Association between use of antidepressants or benzodiazepines and the risk of subsequent fracture among those aged 65+ in the Netherlands

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Abstract
Summary This is the first study to examine the association between antidepressant and benzodiazepine use following a MOF and risk of subsequent fracture in those 65+. Using national data, drug use following MOF showed that the 1-year fully adjusted risk of subsequent MOF in those on antidepressants was more than doubled.

Introduction We evaluated the association between the use of antidepressants or benzodiazepines and the risk of a subsequent major osteoporotic fracture.

Methods A cohort study was performed using the Dutch PHARMO Database Network. Between 2002 and 2011, a total of 4854 patients sustained a first major osteoporotic fracture after the age of 65 years, of which 1766 sustained a hip fracture. Incidence rates and adjusted hazard ratios were calculated using Cox proportional hazards models.

Results Within 1 year following a major osteoporotic fracture, 15% (95% CI 13.7–15.7) and 31% (95% CI 30.1–32.8) of patients were dispensed an antidepressant or benzodiazepine, respectively. Current use of antidepressants in the first year following a major osteoporotic fracture was associated with subsequent fracture (adjusted HR 2.17 (95% CI 1.37–3.43)). Recent and past use of antidepressants were also associated with an increased risk of subsequent fracture. When the complete follow-up period was included, only the current use of antidepressants was associated with subsequent fracture following a major osteoporotic fracture (adjusted HR 1.48; 95% CI 1.06–2.06). Current benzodiazepine use was not associated with an increased risk of fracture within 1 year following a major osteoporotic fracture (adjusted HR 1.18; 95% CI 0.76–1.81) or during the complete follow-up period (adjusted HR 1.18; 95% CI 0.90–1.55).

Conclusion This study provides evidence that antidepressants should be used with caution following a major osteoporotic fracture. It provides needed insights that can be used to inform clinicians when assessing subsequent fracture risk in patients.

Keywords Antidepressants · Benzodiazepines · Hip fracture · Major osteoporotic fracture · Subsequent fracture

Introduction

Osteoporosis is a devastating disease that affects over 200 million women in the world [1]. The major clinical outcome associated with osteoporosis is a bone fracture. Worldwide, osteoporosis causes over 9 million fractures annually [2]. In particular, hip fractures are a devastating consequence as they are associated with increased mortality and healthcare costs. Moreover, both the incidence and healthcare costs are projected to increase 40–50% by the year 2030 [3].

It is established that psychotropic drugs, such as antidepressants or benzodiazepines, are associated with an increased risk of hip fracture due to a higher risk of falls [4]. Antidepressants have a direct action on bone metabolism and are associated with decreased bone mineral density [5, 6]. SSRI and SNRI use are

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associated with a twofold increased risk for incident fragility fracture over 5 and 10 years in a randomly sampled population cohort over age 50 [7, 8]. Also, depression itself is related to higher cortisol levels that are associated with increased risk for incident fractures [9]. Previous literature has identified that the use of antidepressants or benzodiazepines increases the risk for hip fracture by 47 and 35%, respectively [10, 11]. Following an osteoporotic fracture, a major concern among osteoporotic fractures is the risk for having a subsequent fracture. Indeed, previous literature has identified that an important predictor of fracture is having had a previous fracture. In meta-analyses, the risk of a fracture was approximately twofold higher among those with a prior fracture, as compared to those without a history of fracture [12–14]. This risk appears to be further increased if the initial fracture was of the hip, as a 2011 study identified a threefold increased risk of subsequent fracture following a hip fracture [15].

However, while both a prior fracture and use of psychotropic medications are known predictors of osteoporotic fractures, little research has been conducted to evaluate the association between the use of antidepressants or benzodiazepines and the risk of subsequent fracture. To date, only two studies have identified the frequency of prescribing of antidepressants or benzodiazepines following an initial hip fracture. Both studies identified that, among patients with a subsequent fracture, the proportion of patients using at least one psychotropic drug regularly was significantly increased at the time of the second fracture [16, 17]. Yet, there remains little understanding of the effect of psychotropic drug use and the risk for a subsequent osteoporotic fracture. Therefore, the objective of this study was to evaluate the association between the use of antidepressants or benzodiazepines and the risk of a subsequent major osteoporotic fracture following an initial hip or major osteoporotic fracture.

Methods

Source population

A cohort study was performed using the Dutch PHARMO Database Network [Institute for Drug Outcome Research, www.pharmo.nl]. This population-based network of Dutch electronic healthcare databases combines rich, patient-centric from different primary and secondary healthcare settings. These different data types, including primary care, outpatient pharmacy, and hospital data from the Dutch Hospital Data Foundation (DHD, www.dutchhospitaldata.nl), are linked on a patient level through validated algorithms and contains approximately 660,000 community-dwelling individuals in the Netherlands. Primary care diagnoses are coded according to International Classification of Primary Care (ICPC) codes. Drug-dispensing records contain information concerning the dispensed drug according to the Anatomical Therapeutic Chemical (ATC) Classification system codes and include information on amount, dose, dosage regimen, and date of dispensing. Hospital records include dates of hospital admission and discharge, diagnoses, and procedures recorded according to the International Classification of Disease, 9th or 10th revision codes (ICD-9 or ICD-10). High validity of hip fracture coding has been shown previously in the PHARMO Database Network, whereby > 90% of recorded hip fractures represented true hip fractures [18].

Study population

All patients aged 65 years or older with a first record of a major osteoporotic fracture that came to clinical attention since the start of data collection were included. Major osteoporotic fractures were defined as a fracture of the hip, forearm, humerus, or clinical vertebra. Fractures were classified into the following categories using ICPC code or ICD-9 and ICD-10 codes and categorized as follows: hip (ICPC L75.01; ICD-9 820; ICD-10 S72.0, S72.1, S72.2), forearm (ICPC L74.04; ICD-9 812; ICD-10 S42.2–S42.4, S42.7), vertebral (ICPC L76.06; ICD-9 805, 806; ICD-10 S12.0–S12.2, S12.7, S22.0, S22.1, S32.0–S32.2). Fractures were identified between 1 January 2002 and 31 December 2011 from the primary care records and hospitalization data. The index date was the date (i.e., start of follow-up) of the first fracture, and all patients were required to have at least 1 year of valid data collection before their index date.

All patients were followed from the index date until the first occurrence of a subsequent major osteoporotic fracture, migration out of the data source, death, or end of the study period [31 December 2011 the latest]. Fractures that occurred within the first month (30 days) after index date were excluded to avoid misclassification of prevalent fractures, as these may be codes for follow-up appointments for the first fracture.

Exposure

Oral use of antidepressants and benzodiazepines was determined using pharmacy-dispensing data. The World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification codes were used for selecting the drug classes. The following drug classes (ATC codes) were included: antidepressants (N06A) and benzodiazepines (N05BA, N05CD, N05CF). Use of these drugs was defined in a time-dependent manner, and patients were categorized into three groups: antidepressant user, benzodiazepine user, or a combination user if patients were using both antidepressants and benzodiazepines.

To classify exposure time-dependently, follow-up was divided into 30-day periods, starting from the index date. The
presence of a dispensing for an antidepressant and/or benzodiazepine was identified at the start of each 30-day period, and based on the recency of the last dispensing patients, was classified as current, recent, or past users. Current users were patients who had a dispensing record in the 30 days before the start of a period. Recent users were those with a record between 31 and 92 days before the start of a period. Past users were those with the last dispensing record being more than 92 days before the start of a period. Patients could move between current, recent, and past exposure throughout follow-up. Patients who did not have a dispensing for an antidepressant or benzodiazepine were classified as non-users.

**Potential confounders**

Potential confounders for this study are factors that have been associated with fracture risk. Sex was determined at baseline, while all other confounders were identified time-dependently. The following confounders were identified at the start of each 30-day period: a history of chronic diseases (ischemic heart disease, cerebrovascular disease, heart failure, chronic kidney disease, chronic obstructive pulmonary airway disease [COPD], dementia), malignant neoplasms, depression, secondary osteoporosis (type I diabetes mellitus, osteogenesis imperfecta, osteomalacia, hypogonadism, premature menopause, malnutrition, gastrointestinal tract mal-absorption, celiac disease, anorexia, and liver diseases including chronic liver disease, hepatitis, cirrhosis, neoplasms of the liver). In addition, a dispensing record for the following medications in the 6 months before the start of an interval was identified: anticonvulsants, antipsychotics, lithium, glucocorticoids, anti-arrhythmic drugs, opioids, NSAIDs, β-blockers, thiazide diuretics, loop diuretics, renin-angiotensin-aldosterone system (RAAS) inhibitors, statins, diastolic drugs, calcium and vitamin D, and antirheumatic drugs. Potential confounders were included in the final model if they independently changed the β-coefficient for the exposure by at least 5% (change-in-estimate method [19]).

**Statistical analysis**

Kaplan-Meier life-table analyses were used to visualize the probability of being prescribed antidepressants and/or benzodiazepines in the year following fracture. Cox proportional hazards regression was used to model subsequent fracture in users of antidepressants and/or benzodiazepines versus non-users (PHREG procedure, SAS 9.4; SAS Institute). Risk of subsequent fracture was assessed by recency of use (current, recent, past use). This was performed for the total follow-up duration, but also restricted to the first year after the index date of major osteoporotic fracture (hip fracture had too few events). Analyses were performed separately for the composite major osteoporotic fracture and hip fracture alone, and following suggestions during peer review baseline characteristics and the proportion of patients receiving antidepressants and benzodiazepines during follow-up were stratified by sex.

**Results**

A total of 4854 patients sustained a first major osteoporotic fracture after the age of 65 years (Table 1), of which 1766 (36%) sustained a hip fracture (Table 2). The mean age of patients with a major osteoporotic fracture was 78 years (SD = 7.5), while the mean age of hip fracture patients was 81 years (SD = 7.4). Among both major osteoporotic and hip fracture patients, the majority were women, 78 and 73%, respectively. Mean follow-up time was 2.7 years (SD = 2.2) for major osteoporotic fractures and 2.6 years (SD = 2.2) for hip fractures.

Within 1 year following a major osteoporotic fracture, 15% (95% CI 13.7–15.7) and 31% (95% CI 30.1–32.8) of patients were dispensed an antidepressant or benzodiazepine, respectively (Table 3). This percentage was higher for women than that for men, with 16% of women and 11% of men receiving antidepressants and 34% of women and 24% of men receiving benzodiazepines (Table 3). Among hip fracture patients, 16% (95% CI 14.3–17.9) and 36% (95% CI 33.4–38.1) of patients were dispensed an antidepressant or benzodiazepine, respectively (Table 4). Similar to osteoporotic fracture patients, the percentage was higher for women than that for men; with 18% of women and 12% of men receiving antidepressants and 39% of women and 28% of men receiving benzodiazepines (Table 4). Within 1 year following a major osteoporotic fracture or hip fracture, 8% (95% CI 7.5–9.1) and 10%, respectively, were dispensed both an antidepressant and benzodiazepine (Table 4). Similar to the individual medications, the proportion of women receiving both medications was higher among women than men in both fracture groups.

Current use of antidepressants in the first year following a major osteoporotic fracture was significantly, and independently, associated with subsequent fracture (adjusted HR 2.17; 95% CI (1.37–3.43)), as compared to non-use of these medications (Table 5). Recent and past use of antidepressants were also associated with an increased risk of subsequent fracture. However, when the complete follow-up period was included, only current use of antidepressants was associated with subsequent fracture following a major osteoporotic fracture (adjusted HR 1.48; 95% CI 1.06–2.06).

Current benzodiazepine use was not associated with an increased risk of fracture within 1 year following a major osteoporotic fracture (adjusted HR 1.18; 95% CI 0.76–1.81) or during the complete follow-up period (adjusted HR 1.18; 95% CI 0.90–1.55), as compared to non-users (Table 5). Within 1 year following a major osteoporotic fracture, past use of benzodiazepines was associated with an increased risk
for subsequent fracture (adjusted HR 1.48; 95% CI 1.06–2.07); however, this was not observed when the entire follow-up period was considered (adjusted HR 1.11; 95% CI 0.89–1.38).

Following a hip fracture, none of the exposure categories of antidepressants or benzodiazepines were significantly associated with a subsequent fracture, as compared to non-use (Table 6).

Use of both antidepressants and benzodiazepines in the first year following a major osteoporotic fracture was significantly and independently associated with subsequent fracture for both current, recent, and past use (adjusted HR current use 1.93 (1.00–3.73)). This significant increased risk was not observed following a hip fracture or including the complete follow-up period after a major osteoporotic fracture.

**Discussion**

This study is the first study to demonstrate that the use of antidepressants following a major osteoporotic fracture was...
significantly, and independently, associated with subsequent fracture. In addition, results identify that the use of benzodiazepines was not associated with a subsequent major osteoporotic fracture. However, following a hip fracture, neither antidepressants nor benzodiazepines were associated with a subsequent fracture. To our knowledge, this is the first study to examine the association between the use of antidepressants or benzodiazepines individually on the risk of a second fracture.

We identified a twofold increased risk of fracture among current users of antidepressants in the first year following a major osteoporotic fracture, and only current use of antidepressants was associated with subsequent fracture following major osteoporotic fracture when the entire follow-up period was included in the analysis. While the exact mechanism why antidepressants may increase the risk of fractures has not been elucidated, antidepressants do increase the risk of falls and are also associated with decreased bone mass density (BMD) [20–22]. Both are known risk factors for fracture, although evidence is mixed for antidepressants and BMD [23]. Surprisingly, we did not identify a significant increased risk

| Table 2 Baseline characteristics for hip fracture |
|-----------------------------------------------|
|                                              |
|                                              |
| Sex, n (%)                                   |
| Total | Men | Women |
|-------|-----|-------|
| 1766  | 484 | 27.4  |
| 1282  | 72.6|       |
| Age, years (mean, SD)                        |
| Total | Men | Women |
| 81    | 7.4 |       |
| 65–74 | 22.6|       |
| 399   | 232 | 48    |
| 48    | 20  |       |
| 75–84 | 45.1|       |
| 797   | 214 | 44    |
| 44    | 20  |       |
| ≥85   | 32.3|       |
| 570   | 38  | 8     |
| 451   | 35  |       |
| Diseases, ever before index date, n (%)      |
| Cerebrovascular disease                      |
| 199   | 11.3| 13    |
| 64    | 13  |       |
| 135   | 11  |       |
| COPD                                          |
| 101   | 5.7 |       |
| 55    | 4   |       |
| Dementia                                     |
| 126   | 7.1 |       |
| 85    | 7   |       |
| Depression                                   |
| 84    | 4.8 |       |
| 68    | 5   |       |
| Diabetes mellitus                            |
| 11    | 0.6 |       |
| 7     | 1   |       |
| Heart failure                                |
| 157   | 8.9 |       |
| 110   | 9   |       |
| Ischemic heart disease                       |
| 219   | 12.4|       |
| 147   | 11  |       |
| Neurological disease                         |
| 23    | 1.3 |       |
| 15    | 1   |       |
| Rheumatoid arthritis                         |
| 9     | 0.5 |       |
| 8     | 1   |       |
| Secondary osteoporosis                       |
| 49    | 2.8 |       |
| 36    | 3   |       |
| Ulcer and dyspepsia                          |
| 275   | 15.6|       |
| 192   | 15  |       |
| Drug use, 6 months prior index date, n (%)   |
| Antidepressants                               |
| 256   | 14.5| 10    |
| 207   | 16  |       |
| Anti-epileptic drugs                         |
| 65    | 3.7 | 4     |
| 44    | 3   |       |
| Antipsychotics                               |
| 96    | 5.4 | 5     |
| 70    | 5   |       |
| Benzodiazepines                              |
| 496   | 28.1| 19    |
| 405   | 32  |       |
| Beta blockers                                |
| 519   | 29.4| 28    |
| 385   | 30  |       |
| Bone/mineral drugs                           |
| 154   | 8.7 | 4     |
| 135   | 11  |       |
| Calcium + vitamin D                          |
| 79    | 4.5 | 1     |
| 73    | 6   |       |
| Diuretics                                    |
| 596   | 33.7| 30    |
| 449   | 35  |       |
| DMARDs                                       |
| 22    | 1.2 | 1     |
| 19    | 1   |       |
| Glucocorticosteroids                         |
| 156   | 8.8 | 10    |
| 107   | 8   |       |
| Lithium                                      |
| 6     | 0.3 | 4     |
| 0     | 0   |       |
| NSAID                                        |
| 215   | 12.2| 11    |
| 160   | 12  |       |
| Opioids (with tramadol)                      |
| 194   | 11.0| 7     |
| 161   | 13  |       |
| Opioids (stronger than tramadol)             |
| 59    | 3.3 | 2     |
| 49    | 4   |       |
| Oral antidiabetic drugs                      |
| 204   | 11.6| 11    |
| 150   | 12  |       |
| RAAS inhibitors                              |
| 580   | 32.8| 30    |
| 436   | 34  |       |
| Statins                                      |
| 373   | 21.1| 24    |
| 259   | 20  |       |
of subsequent fractures following a hip fracture. However, this may have been due to a lack of power.

Previous literature has identified that benzodiazepines increase the risk for initial major osteoporotic fracture. However, we did not identify an association between benzodiazepine use and risk of subsequent fracture in this study for current and recent users, only for past users. Benzodiazepines enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABA receptor which results in sedative, sleep-inducing, anti-anxiety, and anticonvulsant properties [24]. Similar to antidepressants, the mechanism of action for increased fracture risk in benzodiazepines users is not fully understood, but an increased propensity to fall is a likely contributor [25]. We expected increased fracture risk to be associated with an immediately increased risk of falling, and therefore hypothesized that current users would be at highest risk. Surprisingly, as noted, only past users of benzodiazepines are at risk. It is unclear why this may be the

### Table 3 Percentage of patients using antidepressants/benzodiazepines following first major osteoporotic fracture

|                      | Cumulative incidence, % (95% CI)* | Cumulative incidence, % (95% CI)* |
|----------------------|-----------------------------------|-----------------------------------|
|                      | Total                             | Men                               | Women                             |
| **Antidepressant**   |                                   |                                   |
| 3 months             | 10.6 (9.8–11.6)                   | 7.5 (6.0–9.2)                     | 11.5 (10.5–12.6)                  |
| 6 months             | 12.6 (11.7–13.6)                  | 8.9 (7.3–10.9)                    | 13.6 (12.6–14.8)                  |
| 12 months            | 14.7 (13.7–15.7)                  | 11.0 (9.2–13.1)                   | 15.7 (14.5–16.9)                  |
| **Benzodiazepine**   |                                   |                                   |
| 3 months             | 24.0 (22.8–25.3)                  | 16.8 (14.7–19.2)                  | 26.0 (24.6–27.4)                  |
| 6 months             | 27.7 (26.4–29.0)                  | 19.9 (17.5–22.4)                  | 29.9 (28.5–31.4)                  |
| 12 months            | 31.4 (30.1–32.8)                  | 24.4 (21.8–27.2)                  | 33.4 (31.9–35.0)                  |
| **Both use**         |                                   |                                   |
| 3 months             | 5.3 (4.8–6.0)                     | 2.8 (2.0–4.0)                     | 6.1 (5.3–6.9)                     |
| 6 months             | 6.6 (5.9–7.3)                     | 3.2 (2.3–4.5)                     | 7.5 (6.7–8.4)                     |
| 12 months            | 8.2 (7.5–9.1)                     | 4.8 (3.6–6.3)                     | 9.2 (8.3–10.2)                    |

CI confidence interval
*1-KM-estimate × 100%

### Table 4 Percentage of patients using antidepressants/benzodiazepines following first hip fracture

|                      | Cumulative incidence, % (95% CI)* | Cumulative incidence, % (95% CI)* |
|----------------------|-----------------------------------|-----------------------------------|
|                      | Total                             | Men                               | Women                             |
| **Antidepressant**   |                                   |                                   |
| 3 months             | 10.9 (9.5–12.5)                   | 8.0 (5.9–10.9)                    | 12.0 (10.3–13.9)                  |
| 6 months             | 13.7 (15.4–12.1)                  | 9.9 (7.5–13.0)                    | 15.1 (13.2–17.3)                  |
| 12 months            | 16.0 (14.3–17.9)                  | 11.7 (9.0–15.1)                   | 17.6 (15.5–19.9)                  |
| **Benzodiazepine**   |                                   |                                   |
| 3 months             | 27.8 (25.7–30.0)                  | 19.9 (16.5–23.8)                  | 30.7 (28.2–33.4)                  |
| 6 months             | 32.4 (30.2–34.7)                  | 23.2 (19.6–27.4)                  | 35.8 (33.2–38.6)                  |
| 12 months            | 35.7 (33.4–38.1)                  | 27.7 (23.7–32.1)                  | 38.7 (36.0–41.6)                  |
| **Both use**         |                                   |                                   |
| 3 months             | 6.2 (5.1–7.4)                     | 3.7 (2.3–5.9)                     | 7.1 (5.8–8.7)                     |
| 6 months             | 7.8 (6.6–9.2)                     | 4.2 (2.7–6.5)                     | 9.1 (7.6–10.9)                    |
| 12 months            | 9.7 (8.4–11.3)                    | 5.8 (3.9–8.5)                     | 11.2 (9.5–13.1)                   |

CI confidence interval
*1-KM-estimate × 100%
This study does have some limitations that are noteworthy. We did not exclude prior use of antidepressants or benzodiazepines prior to the initial fracture (index date). Thus, it is possible that observed risk may be slightly diluted, as daily users may become tolerant to the (side) effects (e.g., fall risk). This may be particularly the case for users of benzodiazepines, where fall risk is known to be high. Additionally, we were unable to differentiate between long half-life and short half-life benzodiazepine users. The relative risk of hip fracture has been found to be increased for long half-life benzodiazepines, in contrast to users of short half-life benzodiazepines [26].

Another limitation is the potential for misclassification of our outcome. As there are no ICD codes identifying a new fracture, it is possible we misclassified a fracture as a subsequent new fracture, when it was a follow-up visit or procedure for the index fracture. To mitigate this effect, we excluded fractures occurring in the first 30 days following index fracture. Although the mean duration of hospitalization after hip fractures has dropped from 20 days in 2000 to 10 days in 2012, we may have misclassified a subsequent fracture as the index fracture [27]. Finally, there is the potential for residual confounding. While participants of randomized controlled trials are highly selected and randomly allocated to one of the treatment options, this is not the case in general practice. While we were able to adjust for a number of possible founders, we could not include lifestyle factors that may be associated with fractures, such as smoking, body weight, exercise, and alcohol intake.

Another limitation is the potential for differential mortality risk between the non-users and the compared exposure groups. However, based on the current literature, we would expect that benzodiazepines or antidepressant users would have a higher mortality risk, as compared to never users. This increased risk would be attributed to higher comorbidities, medication use, and frailty. Under this hypothesis, a higher mortality risk in the exposure groups would expect a lower risk for a subsequent fracture, as compared to the control group of never users, due to depletion of susceptibles. However, this was not observed in our study, where we identified use of antidepressants was associated with significant increased risk of subsequent fracture. As a result, while mortality may always be a competing risk, we do not believe it was a major factor in this study.

Table 5 Antidepressants and benzodiazepines and risk of subsequent fracture within 1 year after major osteoporotic fracture and within complete follow-up period, by recency of use

|                      | Subsequent fracture within 1 year |                       | Subsequent fracture within complete follow-up period |
|----------------------|----------------------------------|-----------------------|------------------------------------------------------|
|                      | Events | Age/sex adj. | HR (95% CI) | Events | Age/sex adj. | HR (95% CI) |
| No use               | 196    | 1.0          | 1.0         | 486    | 1.0          | 1.0         |
| Current usea         |        |              |             |        |              |             |
| Antidepressants      | 23     | 2.10 (1.34–3.27) | 2.17 (1.37–3.43) | d  46 | 1.63 (1.12–2.23) | 1.48 (1.06–2.06) |
| Benzodiazepines      | 32     | 1.35 (0.89–2.07) | 1.18 (0.76–1.81) | e  83 | 1.35 (1.03–1.76) | 1.18 (0.90–1.55) |
| Recent useb          |        |              |             |        |              |             |
| Antidepressants      | 12     | 1.83 (1.01–3.31) | 1.95 (1.07–3.56) | d  24 | 1.58 (1.04–2.34) | 1.44 (0.94–2.21) |
| Benzodiazepines      | 14     | 1.26 (0.71–2.24) | 1.11 (0.62–1.99) | e  30 | 1.12 (0.81–1.77) | 1.08 (0.73–1.60) |
| Past usec            |        |              |             |        |              |             |
| Antidepressants      | 27     | 1.55 (1.02–2.35) | 1.57 (1.03–2.40) | d  55 | 1.14 (0.86–1.52) | 1.08 (0.81–1.45) |
| Benzodiazepines      | 74     | 1.61 (1.16–2.23) | 1.48 (1.06–2.07) | e  154 | 1.18 (0.95–1.47) | 1.11 (0.89–1.38) |

*Analyses adjusted for combination users (current, recent, past)

a Current use defined as a dispensing record in the 30 days before the start of a period

b Recent use was defined as a dispensing record between 31 days and 92 days before the start of a period

c Past use defined as the last dispensing record being more than 92 days before the start of a period.

d Adjusted for age, sex, use of opioids, glucocorticoids, antipsychotics, loop diuretics, beta blockers, a history of secondary osteoporosis, ischemic heart disease, cerebrovascular disease, heart failure, malignant neoplasms, depression
Table 6 Antidepressants and benzodiazepines and risk of subsequent fracture after hip fracture, by recency of use

| Subsequent fracture within complete follow-up period | Events | Age/sex adj. HR (95% CI) | Fully adj. HR (95% CI) |
|-----------------------------------------------------|--------|--------------------------|------------------------|
| No use                                              | 184    | 1.0                      | 1.0                    |
| Current use<sup>a</sup>                             |        |                          |                        |
| Antidepressants                                    | 21     | 1.74 (1.09–2.77)         | 1.52 (0.92–2.51)<sup>d</sup> |
| Benzodiazepines                                    | 36     | 1.22 (0.80–1.84)         | 1.05 (0.69–1.62)<sup>c</sup> |
| Recent use<sup>b</sup>                              |        |                          |                        |
| Antidepressants                                    | 8      | 1.32 (0.64–2.70)         | 1.16 (0.55–2.43)<sup>d</sup> |
| Benzodiazepines                                    | 10     | 0.91 (0.46–1.77)         | 0.81 (0.41–1.60)<sup>c</sup> |
| Past use<sup>c</sup>                                |        |                          |                        |
| Antidepressants                                    | 24     | 1.07 (0.69–1.66)         | 1.00 (0.64–1.57)<sup>d</sup> |
| Benzodiazepines                                    | 61     | 1.14 (0.80–1.61)         | 1.03 (0.72–1.48)<sup>d</sup> |

HR hazard ratio; CI confidence interval; Adj Adjusted
<sup>a</sup>Analyses adjusted for combination users (current, recent, past)
<sup>b</sup>Current use defined as a dispensing record in the 30 days before the start of a period
<sup>c</sup>Recent use defined as a dispensing record between 31 days and 92 days before the start of a period
<sup>d</sup>Past use defined as the last dispensing record being more than 92 days before the start of a period
<sup>e</sup>Adjusted for age, sex, a history of depression
<sup>f</sup>Adjusted for age, sex, use of opioids, glucocorticoids, antipsychotics, loop diuretics, beta blockers, a history of secondary osteoporosis, ischemic heart disease, cerebrovascular disease, heart failure, malignant neoplasms, depression

A major strength of this study is the long follow-up period in the PHARMO Database Network. Additionally, the PHARMO Database Network has high-quality information for a wide range of confounding factors. Thus, while we could not adjust for lifestyle factors, we were able to identify and adjust for a number of possible confounding factors, such as comorbidities and drug use. We were also able to classify exposure and confounders time-dependently. This is particularly important for our exposure groups as patients were able to move between current, recent, and past use of antidepressants, benzodiazepines or both medications, and person-time in each exposure category was used in our analysis. Thus, the potential for exposure misclassification that can result from an ever–never design was minimized.

To our knowledge, this is the first study to examine the association between antidepressant and benzodiazepine use following a major osteoporotic fracture and the risk of a subsequent major fracture. While current guidelines to reduce inappropriate prescribing following a major osteoporotic fracture have been introduced [28], our findings suggest that approximately 15% of patients receive an antidepressant and over 30% receive a benzodiazepine following a major osteoporotic fracture. Given the risk of subsequent fracture in the antidepressant users in this study, our research compliments the recommendations of the current treatment guidelines. Patients should go through a process of medication reconciliation at or after hospital admissions for major osteoporotic fractures. A review to identify potentially hazardous drugs should be done to reduce the risk of subsequent fractures. Doctors should be cautious initiating these drugs as well, particularly in the first year following a major osteoporotic fracture.

In conclusion, while there are limitations to the data, as mentioned, this study provides evidence that patients receiving antidepressants following a fracture should be monitored. While evidence has suggested benzodiazepines to be a major risk factor for fracture, we did not confirm this in our results. Thus, more research is likely required before a concrete decision can be made. This study provides needed insights that can be used to inform clinicians when assessing subsequent fracture risk in patients, particularly with the use of antidepressants. In particular, this may be an area whereby medication reconciliation strategies can be implemented to minimize the risk of subsequent fracture.

Compliance with ethical standards

Conflicts of interest None.

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