Clinical Epidemiology

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ORIGINAL RESEARCH

Individual Antidepressants and the Risk of Fractures in Older Adults: A New User Active Comparator Study

This article was published in the following Dove Press journal:
Clinical Epidemiology

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Objective: To determine the risk of hip–pelvis and other non-vertebral fractures in older adults using antidepressants (ADs).

Methods: We conducted a case–control study nested in a cohort of new users of ADs aged ≥65 years without prior hip–pelvis or other non-vertebral fractures, identified in the German Pharmacoepidemiological Research Database (GePaRD) during 2005–2014. Cases were patients first hospitalized for hip–pelvis or other non-vertebral fractures. Up to 100 controls per case were selected using incidence density sampling. AD use was ascertained at index date (ID) based on the supply of last dispensing. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression with current users of mirtazapine as reference (active comparator).

Results: A total of 39,853 cases of hip–pelvis fracture (80% women, median age 81 years) and 31,577 cases of other fractures (84% women, median age 79 years) were matched to >3 million controls. For hip–pelvis fracture, aORs in current users were about 1.3 with little variation between individual ADs, ranging from 1.33 for citalopram (95% CI 1.27–1.39) to 1.28 for amitriptyline (1.21–1.35). For other fractures, the aORs were highest in current users of citalopram (1.50; 1.42–1.58) and duloxetine (1.54; 1.39–1.71) and lowest for amitriptyline (1.18; 1.11–1.26) and trimipramine (1.16; 1.03–1.29). For all examined ADs, the aORs were higher for other fractures than for hip–pelvis fracture.

Conclusion: The risk of fractures varies between ADs, but for most agents is higher than the risk for mirtazapine. When treating older adults with ADs, prescribers should carefully consider the risk profile of individual ADs regarding fractures, which are a major health problem in this population.

Keywords: antidepressants, fractures, hip fracture, pelvis fracture, older adults, health-care databases, pharmacoepidemiology

Introduction

Antidepressants (ADs) are frequently used in older adults, for example, to treat late-life depression, anxiety disturbance, sleep problems or neuropathic pain.[1] The prevalence of AD use in older adults ranges from 15% to up to 30% in different populations.[2–6] However, ADs have been consistently associated with an increased risk of fractures in older adults,[7–13] in particular with fractures of the hip.[13–19] Since fractures are a major health issue in older adults, leading to reduced autonomy and increased short-term mortality, possibilities to reduce the risk of fractures need to be explored. This includes a careful characterization of the safety profile of individual ADs regarding fractures.

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submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/CLEP.S222888

However, prior studies mainly focused on differences in risk between AD classes rather than between individual ADs. Meta-analyses of observational studies showed a higher risk for selective serotonin reuptake inhibitors (SSRIs) than for tricyclic antidepressants (TCAs).[20–24] For example, the summary risk of hip fracture was increased by 60% to 100% in users of SSRI,[22–24] while it was increased by 40% to 70% in users of TCAs;[23,24] the risk of any fracture was increased by 70%[20,22] for SSRIs and by 40%[21,24] for TCAs. These risk patterns were again confirmed by a more recent multi-database study.[17]

Only two cohort studies have compared the risk of fracture between individual ADs and showed differences in risk within the AD classes. In a French cohort[7] of persons aged 65 years or older, the risk of fractures associated with SSRIs was increased twofold for fluoxetine, by 50% for citalopram and by 30% for sertraline and paroxetine. In another cohort of older adults with depression based on a UK primary care database,[8] the risk was increased by 80% for venlafaxine, between 70% and 60% for citalopram, fluoxetine, and sertraline, by about 50% for mirtazapine and paroxetine, and by 30% for amitriptyline and escitalopram. However, these studies compared the risk in persons currently using AD with that of persons not currently treated. Moreover, the first study[7] evaluated four SSRIs and the second one[8] did not evaluate frequently used ADs such as duloxetine.

Improved knowledge of the fracture risk associated with individual ADs is important for clinicians to adequately balance risks and benefits in the decisions of prescribing ADs to older adults and of monitoring treated patients. It ultimately will help to reduce the risk of fractures in this vulnerable population.

We aimed to add knowledge on the risk of individual ADs regarding the risk of hip–pelvis and other non-vertebral fractures in older adults by conducting an active comparator case–control study nested in a cohort of new users of ADs aged ≥65 years without prior hip–pelvis or other non-vertebral fractures.

Methods

Data Source

This study was conducted using the German Pharmacoepidemiological Research Database (GePaRD). GePaRD is based on claims data from four statutory health insurance providers in Germany and currently includes information on about 25 million persons who have been insured with one of the participating providers since 2004 or later. In addition to demographic data, GePaRD contains information on drug dispensations (including Anatomical and Therapeutic Code – ATC, defined daily dose – DDD, strength, packaging size, generic and brand name), outpatient and inpatient services and diagnoses. Per data year, there is information on approximately 17% of the general population and all geographical regions of Germany are represented. In- and outpatient diagnoses are coded according to the International Classification of Diseases, 10th revision, German Modification (ICD-10-GM). GePaRD data are representative of the German general population with respect to age, sex, region of residence and medication dispensations.[25,26]

The suitability of GePaRD data for pharmacoepidemiological research has been assessed methodologically and by validation studies.[25,27,28] GePaRD has been used for various types of pharmacoepidemiological studies including drug utilization studies in the elderly[29,30] and studies investigating the risks of antidepressants.[27,31-33]

Study Design

We conducted a case–control study nested in a cohort of persons aged ≥65 years who initiated the use of an AD (new users) between January 1, 2005 and December 31, 2014 (study period). We applied an active comparator new user design,[34] comparing the risk of persons initiating a certain AD to the risk of persons initiating mirtazapine (active comparator) which is frequently used and has been associated with a low risk of hip fractures.[35]

To be eligible, persons had to be older than 65 years and have at least 12 months of continuous enrollment before cohort entry. Patients entered the cohort at the date of the first AD dispensation after 365 days without such a dispensation ("initiation"). We defined two not mutually exclusive cohorts, one for the outcome hip–pelvis fracture and one for other non-vertebral fractures (the same person could be in both cohorts if he/she experienced both types of fractures during follow-up). We excluded from each cohort persons who experienced the outcome any time before cohort entry. Each person was followed from cohort entry to the date of the first hospitalization for the respective outcome, disenrollment from insurance, end of study period or death, whichever occurred first.

A case was defined as any cohort member (i) hospitalized for a fracture of the hip or pelvis, or (ii) hospitalized for other fractures (excluding hip, pelvis and vertebral fractures). Cases were identified by the main discharge codes (Supplementary Table S1). The day of admission

was defined as the index date (ID). We randomly selected up to 100 controls per case using incidence-density sampling[36] with matching on sex, age and time in the cohort. Controls were eligible to be selected more than once and could become cases later on during follow-up.[36] For controls, the ID was defined as the ID of the corresponding case. Eligible patients hospitalized for any reason at the ID of the case were not at risk of being hospitalized for the outcome and were thus excluded from the set of potential controls (risk-set).[36]

Exposure Definition

Dispensations of ADs were identified through the ATC code N06A and categorized into the following classes (Table S2): tricyclics (TCAs), selective serotonin reuptake inhibitors (SSRIs), selective serotonin-noradrenaline reuptake inhibitors (SSNRIs), noradrenergic and specific serotonergic antidepressants (NASSAs), noradrenaline reuptake inhibitors (NARIs), monoamine oxidase inhibitors (MAOs), as well as herbal and other ADs.

Treatment episodes were defined based on the estimated supply, as the intended treatment duration and daily dose are not registered. To account for lower dosage and compliance in the elderly, supply was estimated as the dispensed amount of defined daily doses (DDDs) plus 150% of the DDDs.[29,37,38] A new dispensation starting during the supply of the previous one marked the start of the new treatment episode. Exposure to ADs was ascertained at ID based on the interval between ID and the end of the most recent prior treatment episode and classified in the following mutually exclusive categories: (i) current use (supply overlapped ID), (ii) recent use (supply ended within 30 days before ID), (iii) past use (supply ended 31 through 90 days before ID) and (iv) remote use (supply ended ≥91 days before ID) (Figure S1). This latter category encompassed use of any AD, while the others were defined separately for selected individual agents. We defined two additional exposure categories: multiple use (encompassing users of two or more ADs within one exposure category) and switching (encompassing current users of an AD with recent use of an AD of a different class).

Covariates and Potential Confounders

We accounted for a wide range of potential confounders, including risk factors of fractures,[39–45] co-morbidities (eg, vision disorders, Parkinson´s disease),[46,47] co-medications (eg, antipsychotics, antiepileptics, hypnotics and sedatives),[48] as well as indicators of life-style habits and of overall health status.

Co-morbidities were ascertained based on inpatient and confirmed outpatient diagnoses occurring (i) any time before ID for chronic diseases and some potentially recurrent conditions, such as syncope and dizziness, (ii) within 6 months before and at ID for acute infectious diseases (eg urinary tract infections or influenza which increase the risk of falling[49–51]) and (iii) within 1 year before and at ID for co-morbidities that are also proxies of indications, such as depression and anxiety disorder. The use of co-medications was ascertained based on dispensations occurring (i) any time before ID or (ii) within 6 months before and at ID for medications potentially affecting the risk of fractures, such as hypnotics and sedatives. Indicators of lifestyle habits were assessed based on diagnoses and medications related, respectively, to alcohol abuse, illicit drug use, obesity, and smoking, and occurring any time before ID. As indicators of overall health status, frailty and use of health care, we calculated the Charlson Co-morbidity Index,[52] the number of different medication classes dispensed within 1 year before ID, nursing home residence (yes/no), and percentage of hospitalized time within 1 year before ID (excluding ID).

Statistical Analysis

Conditional logistic regression was used to estimate matched and confounder-adjusted odds ratios (aORs), with 95% confidence intervals (95% CI), comparing current, recent and past use of each AD with current users of mirtazapine as reference.

In the model, we included all potential confounders (full model) to further reduce the likelihood of residual confounding. Stratified analyses were performed by age (65–74, 75–84 and ≥ 85 years), sex, and prior diagnosis of depression. We performed sensitivity analyses (i) estimating supply based on the dispensed DDDs without any addition and (ii) using remote use of any AD as reference.

Ethics and Approvals

In Germany, the utilisation of health insurance data for scientific research is regulated by the Code of Social Law. All involved health insurance providers as well as the German Federal (Social) Insurance Office and the Senator for Science, Health, and Consumer Protection in Bremen as their responsible authorities approved the use of GePaRD data for this study. Informed consent for studies based on claims data is required by law unless obtaining consent appears unacceptable and would bias

results, which was the case in this study. GePaRD does not include any identifying patient data. According to the Ethics Committee of the University of Bremen studies based on GePaRD are exempt from institutional review board review.

Results

The cohort addressing incident hip–pelvis fracture comprised 706,561 new users and the outcome of interest occurred in 39,853 persons (5.6%); of these, 80% were women and median age was 81 years (25–75% percentile 76–86). The cohort addressing other incident fractures comprised 628,780 new users and the outcome of interest occurred in 31,577 persons (5.0%); of these, 84% were women and median age was 79 years (73–84). Each cohort had approximately 2.9 million person-years of observation (hip fracture cohort 2,916,400 person-years; other fracture cohort 2,912,300 person-years).

Compared to respective controls, cases of both hip–pelvis and other fractures were hospitalized for a longer time, more likely used five or more different medications and had conditions potentially affecting the risk (Table 1). For instance, 32.3% of hip–pelvis fracture cases and 23.5% of other fracture cases had dementia vs 19.6% and 16.3% of controls; 48.7% of hip–pelvis cases and 46.8% of other fracture cases had osteoporosis vs 39.3% and 39.1% of controls. Cases were also more likely to have had prior injuries, to use antipsychotics (35.6% of hip–pelvis cases and 29.7% of other fracture cases vs 25.9% and 24.2% of controls, respectively), antiepileptics (11.1% and 10.3% vs 8.2% and 8.1%), and to have a history of alcohol abuse (5.4% and 4.8% vs 2.9% and 3.0%).

Compared with current users of mirtazapine, the aOR of hip–pelvis fracture was increased by about 30% in current users of citalopram, duloxetine, escitalopram, venlafaxine, amitriptyline, and fluoxetine and by 20% for paroxetine (Table 2). The aOR of other fractures was increased by 50% in current users of duloxetine, citalopram, and paroxetine; it was increased by 40% for venlafaxine and escitalopram, and by 30% for sertraline. The aOR was lower for amitriptyline and trimipramine.

The pattern of risk of both hip–pelvis fracture (Figure 1) and other fractures (Figure 2) was similar in persons with and without depression, between men and women (Figures S2 and S3) and across age categories (Figures S4 and S5).

Sensitivity analysis using the DDDs without any addition to estimate supply confirmed the results in current users of all examined ADs (Table S3). Using remote users of any AD as a reference, the aORs of both outcomes were higher in current users of almost all the examined ADs, except for the aOR of hip fracture in current users of trimipramine (Table S4).

Discussion

Based on a cohort of more than 700,000 new users, we were able to estimate the risk of hip–pelvis fractures and other non-vertebral fractures in current users of 11 individual ADs, compared with current users of mirtazapine. Accounting for a wide range of co-morbidities, use of co-medications and other potential confounding factors, we found that current users of duloxetine and citalopram had the highest risk, increased by more than 30% for hip–pelvis fracture and by 50% for other fractures. Users of paroxetine had a 50% increased risk of other fractures and a 20% increased risk for hip–pelvis fractures. Among the other examined SSRIs and SSNRI, current users of sertraline, fluoxetine, escitalopram, and venlafaxine had a risk increased by approximately 30% for hip–pelvis fracture and between 30% and 40% for other fractures. Among the examined TCAs, the increase in risk was statistically significant only for amitriptyline (28% for hip–pelvis and 18% for other fractures), and trimipramine (16% for other fractures). The pattern of risk was similar for both hip–pelvis and other fractures, in men and women and across all included age groups, suggesting that the risk was not restricted to specific fractures or sub-populations.

To our knowledge, no study has evaluated the risk of hip fracture associated with individual ADs so far and only two other studies have evaluated the risk of other fractures associated with individual ADs.[7,8] The first of these studies conducted among community-dwelling older adults in France[7] compared the risk of any fractures of four individual SSRIs compared with never users of any AD. For citalopram and sertraline, this study found a risk of other fractures similar to our study, but a lower risk for fluoxetine and a slightly higher risk for paroxetine. The other study conducted among older adults with depression in the UK[8] found that the risk of a composite outcome (encompassing fractures of upper and lower limb, ribs, skull, vertebrae, and pelvis) was increased by 60–70% in users of citalopram, fluoxetine, and sertraline, by about 50% in users of mirtazapine and paroxetine, and by 30% for amitriptyline and escitalopram. Similarly, we found a 50% increased risk for citalopram and paroxetine; amitriptyline also had a lower risk in our study. Conversely, in our cohort venlafaxine was not among the ADs with the highest risk, while in the study

Table 1 Characteristics of Cases of Hip and Pelvis Fracture and of Other Fractures and Matched Controls

Demographics	Hip and Pelvis Fracture					Other Fractures				
	Cases (N= 39,853)		Controls (N= 3,979,510)		aOR[a] (95% CI[b])	Cases (N= 31,577)		Controls (N= 3,153,900)		aOR (95% CI)
	N	%	N	%		N	%	N	%	
Sex										
Women	31,789	79.8	3,175,471	79.8	–	26,528	84.0	2,650,493	84.0	–
Men	8064	20.2	804,039	20.2	–	5049	16.0	503,407	16.0	–
Age (years)										
65–74	8213	20.6	821,147	20.6	–	10,130	32.1	1,012,959	32.1	–
75–84	18,296	45.9	1,829,613	46.0	–	13,562	42.9	1,355,996	43.0	–
≥85	13,344	33.5	1,328,750	33.4	–	7885	25.0	784,945	24. 9	–
Co-morbidities										
Depression[c]	21,057	52.8	1,918,013	48.2	1.21 (1.18–1.23)	16,539	52.4	1,534,934	48.7	1.16 (1.14–1.19)
Dementia[c]	12,891	32.3	780,268	19.6	2.12 (2.07–2.17)	7405	23.5	513,432	16.3	1.67 (1.62–1.72)
Anxiety disorders[c]	4481	11.2	459,921	11.6	0.97 (0.94–1.00)	72	0.2	8097	0.3	0.97 (0.94–1.00)
Bipolar disorders[c]	374	0.9	25,965	0.7	1.44 (1.30–1.60)	350	1.1	23,718	0.8	1.34 (1.19–1.50)
Schizophrenia[c]	490	1.2	28,576	0.7	1.72 (1.57–1.88)	1650	5.2	126,852	4.0	1.48 (1.33–1.65)
Obsessive compulsive disorders[c]	114	0.3	9433	0.2	1.21 (1.00–1.45)	3905	12.4	396,079	12.6	0.89 (0.70–1.12)
Parkinson's disease and movement disorders[c]	16,386	41.1	1,347,913	33.9	1.37 (1.35–1.40)	11,241	35.6	1,009,029	32.0	1.18 (1.15–1.21)
Delirium[c]	923	2.3	38,395	1.0	2.45 (2.29–2.62)	3018	9.6	292,845	9.3	2.11 (1.93–2.31)
Pain[d]	37,011	92.9	3,698,908	92.9	0.99 (0.95–1.03)	2694	8.5	198,481	6.3	1.00 (0.95–1.04)
Myocardial infarction[d]	4698	11.8	415,653	10.4	1.15 (1.11–1.19)	3018	9.6	292,845	9.3	1.03 (0.99–1.07)
Other coronary heart disease[d]	19,550	49.1	1,914,710	48.1	1.04 (1.02–1.06)	14,074	44.6	1,433,384	45.4	0.96 (0.94–0.99)
Atrial fibrillation[d]	9219	23.1	772,549	19.4	1.26 (1.23–1.29)	5815	18.4	555,384	17.6	1.06 (1.03–1.09)
Other arrhythmias and conduction disorders[d]	18,362	46.1	1,835,765	46.1	1.00 (0.98–1.02)	13,765	43.6	1,414,554	44.9	0.95 (0.93–0.97)
Valvular disorders and endocarditis[d]	10,326	25.9	997,520	25.1	1.05 (1.02–1.07)	7465	23.6	759,229	24.1	0.98 (0.95–1.00)
Pericardial disorders[d]	464	1.2	39,543	1.0	1.18 (1.07–1.29)	322	1.0	32,259	1.0	1.00 (0.89–1.11)
Myocarditis[d]	210	0.5	20,490	0.5	1.02 (0.89–1.17)	181	0.6	16,684	0.5	1.09 (0.94–1.26)
Peripheral vascular disease[d]	14,890	37.4	1,373,202	34.5	1.14 (1.11–1.16)	10,681	33.8	1,027,333	32.6	1.06 (1.03–1.08)
Hypertension[d]	34,617	86.9	3,475,107	87.3	0.96 (0.93–0.99)	26,960	85.4	2,713,574	86.0	0.95 (0.92–0.98)
Chronic pulmonary disease[d]	19,419	48.7	1,958,446	49.2	0.98 (0.96–1.00)	15,131	47.9	1,541,941	48.9	0.96 (0.94–0.98)
Pulmonary circulation disorders[d]	2860	7.2	235,671	5.9	1.23 (1.18–1.28)	1908	6.0	175,665	5.6	1.09 (1.04–1.14)
Rheumatoid arthritis, arthropathies and connective tissue disorders[d]	9841	24.7	966,583	24.3	1.02 (1.00–1.05)	7831	24.8	783,674	24.8	1.00 (0.97–1.02)
Liver insufficiency[d]	9963	25	958,498	24.1	1.05 (1.03–1.08)	7906	25	784,447	24.9	1.01 (0.98–1.04)
Renal insufficiency[d]	9176	23	777,839	19.5	1.24 (1.21–1.27)	5851	18.5	552,253	17.5	1.07 (1.04–1.10)
Cancer[d,e]	12,136	30.5	1,152,267	29.0	1.08 (1.05–1.10)	9234	29.2	896,549	28.4	1.04 (1.02–1.07)
Diabetes[d,f]	14,750	37	1,409,909	35.4	1.07 (1.05–1.09)	10,941	34.6	1,072,758	34.0	1.03 (1.01–1.05)
Osteoporosis and other diseases of bone density and structure[d]	19,393	48.7	1,565,117	39.3	1.52 (1.49–1.55)	14,772	46.8	1,232,731	39.1	1.41 (1.38–1.44)
Syncope and dizziness[d]	21,211	53.2	1,945,839	48.9	1.20 (1.17–1.22)	15,417	48.8	1,472,308	46.7	1.09 (1.07–1.12)
Vision disorders[d]	32,204	80.8	3,270,698	82.2	0.91 (0.89–0.93)	25,294	80.1	2,558,450	81.1	0.94 (0.91–0.96)
Dyslipidemia[d]	24,731	62.1	2,578,665	64.8	0.89 (0.87–0.91)	19,972	63.2	2,065,600	65.5	0.91 (0.89–0.93)
Infectious diseases[g]	15,378	38.6	1,481,169	37.2	1.06 (1.04–1.08)	512	1.6	24,548	0.8	0.99 (0.97–1.02)
Hip and pelvis fracture[d]	0	-	0	-	–	14,265	45.2	243,315	7.7	11.43 (11.16–11.70)
Other fractures[d]	31,025	77.8	862,005	21.7	13.72 (13.40–14.06)	0	-	0	-	–
Traumatic brain injury[d]	7717	19.4	544,903	13.7	1.53 (1.49–1.57)	5104	16.2	370,959	11.8	1.46 (1.42–1.51)

(*Continued*)

Table 1 (Continued).

Demographics	Hip and Pelvis Fracture					Other Fractures				
	Cases (N= 39,853)		Controls (N= 3,979,510)		aOR[a] (95% CI[b])	Cases (N= 31,577)		Controls (N= 3,153,900)		aOR (95% CI)
	N	%	N	%		N	%	N	%	
Co-medications										
Insulin[d]	3668	9.2	273,290	6.9	1.38(1.33–1.42)	2526	8.0	204,483	6.5	1.26 (1.21–1.31)
Antidiabetic drugs[d]	6713	16.8	617,003	15.5	1.10 (1.08–1.13)	4877	15.4	473,352	15.0	1.04 (1.00–1.07)
Antithrombotic drugs[d]	23,938	60.1	2,132,977	53.6	1.31 (1.29–1.34)	16,965	53.7	1,577,306	50.0	1.17 (1.14–1.19)
Cardiac glycosides[d]	5895	14.8	527,646	13.3	1.14 (1.11–1.17)	3543	11.2	369,746	11.7	0.95 (0.92–0.98)
Anti-arrhythmic drugs[d]	1928	4.8	151,544	3.8	1.29 (1.23–1.35)	1240	3.9	117,680	3.7	1.06 (1.00–1.12)
Other antihypertensive drugs[d]	3753	9.4	372,944	9.4	1.01 (0.97–1.04)	2720	8.6	285,925	9.1	0.95 (0.91–0.98)
Diuretics[d]	25,160	63.1	2,258,086	56.7	1.33 (1.30–1.36)	17,630	55.8	1,666,077	52.8	1.14 (1.11–1.17)
Vasodilators[d]	13,871	34.8	1,391,925	35.0	0.99 (0.97–1.01)	9963	31.6	1,028,486	32.6	0.95 (0.93–0.97)
Beta-adrenergic agonists[d]	24,850	62.4	2,456,283	61.7	1.03 (1.01–1.05)	19,091	60.5	1,934,631	61.3	0.96 (0.94–0.99)
Calcium antagonists[d]	17,722	44.5	1,779,622	44.7	0.99 (0.97–1.01)	13,333	42.2	1,347,792	42.7	0.98 (0.96–1.00)
ACE inhibitors[d]	25,394	63.7	2,440,606	61.3	1.11 (1.09–1.13)	18,762	59.4	1,855,914	58.8	1.02 (1.00–1.05)
Angiotensin II antagonists[d]	10,763	27.0	1,194,188	30.0	0.86 (0.84–0.88)	8708	27.6	946,872	30.0	0.89 (0.87–0.91)
Lipid-lowering drugs[d]	16,536	41.5	1,678,964	42.2	0.97 (0.95–0.99)	12,884	40.8	1,331,916	42.2	0.94 (0.92–0.96)
Hormone therapy[d]	10,467	26.3	1,155,009	29.0	0.85 (0.83–0.87)	9763	30.9	1,063,627	33.7	0.86 (0.84–0.89)
Drugs for the treatment of bone diseases[d]	8345	20.9	601,777	15.1	1.51 (1.47–1.55)	14,772	46.8	1,232,731	39.1	1.41 (1.38–1.44)
Glucocorticoids[d]	15,141	38.0	1,446,436	36.3	1.07 (1.05–1.10)	11,702	37.1	1,169,528	37.1	1.00 (0.98–1.02)
Anti-Parkinson drugs[d]	6548	16.4	495,063	12.4	1.39 (1.35–1.43)	4477	14.2	379,303	12.0	1.21 (1.17–1.25)
Respiratory drugs[d]	11,836	29.7	1,184,752	29.8	1.00 (0.98–1.02)	9185	29.1	943,351	29.9	0.96 (0.94–0.99)
Non-steroidal anti-inflammatory drugs[d]	33,448	83.9	3,333,556	83.8	1.01 (0.99–1.04)	26,560	84.1	2,647,158	83.9	1.01 (0.98–1.05)
Antipsychotics[g]	14,169	35.6	1,032,325	25.9	1.60 (1.57–1.64)	9370	29.7	763,695	24.2	1.33 (1.30–1.37)
Antiepileptic drugs[g]	4432	11.1	327,887	8.2	1.40 (1.35–1.44)	3262	10.3	254,939	8.1	1.31 (1.27–1.36)
Anxiolytics[g]	5351	13.4	428,011	10.8	1.29 (1.25–1.33)	3671	11.6	324,785	10.3	1.15 (1.11–1.19)
Hypnotics and sedatives[g]	4999	12.5	379,701	9.5	1.36 (1.32–1.40)	3448	10.9	286,248	9.1	1.23 (1.19–1.27)
Muscle relaxants[g]	1449	3.6	118,460	3.0	1.23 (1.17–1.30)	980	3.1	100,498	3.2	0.97 (0.91–1.04)
Indicators of lifestyle habits										
Alcohol abuse	2144	5.4	115,741	2.9	1.92 (1.83–2.00)	1520	4.8	93,433	3.0	1.67 (1.58–1.76)
Illicit drug abuse	1515	3.8	116,821	2.9	1.31 (1.24–1.38)	1197	3.8	92,681	2.9	1.30 (1.23–1.38)
Obesity	7670	19.2	883,250	22.2	0.83 (0.81–0.85)	6871	21.8	742,756	23.6	0.90 (0.88–0.93)
Smoking	2318	5.8	139,544	3.5	1.72 (1.65–1.79)	1650	5.2	126,852	4.0	1.32 (1.26–1.39)
Indicators of health status, frailty and use of health care										
Charlson Comorbidity Index >2[d,h]	27,563	69.2	2,493,742	62.7	1.35 (1.32–1.38)	19,786	62.7	1,881,284	59.6	1.14 (1.11–1.17)
Hospitalized time >5%[c,h]	10,458	26.2	506,059	12.7	2.53 (2.47–2.59)	5992	19.0	372,883	11.8	1.78 (1.73–1.83)
Number of medications[h,i]										
1–4	12,372	31.0	1,649,310	41.4	0.63 (0.62–0.64)	12,136	38.4	1,367,912	43.4	0.81 (0.79–0.83)
5–8	20,300	50.9	1,814,090	45.6	1.24 (1.22–1.27)	14,846	47.0	1,379,623	43.7	1.14 (1.12–1.17)
≥10	6344	15.9	38,2808	9.6	1.79 (1.75–1.84)	3667	11.6	286,402	9.1	1.32 (1.28–1.37)
Nursing home residence[c,h]	3397	8.5	17,2028	4.3	2.15 (2.07–2.23)	1725	5.5	109,779	3.5	1.64 (1.56–1.73)

Notes: [a]Model adjusted for all listed covariates. [b]95% confidence interval. [c]Assessed within 365 days before index date and at index date. [d]Assessed any time before the index date. [e]Except for malignant neoplasm of the skin. [f]Includes both type 1 and type 2 diabetes. [g]Assessed within 181 days before and at index date. [h]Cut-offs were defined as follows: for Charlson Comorbidity Index the first tertile among controls, for a number of medications prior studies, for hospitalized time the first decile among controls. [i]Medication of different therapeutic classes.

Abbreviations: aOR, adjusted odds ratio; 95% CI, 95% confidence interval; ACE, angiotensin-converting enzyme.

Table 2 Odds Ratio (OR), with 95 Confidence Interval (95% CI), of Hip–Pelvis Fracture and Other Non-Vertebral Fractures in Users of Individual Antidepressants (AD) Compared with Current Users of Mirtazapine and with Remote Users of Any AD. Main Analysis (DDDs + 150%)

	Hip–Pelvis Fractures				Other Non-Vertebral Fractures			
	Cases	Controls	Matched OR[a] (95% CI)	Adjusted OR[b] (95% CI)	Cases	Controls	Matched OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Current users	(N=39,853)	(N= 3,979,510)			(N= 31,577)	(N= 3,153,900)		
TCA								
Doxepin	640 (1.6)	64,954 (1.6)	0.71 (0.63–0.80)	0.87 (0.77–0.98)	468 (1.5)	49,843 (1.6)	0.80 (0.70–0.93)	0.91 (0.78–1.05)
Amitriptyline	2231 (5.6)	168,378 (4.2)	1.10 (1.04–1.16)	1.28 (1.21–1.35)	1592 (5.0)	129,821 (4.1)	1.14 (1.07–1.22)	1.18 (1.11–1.26)
Opipramol	914 (2.3)	124,842 (3.1)	0.60 (0.56–0.65)	0.88 (0.82–0.95)	774 (2.5)	100,276 (3.2)	0.72 (0.66–0.78)	0.94 (0.87–1.02)
Trimipramine								
Trimipramine	449 (1.1)	48,263 (1.2)	0.77 (0.69–0.85)	1.00 (0.91–1.11)	381 (1.2)	37,116 (1.2)	0.95 (0.85–1.06)	1.16 (1.03–1.29)
SSRI								
Sertraline	866 (2.2)	55,329 (1.4)	1.28 (1.19–1.38)	1.27 (0.17–1.37)	566 (1.8)	40,991 (1.3)	1.28 (1.17–1.40)	1.33 (1.21–1.46)
Citalopram	6082 (15.3)	371,599 (9.3)	1.35 (1.30–1.41)	1.33 (1.27–1.39)	4274 (3.5)	263,557 (8.4)	1.51 (1.44–1.59)	1.50 (1.42–1.58)
Paroxetine	260 (0.7)	20,035 (0.5)	1.05 (0.92–1.19)	1.20 (1.05–1.36)	244 (0.8)	16,935 (0.5)	1.32 (1.16–1.51)	1.49 (1.30–1.71)
Fluoxetine	232 (0.6)	17,115 (0.4)	1.11 (0.97–1.27)	1.27 (1.11–1.46)	190 (0.6)	13,724 (0.4)	1.28 (1.10–1.48)	1.45 (1.24–1.68)
Escitalopram	465 (1.2)	28,908 (0.7)	1.34 (1.21–1.47)	1.30 (1.17–1.43)	326 (1.0)	21,690 (0.7)	1.40 (1.25–1.58)	1.40 (1.24–1.58)
SSNRI								
Duloxetine	548 (1.4)	32,334 (0.8)	1.37 (1.25–1.50)	1.32 (1.21–1.45)	444 (1.4)	26,150 (0.8)	1.56 (1.41–1.73)	1.54 (1.39–1.71)
Venlafaxine	581 (1.5)	36,245 (0.9)	1.29 (1.18–1.40)	1.29 (1.18–1.41)	454 (1.4)	29,787 (0.9)	1.39 (1.26–1.54)	1.41 (1.27–1.56)
NASSA								
Mirtazapine[c]	3362 (8.4)	283,463 (7.1)	(Reference)	(Reference)	2094 (6.6)	200,487 (6.4)	(Reference)	(Reference)

Notes: [a]Adjusted for age, sex and length of follow-up by matching. [b]Model adjusted for myocardial infarction, other coronary heart disease, atrial fibrillation, other cardiac arrhythmias and conduction disorders, valvular disorders and endocarditis, pericardial disorders, myocarditis, peripheral vascular disease, hypertension, dementia, chronic pulmonary disease, pulmonary circulation disorders, rheumatic arthritis/collagen vascular disease, liver disease, Parkinson's disease, other extrapyramidal and movement disorders, depression, diabetes, renal failure, cancer (except malignant neoplasm of skin), obesity, alcohol abuse, drug abuse, osteoporosis and other disorders of bone density and structure, syncope, dizziness and tendency to fall, vision disorders, dyslipidemia, bipolar disorders, schizophrenia, smoking, anxiety disorders, obsessive compulsive disorders, other movement disorders, pain, infectious diseases, delirium, use of insulin, antidiabetic medications, antithrombotic medications, cardiac glycosides, anti-arrhythmic medications, other antihypertensive medications, diuretics, vasodilators, beta-adrenergic agonists, calcium antagonists, ACE inhibitors, angiotensin II antagonists, lipid-lowering medications, hormone therapy, glucocorticoids, anti-Parkinson medications, respiratory medications, non-steroidal anti-inflammatory medications, antipsychotics, antiepileptic medications, anxiolytics, hypnotics and sedatives, muscle relaxants, number of medications (1 to 4; 5 to 8, 9 and more), hospitalized time (≤5%; >5%), Charlson Comorbidity Index (≤2; >2), nursing home residence. [c]Reference category.

Abbreviations: TCA, tricyclics; SSRI, selective serotonin reuptake inhibitors; SSNRI, selective serotonin-noradrenaline reuptake inhibitors; NASSA, noradrenergic and specific serotonergic antidepressants.

by Schneeweiss and Wang it had an 80% increased risk. Additionally, our study provides results for duloxetine, which was not evaluated in that cohort. The lower risks observed in our study might be explained by the different reference. Patients treated with an active comparator are probably more similar than non-users to exposed patients regarding the indication as well as measured and partly unmeasured characteristics (eg severity of depression, cognitive or functional impairment, or frailty). For that reason, using an active comparator is expected to result in less residual confounding, including confounding by indication. In support of this interpretation, one study[53] showed that the risk of hip fracture associated with SSRIs decreased, albeit remaining statistically significant, when unmeasured confounding was accounted for.

Indeed, different ADs may have partially different indications and related different dosages. Although depression is the main indication, some ADs are prescribed for anxiety, sleep disturbances (eg mirtazapine, trazodone), or pain (eg amitriptyline), in addition to depression. These indications often overlap, as anxiety, pain and sleep disturbances are commonly associated with depression, particularly in older adults. In addition to using an active comparator, our study extensively adjusted for potential confounders including indications such as depression, other indications (eg anxiety disorders, pain, cancer, rheumatoid arthritis, arthropathies and connective tissue disorders), and medications to treat such indications (anxiolytics, hypnotics and sedatives, non-steroidal anti-inflammatory drugs, muscle relaxants).

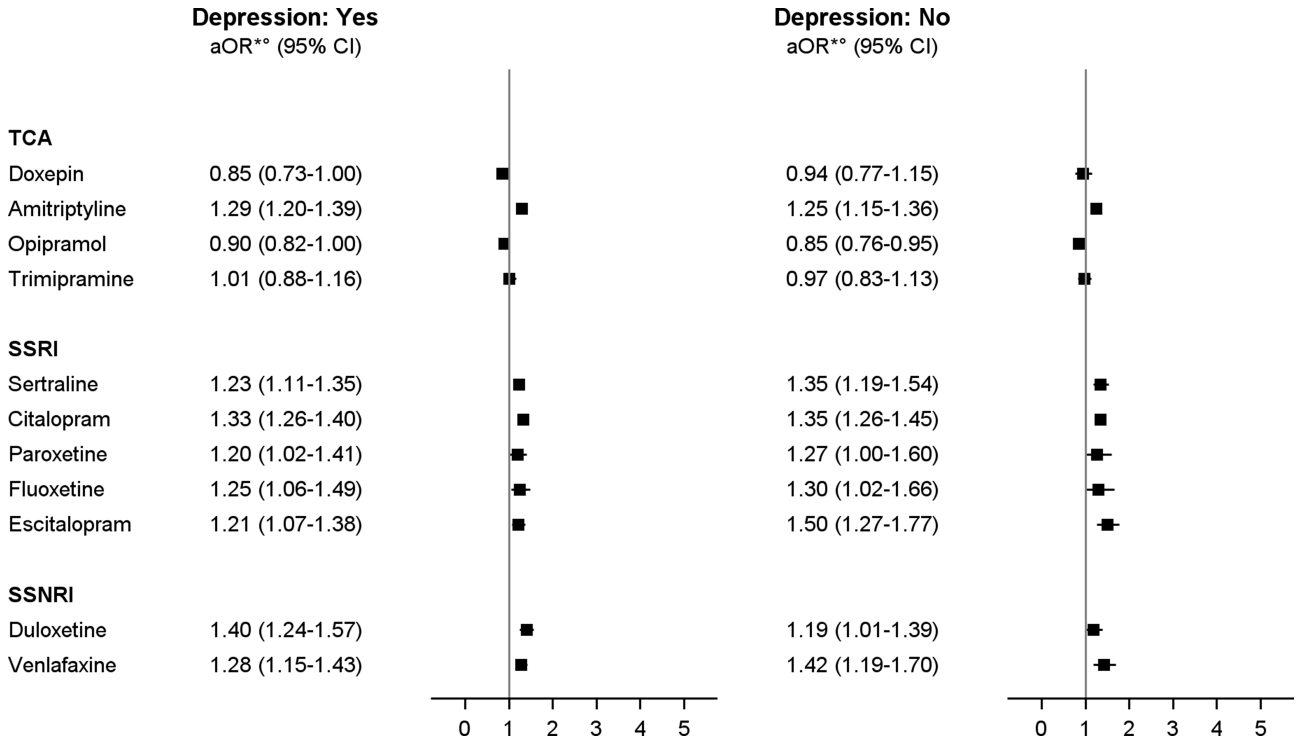

Figure 1 Odds ratio (OR) with 95% confidence interval (95% CI) of hip–pelvis fracture in current users of antidepressants (ADs) compared with current users of mirtazapine, by depression.

Notes: The model did not converge in the group of age 85 years and above. *Model adjusted for all variables listed in Table 1.

Abbreviations: TCA, tricyclics; SSRI, selective serotonin reuptake inhibitors; SSNRI, selective serotonin-noradrenaline reuptake inhibitors; NASSA, noradrenergic and specific serotonergic antidepressants; NARI, noradrenaline reuptake inhibitors; MAO, monoamine oxidase inhibitors.

It is thus a strength of our study that we used an active comparator design[34] and extensively adjusted for potential indications and contraindications as well as co-morbidities, co-medications, indicators of health status and use of health care to reduce possible confounding. Our results did not change when we restricted the analysis to the more homogeneous group of patients with depression, suggesting that residual confounding by indication was small.

Differences between individual ADs regarding the risk of falls and consequences of falls such as fractures[7,8] and traumatic brain injuries[33] have consistently been reported, but the underlying mechanism is still unclear. Although almost all ADs may cause side effects that increase susceptibility to falls (eg sedation, dizziness, orthostatic hypotension),[54] and thus increase the risk of fractures, the intensity of such effects may vary. Considering AD classes, SSRIs generally have less pronounced anticholinergic effects (such as confusion, delirium, and reduced visual acuity) than TCAs, but they can induce sleep disturbances and dizziness.[55,56] Differences in fracture-related side effects are poorly characterized, particularly in older adults. In a meta-analysis of randomized controlled trials, examining several individual SSRIs and SSNRIs,[57] older patients with major depression treated with duloxetine or venlafaxine reported dizziness three-times more frequently than placebo-treated patients. In patients treated with citalopram, escitalopram, and paroxetine the frequency of dizziness was 45–60% higher, while it was 30% and 10% higher for sertraline. This gradient is compatible with the differences between ADs regarding the risk of fractures observed in our study except for venlafaxine, which showed only an intermediately elevated risk in our study.

Our findings showing a higher risk of fractures associated with SSRIs than with TCAs are also consistent with prior studies.[17,20-24] Potential mechanism explaining this difference is unclear; selective prescribing of TCAs to the less frail older adults or those with a lower baseline risk of falling may partially account for this result. Pharmacological properties may partly explain the large difference in risk between individual TCAs observed in our study. For instance, amitriptyline and trimipramine are considered to have relevant sedative, anticholinergic and hypotensive effects, while other TCAs− also with relevant sedative effects− have weaker anticholinergic properties as is the case for doxepin.[58] In our study, users of doxepin did not have an increased risk of fractures.

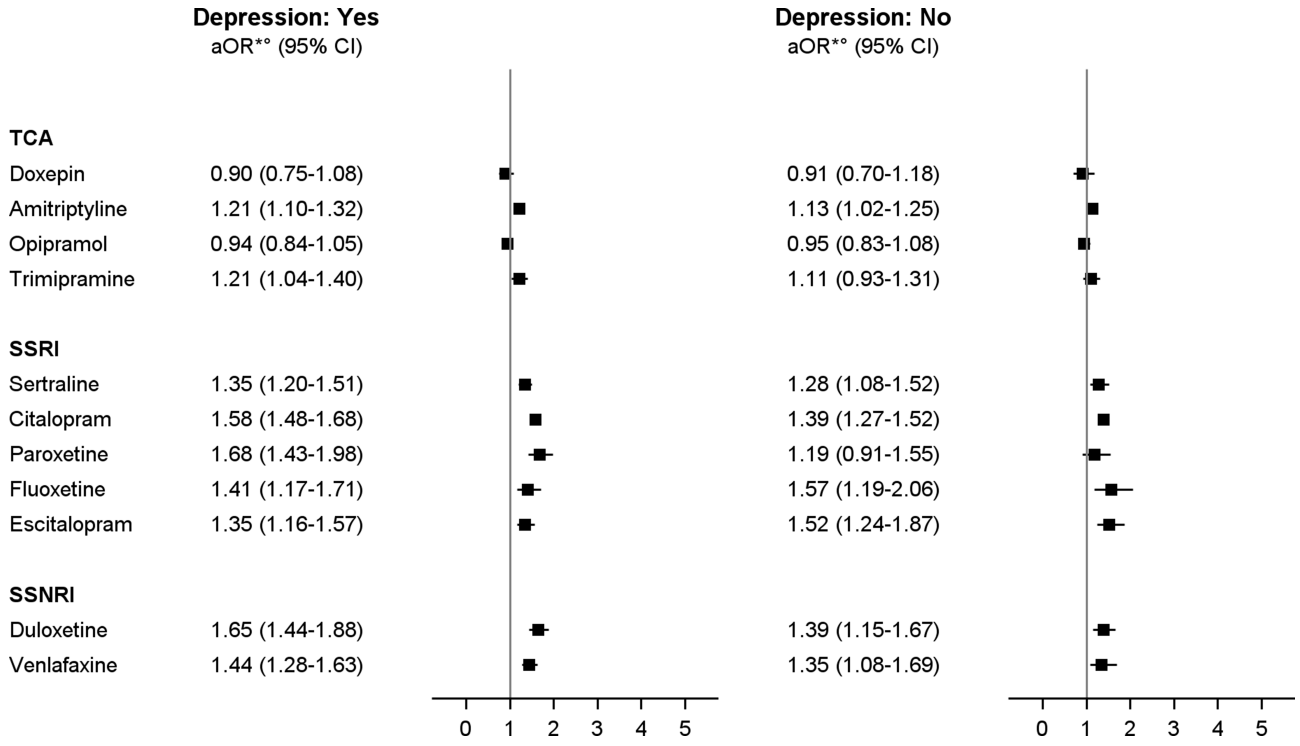

Figure 2 Odds ratio (OR) with 95% confidence interval (95% CI) of other non-vertebral fractures in current users of antidepressants (ADs) compared with current users of mirtazapine, by depression.

Notes: The model did not converge in the group of age 85 years and above. *Model adjusted for all variables listed in Table 1.

Abbreviations: TCA, tricyclics; SSRI, selective serotonin reuptake inhibitors; SSNRI, selective serotonin-noradrenaline reuptake inhibitors; NASSA, noradrenergic and specific serotonergic antidepressants; NARI, noradrenaline reuptake inhibitors; MAO, monoamine oxidase inhibitors.

In interpreting our results, limitations due to the nature of secondary data have to be considered including lack of direct information on the intended treatment duration and daily dose as well as on clinical aspects of the fractures (eg radiology confirmation, bone density data). We used elaborate methods to overcome these limitations as much as possible. Assessment of AD use was based on dispensations. On the one hand, this approach has the advantage of reflecting medications actually redeemed at the pharmacy level, contrary to prescriptions or medical records. On the other hand, we had to estimate treatment duration based on the dispensed DDDs but we took into account that dose and compliance are lower in older patients[37,59] and further varied these assumptions in sensitivity analyses which supported the robustness of our findings in this regard. The assumptions regarding daily dose were varied uniformly for all study participants; thus, potential differences in dose related to different indications were not examined. However, the results did not change in the more homogeneous group of persons with depression suggesting that differential misclassification of the exposure was small, if there was any.

We defined the outcome as fractures leading to hospitalization, thus focusing on clinically relevant events, and we identified the outcome using hospital main discharge diagnoses. In Germany, hospital main discharge diagnoses are considered to have a high validity since they are based on all information relevant to diagnosis gathered during the in-hospital stay (including imaging results) and are subject to regular inspection. We addressed fractures of hip–pelvis as an outcome because they are the most frequent fractures in old age and in 90% of cases are due to falls,[60–62] To comprehensively characterize the risk, we also addressed other non-vertebral fractures as a composite outcome. This encompasses fractures of all sites to capture clinically relevant events with high sensitivity. However, to avoid outcome misclassification, we excluded vertebral fractures because up to two thirds of them remain undiagnosed in older adults.[63–65] As fractures of the hip and pelvis usually present with severe pain and inability and need surgery, they are generally accurately diagnosed and coded. This also holds true for other non-vertebral fractures in older patients, since even milder or suspect cases usually undergo diagnostic assessment in order to clarify symptoms and avoid complications due to lack or delay of treatment.

In conclusion, our study showed that the risk of fractures varied between ADs, but for most agents was higher

than the risk for mirtazapine. When treating older adults with ADs, prescribers should carefully consider the risk profile of individual ADs regarding the risk of fractures, which are a major health problem in this population.

Funding

The initial phase of this study was financed by the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte – BfArM). The publication of this article was funded by the Open Access Fund of the Leibniz Association. Regarding this study, the funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure

JR, BK, UH and TS are working at an independent, non-profit research institute, the Leibniz Institute for Prevention Research and Epidemiology – BIPS. Unrelated to this study, BIPS occasionally conducts studies financed by the pharmaceutical industry. Almost exclusively, these are post-authorization safety studies (PASS) requested by health authorities. The design and conduct of these studies, as well as the interpretation and publication, are not influenced by the pharmaceutical industry. At the time of performing the study, writing the manuscript and submission, FEP worked at the Leibniz Institute for Prevention Research and Epidemiology – BIPS. Unrelated to the work presented in this article, she worked from 1st August 2019 to 24th February 2020 at UCB Pharma and since 1st March 2020 she is working at Bayer AG. The authors report no other conflicts of interest in this work.

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