducted between 1986 and 1992.¹⁵ The study sample was recruited from a random sample of men and women aged 65 and older enrolled in Group Health Cooperative of Puget Sound (GHC). GHC is a large staff-model health maintenance organization providing medical care to more than 370,000 people, including more than 40,000 older adults. From a random sample of 5,240 participants aged 65 and older who received care from three large Seattle GHC clinics, primary care physicians excluded those too ill to participate (8%), and mailed questionnaires (up to two mailings) were sent to the remainder. Of this sample, 36% returned completed consent forms and questionnaires; 13% refused participation; 2% were ineligible because they were institutionalized, seriously ill, or out of the area; and 41% failed to respond. Of those returning completed questionnaires, 400 were excluded because they reported difficulty with ambulation or with one or more self-care activities of daily living (ADL), thus providing a sample of 1,559 for the original trial. For this analysis, only subjects who were continuously enrolled in GHC for the follow-up period or until censored were included (n = 1,519).

The details of the trial design, intervention, and enrollment statistics have been previously described.¹⁵ Briefly, participants were randomized to an active intervention (nurse assessment and intervention), active control (single nurse visit for general health promotion), or usual care. The intervention was a brief low-intensity intervention focused on the reduction of six risk factors for disability and falls: physical inactivity, excess alcohol consumption, home hazards, use of psychotropic or cardiovascular medications, and uncorrected hearing or visual impairments.

Data Collection

Questionnaires were mailed to participants at baseline and at follow-up Years 1, 2, and 4. Participants were asked to provide information about demographics, health status, and health behaviors. A telephone interview was conducted if respondents did not return questionnaires.

Dependent Variable—Functional status was assessed using the Medical Outcome Study (MOS) Physical Function Scale.¹⁶ Participants were asked whether their health had limited them in six hierarchical domains of functioning: vigorous activity; moderate activity; bending, lifting or stooping; climbing stairs; walking across a room; and several self-care ADLs (bathing, toileting, feeding, and dressing). The MOS was scored using a Guttman scale, with 0 indicating no impairments and 6 indicating impairments in self-care ADLs. Individuals were excluded from the original trial if they reported difficulty with ambulation

or one or more self-care ADLs, thus the most-impaired subjects had a baseline score of 4 on the MOS scale.

Two disability outcomes were examined. First, overall decline in physical function was defined as an increase by two or more points on the MOS (six-item Guttman scale). A decline of two points or more discriminated between those who had major intervening illness and those who did not.¹⁷ The second outcome was becoming limited in self-care ADLs, a specific question on the MOS (MOS score of 6). In these analyses, subjects were censored at the time of first occurrence of each disability outcome; therefore, we did not consider future functional recovery.

Benzodiazepine Exposure—Exposure to benzodiazepines was determined from GHC automated pharmacy files. The pharmacy files included information regarding the therapeutic class, drug form, strength, date dispensed, and quantity dispensed for each prescription filled or refilled at GHC's outpatient pharmacies since March 1977. Most medications prescribed by GHC physicians are filled in GHC pharmacies. A survey of GHC enrollees treated for various types of pain during 1989/1990 found that 93% of prescriptions for diazepam were filled at GHC pharmacies.¹⁸

The exposure period examined was the 6 months before each interview (baseline and 1-year and 2-year interviews). Each participant was classified as using or not using a benzodiazepine during each period. For users, the intensity of benzodiazepine use was calculated according to the following three steps. First, the total milligrams for each benzodiazepine prescription was calculated by multiplying the number of pills dispensed by the tablet 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), chlorazepate (15 mg), lorazepam (2 mg), flurazepam (15 mg), oxazepam (30 mg), temazepam (15 mg), triazolam (0.125 mg), clonazepam (0.5 mg), and chlordiazepoxide (15 mg). Third, all standardized doses were summed to create the total standardized dose (TSD). The TSD represents the number of days of use of the benzodiazepine over 6 months if used at the minimum effective dose.

The primary exposure variable was any use of a benzodiazepine versus no use. Secondary analyses were conducted using additional prespecified definitions of exposure to examine the robustness of the associations (intensity, number of prescriptions, indication for use). The minimal duration or intensity of benzodiazepine exposure that might contribute to functional decline is unknown, but it was hypothesized that low dose or brief exposure (single prescription) would not increase risk for functional decline. Two variables were created to examine this issue: (1) intensity of use: high intensity (≥ 90 TSD (≥ 90 days of use if used at the minimum effective dose)), low intensity (<90 TSD), or no use and (2) number of benzodiazepine dispensings within each period: 0, 1, or 2 or more.

Accounting for indication for benzodiazepine use is important to minimize confounding by indication. In this study, the indication for benzodiazepine use was not known. Therefore, drugs were classified according to their Federal Drug Administration (FDA)-approved indications: hypnotic (triazolam, flurazepam, temazepam) or anxiolytic (diazepam,

alprazolam, lorazepam, chlorthalidone, clonazepam, oxazepam). We hypothesized that risk would be similar for both types, and if a difference was found this could represent confounding. Lastly, a person was classified as using an agent with a short half-life ($t_{1/2} < 24$ hours), long half-life ($t_{1/2} \geq 24$ hours), or both. Benzodiazepines with a longer half-life may increase the likelihood of adverse outcomes.⁵

Potential Confounding Variables—Several demographic, health status, and health behavior factors were identified from the literature that may be confounders of the association between benzodiazepine use and disability.^{1,2,19,20} Demographic variables included age, sex, education (completed high school, did not complete high school), and annual income ($< \$15,000$, $\geq \$15,000$). Health behavior variables included smoking status at baseline (current, past, never) and alcohol use (nondrinker, 1 drink/day, > 1 drink/day). Body mass index (kg/m^2) was calculated from self-reported weight and height.

The Chronic Disease Score (CDS) is a measure derived from computerized pharmacy data reflecting the number and severity of several chronic conditions. The CDS has been shown to be highly predictive of death, hospitalization, and ambulatory utilization of health care in a variety of GHC study populations.²¹ The positive affect score, a measure of psychological distress and well-being, was obtained from a 10-item scale with items adapted from Veit et al.²² This scale correlated moderately with depressive symptoms assessed by the Geriatric Depression Scale ($r = -.59$).²³ Subjects were asked about degree of pain they experienced on a daily basis using a Likert scale (0 = no pain, 10 = very severe pain). In addition, subjects were asked about how much stress they had experienced in the past year (0 = none, 10 = a great deal).

Statistical Methods

Missing Data—Multiple imputation was performed to accommodate missing values for nine of the covariates using Statistical Solutions software.^{24,25} Table 1 identifies the variables that were imputed and the sample size for each variable. The proportion of data that was imputed for an individual variable did not exceed 16%. The problem with only including individuals with complete data (complete case analysis) in the analyses is that the remaining sample may not be representative of the target population and the estimates may be biased. Using the method of propensity scores and Bayesian predictive distributions, missing data were randomly imputed and five complete data sets were obtained. Each model was estimated using each of the five data sets, and the results were combined. This method assumes missing data are missing at random and takes into account the uncertainty in imputing missing values, resulting in conservative estimates of standard errors. Specifically, estimated standard errors of corresponding hazard ratios include uncertainty within a complete imputed data set (between individual) and uncertainty between different imputations (within individual). In this way, a rigorous approach to “filling in” missing data is achieved.

Statistical Analysis—SAS statistical software was used to perform all statistical analyses (SAS Institute Inc., Cary, NC). Differences in baseline characteristics between users and nonusers of benzodiazepines before baseline were assessed using chi-square and two-sample

t test for categorical and continuous variables, respectively. Discrete time hazards models were used to determine the unadjusted and adjusted hazard ratios for the two disability outcomes. Exact time to decline was unobserved; the outcome was only known to have occurred between administration of questionnaires (interval censored). To model this structure appropriately, a binomial model was used with the complementary log-log link function.²⁶ To accommodate unequal time intervals between questionnaires, the length of time interval in days was included in the model. A squared term was also included to allow for nonlinearity.²⁷ Furthermore, to adjust for late entry into the risk set (left-truncation), time since first use of benzodiazepine was included in the model.²⁷ Left truncation occurs in these data because first use of benzodiazepine could have occurred before baseline.

The five exposure variables were modeled as time-dependent variables; therefore, an individual could have had a different exposure before each interview. Other covariates also modeled as time-dependent covariates were stress, pain, positive affect score, and alcohol use. Analyses were conducted to examine specifically the effect of confounding by disease status. First, separate age- and sex-adjusted models were built to examine the effect of confounding by demographics, health status, and health behaviors. The health status variables were grouped into two distinct categories: variables associated with emotional health or pain and indicators of overall health status.

We conducted additional analyses to evaluate the sensitivity of our results to various analytical decisions. First, the analyses were repeated restricting the sample to those filling more than one benzodiazepine prescription during the study period ($n = 1,337$). Because information regarding actual use is not available, restricting the analyses to those who filled more than one prescription is likely to represent those who actually took the benzodiazepine. Second, the exposure window was increased to the 1 year before each interview. A longer exposure duration was examined because the minimal duration of benzodiazepine exposure necessary to adversely affect functional status is unknown. Third, a sensitivity analysis was conducted to informally assess whether the censoring was informative. Each model was run two ways: first with decline in function assumed to occur just before death in those individuals who died (that is, were censored) and second without this assumption. Results differed little, indicating that censoring was noninformative.²⁷

RESULTS

Of the 1,519 participants, 124 (8.2%) had filled a prescription for a benzodiazepine in the 6 months before the baseline interview. Most users had low intensity of use over this period, with 90 (72.6%) receiving less than 90 TSD. Fifty-two percent of users were taking an agent with a short half-life, and 54% were using a hypnotic benzodiazepine.

Baseline characteristics of the participants according to use of benzodiazepines in the 6 months before baseline are shown in Table 1. Users were more likely to be female and have a high school education and an income of less than \$15,000. Furthermore, users of benzodiazepines differed from nonusers on many health-related variables; they were more likely to report fair or poor health and had higher average levels of pain and stress, lower scores on the positive affect scale, and higher chronic disease scores.

Overall, 132 (8.7%) and 545 (35.9%) participants experienced incident limitations in self-care ADLs and loss in physical function, respectively. When examining risk of disability considering baseline benzodiazepine use only, risk of becoming limited in self-care ADLs was 12.9% versus 8.3% for users and nonusers, respectively ($\chi^2 = 3.02$, $P = .082$), and risk of loss of physical function was 38.7% versus 35.6% for users and nonusers, respectively ($\chi^2 = 0.47$, $P = .493$).

Table 2 displays the crude and adjusted hazard ratio (HR) for developing incident limitation in ADLs and loss of physical function over the follow-up period according to use of benzodiazepines. The unadjusted HR associated with benzodiazepine use was 2.27 (95% confidence interval (CI) = 1.17–4.39) for limitations in ADLs, which was no longer significant after adjusting for all potential confounders (HR = 1.71, 95% CI = 0.87–3.34). The unadjusted HR associated with benzodiazepine use was 1.70 (95% CI = 1.16–2.52) for loss in overall physical function, which remained significant in the fully adjusted model (HR = 1.51, 95% CI = 1.02–2.24). To examine the influence of potential confounders on the relationship between benzodiazepine use and incident disability, we built separate age- and sex-adjusted Cox proportional models for demographic, health status, and health characteristics (Table 2). The strength of the association between benzodiazepine use and both disability outcomes was reduced when adjusting for health status variables.

Table 3 displays the results for the additional classifications of benzodiazepine exposure. A dose-response relationship was not apparent for either outcome. In fact, for incident limitations in ADLs, a stronger association existed for low-intensity use than high-intensity use (HR = 2.03, 95% CI = 1.02–4.02 for low-intensity use compared with nonusers). For both outcomes, a stronger association was found between nonusers and those filling two or more prescriptions than between nonusers and those filling only one prescription. When adjusting for all possible confounders, the association between two or more benzodiazepine prescriptions and decline was no longer significant for either outcome.

Type of benzodiazepine was significantly related to incident disability (Table 3). Anxiolytic use (HR = 1.95, 95% CI = 1.24–3.07), but not hypnotic use (HR = 1.21, 95% CI = 0.73–2.00), was associated with loss of physical function. After observing this significant finding, we statistically compared the model with benzodiazepine use categorized according to indication for use with the model including the exposure as use versus no use to determine which exposure categorization provided the best fit of the data. Categorizing the benzodiazepine according to indication for use provided a significantly better fit than the latter model (likelihood ratio test, $P < .01$) for the loss of physical function outcome only. Risk of loss of physical function was not increased with use of a short-acting agent or long-acting agents. We were unable to examine whether the half-life of the agent was associated with incident limitations in ADLs because there were only a few events in one of the subgroups.

Additional Analyses

Additional adjustment for assignment to intervention resulted in similar HRs (data not shown). Similar results were obtained for all exposure variables (any use, intensity, indication for use, and half-life) when eliminating subjects who had filled only one

benzodiazepine prescription during the study period ($n = 149$) (data not shown). When extending the exposure window to 1 year before each interview, the HRs tended to be closer to the null and no exposure variables were significant in fully adjusted models (data not shown).

DISCUSSION

In this prospective study, use of benzodiazepines, particularly agents classified as anxiolytics was significantly associated with incident loss of physical function. An association with benzodiazepine use and limitations in ADLs was also observed, but the CI was wide and not statistically significant in the fully adjusted model, perhaps because of the smaller number of events. A dose-response relationship was not observed; in fact, low-intensity use but not high intensity was significantly associated with developing limitations in ADLs. When limiting the sample to those who filled more than one benzodiazepine prescription during the study period, the association between benzodiazepine use and loss of physical function remained significant.

Only two longitudinal studies have examined whether benzodiazepine use is associated with functional decline. Levielle et al. reported that users of sedatives were twice as likely to experience functional decline over the subsequent year as nonusers after adjusting for age, but this finding was no longer significant after adjusting for other variables.¹¹ More recently, Sarkisian et al. reported that use of short-acting benzodiazepines was associated with decline in vigorous and basic activities, and use of long-acting agents was associated with decline in ADLs over a 4-year period.¹² The major limitation of these studies is that consideration of potential confounders was limited.

Although we found a modest increased risk for functional decline in those using benzodiazepines, several findings are consistent with the interpretation that the medical reasons for which benzodiazepines are prescribed, rather than an adverse effect of benzodiazepine use, may partially or fully account for disability. First, the association between benzodiazepine use and disability varied when agents were classified according to indication for use (anxiolytic, hypnotic). If benzodiazepine use increases risk of disability, the increased risk should be apparent for both hypnotic and anxiolytic use. Our finding that anxiolytic use, but not hypnotic use, was associated with loss of physical function may suggest confounding by indication. Differences in health status are likely to exist between anxiolytic and hypnotic users that we were unable to account for in this study that may explain the significant association.¹ We classified medications according to the FDA-approved indication, acknowledging that medications are not always prescribed according to FDA-approved indications.

Second, the inclusion of health-related variables in the multivariate models reduced the strength of the association between benzodiazepine use and the disability outcomes. It is likely that we have not eliminated confounding by related disease and symptom states. For example, presence of depressive symptoms has been found to be associated with incident disability.^{12,19} Although we adjusted for mood by using the positive affect scale, which is

moderately associated with the Geriatric Depression Scale, confounding by depressive symptoms is still possible.

Third, intensity of benzodiazepine use was not related to disability. The existence of a dose-response relationship would have strengthened the case for a causal interpretation over alternate explanations. It is not clear why low intensity, but not high intensity, of use was significantly associated with incident limitations in ADLs when compared with nonusers. It is possible that those individuals who had adverse events attributed to benzodiazepine use were identified early and only received a few prescriptions or were given low doses. The intensity of exposure used in this study made no assumptions about duration of benzodiazepine use or dose or whether use was continuous. The TSD represents the number of days of benzodiazepine use over 6 months if used at the minimum effective dose; thus, high-intensity users, defined as at least 90 TSD, could be considered to have used benzodiazepines for, at a minimum, half the days during the 6-month period.

We have expanded on prior research by using a time-varying exposure, defining exposure in several ways, and including several factors that may explain reasons for use of benzodiazepines to attempt to adequately control for confounding. By modeling benzodiazepine use as a time-varying exposure, we allowed use to change over time and attempted to capture use of benzodiazepines that was proximal to the functional assessments. It may not be reasonable to assume that benzodiazepine use at baseline would have an effect on functional status 3 or 4 years later,¹² especially if use was discontinued. This is supported by the fact that, in the univariate analyses, we did not find significant differences between rates of functional decline when considering baseline benzodiazepine use only, especially for decline in overall function. Use of a time-varying exposure is especially important if the negative effect on function is greatest during the time the drug is being consumed and the effects are reversible upon discontinuation. Although we improved upon methodology used in prior research, our definition of exposure still allowed a delay of up to several months before the assessment of functional status.

The mechanisms through which benzodiazepines might increase risk of disability are not entirely known but are likely to be multifaceted and complex. Disability may occur because of a single event (e.g., hip fracture), which could occur with short-term exposure, but the incidence of disability due to benzodiazepine-induced hip fracture would be expected to be low. For example, it was estimated that approximately 10% of all hospitalizations for femur fractures resulting from accidental falls were caused by benzodiazepine use.⁴ Approximately 40% to 50% of these individuals would be expected to develop disability.²⁸ Benzodiazepine use may result in disability through its adverse effects on cognition⁷ and mood;⁶ conditions associated with functional decline.²⁰ Disability caused by these mechanisms would likely require more-extended benzodiazepine use. We examined exposure periods of 6 months and 1 year to gain a better understanding of the relevant duration of benzodiazepine use. The strength of association was stronger when benzodiazepine use was ascertained for the 6-month window.

Several limitations should be noted. First, misclassification of exposure is possible. Information about prescription drug use was obtained from a computerized pharmacy

database, which cannot discern whether individuals actually took the benzodiazepine. We attempted to address this problem by creating an exposure variable based on number of prescriptions and including in the sensitivity analysis only subjects who filled two or more prescriptions during the study period. These analyses are more likely to reflect actual usage of the medications of interest than would receipt of a single isolated prescription. Second, the database only provides information about prescriptions filled at GHC pharmacies. It seems likely that this misclassification would be nondifferential, which would tend to bias risk estimates toward the null and reduce our power to detect differences. Third, the ability to detect small increases in risk, especially for limitations in ADLs would require a much larger sample size or higher levels of exposure to benzodiazepines than available in our study. We cannot discount that use of benzodiazepines is associated with a small increase in developing incident limitations in ADLs, because the CIs are wide. Fourth, this study was conducted among predominately white, relatively healthy, middle-class older adults, and our results may not be generalizable to other populations.

In summary, we found a moderate increase in risk for decline in physical function associated with benzodiazepine use, especially anxiolytic agents. Several of our findings suggest that the medical reasons for which these medications are prescribed might partially or fully explain this association. Although there are many reasons for avoiding benzodiazepines in older adults, it is still unclear whether use contributes independently to functional decline.

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References

1. 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]
2. 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]
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. 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]
5. 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]
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. Simon GE, VonKorff M, Barlow W, et al. Predictors of chronic benzodiazepine use in a health maintenance organization sample. *J Clin Epidemiol*. 1996; 49:1067–1073. [PubMed: 8780618]
9. Ried LD, Johnson RE, Gettman DA. Benzodiazepine exposure and functional status in older people. *J Am Geriatr Soc*. 1998; 46:71–76. [PubMed: 9434668]

10. 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]
11. Leveille SG, LaCroix AZ, Hecht JA, et al. The cost of disability in older women and opportunities for prevention. *J Womens Health.* 1992; 1:53–61.
12. 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]
13. Olfson M, Pincus HA. Use of benzodiazepines in the community. *Arch Intern Med.* 1994; 154:1235–1240. [PubMed: 7911297]
14. Mayer-Oakes SA, Kelman G, Beers MH, et al. Benzodiazepine use in older, community-dwelling southern Californians: Prevalence and clinical correlates. *Ann Pharmacother.* 1993; 27:416–421. [PubMed: 8097415]
15. Wagner EH, LaCroix AZ, Grothaus L, et al. Preventing disability and falls in older adults: A population-based randomized trial. *Am J Public Health.* 1994; 84:1800–1806. [PubMed: 7977921]
16. Ware, JE.; Sherbourne, CD.; Davies, A., et al. The MOS Short-Form General Health Survey: Development and Test in a General Population. Santa Monica, CA: Rand Corporation; 1988.
17. Wagner EH, LaCroix AZ, Grothaus LC, et al. Responsiveness of health status measures to change among older adults. *J Am Geriatr Soc.* 1993; 41:241–248. [PubMed: 8440846]
18. Saunders, KW.; Stergachis, A.; VonKorff, M. Group Health Cooperative of Puget Sound. In: Strom, BL., editor. *Pharmacoepidemiology*. London: John Wiley; 1994.
19. 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]
20. 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]
21. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. *J Clin Epidemiol.* 1992; 45:197–203. [PubMed: 1573438]
22. Veit CT, Ware JE. The structure of psychological distress and well-being in general populations. *J Consult Clin Psychol.* 1985; 51:730–742. [PubMed: 6630688]
23. Scholes D, LaCroix AZ, Wagner EH, et al. Tracking progress toward national health objectives in the elderly: What do restricted activity days signify? *Am J Public Health.* 1991; 81:485–488. [PubMed: 2003629]
24. Statistical Solutions for Data Analysis. Systems Manual. Cork, Ireland: Statistical Solutions Ltd; 1999.
25. Little, RJA.; Rubin, DB. *Statistical Analysis with Missing Data*. New York, NY: John Wiley and Sons; 1987. p. 255-259.
26. Collett, D. *Modelling Survival Data in Medical Research*. London: Chapman and Hall; 1994. p. 114-115.
27. Allison, PD. *Survival Analysis Using the SAS System: A Practical Guide*. Cary: SAS Institute, Inc; 1995. p. 225-231.
28. Huddleston JM, Whitford KJ. Medical care of elderly patients with hip fractures. *Mayo Clin Proc.* 2001; 76:295–298. [PubMed: 11243276]

Table 1

Characteristics of Benzodiazepine Users and Nonusers at Baseline

Characteristic	n	Benzodiazepine Use Before Baseline		P-value
		No n = 1,395	Yes n = 124	
Demographic, %				
Age	1,519			.087
65–69		36.1	28.2	
70–74		32.6	31.5	
75		31.3	40.3	
Female	1,519	57.4	75.8	.000
Graduated from high school *	1,485	83.5	90.8	.037
Income <15,000 *	1,275	32.5	51.9	.000
Health status				
Positive affect, [†] mean (±SD)	1,452	45.4 (±0.2)	41.4 (±0.8)	.000
Pain, [‡] mean (±SD)	1,353	20.1 (±0.6)	30.7 (±2.3)	.000
Stress, [‡] mean (±SD)	1,455	35.0 (±0.7)	47.9 (±2.7)	.000
Fair or poor self-rated health, % *	1,501	10.2	18.7	.004
Chronic disease score, %	1,519			.000
0		41.6	21.0	
1–3		35.2	42.7	
4		23.2	36.3	
Health behaviors, %				
Smoking status *	1,487			
Current		7.2	6.7	.976
Former		36.9	37.5	
Never		55.9	55.8	
Alcohol use *	1,450			
Nondrinker		30.6	31.9	.630
1 drink/day		43.5	39.5	
1 drink/day		25.9	29.4	
Body mass index				
<24.9 *	1,405	48.6	61.9	.006

Note: Total number observations were specified for variables with missing values. Chi-square testing and Student *t* test were used to analyze categorical and continuous variables, respectively.

* Imputed variables.

[†] Range 0–60; higher score is better.

[‡] Range 0–100.

SD = standard deviation.

Table 2

Association of Benzodiazepine Use with Risk of Developing Limitations in Activities of Daily Living and Loss of Physical Function

Characteristic	Limitations in ADLs		Loss of Physical Function	
	HR	95% CI	HR	95% CI
Unadjusted	2.27	1.17–4.39	1.7	1.15–2.52
Adjusted for potential confounders *				
Demographic				
Age and sex	2.17	1.13–4.18	1.71	1.16–2.52
All demographic	2.09	1.08–4.04	1.69	1.15–2.50
Health status				
Factors related to emotional health/pain [†]	1.83	0.95–3.52	1.55	1.05–2.28
Indicators of general health status [‡]	2.06	1.06–4.00	1.62	1.09–2.39
All health status	1.79	0.92–3.48	1.50	1.02–2.22
Health behaviors [§]	2.20	1.13–4.27	1.70	1.15–2.51
Fully adjusted ^{//}	1.71	0.87–3.34	1.51	1.02–2.24

* All models adjusted for age, sex, and past benzodiazepine use.

[†] Adjusted for positive affect, pain, stress, age, sex, and past benzodiazepine use.

[‡] Adjusted for self-rated health, chronic disease score, age, sex, and past benzodiazepine use.

[§] Adjusted for alcohol use, smoking status, body mass index, age, sex, and past benzodiazepine use.

^{//} Adjusted for body mass index, income, education, alcohol use, smoking status, positive affect, stress, pain, chronic disease score, self-reported health, age, sex, and past benzodiazepine use.

CI = confidence interval; HR = hazard ratio.

Table 3

Hazard Ratios (HR) for Developing Limitations in Activities of Daily Living (ADL) and Loss of Physical Function According to Intensity of Benzodiazepine Use, Number of Benzodiazepine Prescriptions, and Indication for Benzodiazepine Use

Exposure	Baseline n (%)	ADL Limitations*		Loss of Physical Function*	
		HR	95% CI	HR	95% CI
Intensity of use					
Low (<90 TSD)	90 (5.9)	2.03	1.02–4.02	1.40	0.94–2.08
High (≥ 90 TSD)	34 (2.2)	0.82	0.23–2.95	1.10	0.56–2.16
Number of prescriptions					
1	61 (4.0)	1.48	0.65–3.37	1.43	0.92–2.23
2 or more	63 (4.1)	2.05	0.87–4.82	1.66	0.99–2.80
Indication†					
Anxiolytic	50 (3.3)	1.43	0.61–3.39	1.95	1.24–3.07
Hypnotic	67 (4.4)	2.09	0.94–4.63	1.21	0.73–2.00
Half-life‡§					
Long	53 (3.5)	—	—	1.64	0.97–2.80
Short	65 (4.3)	—	—	1.35	0.86–2.13

^{*} Adjusted for body mass index, income, education, alcohol use, smoking status, positive affect, stress, pain, chronic disease score, self-reported health, age, sex, and past benzodiazepine use.

[†] Those using both anxiolytics and hypnotics were included in the model as a separate category for completeness, but the results are not shown because of significant imprecision of the estimates secondary to the small number of individuals in this subgroup (n = 7).

[‡] Those using a benzodiazepine with a short and a long half-life were included in the model as a separate category for completeness, but the results are not shown because of the significant imprecision of the estimates secondary to small number of individuals in this subgroup (n = 6).

[§] We were unable to examine whether the half-life of the agent was associated with incident limitations in ADLs because of few events in one of the subgroups.

CI = confidence interval; TSD = total standardized daily dose in 6 months before interviews.