Benzodiazepine Use and Hip Fractures in the Elderly

Who Is at Greatest Risk?

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Background: It remains unclear whether benzodiazepine use increases hip fracture incidence. We studied this relationship in a large cohort, controlling for multiple potential confounders.

Methods: We analyzed 42 months of New Jersey Medicaid health care claims data for all enrollees. Each eligible person-day was assigned to categories of benzodiazepine exposure and categories of other predictors, based on prior and current medication dispensing and diagnosis information. Hip fractures were identified based on hospital claims with primary discharge diagnosis International Classification of Diseases, Ninth Revision (ICD-9) codes 820.xx.

Results: Cohort members (n=125203) contributed 194071 person-years and had 2312 eligible hip fractures. After adjustment for age, sex, race, Medicaid nursing home residence, exposure to other psychoactive medications, including antiparkinsonian medications, diagnoses of epilepsy and dementia, and hospitalization in the previous 6 months, the incidence rate of hip fracture was significantly higher compared with no benzodiazepine use for exposure to any benzodiazepine (incidence rate ratio [IRR], 1.24; 95% confidence interval [CI], 1.06-1.44), to a short half-life, high-potency benzodiazepine (IRR, 1.27; 95% CI, 1.01-1.59), during the first 2 weeks after starting a benzodiazepine (IRR, 2.05; 95% CI, 1.28-3.28), during the second 2 weeks after starting a benzodiazepine (IRR, 1.88; 95% CI, 1.15-3.07), and for continued use (IRR, 1.18; 95% CI, 1.03-1.35).

Conclusions: The incidence of hip fracture appears to be associated with benzodiazepine use. Contrary to several previous studies, short half-life benzodiazepines are not safer than long half-life benzodiazepines. Hip fracture risk is highest during the first 2 weeks after starting a benzodiazepine and declines thereafter.

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With 71 million prescriptions dispensed in 2002, and an annual growth rate of 3%, benzodiazepines are currently the 13th leading therapeutic class of medications in the United States, despite well-publicized concerns about their adverse effects, which include an increased risk of hip fracture among the elderly. Because hip fractures frequently lead to disability and death among the elderly, this concern has prompted recent interventions to decrease benzodiazepine use in elderly patients.6,7 Data about the relationship between benzodiazepine use and the incidence of hip fracture remain conflicting.8 Two landmark case-control studies published almost 15 years ago suggested that use of long elimination half-life hypnotic- anxiolytic agents9 in general and use of long elimination half-life benzodiazepines10 in particular increase elderly patients’ risk for hip fracture. Since then, some studies have confirmed associations between benzodiazepine use and falls,11,14 and benzodiazepine use and risk of fall15,16 and hip fracture.17 Others found increased risk of hip fracture only with short elimination half-life benzodiazepines,18-20 while some studies failed to detect a relationship between benzodiazepine use and incidence of fall21,22 or hip fracture.23-24 Studies that investigated the effects of duration of use on risks of fall,15 fall-related hospitalization,14 and hip fracture20 found increased risks during the first 2 weeks of benzodiazepine treatment but differ in conclusions regarding the risk of benzodiazepine use after that time. Confounding by indication25 and benzodiazepine exposure misclassification26 may account for some of the differences in results.

To evaluate hip fracture risk when a benzodiazepine would be clinically useful, clinicians and patients need to know which situations of benzodiazepine use carry the highest risk of hip fracture. We studied the association between benzodiazepine dispensing and hip fracture incidence among a cohort of elderly Medicaid enrollees in New Jersey. In particular, we were interested in filling existing

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knowledge gaps by confirming the association between benzodiazepine use and hip fracture in a large cohort study, controlling for multiple time-varying potential founders; assessing whether hip fracture risk differed across benzodiazepines differing in half-life and potency; and whether hip fracture risk changed with duration of therapy.

**METHODS**

We conducted a cohort study of all members in the New Jersey Medicaid program who met inclusion criteria. Medicaid is a program of national health assistance, funded by the US federal government and the states, for low-income individuals who are aged, blind, or disabled, and their families, or members of families with dependent children.

**DATA SOURCES**

We obtained monthly Medicaid enrollment and Medicaid and Medicare claims files from the computerized New Jersey Medicaid Management Information Systems (MMIS) for all elderly Medicaid enrollees between January 1987 and June 1990. We used data from this period because it largely predates the publication of a landmark study in December 1989 reporting the risk of hip fracture associated with long half-life benzodiazepine use (and should make bias due to selection of short half-life benzodiazepines for patients at higher hip fracture risk less likely).

We extracted enrollee characteristics (date of birth, sex, race) from the MMIS enrollment files. From drug claims files, we extracted the National Drug Code number of each dispensed medication and the date of dispensing. National Drug Code numbers were cross-referenced to data on ingredients using information in the First Databank database and Food and Drug Administration National Drug Code Directory. Medic aid prescribing data have been shown to be reliable and valid, yielding measures of medication use that are internally consistent and stable over time for both individual drugs and broader therapeutic classes.

From MMIS institutional claims files we extracted data on acute care hospitalization, and admissions to long-term care facilities and nursing homes. We created hospitalization and nursing home episodes by combining hospital claims and nursing home claims, respectively, with overlapping and adjacent dates (which may result when patients are transferred from one service to another).

**COHORT**

The cohort consisted of all 125203 individuals enrolled in the New Jersey Medicaid program for at least 6 continuous months between January 1987 and June 1990 who were at least 65 years old at entry into the cohort. Individuals contributed person-days as occurring within days 1 through 15 or within days 16 through 30 of the new benzodiazepine episode. Exposed person-days were calculated by subtracting the clinical episode from the start of the new benzodiazepine episode. A new benzodiazepine treatment episode started with a benzodiazepine dispensing (and should make bias due to selection of short half-life benzodiazepines for patients at higher hip fracture risk less likely).

For each day of benzodiazepine exposure, we calculated the diazepam milligram equivalent (DME) doses for each benzodiazepine, which allowed us to convert total milligrams dispensed to therapeutically equivalent DME doses, based on equivalencies previously validated by Shader et al.

**BENZODIAZEPINE EXPOSURE**

We classified each person-day into different benzodiazepine exposure categories. Exposed person-time started on the day a benzodiazepine was dispensed. To determine duration of exposure, we first calculated for each type of benzodiazepine (long half-life; short half-life, high potency; short half-life, low potency) the median number of days between 2 consecutive dispensings for the subgroup of the study population who were continuously enrolled in Medicaid during the baseline year and received more than 1 benzodiazepine dispensing during that time. Median duration between dispensings was 29 days for each benzodiazepine type. We therefore classified as exposed the dispensing day and the 29 days following each dispensing day. One exposure variable categorized days into days exposed to any benzodiazepine or not exposed to a benzodiazepine.

We further categorized each exposed person-day by type of benzodiazepine into exposure to only a long (>20 hours) half-life benzodiazepine (quazepam, chlordiazepoxide, clonazepam, diazepam, halazepam, prazepam, clorazapate, flurazepam); only a short half-life, high-potency benzodiazepine (approximate dosage equivalents below 2 mg: alprazolam, lorazepam, triazolam); only a short half-life, low-potency benzodiazepine (approximate dosage equivalents of 30 mg: oxazepam, temazepam); or exposure to more than 1 benzodiazepine type on that day.

We also classified exposed person-days by time since the start of a new benzodiazepine treatment episode. A new benzodiazepine episode started with a benzodiazepine dispensing at least 6 benzodiazepine-free months (ie, 210 days without a benzodiazepine prescription dispensed). We classified person-days as occurring within days 1 through 15 or within days 16 through 30 of the new benzodiazepine episode. Exposed person-days that occurred after day 30 of the new benzodiazepine episode and exposed days that occurred earlier than 210 days after the last dispensing were classified as continued benzodiazepine use days.

For each day of benzodiazepine exposure, we calculated the diazepam milligram equivalent (DME) doses for each benzodiazepine, which allowed us to convert total milligrams dispensed to therapeutically equivalent DME doses, based on equivalencies previously validated by Shader et al.

We calculated the number of persons with average daily doses during their exposed days above and below 10 DME.

**OTHER PREDICTORS**

We classified each person-day into categories of other predictors. For time-varying characteristics that continue to change over time (age, Medicaid nursing home residence, and exposure to psychoactive medications other than benzodiazepine [sedating antihistamines, barbiturates and nonbarbiturate sedative hypnotics, antidepressants, lithium, neuroleptics, anticonvulsants]), we classified each day according to exposure on that day. As for benzodiazepine exposure, we defined duration of psychoactive medication exposure as median time between 2 consecutive dispensings in each class of medications. For characteristics that, once acquired, remain (sex, race, epilepsy, Parkinson disease, dementia), we categorized each person-day as exposed from the time point onward on which the definition of exposure was met (first presence of a discharge diagnosis of epilepsy, first receipt of an antiparkinsonian medication [levodopa with or without carbidopa, bromocriptine, pergolide, selegiline], and first presence of an inpatient diagnosis of dementia or first receipt of ergoloid mesylates). Lastly, we classified person-days according to whether the enrollee had spent 1 or more days in a hospital or long-term care facility in the preceding 6 months.
For initial analyses, we had also categorized each person-day into current exposure to cardiac glycosides, type 1A antiarrhythmics, thiazides, other diuretics, and oral glucocorticoids, and past diagnoses of wrist fracture and bone metastases. We excluded these covariates from final analyses because their inclusion did not change results.

OUTCOME

We defined hip fractures based on Medicaid or Medicare claims for acute care hospitalization that lasted longer than 1 day (to avoid misclassifying emergency department admissions for hip fracture rule-out as admission for hip fracture treatment) and had a primary discharge diagnosis of hip fracture (International Classification of Diseases, Ninth Revision (ICD-9) codes 820.xx). We defined eligible hip fractures as first hip fractures for individuals during the study period and occurring after 6 months of continuous Medicaid eligibility without a hip fracture. We excluded hip fractures that occurred on days when individuals were not enrolled in Medicaid. The hospital admission date was used as the date of the hip fracture.

ANALYSIS

We created a person-day level data set with indicators on each day of benzodiazepine exposures, other predictors, and hip fracture status for each enrollee. We summed person-days and hip fractures for each category of benzodiazepine exposure and other predictors. We divided person-days by 365.25 and expressed crude incidence rates as number of hip fractures per 1000 person-years.

To estimate the measures of interest to our study—the overall incidence rate of hip fracture associated with any benzodiazepine use, the incidence rates associated with use of different types of benzodiazepine, and with different durations of benzodiazepine use—we defined 3 sets of mutually exclusive binary exposure variables and classified each person-day accordingly. One binary variable indicated exposure to any benzodiazepine or no benzodiazepine. A set of 4 binary variables indicated exposure to a long half-life benzodiazepine only; a short half-life, high-potency benzodiazepine only; a short half-life, low-potency benzodiazepine only; more than 1 benzodiazepine type; and no benzodiazepine. A set of 3 binary variables indicated exposure to a benzodiazepine within 15 days of the start of a new benzodiazepine treatment; exposure to a benzodiazepine within 16 to 30 days of the start of a new benzodiazepine; continuous benzodiazepine exposure, and no benzodiazepine exposure.

For multivariate analyses of relative incidence rates, we conducted Poisson regressions, using the GENMOD procedure in SAS statistical software (version 8.2, SAS Institute Inc, Cary, NC). We specified 3 models, one for each set of exposure variables. Each final model included the respective benzodiazepine exposure main effects, the other predictor (covariate) main effects (listed in Table 1), and all pairwise interactions among covariates other than the exposures of interest. The 95% confidence intervals (CIs) are based on the standard errors of the regression coefficients adjusted for overdispersion using the Pearson χ² statistic.

RESULTS

DISTRIBUTION OF PERSONS AND PERSON-TIME

The cohort consisted of 125,203 New Jersey Medicaid enrollees who contributed 194,071 person-years to the study. Table 1 shows the distribution of persons and person-time over categories of demographic and other predictors, while Table 2 shows the distributions over categories of benzodiazepine exposure. The population consisted mostly of elderly white women. Almost half (45%) of all benzodiazepine exposed person-time was associated with use of short half-life, high-potency benzodiazepine only, and 31% with use of long half-life benzodiazepine only. Seventy-five percent of benzodiazepine recipients received up to 10 DME per day and 95% of

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*For time-varying exposures, the number of persons exceeds the total number of enrollees because each person may contribute time to more than one time-varying predictor category.
benzodiazepine recipients received up to 20 DME per day. The mean (SD) benzodiazepine dose among benzodiazepine recipients was 8.0 (8.0) DME.

**CRUDE EFFECTS OF BENZODIAZEPINE EXPOSURE**

There were 2312 first hip fractures during the observation period (Table 2). Compared with not being exposed to a benzodiazepine, exposure to any benzodiazepine was associated with a 54% higher rate of hip fracture (unadjusted incidence rate ratio [IRR], 1.54; 95% CI, 1.37-1.73). Crude incidence rate ratios also indicated increased hip fracture incidence associated with exposure to high- and low-potency short half-life benzodiazepines and exposure to more than 1 benzodiazepine type. All durations of new and continued benzodiazepine exposure were associated with higher hip fracture incidence than not being exposed but crude incidence rate ratios declined with increasing duration of use. We did not observe an association between exposure to a long half-life benzodiazepine and hip fracture.

**HIP FRACTURES AND USE OF ANY BENZODIAZEPINE, ADJUSTED FOR POTENTIAL CONFOUNDERS**

Adjusting for age, sex, race, Medicaid nursing home residence, use of other psychoactive medications, epilepsy, use of antiparkinsonian medications, dementia, and recent hospitalization lowered the estimated incidence rates of hip fracture associated with benzodiazepine use (Table 2). In adjusted models, benzodiazepine use was associated with a 24% increased rate of hip fracture, compared with not using a benzodiazepine (IRR, 1.24; 95% CI, 1.06-1.44). Our original models contained more finely classified categories of these covariates as well as additional potential confounders. Reducing the number and categories of covariates did not noticeably change parameter estimates.

**HIP FRACTURES AND USE OF BENZODIAZEPINE DIFFERING IN HALF-LIFE AND POTENCY**

Compared with no benzodiazepine use, adjusted hip fracture incidence rates for exposure to benzodiazepines in different categories were similar (Table 2). Exposure to short half-life, high-potency benzodiazepines (IRR, 1.27; 95% CI, 1.01-1.59) reached statistical significance, while exposure to short half-life, low-potency benzodiazepines, mid-/long half-life benzodiazepines, and mixed benzodiazepine type exposure did not (Table 2). Comparing the risks associated with exposure to different benzodiazepine types to each other did not reveal significantly elevated incidence rate ratios associated with any one benzodiazepine type (Table 3).

**HIP FRACTURES AND NEW USE OF BENZODIAZEPINES**

The adjusted incidence rate of hip fracture compared with no benzodiazepine use was greatest during the first 2 weeks of starting a benzodiazepine (IRR, 2.05; 95% CI, 1.28-3.28), less during the second 2 weeks (IRR, 1.88; 95% CI, 1.15-3.07), and less for continued users (IRR, 1.18; 95% CI, 1.03-1.35) (Table 2). Compared with continued benzodiazepine use, new use was associated with a significantly higher hip fracture rate (IRR, 1.74; 95% CI, 1.07-2.82) for the first 15 days. During the second 15 days of new use, the hip fracture incidence rate did not differ significantly from that during the first 15 days or from the incidence rate ratio during continued use (Table 3). A linear trend test (scoring: 0=no benzodiazepine use, 1=less than or equal to 15 days use; 2=16-30 days use, and 3=continued use, and a binary overall exposure variable), however, showed a significant (P=.006) negative association between hip fracture incidence and duration of use when there is benzodiazepine exposure. The incidence rate declined by 26.4% with transition from the first 2 weeks of use to the second, and to continued use.
In this study of more than 125,000 elderly Medicaid enrollees, contributing almost 200,000 person-years, we observed a significant, modestly elevated rate of hip fracture when enrollees were exposed to benzodiazepines, compared with not being exposed, after controlling for a large number of potential confounders. Of the different benzodiazepine types, short half-life, high-potency benzodiazepine exposure was associated with a statistically significant higher incidence rate compared to no benzodiazepine use, although hip fracture incidence rates were similar across benzodiazepine types. Incidence was particularly high when a new benzodiazepine was started and declined with continued use.

The present results confirm the previously reported association between benzodiazepine use and hip fracture incidence using a large cohort study. As mentioned by Ray and colleagues,3,9 prospective cohort studies of falls and related injuries12,17,21,38-43 measured benzodiazepine exposure at baseline only, most with follow-up of 1 year or longer. In contrast to these studies, we were able to account for the time-varying nature of exposure to benzodiazepines, while controlling for exposure to other medications and comorbid conditions that may confound the hip fracture association. We did so by classifying each person-day into the appropriate exposure and covariate categories, based on prior dispensing and diagnostic information. Day-by-day definition of exposure status—although not based on medication administration records—should decrease the likelihood of potentially serious exposure27 and covariate misclassification.

Consistent with some18-20 but not all9,10,15-17 previous studies, our results suggest that short half-life benzodiazepines, which are often considered the best choice for elderly patients among this class of drugs,33 carry significant risk of hip fracture. In contrast to the recent studies which also suggest increased risk associated with short half-life benzodiazepine use, bias due to prescribing of these benzodiazepines to patients at higher risk for hip fracture is a less likely explanation for our results because our data predate the landmark publication of the finding of increased risk associated with long half-life benzodiazepines.10 However, differences across types of benzodiazepine were small. We did not find significant differences when we compared incidence rate ratios associated with exposure to the different benzodiazepine types to each other. Given the cumulative published data reporting increased hip fracture risk with exposure to all types of benzodiazepines, short half-life benzodiazepines should not be considered safer than long half-life benzodiazepines. The best estimate of hip fracture incidence may be that associated with any benzodiazepine exposure. We have not studied the effects of dose on hip fracture. The majority of benzodiazepine recipients in our study received less than 20 DME per day. Recently, however, Wang et al20 suggested that hip fracture risk increases with benzodiazepine doses equal to or greater than 3 DME; however, this finding merits replication.

Finally, and of most clinical relevance, our results add to the findings from other studies14,15,20 that suggested greater hip fracture risk during the first few weeks after benzodiazepines are started. Patients should receive increased surveillance and support mechanisms during the beginning of therapy. However, we need to keep in mind that such measures may only prevent a small percentage of hip fractures among the elderly. In our study, only 42 hip fractures occurred in the first 30 days after starting a benzodiazepine.

We need to consider 3 sets of potential limitations when interpreting the present results. We inferred exposure from pharmacy dispensing claims. We do not know whether patients actually took the dispensed medications. It is conceivable that the increased incidence of hip fracture during the first 15 days of new use is due to patients’ higher compliance during the initial days of therapy. However, our classification of continued use required repeated benzodiazepine dispensings, which would be unlikely for patients who do not actually take their benzodiazepine.

Lack of power could account for the lack of significant associations between long half-life and short half-life, low potency benzodiazepine use and hip fracture incidence. With more person-time exposed to short half-life, low potency benzodiazepines, we may have found a significant association after adjusting for potential confounders. However, results of unadjusted analyses, with more degrees of freedom, did not suggest a significantly increased incidence of hip fracture associated with long half-life benzodiazepines.

Despite controlling for a broad array of confounders, our results may still suffer from under-adjustment for potential confounders. Adjustment for factors we were able to measure halved the estimated crude effect. Residual confounding by factors for which we only had incomplete proxy measures (eg, dementia) or factors that we could not measure at all in claims data (eg, smoking status, body mass index, bone density) would be expected to confound the results in the same direction and further adjustment would be expected to further decrease the association.

Since a randomized controlled trial to study hip fracture incidence following benzodiazepine use will never be conducted, a quasi-experimental study is the next best...
option to arrive at an estimate of the association that is less subject to this source of confounding. We are currently conducting a longitudinal, controlled, quasi-experimental study to explore changes in hip fracture incidence after New York State implemented a prescribing restriction that resulted in a 50% decline in benzodiazepine use across all subgroups of patients. An observed reduction in hip fracture incidence concomitant with this reduction in benzodiazepine use would validate previous described epidemiological associations including the results of the present study.

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