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ORIGINAL ARTICLE

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

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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

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 L72; ICD-9 813, 814; ICD-10 S52), humerus (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, antidiabetic 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

Table 1 Baseline characteristics for major osteoporotic fracture

	Major osteoporotic fracture					
	Total		Men		Women	
Sex, *n* (%)	4854		1063	22	3791	78
Age, years (mean, SD)	78	7.5	77	7.1	78	7.6
Age, years, *n* (%)						
65–74	1783	37	424	40	1359	36
75–84	2050	42	452	43	1598	42
≥85	1021	21	187	18	834	22
Diseases, ever before index date, *n* (%)						
Cerebrovascular disease	464	9.6	129	12	335	9
COPD	251	5.2	93	9	158	4
Dementia	220	4.5	55	5	165	4
Depression	208	4.3	32	3	176	5
Diabetes mellitus	34	0.7	5	0	29	1
Heart failure	328	6.8	95	9	233	6
Ischemic heart disease	574	11.8	177	17	397	10
Neurological disease	43	0.9	11	1	32	1
Rheumatoid arthritis	16	0.3	2	0	14	0
Secondary osteoporosis	154	3.2	22	2	132	3
Ulcer and dyspepsia	806	16.6	193	18	613	16
Drug use, 6 months prior index date, *n* (%)						
Antidepressants	617	12.7	94	4	524	14
Anti-epileptic drugs	188	3.9	45	4	143	4
Antipsychotics	170	3.5	43	4	128	3
Benzodiazepines	1230	25.3	180	17	1054	28
Beta blockers	1433	29.5	312	29	1122	30
Bone/mineral drugs	517	10.7	51	5	467	12
Calcium + vitamin D	258	5.3	22	2	236	6
Diuretics	1415	29.2	293	28	1124	30
DMARDs	74	1 .5	11	1	63	2
Glucocorticosteroids	424	8.7	106	10	319	10
Lithium	12	0.2	0	0	12	0
NSAID	716	14.8	136	13	585	15
Opioids (with tramadol)	547	11.3	88	8	459	12
Opioids (stronger than tramadol)	168	3.5	27	3	141	4
Oral antidiabetic drugs	555	11.4	121	11	435	11
RAAS inhibitors	1573	32.4	334	31	1241	33
Statins	1246	25.7	308	29	939	25

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

Table 2 Baseline characteristics for hip fracture

	Hip fracture					
	Total		Men		Women	
Sex, *n* (%)	1766		484	27.4	1282	72.6
Age, years (mean, SD)	81	7.4	75	6.8	81	7.5
Age, years, *n* (%)						
65–74	399	22.6	232	48	262	20
75–84	797	45.1	214	44	569	44
≥85	570	32.3	38	8	451	35
Diseases, ever before index date, *n* (%)						
Cerebrovascular disease	199	11.3	64	13	135	11
COPD	101	5.7	46	10	55	4
Dementia	126	7.1	41	8	85	7
Depression	84	4.8	16	3	68	5
Diabetes mellitus	11	0.6	4	1	7	1
Heart failure	157	8.9	47	10	110	9
Ischemic heart disease	219	12.4	72	15	147	11
Neurological disease	23	1.3	8	2	15	1
Rheumatoid arthritis	9	0.5	1	0	8	1
Secondary osteoporosis	49	2.8	13	3	36	3
Ulcer and dyspepsia	275	15.6	83	17	192	15
Drug use, 6 months prior index date, *n* (%)						
Antidepressants	256	14.5	49	10	207	16
Anti-epileptic drugs	65	3.7	21	4	44	3
Antipsychotics	96	5.4	26	5	70	5
Benzodiazepines	496	28.1	91	19	405	32
Beta blockers	519	29.4	134	28	385	30
Bone/mineral drugs	154	8.7	19	4	135	11
Calcium + vitamin D	79	4.5	6	1	73	6
Diuretics	596	33.7	147	30	449	35
DMARDs	22	1.2	3	1	19	1
Glucocorticosteroids	156	8.8	49	10	107	8
Lithium	6	0.3	2	0	4	0
NSAID	215	12.2	55	11	160	12
Opioids (with tramadol)	194	11.0	33	7	161	13
Opioids (stronger than tramadol)	59	3.3	10	2	49	4
Oral antidiabetic drugs	204	11.6	54	11	150	12
RAAS inhibitors	580	32.8	146	30	436	34
Statins	373	21.1	114	24	259	20

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

	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%

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

	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%

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)	Fully adj. HR (95% CI)	Events	Age/sex adj. HR (95% CI)	Fully adj. HR (95% CI)
No use	196	1.0	1.0	486	1.0	1.0
Current use[a]						
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)[d]
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)[e]
Recent use[b]						
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)[d]
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)[e]
Past use[c]						
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)[d]
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)[e]

HR hazard ratio; *CI* confidence interval; *Adj* Adjusted

*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, a history of depression

[e] 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

case, but it could be that those at the highest risk for falling (or most frail) were removed from benzodiazepine, therefore making them a past user. However, we were not able to identify the effect on fall risk since falls are not reliably recorded in the PHARMO Database Network. If you look at the whole period, it disappears, which may suggest that the early discontinued users are those with characteristics that place them at the highest risk. However, this is only a hypothesis and could warrant further investigation.

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 confounders, 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 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[a]			
Antidepressants	21	1.74 (1.09–2.77)	1.52 (0.92–2.51)[d]
Benzodiazepines	36	1.22 (0.80–1.84)	1.05 (0.69–1.62)[e]
Recent use[b]			
Antidepressants	8	1.32 (0.64–2.70)	1.16 (0.55–2.43)[d]
Benzodiazepines	10	0.91 (0.46–1.77)	0.81 (0.41–1.60)[e]
Past use[c]			
Antidepressants	24	1.07 (0.69–1.66)	1.00 (0.64–1.57)[d]
Benzodiazepines	61	1.14 (0.80–1.61)	1.03 (0.72–1.48)[e]

HR hazard ratio; *CI* confidence interval; *Adj* Adjusted

*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, a history of depression

[e] 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 conciliation strategies can be implemented to minimize the risk of subsequent fracture.

Compliance with ethical standards

Conflicts of interest None.

References

1. Kanis JA (2007) WHO technical report, University of Sheffield, UK:66
2. Johnell O, Kanis JA (2006) An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int 17(12):1726–1733
3. Lötters FJ, van den Bergh JP, de Vries F, Rutten-van Mölken MP (2016) Current and future incidence and costs of osteoporosis-related fractures in the Netherlands: combining claims data with BMD measurements. Calcif Tissue Int 98(3):235–243
4. Takkouche B, Montes-Martínez A, Gill SS, Etminan M (2007) Psychotropic medications and the risk of fracture: a meta-analysis. Drug Saf 30(2):171–184
5. Diem SJ, Blackwell TL, Stone KL, Yaffe K, Haney EM, Bliziotes MM, Ensrud KE (2007) Use of antidepressants and rates of hip bone loss in older women: the study of osteoporotic fractures. Arch Intern Med 167(12):1240–1245
6. Rauma PH, Honkanen RJ, Williams LJ, Tuppurainen MT, Kröger HP, Koivumaa-Honkanen H (2016) Effects of antidepressants on postmenopausal bone loss—a 5-year longitudinal study from the OSTPRE cohort. Bone 89:25–31

7. Richards JB, Papaioannou A, Adachi JD, Joseph L, Whitson HE, Prior JC, Goltzman D, Canadian Multicentre Osteoporosis Study Research Group (2007) Effect of selective serotonin reuptake inhibitors on the risk of fracture. Arch Intern Med 167(2):188–194
8. Moura C, Bernatsky S, Abrahamowicz M, Papaioannou A, Bessette L, Adachi J, Goltzman D, Prior J, Kreiger N, Towheed T, Leslie WD, Kaiser S, Ioannidis G, Pickard L, Fraser LA, Rahme E (2014) Antidepressant use and 10-year incident fracture risk: the population-based Canadian Multicentre Osteoporosis Study (CaMoS). Osteoporos Int 25(5):1473–1481
9. Greendale GA, Unger JB, Rowe JW, Seeman TE (1999) The relation between cortisol excretion and fractures in healthy older people: results from the MacArthur studies-Mac. J Am Geriatr Soc 47: 799–803
10. Rabenda V, Nicolet D, Beaudart C, Bruyère O, Reginster JY (2013) Relationship between use of antidepressants and risk of fractures: a meta-analysis. Osteoporos Int 24(1):121–137
11. Xing D, Ma XL, Ma JX, Wang J, Yang Y, Chen Y (2014) Association between use of benzodiazepines and risk of fractures: a meta-analysis. Osteoporos Int 25(1):105–120
12. Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, Eisman J, Fujiwara S, Garnero P, Kroger H, McCloskey EV, Mellstrom D, Melton LJ, Pols H, Reeve J, Silman A, Tenenhouse A (2004) A meta-analysis of previous fracture and subsequent fracture risk. Bone 35(2):375–382
13. Haentjens P, Autier P, Collins J, Velkeniers B, Vanderschueren D, Boonen S (2003) Colles fracture, spine fracture, and subsequent risk of hip fracture in men and women. A meta-analysis. J Bone Joint Surg Am 85-A(10):1936–1943
14. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA 3rd, Berger M (2000) Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res 15(4):721–739
15. Warriner AH, Patkar NM, Yun H, Delzell E (2011) Minor, major, low-trauma, and high-trauma fractures: what are the subsequent fracture risks and how do they vary? Curr Osteoporos Rep 9(3): 122–128
16. Lönnroos E, Kautiainen H, Karppi P, Hartikainen S, Kiviranta I, Sulkava R (2007) Incidence of second hip fractures. A population-based study. Osteoporos Int 18(9):1279–1285
17. Kaukonen JP, Lüthje P, Nurmi-Lüthje I, Kataja M, Naboulsi H (2011) Second hip fracture and patients' medication after the first hip fracture: a follow-up of 221 hip fracture patients in Finland. Arch Gerontol Geriatr 52(2):185–189
18. Herings RMC, Stricker BHC, de Boer A, Bakker A, Stmnum F, Stergachis A (1996) Current use of thiazide diuretics and prevention of femur fractures. J Clin Epidemiol 49:115–119
19. Mickey RM, Greenland S (1989) The impact of confounder selection criteria on effect estimation. Am J Epidemiol 129(1):125–137
20. Leipzig RM, Cumming RG, Tinetti ME (1999) Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. J Am Geriatr Soc 47(1):30–39
21. Rauma PH, Honkanen RJ, Williams LJ, Tuppurainen MT, Kröger HP, Koivumaa-Honkanen H (2016) Effects of antidepressants on postmenopausal bone loss—a 5-year longitudinal study from the OSTPRE cohort. Bone 89:25–31
22. Diem SJ, Blackwell TL, Stone KL, Yaffe K, Haney EM, Bliziotes MM, Ensrud KE (2007) Use of antidepressants and rates of hip bone loss in older women: the study of osteoporotic fractures. Arch Intern Med 167(12):1240–1245
23. Diem SJ, Ruppert K, Cauley JA, Lian Y, Bromberger JT, Finkelstein JS, Greendale GA, Solomon DH (2013) Rates of bone loss among women initiating antidepressant medication use in midlife. J Clin Endocrinol Metab 98(11):4355–4363
24. Mehdi T (2012) Benzodiazepines revisited. BJMP 5(1):a501
25. van Strien AM, Koek HL, van Marum RJ, Emmelot-Vonk MH (2013) Psychotropic medications, including short acting benzodiazepines, strongly increase the frequency of falls in elderly. Maturitas 74(4):357–362
26. Donnelly K, Bracchi R, Hewitt J, Routledge PA, Carter B (2017) Benzodiazepines, Z-drugs and the risk of hip fracture: a systematic review and meta-analysis. BPLoS One 12(4):e0174730
27. Statistics Netherlands, STATLINE: "hospitalizations by sex, age, region and diagnosis ISHTM classification". www.statline.cbs.nl, accessed 17 January 2018
28. Nederlands Huisartsen Genootschap (NHG), de Nederlandse Vereniging voor Klinische Geriatrie (NVKG), Orde van Medische Specialisten (OMS). Multidisciplinaire richtlijn polyfarmacie bij ouderen 2012, https://www.nhg.org/themas/publicaties/multidisciplinaire-richtlijn-polyfarmacie-bij-ouderen assessed 05-02-2017