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Impact of drug interactions, dosage, and duration of therapy on the risk of hip fracture associated with benzodiazepine use in older adults

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Abstract

Purpose—To determine how concomitant use of potentially interacting drugs, drug dosage, and duration of therapy modify the risk of hip fracture associated with use of benzodiazepines and related drugs (BDZ) in older adults.

Methods—A nested case-control study was conducted in Medicare patients 65 years or older, enrolled in the Pennsylvania drug assistance program (PACE) between 1994 and 2005. We included 17,198 patients with a hip fracture leading to hospitalization and 85,990 controls matched on hospitalization (index date). BDZ and interacting drug use within two weeks preceding the index date was determined using information on date of drug dispensing, days supplied, quantity dispensed, and strength. Date of the first BDZ prescription within the year preceding the index date was used as surrogate for duration of therapy.

Results—While the adjusted relative risk (RR) for overall BDZ use and hip fracture was 1.2 (95% confidence interval 1.1, 1.2), the RRs for concomitant use of alprazolam, lorazepam, and zolpidem and their interacting drugs were 1.5 (1.3, 1.7), 1.9 (1.7, 2.2), and 1.7 (1.4, 2.0), and 2.1 (1.5, 2.8) for BDZ use initiated within 14 days preceding the index date. RR increased with increasing BDZ dose and was highest for defined daily BDZ doses >1 (RR: 1.3 (1.2, 1.5)).

Conclusions—BDZ associated hip fracture risk increases with concomitant use of interacting drugs, higher doses, and is highest at initiation. Clinicians should avoid concomitant use of BDZ and interacting drugs, because their impact on hip fracture risk is at least additive.

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Conflict of interest
Kristina Zint is an employee of Boehringer Ingelheim.

Keywords

Aged; benzodiazepines; case-control studies; drug interactions; hip fractures; zolpidem

INTRODUCTION

The association between benzodiazepine use in older adults and the risk of hip fracture is well established.[1,2] However, the risk of hip fracture is likely to be heterogeneous in this population. Earlier studies indicated an increased risk of hip fracture with long-acting compounds while short-acting benzodiazepines were not associated with an increased risk.[3,4] More recent studies also reported a higher risk of falls or hip fracture with short-acting benzodiazepines or zolpidem, a short-acting benzodiazepine related drug.[5–8] One explanation for the apparent discrepancy is that prescribers learned to avoid long-acting substances in vulnerable older adults.[7] For sake of clarity, we will use BDZ from now on to refer to benzodiazepines and benzodiazepine related drugs.

The increased risk of hip fracture might, however, be rather a function of the concentration achieved than a function of the half-life of the BDZs and may be highest immediately after initiation.[7,9] The impact of a given dose may be modified by different factors like concomitant use of interacting drugs altering BDZ plasma concentrations and subsequently sedative effects. Patient characteristics like liver and renal dysfunction can reduce the clearance of BDZs or their active metabolites[10] and interacting drugs and thereby alter BDZ effects.

Pharmacodynamic interactions might also lead to an increased risk for adverse effects. Seventy-one percent of individuals with at least one benzodiazepine prescription who experienced an injury, including fractures, had used a benzodiazepine-drug combination classified as a major interaction within 30 days prior to the injury.[11] In this population concomitant use of interacting drugs increased the odds of an injury more than two-fold.[11] Neither the association between individual BDZs nor the association between interacting drugs alone (without BDZs) and the risk of hip fracture were assessed in that study, however.[11]

The aim of this study was therefore to determine how factors that are likely to modify (a) BDZ plasma concentrations like drug dose, concomitant use of pharmacokinetically interacting drugs, and co-morbidity known to affect clearance, or (b) the effect of BDZs (i.e. pharmacodynamically interacting drugs and duration of therapy) modify the risk of hip fracture associated with BDZ use. In particular, we wanted to assess the impact of drugs potentially interacting with BDZ on the risk of hip fracture in more detail.

METHODS

Study design

We performed a case-control study nested within a cohort of all Medicare patients who were 65 years or older and enrolled in the Pennsylvania drug assistance program (PACE) between 1994 and 2005. We defined cases as hip fracture among outpatients between 1995 and 2005

leading to hospitalization.[12] In case of multiple admissions with hip fracture per person, only the first was considered.

For each case of hip fracture (N=17,198), five controls (N=85,990) were individually matched on the month of hospitalization. All controls were assigned the same index date as the hospital admission date of the corresponding case.

In order to assure that the patients were eligible for medical services and drug benefits for at least a 12-month period, cases and controls had to have at least one claim for both a non-prescription service and a prescription each within three 6-month periods before the index date. To ensure a full drug exposure history,[13] cases and controls hospitalized or staying in a nursing home any time during the three months before the index date were excluded.

The study protocol was approved by the IRB of the Brigham and Women's Hospital and the Ethics Committee of the Medical Faculty of the University of Heidelberg.

BDZ exposure

The primary exposure of interest was BDZ use during the 2 weeks prior to the index date. To categorize use during this time window, we considered all available BDZ (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, eszopiclone, flurazepam, halazepam, lorazepam, oxazepam, quazepam, temazepam, triazolam, zaleplon, zolpidem) dispensed within the 90 days before the index date. We then defined BDZ exposure as having at least one prescription of a BDZ dispensed extending into the 14 days before the index date based on the information on the dispensing date and the days supplied. In agreement with earlier studies[7,8,14] a grace period after the calculated end of supply was chosen because some BDZ have increased half-lives in the elderly or active metabolites exceeding the half-life of the BDZ by far.[10,15] BDZ users were further classified with respect to BDZ half-life, prescribed dose, and duration of BDZ therapy.

BDZ half-life

Appropriateness of BDZ therapy in the elderly is dichotomously defined depending on BDZ half-life;[16] BDZ were therefore classified as short-acting (half-life ≤24h: alprazolam, estazolam, lorazepam, oxazepam, temazepam, triazolam, eszopiclone, zaleplon, zolpidem) and long-acting substances (half-life >24h: chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, halazepam, quazepam). BDZ users with long- and short-acting BDZ prescriptions were classified as long-acting BDZ users.

BDZ dose

We calculated the BDZ daily dose from the strength dispensed and by dividing the quantity of drug dispensed by the days of supply. To standardize daily dose over all BDZ, we divided the daily dose by the defined daily dose (DDD - World Health Organization). In case of BZD prescriptions with more than 7 days of overlap based on the days supplied, the overall daily dose was calculated adding the different prescriptions. With 7 or fewer days of overlap they were assumed to be early fillings rather than parallel use. The dose was categorized into

low (daily dose ≤0.5 DDD), medium (0.5 DDD < daily dose ≤1 DDD), and high (daily dose >1 DDD).

Duration of BDZ use

Duration of BDZ therapy within the year prior to the index date was defined depending on the first BDZ prescription during the 12 months before the index date. If the first BDZ script was filled within the 14 days prior to the index date this corresponds to a new user design[17] with a wash-out period of approximately 12 months in case of prior exposure. If the first script was between 10 and 12 months before the index date, however, prevalent use for many years prior to the exposure assessment period cannot be excluded. BDZ users were grouped into seven different categories according to the timing of the first BDZ script before the index date: within 271–360 days, 181–270 days, 91–180 days, 61–90 days, 31–60 days, 15–30 days, and first script within 14 days before the index date.

BDZ-drug interactions

We assessed pharmacokinetic and pharmacodynamic interactions potentially leading to an increased effect of alprazolam, lorazepam, and zolpidem (the most commonly prescribed BDZ). We considered strong and moderate inhibitors of cytochrome P450 3A4, the main isozyme, by which alprazolam and zolpidem are metabolized,[18] and all drug-drug interactions mentioned in Stockley´s,[19,20] DRUGDEX,[21,22] or summary of product characteristics of the originator brand.[23] The following pharmacokinetically interacting substances were considered:

Alprazolam [18,19,21,23]: Aprepitant, amiodarone, cimetidine, clarithromycin, cyclosporine, dextropropoxyphen, diltiazem, ergotamine, erythromycin, esomeprazole, fluconazole, fluoxetine, fluvoxamine, indinavir, isoniazid, itraconazole, ketoconazole, nefazodone, nelfinavir, nicardipine, nifedipine, omeprazole, paroxetine, propoxyphene, ritonavir, saquinavir, telithromycin, troleandomycin, and verapamil.

Lorazepam [19,21,23]: Valproate and probenecid.

Zolpidem [18,20,22,23]: Aprepitant, cimetidine, clarithromycin, diltiazem, erythromycin, fluconazole, indinavir, itraconazole, ketoconazole, nelfinavir, nefazodone, telithromycin, ritonavir, saquinavir, and verapamil.

As pharmacodynamically interacting with all BZD we considered the following substances: Opioids, H_1-antihistamines, barbiturates, anticonvulsants, non-benzodiazepine non-barbiturate hypnotics, antidepressants, neuroleptics, and muscle relaxants.

Presence of a drug-drug interaction was defined as concomitant use of the corresponding BDZ and at least one prescription of an interacting compound extending into the 14 days before the index date using the information on the service start date and the days supplied.

BDZ-disease interactions

For alprazolam we assessed the presence of liver disease and chronic renal failure (International Classification of Diseases (ICD-9) code within the 12 months before the index

date) as they might modify alprazolam exposure.[23] For lorazepam and zolpidem we only considered liver disease as a condition potentially modifying drug exposure.[23]

Potentially confounding variables

All potential confounders were defined during the 12-month period before the index date. For the definition of potential confounders, any ICD-9 code corresponding to the diseases during the 12 months prior to the index date and dispensed prescription of a drug class during the 3 months prior to the index date was considered as evidence of the corresponding condition or use of the corresponding drug class. Due to this definition, which is standard in analyses of claims data, there are no missing values for any of the confounders except income (missing in 30 cases and 3 controls). We adjusted all multivariable models for a variety of patient characteristics, co-morbidity, co-medication, and health care system use.

Analysis

We used crude, age-, gender-, and race-adjusted, and multivariable adjusted logistic regression models conditioning on each matched set to estimate the incidence rate ratio for BDZ use and hip fracture using the more general term relative risk (RR) for this measure of association. When individual BDZ were analyzed, we excluded patients using combinations of alprazolam, lorazepam, or zolpidem with other BDZs.

The test for dose-response was performed by chi-square test for trend over the ordinal categories only among BDZ users. A P value <0.05 was considered significant.

To analyze interactions, we used the departure-from-additivity method as described earlier.[24] In these analyses, we included the index year as covariate because individual matches were broken; we also excluded patients using combinations of alprazolam, lorazepam, or zolpidem with other BDZs. All analyses were performed using SAS software version 9.1, SAS Institute Inc., Cary, NC, USA.

RESULTS

Table 1 shows characteristics of the study population. The cases were older, more likely to be women, and had more frequent BDZ use in the 14 days before the index date compared to controls. Table 2 lists the characteristics of BDZ use among hip fracture patients and controls. Alprazolam, lorazepam, and zolpidem were the most frequently prescribed BDZ which is reflected also in the fact that the greatest proportion of prescribed BDZ was short-acting. Most of the patients were exposed to low dose BDZ (daily dose ≤0.5 DDD).

The crude and adjusted relative risks (RR) for potential risk factors of hip fracture are shown in Table 3. BDZ exposure was associated with risk of hip fracture (crude RR=1.30; 95% confidence interval (CI): 1.24, 1.36). Controlling for socio-demographics, health care utilization, co-morbidity, and co-medication attenuated the RR for hip fracture (RR=1.16; 95% CI: 1.10, 1.22). Exposure to a short-acting BDZ was associated with an increased adjusted hip fracture risk (RR=1.19; 95% CI: 1.13, 1.26), whereas long-acting BDZ were not associated with an increased fracture risk (RR=1.05; 95% CI: 0.94, 1.16). When focussing on the most frequently prescribed individual substances we found an increased hip

fracture risk for zolpidem (RR=1.26; 95% CI: 1.11, 1.44) and lorazepam (RR=1.29; 95% CI: 1.19, 1.40), but not for alprazolam (Table 3).

Hip fracture risk increased with increasing BDZ dose (P <0.005) and the highest risk was observed for BDZ doses >1 DDD (RR=1.32 (95% CI: 1.17, 1.48) (Table 3). The relation between the date of the first BDZ prescription and the index date as a surrogate of duration of therapy is shown in Table 3. The highest hip fracture risk was found in those users who started BDZ use within 14 days preceding the index date (RR=2.05 (95% CI: 1.52, 2.77).

More than 70% of the exposed cases and controls were already exposed to a BDZ within the 271–360 days before the index date indicating long-term use. Cases were more likely to be on an interacting drug than controls (Table 4). Most potential BDZ-drug interactions were pharmacodynamic interactions (Table 5). Out of the cases exposed to alprazolam, 72% were concomitantly exposed to an interacting drug as opposed to 61 % of the controls (Table 4). The corresponding percentages were 57% of the cases and 43% of the controls for lorazepam and 59% vs. 50% for zolpidem (Table 4).

Risk of hip fracture was increased for concomitant use of alprazolam and interacting drugs (RR=1.51; 95% CI: 1.34, 1.69; Table 4) and we found a tendency toward a positive interaction with a proportion of disease among those with both exposures that is attributable to their interaction (AP) of 13% (95% CI: 0, 27%). Concomitant use of lorazepam and interacting drugs (RR=1.94; 95% CI: 1.74, 2.17; Table 4) increased the risk of hip fracture, too. There was no indication for interaction in terms of a synergistic effect, however, with an AP of only 3% (95% CI: -10%, +16%). Similarly, for zolpidem and concomitant interacting drug use risk was increased without indication for interaction (AP 1% (95% CI: -21%, +22%)).

Combining BDZ-drug interactions and BDZ-disease interactions in separate models had very little effect on the risk associated with concomitant use of the BDZ and interacting drugs and there was no meaningful departure from additive risks (data not shown).

DISCUSSION

This study provides a comprehensive analysis of potential modifiers of the association between BDZ use and risk of hip fracture. Our findings are consistent with previous studies showing an increased risk of hip fracture associated with overall BDZ use.[7,9,25] The risk of hip fracture associated with BDZ use is highest immediately following initiation of therapy and increases with higher doses. Concomitant use of alprazolam, lorazepam, and zolpidem with interacting drugs is associated with an increased risk of hip fracture. In case of lorazepam we observed an almost two-fold increased risk of hip fracture. Our results are likely to be clinically important.

Because many of the interacting drugs belong to substance classes that are associated with an increased risk of hip fracture, a higher risk with concomitant use does not in itself indicate any interaction between the drugs in the sense of a synergistic effect. When assessed alone, the interacting drugs were associated with a similar or even larger risk of hip fracture than BDZ. For lorazepam and zolpidem and their interacting drugs effects appeared

to be additive, whereas for alprazolam and its interacting drugs we found a tendency toward a synergistic effect. In both cases, however, concomitant prescribing should be avoided as it is associated with an increased risk of hip fracture. To our knowledge BDZ-drug interactions and their impact on hip fracture risk were never analyzed in such detail before.

Our results on possible differences between long- and short-acting BDZ with respect to risk of hip fracture confirm data from studies showing an increased risk for short-acting substances.[7,9] An explanation for that finding might be a selective prescribing of short-acting substances to more vulnerable patients. It may also be that patients are preferentially started on short-acting BDZ and only then switched to long-acting compounds so that the increased risk observed at the beginning of BDZ therapy may be preferentially attributed to short-acting BDZ.

We found a dose-response relation over categories of DDD of BDZ use and the risk of hip fracture thus confirming earlier findings.[9] Our findings on changing hazards over time since initiation of BDZ use confirm previous data with the highest risk observed in new BDZ users.[7,25–27] It is unclear whether the risk reduction over time on drug is a consequence of adaptive biologic mechanisms or selection of “resistant” people over time (depletion of susceptibles).[28]

We found no association between use of alprazolam and hip fracture risk confirming earlier findings.[29,30] For lorazepam our finding of an increased risk is consistent with some[9,29] but not all previous studies.[4] For zolpidem we found a smaller risk of hip fracture than an earlier study,[8] which might be due to the larger sample size enabling us to control for a large variety of potential confounders.

This study has several limitations. First, our analysis is based on drug-dispensing data. We therefore do not know whether the patients really took the BDZs. The use of drug dispensing data collected prior to the event for the whole population, however, makes differential misclassification of exposure unlikely. Non-differential misclassification of exposure cannot be ruled out and would tend to bias risk estimates towards the null. We only have information on prescription drugs and thus cannot assess the effects of over-the-counter (OTC) medications. Most of the drugs potentially modifying the risk of hip fracture are prescription drugs, however, cimetidine, omeprazole, and H_1-antihistamines as OTC drugs might have been missed. We estimated the daily dose of BDZ based on information on the days supplied potentially leading to an underestimation of the actual dose if the BDZ is not taken continuously. In our analysis on duration of BDZ use we cannot exclude the possibility of BDZ use prior to the exposure assessment period. As the first prescription date was used as a surrogate for duration of therapy, some misclassification of patients with intermittent BDZ therapy during the 12 months preceding the index date cannot be ruled out. We did not expand the exposure time window beyond 12 months because potential adaptive biologic mechanisms or selection of “resistant” people over time might have already taken place. Drugs which might decrease rather than increase the effect of alprazolam, lorazepam, or zolpidem were not taken into account. We assume that effect-increasing drugs would outweigh the effect of drugs with effect-decreasing properties. The small numbers of pharmacokinetic interactions precluded evaluation of individual subgroups. We used

prescriptions of bisphosphonates and other antiosteoporotic drugs as a proxy for severity of co-morbidity but residual confounding by severity cannot be ruled out. We required prescription and non-prescription services as proof-of-system use. In a study of drug interactions in older adults this is very unlikely to limit the generalizability of our findings. Finally, unmeasured confounding, particularly by indication, is possible, although we adjusted for a large variety of potentially confounding factors. Confounding by indication could be present if e.g. the combinations of BDZ with potentially interacting drugs would have been preferentially prescribed to patients with particularly severe conditions that may have placed these patients at an increased risk of hip fracture.

In conclusion, our study confirmed that higher doses of BDZ should be avoided and that patients should be monitored carefully at the beginning of BDZ therapy. Concomitant prescribing of interacting drugs was associated with a substantially increased risk of hip fractures. Physicians should therefore carefully monitor such patients and prescribe the lowest possible doses if the combination cannot be avoided.

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REFERENCES

1. Cumming RG, Le Couteur DG. Benzodiazepines and risk of hip fractures in older people: a review of the evidence. CNS Drugs. 2003; 17:825–837. [PubMed: 12921493]
2. Takkouche B, Montes-Martínez A, Gill SS, Etminan M. Psychotropic medications and the risk of fracture: a meta-analysis. Drug Saf. 2007; 30:171–184. [PubMed: 17253881]
3. Ray WA, Griffin MR, Schaffner W, et al. Psychotropic drug use and the risk of hip fracture. N Engl J Med. 1987; 316:363–369. [PubMed: 2880292]
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. Ray WA, Thapa PB, Gideon P. Benzodiazepines and the risk of falls in nursing home residents. J Am Geriatr Soc. 2000; 48:682–685. [PubMed: 10855607]
6. Passaro A, Volpato S, Romagnoni F, et al. Benzodiazepines with different half-life and falling in a hospitalized population: The GIFA study. Gruppo Italiano di Farmacovigilanza nell'Anziano. J Clin Epidemiol. 2000; 53:1222–1229. [PubMed: 11146268]
7. Wang PS, Bohn RL, Glynn RJ, et al. Hazardous benzodiazepine regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture. Am J Psychiatry. 2001; 158:892–898. [PubMed: 11384896]
8. Wang PS, Bohn RL, Glynn RJ, et al. Zolpidem use and hip fractures in older people. J Am Geriatr Soc. 2001; 49:1685–1690. [PubMed: 11844004]
9. 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]

10. Bauer TM, Ritz R, Haberthür Ch, et al. Prolonged sedation due to accumulation of conjugated metabolites of midazolam. Lancet. 1995; 346:145–147. [PubMed: 7603229]
11. French DD, Chirikos TN, Spehar A, et al. Effect of concomitant use of benzodiazepines and other drugs on the risk of injury in a veterans population. Drug Saf. 2005; 28:1141–1150. [PubMed: 16329716]
12. Ray WA, Griffin MR, Fought RL, Adams ML. Identification of fractures from computerized Medicare files. J Clin Epidemiol. 1992; 45:703–714. [PubMed: 1619449]
13. Suissa S. Immeasurable time bias in observational studies of drug effects on mortality . Am J Epidemiol. 2008; 168:329–335. [PubMed: 18515793]
14. Vink NM, Klungel OH, Stolk RP, et al. Comparison of various measures for assessing medication refill adherence using prescription data. Pharmacoepidemiol Drug Saf. 2009; 18:159–165. [PubMed: 19109809]
15. Allain H, Bentué-Ferrer D, Polard E, et al. Postural instability and consequent falls and hip fractures associated with use of hypnotics in the elderly: a comparative review. Drugs Aging. 2005; 22:749–765. [PubMed: 16156679]
16. Fick DM, Cooper JW, Wade WE, et al. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med. 2003; 163:2716–2724. [PubMed: 14662625]
17. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol. 2003; 158:915–920. [PubMed: 14585769]
18. Flockhart, DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine; 2007. (http://medicine.iupui.edu/flockhart/table.htm) [Accessed 22 September 2008]
19. Baxter, K. Stockley´s drug interactions. London, Chicago: Pharmaceutical Press; 2006. p. 7
20. Baxter, K. Stockley´s drug interactions. London, Chicago: Pharmaceutical Press; 2007. p. 8
21. Klasco, RK. DRUGDEX® System. Greenwood Village, Colorado: Thomson Reuters; (Edition expires 6/2007)
22. Klasco, RK. DRUGDEX® System. Greenwood Village, Colorado: Thomson Reuters; (Edition expires 9/2008)
23. Fachinformationsverzeichnis Deutschland (einschlieβlich EU-Zulassungen). Rote Liste®. Frankfurt, Germany: Service GmbH; (http://www.fachinfo.de) [Accessed 23 February 2009]
24. Lundberg M, Fredlund P, Hallqvist J, Diderichsen F. A SAS program calculating three measures of interaction with confidence intervals. Epidemiology. 1996; 7:655–656. [PubMed: 8899400]
25. 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]
26. Chang CM, Wu EC, Chang IS, Lin KM. Benzodiazepine and risk of hip fractures in older people: a nested case-control study in Taiwan. Am J Geriatr Psychiatry. 2008; 16:686–692. [PubMed: 18669947]
27. Neutel CI, Hirdes JP, Maxwell CJ, Patten SB. New evidence on benzodiazepine use and falls: the time factor. Age Ageing. 1996; 25:273–278. [PubMed: 8831871]
28. Guess HA. Exposure-time-varying hazard function ratios in case-control studies of drug effects. Pharmacoepidemiol Drug Saf. 2006; 15:81–92. [PubMed: 16287211]
29. Pierfitte C, Macouillard G, Thicoïpe M, et al. Benzodiazepines and hip fractures in elderly people: case-control study. BMJ. 2001; 322:704–708. [PubMed: 11264208]
30. Tamblyn R, Abrahamowicz M, du Berger R, et al. A 5-year prospective assessment of the risk associated with individual benzodiazepines and doses in new elderly users. J Am Geriatr Soc. 2005; 53:233–241. [PubMed: 15673346]

Key points

- The general association between benzodiazepine use in older adults and the risk of hip fracture is well established
- Little is known about the impact of drug-drug interactions on this association
- In this large nested case-control study the risk of hip fracture was substantially higher in patients concomitantly using benzodiazepines and potentially interacting drugs

Table 1

Demographic and clinical characteristics of hip fracture patients and controls

Characteristics	Hip Fracture Patients (n= 17,198)	Controls (n= 85,990)
Mean age, years (SD)	84.3 (6.6)	79.5 (7.0)
	N (%)	**N (%)**
Gender		
female	15,371 (89.4)	70,792 (82.3)
male	1,827 (10.6)	15,198 (17.7)
Race		
white	16,779 (97.6)	80,710 (93.9)
nonwhite	419 (2.4)	5,280 (6.1)
BDZ use	2,840 (16.5)	11,410 (13.3)
Co-medication use[a]		
Antiparkinson drugs	653 (3.8)	1,582 (1.8)
Atypical neuroleptics	677 (3.9)	1,263 (1.5)
Classical neuroleptics	647 (3.8)	1,897 (2.2)
Co-morbidity[a]		
Degenerative muscle disorders	50 (0.3)	140 (0.2)
Hemiplegia	312 (1.8)	759 (0.9)
Delirium	4,121 (24.0)	9,528 (11.1)
Other fractures	2,666 (15.5)	5,496 (6.4)
	mean (SD)	mean (SD)
Days in hospital	3.6 (8.9)	2.1 (6.4)
Days in nursing home	2.4 (10.5)	1.0 (6.9)
Annual income ($)[b]	9,845.5 (3,851.5)	10,293.0 (4,206.0)
Charlson comorbidity score	2.1 (2.1)	1.6 (1.8)
Number of medications	8.7 (5.2)	8.1 (4.9)

Abbreviations: SD, standard deviation; BDZ, benzodiazepines and related drugs.

[a] only potentially confounding covariates with the most pronounced effects on hip fracture risk are shown

[b] missings: hip fracture patients: N= 30; controls: N= 3

Table 2

Characteristics of BDZ use in hip fracture patients and controls

Drug exposure	Hip fracture patients using BDZ (N= 2840)		Controls using BDZ (N=11,410)	
	N	%	N	%
alprazolam	703	24.8	3,289	28.8
chlordiazepoxide	66	2.3	416	3.7
clonazepam	182	6.4	728	6.4
clorazepate	139	4.9	650	5.7
diazepam	105	3.7	624	5.5
estazolam	22	0.8	85	0.7
eszopiclone	5	0.2	10	0.1
flurazepam	33	1.2	135	1.2
halazepam	0	0	2	0.0
lorazepam	1,071	37.7	3,658	32.1
oxazepam	104	3.7	381	3.3
quazepam	5	0.2	25	0.2
temazepam	81	2.9	212	1.9
triazolam	1	0.0	8	0.1
zaleplon	21	0.7	62	0.5
zolpidem	456	16.1	1,608	14.1
dosage				
low dose (≤0.5 DDD)	1,415	49.8	5,704	50.0
medium dose	958	33.7	3,794	33.3
high dose (>1 DDD)	467	16.4	1,912	16.8
half-life				
only long half-life (>24h)	477	16.8	2,412	21.1
only short half-life (≤24h)	2,315	81.5	8,850	77.6
both	48	1.7	148	1.3
duration (first script during 12 months prior to index date)				
0–14 days	77	2.7	181	1.6
15–30 days	60	2.1	182	1.6
31–60 days	80	2.8	269	2.4
61–90 days	149	5.3	601	5.3
91–180 days	150	5.3	495	4.3
181–270 days	284	10.0	779	6.8
271–360 days	2,040	71.8	8,903	78.0

Abbreviation: DDD, defined daily dose.

Table 3

Association between BDZ use during the last 14 days and risk of hip fracture

Risk factor	Crude	Age-, gender-, and race-adjusted	Fully adjusted[a]
	RR (95% CI)	RR (95% CI)	RR (95% CI)
no BDZ use	1.00 (ref)	1.00 (ref)	1.00 (ref)
BDZ use	1.30 (1.24, 1.36)	1.32 (1.26, 1.39)	1.16 (1.10, 1.22)
long-acting BDZ	1.07 (0.97, 1.17)	1.18 (1.07, 1.31)	1.05 (0.94, 1.16)
short-acting BDZ	1.36 (1.30, 1.43)	1.36 (1.29, 1.43)	1.19 (1.13, 1.26)
alprazolam[b]	1.09 (1.00, 1.19)	1.13 (1.03, 1.23)	1.01 (0.92, 1.11)
zolpidem[b]	1.48 (1.32, 1.66)	1.43 (1.26, 1.62)	1.26 (1.11, 1.44)
lorazepam[b]	1.50 (1.39, 1.61)	1.48 (1.37, 1.60)	1.29 (1.19, 1.40)
other BDZ[b]	1.14 (1.05, 1.24)	1.21 (1.10, 1.32)	1.08 (0.98, 1.18)
dosage			
low dose (≤0.5 DDD)	1.29 (1.22, 1.37)	1.23 (1.15, 1.31)	1.09 (1.02, 1.17)
medium dose	1.31 (1.22, 1.41)	1.36 (1.26, 1.47)	1.21 (1.11, 1.31)
high dose (>1 DDD)	1.27 (1.15, 1.41)	1.58 (1.42, 1.76)	1.32 (1.17, 1.48)
1st BDZ prescription during prior 12 months			
0–14 days (new users)	2.21 (1.70, 2.89)	2.27 (1.70, 3.03)	2.05 (1.52, 2.77)
15–30 days	1.72 (1.28, 2.30)	1.69 (1.25, 2.30)	1.42 (1.03, 1.96)
31–60 days	1.55 (1.21, 2.00)	1.71 (1.31, 2.23)	1.34 (1.02, 1.77)
61–90 days	1.29 (1.08, 1.55)	1.52 (1.26, 1.84)	1.05 (0.86, 1.28)
91–180 days	1.58 (1.31, 1.89)	1.57 (1.29, 1.90)	1.21 (0.99, 1.48)
181–270 days	1.90 (1.66, 2.18)	1.89 (1.63, 2.18)	1.53 (1.31, 1.78)
271–360 days	1.19 (1.13, 1.26)	1.21 (1.15, 1.28)	1.10 (1.04, 1.17)

Abbreviations: RR, relative risk; CI, confidence interval; ref, reference category; BDZ, benzodiazepines and related drugs; DDD, defined daily dose.

[a] adjusted for age at the index date, gender, race, income, health care utilization (number of physician visits, number of different generic drugs dispensed, number of nursing home days, number of hospital days, mammography, prostate-specific antigen test, Pap smear test, electrocardiogram, and cholesterol measurement), co-morbidity (delirium, visual impairment, stroke, polyneuropathy, other fractures, osteoporosis, osteomalacia, multiple sclerosis, palsy, disturbances of equilibrium, degenerative muscle disorders, Charlson co-morbidity score, hypoalbuminemia, liver disease, chronic renal failure, congestive heart failure, chronic obstructive pulmonary disease, hypercalciuria, hyperparathyroidism, hyperthyroidism, hypogonadism, hysterectomy, inflammatory bowel disease, lupus erythematosus, oophorectomy, rheumatoid arthritis, cancer), and co-medication (organic nitrates, statins, thiazolidinediones, sulfonylureas, insulin, anticoagulants, digoxin, antiarrhythmics, hormone replacement therapy, corticosteroid use, estrogen receptor modulators, anti-osteoporotic drugs, bisphosphonates, proton pump inhibitors, non-steroidal anti-inflammatory drugs, other anti-inflammatory drugs, acetaminophen, angiotensin II receptor antagonists, angiotensin-converting enzyme inhibitors, calcium-channel blockers, agents acting on the arteriolar smooth muscle, beta-blockers, other peripherally or centrally acting antiadrenergic agents, potassium sparing diuretics, thiazides, other low ceiling diuretics, high-ceiling diuretics, antiparkinson drugs, and the pharmacodynamically interacting substances mentioned above) with a dispensed prescription during the three months before the index date; no missing values except for income (N= 30 cases; N= 3 controls)

[b] patients with a combination of alprazolam, zolpidem, lorazepam, and other BDZ were excluded

Table 4

Association between hip fracture risk and BDZ-drug interactions[a]

Risk factor	Hip fracture patients (N=17,057)		Controls (N=85,553)		Crude	Adjusted for age, gender, and race	Fully adjusted[b]
	N	%	N	%	RR (95% CI)	RR (95% CI)	RR (95% CI)
alprazolam drug interactions							
alprazolam without interacting drug	181	1.1	1,210	1.4	0.91 (0.78, 1.07)	0.92 (0.78, 1.08)	0.90 (0.77, 1.07)
interacting drug without alprazolam[c,d]	8,361	49.0	34,116	39.9	1.45 (1.40, 1.50)	1.47 (1.41, 1.52)	1.40 (1.35, 1.46)
alprazolam and interacting drug	467	2.7	1,883	2.2	1.52 (1.37, 1.68)	1.60 (1.44, 1.79)	1.51 (1.34, 1.69)
lorazepam drug interactions							
lorazepam without interacting drug	431	2.5	1,984	2.3	1.34 (1.20, 1.49)	1.30 (1.16, 1.45)	1.32 (1.18, 1.48)
interacting drug without lorazepam[d,e]	5,892	34.5	19,586	22.9	1.86 (1.79, 1.93)	1.86 (1.79, 1.93)	1.57 (1.50, 1.64)
lorazepam and interacting drug	573	3.4	1,504	1.8	2.36 (2.14, 2.61)	2.37 (2.14, 2.63)	1.94 (1.74, 2.17)
zolpidem drug interactions							
zolpidem without interacting drug	150	0.9	644	0.8	1.43 (1.20, 1.71)	1.28 (1.06, 1.54)	1.26 (1.04, 1.53)
interacting drug without zolpidem[d,f]	7,576	44.4	28,919	33.8	1.57 (1.52, 1.63)	1.58 (1.52, 1.64)	1.44 (1.38, 1.50)
zolpidem and interacting drug	217	1.3	654	0.8	2.04 (1.75, 2.38)	2.04 (1.73, 2.40)	1.71 (1.44, 2.03)

Abbreviations: RR, relative risk; CI, confidence interval.

[a] patients with a combination of alprazolam, zolpidem, lorazepam, and other BDZ were excluded in the interaction model

[b] adjusted for age, gender, race, income, health care utilization, co-morbidity, co-medication; missings: hip fracture patients: N= 30; controls: N= 3

[c] Aprepitant, amiodarone, cimetidine, clarithromycin, cyclosporine, dextropropoxyphen, diltiazem, ergotamine, erythromycin, esomeprazole, fluconazole, fluoxetine, fluvoxamine, indinavir, isoniazid, itraconazole, ketoconazole, nefazodone, nelfinavir, nicardipine, nifedipine, omeprazole, paroxetine, propoxyphene, ritonavir, saquinavir, telithromycin, troleandomycin, and verapamil.

[d] Opioids, H1-antihistamines, barbiturates, anticonvulsants, non-benzodiazepine non-barbiturate hypnotics, antidepressants, neuroleptics, and muscle relaxants.

[e] Valproate and probenecid.

[f] Aprepitant, cimetidine, clarithromycin, diltiazem, erythromycin, fluconazole, indinavir, itraconazole, ketoconazole, nelfinavir, nefazodone, telithromycin, ritonavir, saquinavir, and verapamil.

Table 5

Characteristics of concomitant use of interacting drugs.

Risk factor	Hip fracture patients (N=17,057) N(%)	Controls (N=85,553) N(%)
alprazolam and interacting drug use		
pharmacokinetically interacting co-medication[a]	83(0.5)	535(0.6)
pharmacodynamically interacting co-medication[b]	163(1.0)	554(0.7)
pharmacokinetically and pharmacodynamically interacting co-medication[a,b]	221(1.3)	794(0.9)
lorazepam and interacting drug use		
pharmacokinetically interacting co-medication[c]	0(0.0)	3(0.0)
pharmacodynamically interacting co-medication[b]	571(3.4)	1501(1.8)
pharmacokinetically and pharmacodynamically interacting co-medication[b,c]	2(0.0)	0(0.0)
zolpidem and interacting drug use		
pharmacokinetically interacting co-medication[d]	18(0.1)	90(0.1)
pharmacodynamically interacting co-medication[b]	179(1.1)	480(0.6)
pharmacokinetically and pharmacodynamically interacting co-medication[b,d]	20(0.1)	84(0.1)

[a] Aprepitant, amiodarone, cimetidine, clarithromycin, cyclosporine, dextropropoxyphen, diltiazem, ergotamine, erythromycin, esomeprazole, fluconazole, fluoxetine, fluvoxamine, indinavir, isoniazid, itraconazole, ketoconazole, nefazodone, nelfinavir, nicardipine, nifedipine, omeprazole, paroxetine, propoxyphene, ritonavir, saquinavir, telithromycin, troleandomycin, and verapamil.

[b] Opioids, H1-antihistamines, barbiturates, anticonvulsants, non-benzodiazepine non-barbiturate hypnotics, antidepressants, neuroleptics, and muscle relaxants.

[c] Valproate and probenecid.

[d] Aprepitant, cimetidine, clarithromycin, diltiazem, erythromycin, fluconazole, indinavir, itraconazole, ketoconazole, nelfinavir, nefazodone, telithromycin, ritonavir, saquinavir, and verapamil.