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Original Study

Risk of Hip Fracture in Benzodiazepine Users With and Without Alzheimer Disease

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A B S T R A C T

Objectives: To investigate the association between benzodiazepine and related drug (BZDR) use and hip fracture as well as postfracture mortality and duration of hospital stay in community-dwellers with and without Alzheimer disease (AD).
Design: Retrospective cohort study.
Setting: The register-based Medication Use and Alzheimer's disease (MEDALZ) study, including all community-dwelling persons diagnosed with AD in Finland during 2005–2011 (n = 70,718) and their matched comparison persons without AD.
Participants: Persons without BZDR use during the year preceding the AD diagnosis or the corresponding matching date as well as persons without history of hip fracture were included in this study.
Measurements: We investigated the risk of hip fracture associated with BZDR use compared with nonuse separately in persons with and without AD. Further, we investigated the association between BZDR use during hip fracture and 1-year mortality as well as longer than a 4-month hospital stay after hip fracture. Associations were reported as hazard ratios and odds ratios with 95% confidence intervals (CI).
Results: BZDR use was associated with an increased risk of hip fracture in persons with and without AD (adjusted hazard ratio 1.4 [95% CI 1.2–1.7] and 1.6 [95% CI 1.3–1.9], respectively). BZDR use during hip fracture was associated with longer than 4-month postfracture hospital stay in persons with AD [adjusted odds ratio 1.9 (95% CI 1.3–2.8)] but not in comparison persons. One-year mortality was not associated with BZDR use during hip fracture.
Conclusions: Higher threshold in prescribing BZDRs for neuropsychiatric symptoms might decrease the hip fracture rate and affect the length of hospital stay in persons with AD.

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Hip fracture is a devastating event for an older person, and the risk of hip fracture increases with age.[1] Persons with Alzheimer disease (AD) have an increased risk of hip fracture compared with those without AD.[2] The hip fracture rate was more than twice as high in persons with AD compared with those without AD in a Finnish nationally representative sample. Hip fractures present a growing challenge because of the globally increasing number of persons with AD.[3]

There are several risk factors for hip fractures, including certain drugs often used by older persons.[1] Benzodiazepines and related drugs (BZDRs) are widely used in persons with AD[4] even in long-term use[5]; the use of these drugs is frequently initiated after the AD diagnosis.[6] However, BZDRs impair gait and balance in older persons.[7] Four meta-analyses have demonstrated the association between BZDR use and increased risk of hip fracture; however, none had a focus on persons with dementia or included studies conducted specifically in persons with dementia.[8–11] The studies focusing on benzodiazepines have consistently indicated a 30%–40% increase in the risk of hip fracture associated with drug use.[9–11] The analysis focusing on a benzodiazepine-related drug indicated 180% increase in hip fracture risk associated with drug use.[8]

Hip fractures lead to other adverse health outcomes, especially among frail older persons with dementia. Persons with dementia have an increased risk of institutionalization and mortality after hip fracture, compared with those without dementia.[12,13] Persons with dementia are also at high risk of delirium after hip fracture that can further worsen these outcomes.[14]

To our knowledge, there are no previous studies that investigate the association between BZDR use and risk of hip fracture in community-dwelling persons with AD. Therefore, the aim of this study was to investigate the risk of first hip fracture associated with BZDR use among community-dwelling persons with AD and age- and sex-matched persons without AD. In addition, our aim was to calculate risk estimates and hip fracture rates separately for persons with and without AD. For secondary analyses, we investigated the duration of postfracture hospital stay and mortality after hip fracture.

Methods

Cohort

This study was based on the register-based Medication Use and Alzheimer's Disease (MEDALZ) cohort.[15] This cohort included all community-dwelling persons diagnosed with AD during 2005–2011 (n = 70,718) in Finland. Data on AD diagnoses were obtained from the Special Reimbursement Register. This register contains information on each person's entitlement to higher reimbursement of drugs because of chronic diseases.[15] AD diagnoses were based on the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association and the *Diagnostic and Statistical Manual, Fourth Edition* criteria.[16,17] The diagnoses were confirmed by a neurologist or a geriatrician, and the criteria included symptoms consistent with mild or moderate AD as well as exclusion of alternative diagnoses and confirmation of diagnosis with clinical tests and imaging scans.[15] For this study, the index date was defined as the AD diagnosis date. The MEDALZ cohort included also comparison persons without AD who were identified from a nationwide register including all residents.

No ethics approval or informed consent from the cohort was required by the Finnish legislation as the persons were not contacted and only deidentified data were used. Permissions for data use were received from the maintainers of registers.

Data Sources

In addition to AD diagnosis, we collected data on drug use, comorbidities, hospital stays, socioeconomic position, and death from nationwide registers.[15] Drug use data from 1995 to 2012 was obtained from the Prescription Register, which contains information on all reimbursed drug purchases for each resident in Finland. Hip fractures and other diagnoses related to hospital stay as well as associated duration of stays were obtained from Hospital Discharge Register from 1972 to 2012. Comorbidities were obtained from Special Reimbursement and Hospital Discharge registers from 1972 to 2012. Data on socioeconomic position were obtained from Statistics Finland. Mortality data were obtained from Social Insurance Institution.

Benzodiazepine and Related Drug Exposure

The drug purchases were classified according to the anatomical therapeutic chemical (ATC) classification system.[18] In addition to the ATC code, the Prescription Register data included package size, strength, dosage form, date of purchase, and the purchased amount in defined daily doses.[15]

BZDRs included benzodiazepines (ATC classes N05BA and N05CD) and benzodiazepine-related drugs, so called Z-drugs (N05CF). All BZDRs used by the study participants are listed in the Appendix (Table A1). Two benzodiazepines (midazolam and triazolam) and 1 Z-drug (zaleplon) were excluded from the study as they were not reimbursed during the study period. Further, clobazam (a benzodiazepine) use was excluded because it was indicated only for epilepsy.

We applied the From prescription drug purchases to drug use periods (PRE2DUP) method[19] to calculate drug use periods (ie, when continuous drug use started and ended), from the purchase-based register data for each drug and each person. This method was based on modeling individual drug purchase patterns by calculating the sliding averages of the daily dose, while accounting for regularity of drug purchases, hospital stays, and stockpiling of drugs. After modeling each ATC code, overlapping benzodiazepine and Z-drug use periods were combined to retrieve "BZDR use." During BZDR use, persons were allowed to switch from one drug to another unless there were any breaks in drug use. Similarly, benzodiazepine and Z-drug use periods were constructed for drug class analyses. Concomitant use of 2 or more BZDRs was not investigated separately because of small number of users.

Hip Fractures

The main outcome in this study was the first hospitalization because of hip fracture after the index date. Hip fractures were defined according to the *International Statistical Classification of Diseases and Related Health Problems* (ICD) *10th Revision* (ICD-10) as fracture of neck of femur (S72.0), pertrochanteric fracture (S72.1), and subtrochanteric fracture (S72.2). History of hip fracture before the index date was defined from 1972 according to the ICD-8, ICD-9, and ICD-10 classifications. Persons with a history of hip fracture before the index date were excluded from this study.

Postfracture Hospital Stay and Mortality

We investigated the uninterrupted duration of postfracture hospital stay, including acute care and inpatient rehabilitation in various hospital-based settings, for all persons who experienced hip fracture during the study follow-up. We defined longer than 4-month hospital stay as long-term care.[20] Furthermore, we investigated postfracture mortality during the first year after the hip fracture.