Brief Communication

Mortality Associated With Benzodiazepines and Benzodiazepine-Related Drugs Among Community-Dwelling Older People in Finland: A Population-Based Retrospective Cohort Study

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Objective: To investigate the association between the use of benzodiazepines (BDZs) and BDZ-related drugs and mortality among community-dwelling people aged 65 years and older in Finland.

Method: This was a population-based retrospective cohort study. Records of all reimbursed drugs purchased by all 2224 residents of Leppävirta, Finland, aged 65 years and older in 2000 were extracted from the Finnish National Prescription Register. Diagnostic data were extracted from the Special Reimbursement Register. All-cause mortality was assessed after 9 years using national registers. Cox proportional hazards models were used to compute unadjusted and adjusted hazard ratios (HRs) and 95% confidence intervals for mortality among prevalent users of BDZs and BDZ-related drugs in 2000 (n = 325), compared with nonusers of BDZs and BDZ-related drugs between 2000 and 2008 (n = 1520).

Results: BDZs and BDZ-related drugs were used by 325 out of the 2224 residents (14.6%) in 2000. The 9-year mortality was 50.2% among BDZ and BDZ-related drug users in 2000 and 36.3% among BDZ and BDZ-related drug nonusers between 2000 and 2008 (HR 1.53; 95% CI 1.28 to 1.82). After adjusting for baseline age, sex, antipsychotic drug use, and diagnostic confounders, the HR was 1.01 (95% CI 0.84 to 1.21).

Conclusions: Use of BDZs and BDZ-related drugs was associated with an increased mortality hazard in unadjusted analyses. However, after adjusting for age, sex, antipsychotic drug use, and diagnostic confounders, the use of BDZs and BDZ-related drugs was not associated with excess mortality.


Clinical Implications

- Adverse drug events associated with BDZs are well documented. However, there are conflicting data about mortality hazards.
- In contrast to recent findings from a Canadian study, BDZs and BDZ-related drugs were not associated with excess mortality after adjusting for baseline differences in age, sex, antipsychotic drug use, and diagnoses.
- While BDZs and BDZ-related drugs were not associated with excess mortality, clinicians should maintain a judicious approach when prescribing BDZs and BDZ-related drugs for older people.

Limitations

- The study sample was drawn from a single municipality in Finland and, therefore, may not be generalizable to other populations.
- Only large BDZ and BDZ-related drug pack sizes were reimbursed and included in the Finnish National Prescription Register in 2000. This means BDZ and BDZ-related drug use may have been underestimated.
- Differences in BDZ and BDZ-related drug dose, frequency, and duration of use were not evaluated.

Key Words: hypnotics and sedatives, benzodiazepines, mortality, aged, pharmacoepidemiology
BDZs are among the most frequently used drugs among community-dwelling older people in Europe and North America. However, use of BDZs for insomnia may not improve sleep quality in older people. BDZs have been associated with cognitive impairment, depressive symptoms, poor physical function, falls, and fractures. The responsible prescribing of BDZs in psychiatric disorders has recently been debated. Research into the association between BDZ use and mortality has been inconsistent. A recent study using data from the Canadian National Population Survey reported that anxiolytic and hypnotic drug use was associated with a small but significant increase in mortality. The objective of our study was to investigate the association between use of BDZs and BDZ-related drugs and mortality among community-dwelling people aged 65 years and older in Finland.

Methods

Data Sources

The study protocol was approved by the SII. The study comprised all community-dwelling people aged 65 years and older (n = 2224) residing in Leppävirta on January 1, 2000. Records of reimbursed drugs purchased during 2000 were extracted from the FNPR maintained by the SII. The FNPR includes information on the dispensing date of each prescription and the number of dispensed packages and tablets. Each person’s birthdate and sex are also included. There is high concordance between self-reported drug use and drug use recorded in the FNPR. In Finland, 3-month’s supply of a drug can be reimbursed in a single dispensing. Large packs of BDZs and BDZ-related drugs are reimbursed by the SII and therefore purchases are recorded in the FNPR; however, not all small pack sizes are reimbursed. Death dates were provided by the SII and patient diagnoses in 2000 were extracted from the Special Reimbursement Register also maintained by the SII. To be included in the Special Reimbursement Register, a person’s disease or condition must meet predefined explicit criteria, and supporting evidence must be provided by that person’s clinician. Depending on the diagnoses, this evidence may include laboratory test results, diagnostic imaging, and results from clinical outcome scales. Diagnoses extracted included cancer, cardiovascular disease (heart failure, hypertension, coronary artery disease, and arrhythmias), endocrine disorders (diabetes and hypothyroidism), mental and neurological disorders (epilepsy, persistent depression and [or] psychosis, Alzheimer disease, and Parkinson disease), musculoskeletal disorders (rheumatoid arthritis and other connective tissue diseases), and respiratory disease (persistent asthma and chronic obstructive pulmonary disease).

Measures and Definitions

Drugs were categorized using the ATC classification system. BDZs and BDZ-related drugs (zopiclone and zolpidem) belonging to anxiolytics (ATC code N05B) and hypnotics and sedatives (N05C) were included. BDZs and BDZ-related drug use at baseline was defined as receipt of 1 or more reimbursed prescriptions for a BDZ or BDZ-related drug in 2000 (n = 325). Residents who were nonusers of BDZs and BDZ-related drugs in 2000, but who were dispensed a BDZ or BDZ-related drug between 2001 and 2008 (n = 379), were excluded from the comparison group. The remaining 1845 residents were included in the analyses.

Baseline use of antipsychotics and ADs was defined as receipt of 1 or more reimbursed prescriptions for an antipsychotic (N05A, excluding lithium) or AD (N06A) in 2000, respectively. The number of prescription drugs was defined as the total number of different prescription drugs (according to ATC code) reimbursed by the SII during 2000.

Statistical Analyses

Baseline characteristics of BDZ and BDZ-related drug users and nonusers were compared using chi-square tests for categorical variables and independent sample t tests for continuous variables. Cox proportional hazards models were used to determine unadjusted and adjusted mortality hazards associated with baseline use of BDZs and BDZ-related drugs. HRs and 95% confidence intervals were computed. This statistical technique permitted analyses of days until death over a 9-year follow-up period. The follow-up period for each person commenced on January 1, 2000, and ended at time of death or December 31, 2008, whichever occurred first. The adjusted analysis was performed using the backward stepwise likelihood ratio approach. The model was adjusted for baseline differences in age, sex, number of prescription drugs, and for the following baseline diagnoses: cancer, cardiovascular disease, endocrine disorders, mental and neurological disorders, musculoskeletal disorders, and respiratory disease. The model was also adjusted for antipsychotic and AD use. The sample size was too small to differentiate between mortality associated with specific BDZs and BDZ-related drugs. The covariates relating to AD use and number of prescription drugs were excluded from the final adjusted model as they did not make a significant contribution to mortality (at the 0.05 level). All analyses were conducted using SPSS, Version 18.0 (SPSS Inc, Chicago, IL).
Results
Among the 2224 residents, 325 (14.6%) were BDZ and BDZ-related drug users. Zopiclone (35.4%, n = 115), oxazepam (25.8%, n = 84), temazepam (24.6%, n = 80), and diazepam (15.4%, n = 50) were the most commonly reimbursed BDZs and BDZ-related drugs. Thirty-three residents had a diagnosis of a mental or neurological disorder: 14 (42.4%) had persistent depression and/or psychosis, 11 (33.3%) had Parkinson disease, 7 (21.2%) had epilepsy, and 1 (3.0%) had Alzheimer disease. Baseline demographic and diagnostic differences between BDZ and BDZ-related drug users and nonusers are compared in Table 1. At the end of follow-up, there were 163 (50.2%) recorded deaths among BDZ and BDZ-related drug users and 552 (36.3%) deaths among nonusers. The unadjusted HR for mortality associated with BDZ and BDZ-related drug use was 1.53 (95% CI 1.28 to 1.82). After adjusting for baseline differences in demographic characteristics, antipsychotic drug use and diagnoses, the HR was reduced to 1.01 (95% CI 0.84 to 1.21), indicating that BDZ and BDZ-related drug use was not associated with an increased mortality hazard (Table 2).

Discussion
Our study found that BDZ and BDZ-related drug use among community-dwelling older people was associated with a mortality hazard about 1.5 times greater than nonusers. However, after adjusting for baseline differences in age, sex, antipsychotic drug use, and diagnoses; BDZ and BDZ-related drug use was no longer associated with excess mortality.

In contrast, Belleville10 reported that anxiolytic and hypnotic drug use was associated with a small but significant increase in mortality when adjusting for confounding sociodemographic, lifestyle, and health factors (OR 1.36; 95% CI 1.09 to 1.70). However, our results were consistent with Hausken et al17 who reported higher crude mortality among Norwegian anxiolytic and hypnotic users, but nonsignificant and greatly attenuated HRs after adjusting for lifestyle and socioeconomic factors (HR 1.5; 95% CI 0.9 to 2.7 for men and HR 1.7; 95% CI 1.1 to 2.6 for women). In the studies by Belleville10 and Hausken et al17 the adjusted mortality hazard was lower than the unadjusted mortality hazard for middle-aged adults. Our findings support Hausken et al’s17 conclusions that excess mortality with anxiolytic and hypnotic use may be due to residual confounding.

Methodological differences may explain the inconsistency between our results and Belleville’s findings. First, the main data source used in our study was the FNPR, which provided a complete record of all reimbursed drugs purchased by the residents of Leppävirta. However, drugs purchased in hospitals or institutional settings were not included in the FNPR. Conversely, the main data source in Belleville’s study10 was the Canadian National Population Health Survey, a self-reported questionnaire. Nonparticipation bias is commonly encountered in health surveys,18 although Belleville10 adopted measures to maximize response rates. Nonparticipation bias was not relevant to our study because we used a population-based cohort comprising all residents of Leppävirta instead of a sample of residents. Consequently, our study has a high degree of internal validity, but the

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Table 1 Baseline characteristics for BDZ and BDZ-related drug users in 2000 and BDZ and BDZ-related drug nonusers from 2000–2008

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BDZ and BDZ-related drug user n = 325</th>
<th>BDZ and BDZ-related drug nonuser n = 1520</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>76.1 (7.2)</td>
<td>73.8 (6.9)</td>
</tr>
<tr>
<td>Sex, men</td>
<td>108 (33.2)</td>
<td>656 (43.2)</td>
</tr>
<tr>
<td>9-year mortality</td>
<td>163 (50.2)</td>
<td>552 (36.3)</td>
</tr>
<tr>
<td>Prescription drugs, n, mean (SD)a</td>
<td>9.7 (5.1)</td>
<td>4.3 (3.9)</td>
</tr>
<tr>
<td>Antipsychotic usersb</td>
<td>45 (13.8)</td>
<td>67 (4.4)</td>
</tr>
<tr>
<td>Cancer</td>
<td>10 (3.1)</td>
<td>36 (2.4)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>188 (57.8)</td>
<td>724 (47.6)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>55 (16.9)</td>
<td>217 (14.3)</td>
</tr>
<tr>
<td>Mental and neurological</td>
<td>33 (10.2)</td>
<td>82 (5.4)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>22 (6.8)</td>
<td>67 (4.4)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>41 (12.6)</td>
<td>128 (8.4)</td>
</tr>
</tbody>
</table>

* Defined according to number of different drugs by ATC code
* Defined as drugs included in ATC code N05A, excluding lithium
results may not be generalizable. Definitions of drug exposure differ between the 2 studies. In our study, a BDZ and BDZ-related drug user was defined as any resident who received 1 or more reimbursed BDZs or BDZ-related drugs during 2000. Only large pack sizes were reimbursed by the SII in 2000, therefore small packs were not recorded. This means that regular BDZ and BDZ-related drug users may have been more likely to be included in the FNPR than less frequent users.14 Analysis of reimbursed drug dispensing in our study did not account for possible nonadherence. Meanwhile, Belleville’s10 definition of an anxiolytic and hypnotic user was limited to respondents reporting use in the month prior to survey completion. Drug use assessed using self-reported questionnaires may be prone to recall bias and may inaccurately estimate the prevalence of anxiolytic and hypnotic use.19 The diagnoses used as covariates in our study were clinician-verified according to predefined explicit criteria. This represents an advantage over the use of self-reported diagnoses. However, it is not always possible to ascertain severity for all diagnoses. Although the frequency of anxiolytic and hypnotic use was accounted for by Hausken et al.,17 differences in dose, frequency, and duration of BDZ and BDZ-related drug use were not evaluated either in our study or in Belleville’s study.10

Despite our finding that BDZ and BDZ-related drug use does not contribute to excess mortality, there are a growing number of studies that report the risks and negative consequences of BDZ use in older people.4–7 Use of BDZs and BDZ-related drugs may expose people to unnecessary risks. A larger study that draws data from various countries or regions would provide valuable information.

Conclusions
BDZ and BDZ-related drug use was associated with an increased mortality hazard in unadjusted analyses. However, after adjusting for baseline differences in age, sex, antipsychotic drug use, and diagnoses, BDZ and BDZ-related drug use was not associated with excess mortality. Given that the association between BDZ and BDZ-related drug use and mortality has been inconsistent, and BDZs have been associated with other adverse drug events, clinicians should nevertheless maintain a judicious approach to the prescribing BDZs and BDZ-related drugs to older adults.

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References
Résumé : Mortalité associée aux benzodiazépines et aux médicaments reliés chez des personnes âgées résidant dans la communauté en Finlande : une étude de cohorte rétrospective dans la population

Objectif : Investiguer l’association entre l’utilisation de benzodiazépines (BZP) et de médicaments reliés aux BZP et la mortalité chez des personnes de 65 ans et plus résidant dans la communauté, en Finlande.

Méthode : Il s’agit d’une étude de cohorte rétrospective dans la population. Les dossiers de tous les médicaments remboursés achetés par tous les 2224 résidents de Leppävirta, en Finlande, âgés de 65 ans et plus en 2000, ont été extraits du registre national finlandais des prescriptions. Les données diagnostiques ont été tirées du registre des remboursements spéciaux. La mortalité toutes causes confondues a été évaluée après 9 ans d’usage des registres nationaux. Les modèles de régression des hasards proportionnels de Cox ont servi à calculer les rapports de risques (RR) non corrigés et corrigés et les intervalles de confiance (IC) à 95 % pour la mortalité chez les utilisateurs prévalents de BZP et de médicaments reliés aux BZP en 2000 (n = 325), comparativement aux non-utilisateurs de BZP et de médicaments reliés aux BZP entre 2000 et 2008 (n = 1520).

Résultats : Les BZP et les médicaments liés aux BZP ont été utilisés par 325 sur 2224 résidents (14,6 %) en 2000. Le taux de mortalité sur 9 ans était de 50,2 % chez les utilisateurs de BZP et de médicaments reliés aux BZP en 2000, et de 36,3 % chez les non-utilisateurs de BZP et de médicaments liés aux BZP entre 2000 et 2008 (RR 1,53 ; IC à 95 % 1,28 à 1,82). Après ajustement pour l’âge au départ, le sexe, l’utilisation d’antipsychotiques, et les variables diagnostiques confusionnelles, le RR était de 1,01 (IC à 95 % 0,84 à 1,21).

Conclusions : L’utilisation de BZP et de médicaments reliés aux BZP était associée à un risque accru de mortalité dans les analyses non corrigées. Cependant, après ajustement pour l’âge, le sexe, l’utilisation d’antipsychotiques, et les variables diagnostiques confusionnelles, l’utilisation de BOZ et de médicaments liés aux BOZ n’était pas associée à une mortalité excessive.