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ORIGINAL ARTICLE

Use of anti-depressants and the risk of fracture of the hip or femur

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Abstract
Summary Anti-depressants are used largely, but have serious side effects. We show that both selective serotonin re-uptake inhibitors (SSRIs) and tricyclic anti-depressants (TCAs) increase the risk of hip/femur fracture and that this risk is time related and depends on the degree of serotonin transporter inhibition. This should be considered when prescribing anti-depressants to patients.
Introduction Anti-depressants are known to have serious side effects. We examined the association between the use of anti-depressants and the risk of hip/femur fractures with a special focus on the relation with the degree of 5-hydroxytryptamine transporter (5-HTT) inhibition and the duration of use.
Methods A case–control study was conducted within the Dutch PHARMO-RLS database. Cases (n=6,763) were adult patients with a first hip/femur fracture during the study period. For each case, four controls (n=26341) were matched by age, gender and geographic region.
Results The risk of hip/femur fracture increased with current use of SSRIs (adjusted odds ratio (OR_{adj}) 2.35 [95% confidence interval (CI) 1.94–2.84]) and TCAs (OR_{adj} 1.76 [95% CI 1.45–2.15]). The risk of hip/femur fracture declined rapidly after discontinuation of use. The risk of hip/femur fracture increased as the degree of 5-HTT inhibition of all anti-depressants increased from OR_{adj} 1.64 [95% CI 1.14–2.35] for drugs with low 5-HTT inhibition to OR_{adj} 2.31 [95% CI 1.94–2.76] for those with high 5-HTT inhibiting properties.
Conclusion Current use of both SSRIs and TCAs increase hip/femur fracture risk. Further studies are needed to elucidate the mechanistic pathways and the relation with the underlying pathophysiology. Until then, the elevated fracture risk should be considered when prescribing anti-depressants.

Keywords Duration of use · Fracture · Risk · SSRI · 5-HTT inhibition

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Introduction

Depression is one of the most important mental health problems especially in the elderly and is associated with a

poor natural history, reduced quality of life, increased utilisation of medical health services and high mortality [1–4]. Although depression can be treated effectively with tricyclic anti-depressants (TCAs), many users experience cardiovascular (e.g. orthostatic hypotension) and anti-cholinergic side effects (e.g. visual disturbances), which both may increase the risk of falling and thereby of fractures. The newer generation of anti-depressants, including the selective serotonin re-uptake inhibitors (SSRIs), are considered as effective as the TCAs but with less bothersome side effects. Its use has increased over the last decade [5–7]. Some studies investigating the risk of falls with anti-depressants have reported no significant difference in risk for SSRIs and TCAs [8, 9].

Falls increase the risk of fracture, especially of the hip or femur in the elderly [10], with significant consequences for the individual and healthcare providers in terms of the impact on long-term morbidity, mortality and healthcare costs [11–14]. Several epidemiological studies have reported an increased risk of fracture with anti-depressant use [9, 15–17]. One explanation is that the increased fracture risk is mediated simply by falling [8]. Another explanation lies in the potential for anti-depressants to affect the micro-architecture of bone. Functional serotonin (5-hydroxytryptamine, 5-HT) receptors and transporter systems have been localised on osteoblasts, osteoclasts and osteocytes [18–22] and 5-HT stimulates proliferation of osteoblast precursor cells in vitro [23]. Thus, drugs that block 5-HT re-uptake could affect bone metabolism and have a negative impact on bone micro-architecture. This has been illustrated by a recent case–control study conducted in Denmark, which reported an increased risk of fractures with an increased degree of blocking of the serotonin system [24].

The aim of this study was to examine the association between the use of anti-depressants and the risk of hip/femur fractures, with a special focus on the relation with the degree of 5-hydroxytryptamine transporter (5-HTT) inhibition afforded by different anti-depressants and the duration of use.

Materials and methods

Study design

We conducted a case–control study within the Dutch PHARMO Record Linkage System (RLS) (www.pharmo.nl). The database includes the demographic details and complete medication histories for about one million community-dwelling residents in The Netherlands representing some 7% of the general population. Data are linked to hospital discharge records as well as several other health registries, including pathology, clinical laboratory findings and general practitioner data [25]. Almost every individual in The Netherlands is registered with a single community pharmacy, independent of prescriber and irrespective of their health insurance or socio-economic status. Pharmacy records have a high degree of completeness with regards to dispensed drugs [26, 27]. Pharmacy data include information about the drug dispensed, the date of dispensing, the prescriber, the amount dispensed, the prescribed dosage regimen and the estimated duration of use. Hospital discharge records include detailed information on date of admission, discharge diagnoses and procedures. Validation studies on PHARMO RLS have confirmed a high level of data completeness and validity [28–30]. During data collection, the privacy and confidentiality of patients is maintained and complies with the Dutch Data Protection Act.

Study population

Data were collected for the period 1 January 1991 to 31 December 2002. Cases were patients aged 18 years and older with a record for a first fracture of the hip or femur during the study period. The date of hospital admission was used to define the index date. Each case was matched by year of birth, sex and geographical region to up to four control patients without any evidence of ever having sustained a fracture. The index date for each control was the same as the date of fracture for the matched case.

Exposure assessment

Exposure to anti-depressants was determined by reviewing prescription information before the index date. Current users were defined as individuals who had received a prescription for a TCA, an SSRI or other anti-depressant within a 30-day period before the index date. Recent users were individuals whose most recent prescription was issued 31–90 days before the index date, and past users were those whose most recent prescription had been issued more than 3 months (>90 days) before the index date. Patients with a history of using more than one type of anti-depressant before the index date were classified as appropriate, e.g. a current user of an SSRI may also qualify as a current user of a TCA. The average daily dose was calculated by dividing the cumulative exposure by the total treatment time. Dose equivalencies of anti-depressants were applied from the WHO defined daily dose (DDD) [31] and were expressed as paroxetine equivalents (SSRIs) or amitriptyline equivalents (TCAs). The extent of 5-HTT inhibition was determined for each anti-depressant with reference to Goodman and Gilman's 'The Pharmacological Basis of Therapeutics' [32] (Table 1).

Table 1 Drugs grouped according to the degree of serotonin transporter inhibition [31]

Degree of serotonin transporter inhibition (inhibition constant in nM)			
Low (>10)	Intermediate (>1≤10)	High (≤1)	Not classified
Desipramine	Imipramine	Clomipramine	Opipramol
Nortriptyline	Amitriptyline	Fluoxetine	Dosulepin
Doxepine	Fluvoxamine	Paroxetine	Moclobemide
Maprotiline	Venlafaxine	Sertraline	
Mianserine	Citalopram		
Trazodone			
Nefadozone			
Mirtazapine			

For each prescription, the expected duration of use (in days) was based on how the drug was supplied and the prescribed daily dose. If there were missing data on the total drug supply or written dosage instruction, the expected duration of use (based on the median duration for a prescription from patients of similar age and sex) was taken. When repeat prescriptions were issued, the expected duration of use period was extended according to the expected duration of the repeat prescription. In the event of overlap between two prescriptions (i.e. a repeat prescription given before the expected end date of a previous prescription), the 'overlap' days were added to the theoretical end date of the repeat prescription. If the gap between any consecutive prescriptions was 6 months or less, exposure was deemed to be continuous.

Potential confounders

The records of cases and controls were assessed for potential confounding variables, including use within the 3 months before the index date of a benzodiazepine; use within the 6 months before the index date of an anti-psychotic (other than lithium), lithium, an anti-Parkinson drug, anti-convulsant, oral or inhaled glucocorticoid, bronchodilator, hormone replacement therapy, a disease-modifying anti-rheumatic drug (DMARD), anti-arrhythmic, thiazide diuretic, beta-blocker, drug for diabetes, metoclopramide, morphine/opiate or two or more prescriptions for an non-steroidal anti-inflammatory drug (NSAID); and a history at any time of hospitalisation for cardiovascular disease, malignant neoplasm, inflammatory bowel disease, rheumatoid disease, obstructive airway disease, impaired renal function, mental disorder or cerebrovascular disease. We have chosen a different time window for benzodiazepines, because in The Netherlands, benzodiazepines are dispensed for periods up to 1 month and other drugs for periods up to 3 months.

Statistical analysis

Conditional logistic regression analysis was used to estimate the risk of hip/femur fracture associated with the use of TCAs, SSRIs and the various confounding variables (SAS version 9.1.3, PHREG procedure) and were expressed as odds ratios (OR) with corresponding 95% confidence intervals (CI). Adjusted odds ratios (OR_{adj}) for hip/femur fracture were estimated by comparing anti-depressant use with no use using conditional logistic regression analysis. Final regression models were determined by stepwise backward elimination using a significance level of 0.05. We stratified the study population to assess the risk with current use by age and sex.

Further analyses were conducted to evaluate the risk of fracture associated with current exposure to anti-depressants versus no use grouping current users according to the daily dose of anti-depressant prescribed and according to the degree of 5-HTT inhibition expected. Smoothing spline regression plots (SAS version 9.1.3) were used to visualise the longitudinal relationship between the risk of fracture and (a) the time between the index date and last dispensing of an anti-depressant (recency of use) and (b) the duration of continuous use. The population attributable risk (PAR) was estimated using the following formula:

$$\mathrm{PAR}\% = \frac{\mathrm{Pe}(\mathrm{OR}-1)}{1+\mathrm{Pe}(\mathrm{OR}-1)} \times 100.$$

The prevalence (Pe) of anti-depressant use was derived from national prescribing figures in 2003, www.gipdatabank.nl.

Results

We identified 6,763 patients who suffered a hip/femur fracture. These cases were matched to 26,341 controls. The mean age of cases and controls was 75 years and 73% were female (Table 2). The mean period of time with prescription information before the index date was 4.1 years. Prescriptions for paroxetine accounted for 50% of the prescriptions issued for an SSRI (25,131/50,287). Most of the other SSRI prescriptions were for fluoxetine (23.4%) or fluvoxamine (20.3%). Amitriptyline (46.6%) and clomipramine (23.1%)

Table 2 Baseline characteristics of the study population

	Cases (n=6,763)	Controls (n=26,341)	Crude odds ratio (95% CI)
Age			
18 to 49 years	452 (6.7%)	1,808 (6.9%)	
50 to 69 years	1,061 (15.7%)	4,239 (16.1%)	
≥70 years	5,250 (77.6%)	20,294 (77.0%)	
Mean age in years	75.7	75.3	
Number of females	4,929 (72.9%)	19,138 (72.7%)	
Drug use before the index date			
TCAs	256 (3.8%)	591 (2.2%)	1.75 (1.51–2.04)
SSRIs	315 (4.7%)	582 (2.2%)	2.20 (1.91–2.54)
Anti-psychotics[a]	412 (6.1%)	921 (3.5%)	1.79 (1.58–2.02)
Anti-convulsants[a]	242 (3.6%)	431 (1.6%)	2.23 (1.90–2.61)
Benzodiazepines[b]	967 (14.3%)	2,751 (10.4%)	1.44 (1.33–1.56)
Oral glucocorticosteroids[a]	366 (5.4%)	918 (3.5%)	1.59 (1.40–1.80)
Thiazide diuretics[a]	146 (2.2%)	557 (2.1%)	1.01 (0.84–1.21)
Opiates[a]	253 (3.7%)	455 (1.7%)	2.24 (1.92–2.63)
Anti-Parkinson drugs[a]	397 (5.9%)	833 (3.2%)	1.94 (1.71–2.19)
≥2 NSAID prescriptions[a]	929 (13.7%)	2,584 (9.8%)	1.46 (1.35–1.59)
Hospitalisation before the index date			
Cardiovascular disease	359 (5.3%)	1,289 (4.9%)	1.10 (0.98–1.25)
Cerebrovascular disease	296 (4.4%)	565 (2.1%)	2.12 (1.84–2.45)
Malignant neoplasms	341 (5.0%)	1,021 (3.9%)	1.54 (1.37–1.74)

TCAs tricyclic anti-depressants, *SSRIs* selective serotonin re-uptake inhibitors, *GCs* glucocorticosteroids

[a] Within the 6 months before the index date

[b] Within the 3 months before the index date

accounted for the majority of TCA prescriptions (n= 59,836).

Table 2 shows that compared with controls, cases were significantly more likely to have used a benzodiazepine in the previous 3 months and/or an anti-depressant, an anti-psychotic, anti-convulsant, oral glucocorticoid, opiate or drug for Parkinson's disease within the previous 6 months. In addition, cases were significantly more likely than controls to have a history of cerebrovascular disease or malignant neoplasm.

Table 3 provides crude and adjusted risk estimates for hip/femur fracture associated with anti-depressant use according to recency of use, and the results of analyses amongst current users stratified by sex and age. Compared with individuals who had never used the anti-depressant in question, the risk of hip/femur fracture increased with current use of SSRIs (crude OR 2.88 [95% CI 2.40–3.46]) and TCAs (crude OR 2.22 [95% CI 1.84–2.68]). After adjustment for other variables associated with fracture risk, the ORs remained significantly increased (OR_{adj} 2.35 [95% CI 1.94–2.84] for SSRIs and 1.76 [95% CI 1.45–2.15] for TCAs). Under the assumption that the risk of hip fracture amongst users of SSRIs/TCAs is similar in the period 1991–2002 and 2003, we estimated that the population attributable risk of hip fracture is 1.1% for current users of TCAs and 4.4% for current users of SSRIs. For SSRIs, there was some effect modification by sex (OR_{adj} 2.50 [95% CI 2.03–3.08] for females and 1.72 [95% CI 1.08–2.74] for males) and age (OR_{adj} 2.00 [95% CI 1.21–3.29] for SSRI users aged 18–69 years and 2.39 [95% CI 1.94–2.94] for SSRI users aged ≥70 years).

Figure 1a shows a clear association between the time since the last dispensing of an SSRI and the risk of hip/femur fracture. The risk of hip/femur fracture, which was increased in current users, declined rapidly after discontinuation of use. A similar trend was observed for users of TCAs (Fig. 1b). The risk of hip/femur fracture was increased during the first few months of continuous use of SSRIs, peaking at about 8 months, and remained elevated after about 1.5 years of continuous use (Fig. 2a). Short-term exposure to TCAs showed a rapid increase in hip/femur fracture risk that declined after 1 year of exposure (Fig. 2b).

Table 4 presents the results of analysis amongst current users according to the average daily dose of anti-depressant used. Compared with individuals who had never used an SSRI, medium and high dose SSRI users had a greater risk of fracture than low dose users, although the differences were not statistically significant. There was no evidence to suggest a dose–response relationship for the risk of hip/femur fracture with TCA use.

Table 5 presents the results of analyses amongst all anti-depressant users, where current users were grouped according to the degree of 5-HTT inhibition afforded by the different drugs. The risk of hip/femur fracture increased as the degree of 5-HTT inhibition increased from OR_{adj} 1.64 [95% CI 1.14–2.35] for drugs with low 5-HTT

Table 3 Use of SSRIs and TCAs and the risk of hip/femur fracture

	Cases (n=6,763)	Controls (n=26,341)	Crude OR	95% CI	Adjusted OR[a]	95% CI
Exposure to SSRIs						
Never exposed	6,174	25,041	1.00	–	Referent	
Past use (>90 days before the index date)	303	820	1.52	1.33–1.75	1.23	1.07–1.42
Recent use (31–90 days before the index date)	86	193	1.87	1.45–2.42	1.48	1.14–1.93
Current use (1–30 days before the index date)	200	287	2.88	2.40–3.46	2.35	1.94–2.84
Males	33	59	2.30	1.48–3.59	1.72	1.08–2.74
Females	167	228	3.02	2.46–3.70	2.50	2.03–3.08
Age 18–69 years	33	44	3.07	1.95–4.82	2.00	1.21–3.29
Age ≥70 years	167	243	2.84	2.32–3.48	2.39	1.94–2.94
Exposure to TCAs						
Never exposed	6,175	24,864	1.00	–	Referent	
Past use (>90 days before the index date)	360	978	1.52	1.34–1.72	1.14	1.00–1.30
Recent use (31–90 days before the index date)	56	176	1.32	0.97–1.79	0.98	0.72–1.34
Current use (1–30 days before the index date)	172	323	2.22	1.84–2.68	1.76	1.45–2.15
Males	29	43	2.85	1.76–4.62	2.19	1.31–3.67
Females	143	280	2.11	1.72–2.60	1.69	1.36–2.09
Age 18–69 years	31	60	2.18	1.40–3.40	1.31	0.80–2.14
Age ≥70 years	141	263	2.22	1.80–2.74	1.81	1.46–2.25

[a] SSRI use was adjusted for (a) current use of an anti-depressant other than SSRI, (b) use in the past 3 months of a benzodiazepine; (c) use in the past 6 months of oral corticosteroids, hormone replacement therapy, anti-psychotics, beta-blockers, opioids, anti-convulsants, drugs for diabetes, more than two dispensings of an NSAID, DMARDs and metoclopramide and (d) a history of malignant neoplasms, mental disorders, cerebrovascular diseases, obstructive airway diseases or inflammatory bowel diseases. TCA use was adjusted for current use of an anti-depressant other than TCA and other potential confounders as listed above (b)–(d) for SSRI use

inhibition to OR_{adj} 2.31 [95% CI 1.94–2.76] for those with high 5-HTT inhibiting properties. Users of anti-depressants with stronger anti-cholinergic properties, or a strong potential to induce orthostatic hypotension, did not have higher risks of hip fracture compared to users of anti-depressants with weaker properties (data not shown).

Discussion

This study has demonstrated an increased risk hip/femur fracture for current users of SSRIs and TCAs. For both SSRIs and TCAs, the increased risk declined rapidly about 6 months after discontinuation of use. Fracture risk associated with SSRIs and TCAs was the greatest during the first few months of use and an elevated risk persisted with continuous use of SSRIs. We found some evidence for a dose effect with SSRIs but not TCAs. Furthermore, we found evidence to suggest that the risk of fracture was greater amongst people using anti-depressants with a higher degree of 5-HTT inhibition.

The magnitude of increased fracture risk with anti-depressant use described here is in line with findings from other epidemiological studies [9, 15–17, 24]. Those studies that compared risk with SSRIs and TCAs [9, 15, 16] similarly reported no difference in risk. There is also evidence to support our observation of an increased risk during the initial period of exposure [15, 16]. Richards et al. [17] investigated fracture risk with SSRIs and reported a dose effect and a sustained elevation in risk with prolonged use. Vestergaard et al. reported a dose-dependent increase in fracture risk for sedating TCAs and most SSRIs. Furthermore, they also found an association between the increase in risk of any fracture and the inhibition of the serotonin transporter system [24].

We observed a similar increase in fracture risk for users of SSRIs and TCAs. The explanation for that increased fracture risk may be related simply to an increase in the risk of falls associated with anti-depressant use, especially as there is evidence to suggest that both SSRIs and TCAs are associated with an increased risk of fall. A large study of nursing home residents showed that, compared with non-users and after adjusting for potential confounders, the risk of falls was similar in new users of TCAs and SSRIs. The association was dose dependent and the increased risk persisted through the first 180 days of use and beyond [8]. TCAs are known to inhibit cardiovascular Na+, Ca2+ and K+ channels which can lead to life-threatening arrhythmias. SSRI use has been associated with an increased risk of syncope [33], postural hypotension and dizziness [34]

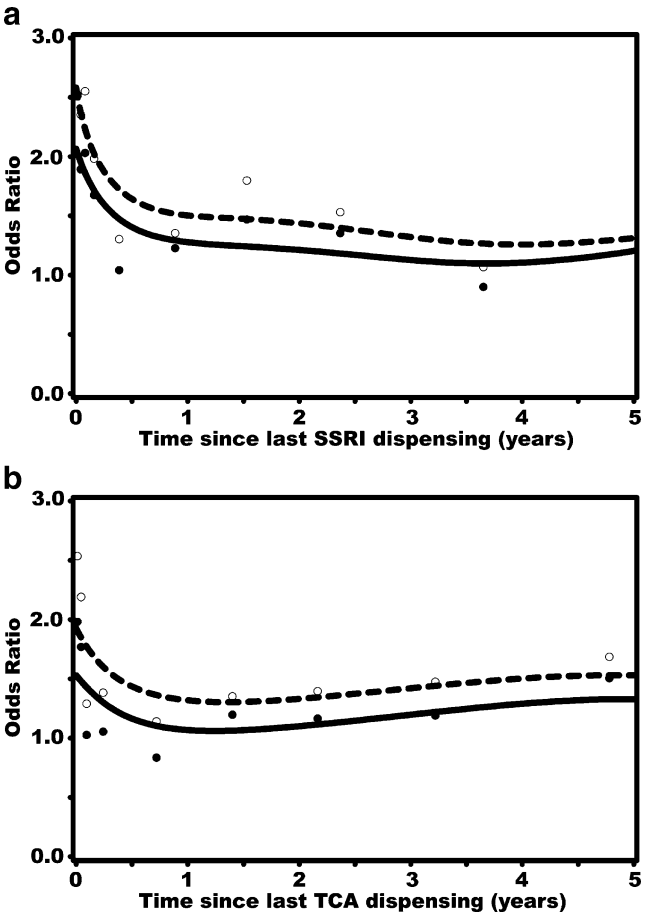

Fig. 1 **a**, **b** Recency of SSRI (**a**) and TCA (**b**) use before the index date and risk of hip/femur fracture. *Dashed lines* and *open dots*: crude ORs with 95% CI; *solid lines* and *solid dots*: adjusted ORs with 95% CI. Adjustments were made for the same confounders as in Table 3

during the early days of exposure, and both SSRIs and TCAs can affect sleep patterns [35, 36], thereby increasing the risk of falls [37].

Another explanation for the increased fracture risk observed here is the effect of anti-depressants on bone physiology. Functional 5-HT receptors are present in bone cells and 5-HT stimulates proliferation of osteoblast precursor cells in vitro [23]. There is emerging evidence from animal studies that 5-HT is involved in bone remodelling and can alter bone mineral density (BMD) [18–20, 22]. Indeed, recent findings have shown that SSRIs decrease BMD in animal models [38] and humans [17, 39–41]. Such studies that compared BMD changes with different anti-depressants reported no association between TCA use and BMD [39, 40]. In a recent study of osteoporotic fractures, it was observed that the use of SSRIs (but not TCAs) in older women was independently associated with an increased rate of hip bone loss (0.82% reduction per year) [41], although there was limited information on dose and duration of use.

To explore the possibility that fracture risk may be directly related to inhibition of the 5-HTT system, we grouped together the anti-depressants used according to the degree of 5-HTT inhibition afforded. It was apparent that the risk of hip/femur fracture increased as the degree of 5-HTT inhibition increased. Whilst none of the risk estimates was significantly different, a clear trend was evident and this supports the possibility that stronger inhibition of the 5-HTT system on the bone could cause a greater disruption of the balance between osteoblasts and osteoclasts and hence have a greater detrimental effect on bone micro-architecture.

Drug-induced changes in bone micro-architecture can be rapid. Analysis of the micro-architecture of femur bone in rats treated with 5-HT showed changes in trabecular bone volume and an increased femoral stiffness after just 3 months [10]. Other drug exposures had demonstrated similarly rapid effects on human bone, e.g. corticosteroids [42, 43]. It is possible that a rapid change in bone micro-architecture affected by anti-depressant use accounted for,

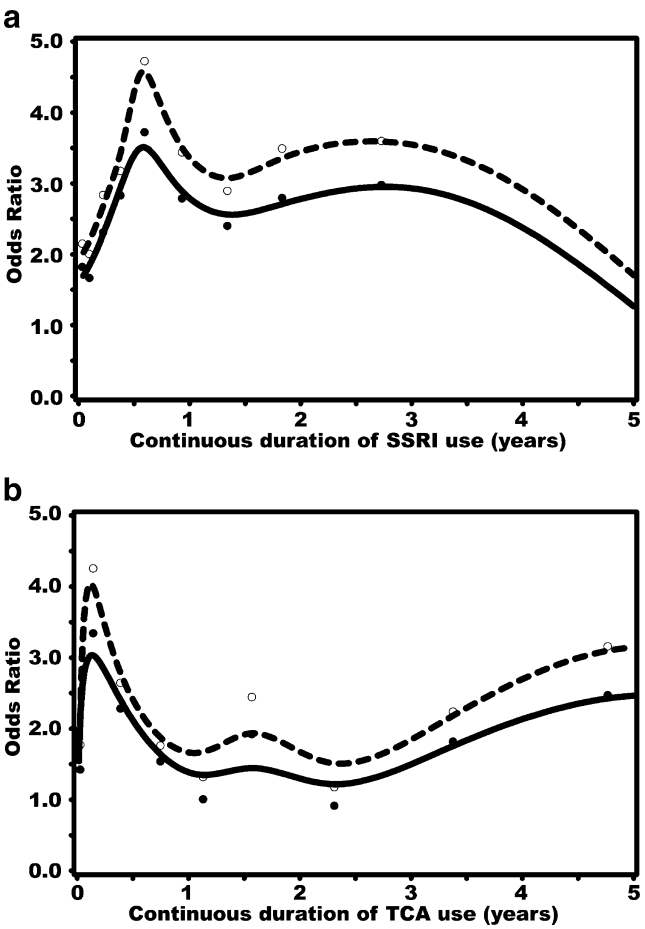

Fig. 2 **a**, **b** Recency of SSRI (**a**) and TCA (**b**) duration of continuous use amongst current users before the index date and risk of hip/femur fracture. *Dashed lines* and *open dots*: crude ORs with 95% CI; *solid lines* and *solid dots*: adjusted ORs with 95% CI. Adjustments were made for the same confounders as in Table 3

Table 4 Current use of SSRIs and TCAs and the risk of hip/femur fracture by average daily dose

Average daily dose (DDD)	Cases	Controls	Crude OR	95% CI	Adjusted OR[c]	95% CI
Current SSRI use[a]						
One prescription before the index date	16	30	2.15	1.17–3.96	1.72	0.92–3.21
Low (<0.5)	22	47	1.88	1.13–3.13	1.50	0.89–2.53
Medium (0.5–1.0)	77	95	3.40	2.51–4.62	2.77	2.03–3.80
High (>1.0)	85	115	3.08	2.31–4.09	2.49	1.86–3.34
Current TCA use[b]						
One prescription before the index date	12	21	2.39	1.17–4.86	1.95	0.94–4.06
Low (<0.5)	95	186	2.13	1.66–2.74	1.73	1.33–2.24
Medium (0.5–1.0)	53	91	2.41	1.71–3.38	1.82	1.28–2.58
High (>1.0)	12	25	1.99	1.00–3.97	1.35	0.66–2.79

[a] Referent: never exposed to SSRIs

[b] Referent: never exposed to TCAs

[c] Adjustments were made for the confounders listed in the footnote of Table 3

or at least contributed to, the increased fracture risk during the early months of exposure.

We found that as the duration of treatment with TCAs increased, the risk of fracture declined, whereas the risk for fracture with continuation of SSRIs fell after the initial increase but remained somewhat elevated thereafter. It may be that with chronic administration of anti-depressants, adaptive changes occur [44]. These may result in an adjustment to the cardiovascular effect of TCAs and SSRIs, explaining the decrease in fracture risk after a few months of use, whereas changes in bone physiology are not subject to adaptive changes, explaining the sustained fracture risk in SSRI users.

Limitations of our study include absence of potentially confounding data on body mass index (BMI), smoking status and exercise. In a US/Puerto Rican cohort study, it was likely that lack of adjustment for BMI, current smoking status, activities of daily living score, cognitive impairment and Rosow–Breslau physical impairment scale accounted for up to 30% of the increased risk of hip fractures amongst users of SSRIs [45]. We do not anticipate that missing data on these variables would have an important impact on our findings; therefore, as if our ORs were decreased by 30%, a positive association would remain. Another limitation lies in the potential for confounding by indication, as depression itself is associated with an increased risk of falls and fractures [46]. There is also the possibility of a channelling effect whereby, for some frail patients with depression, an SSRI was prescribed instead of a TCA because of the more favourable side-effect profile anticipated. This could have overestimated the risk associated with SSRIs observed here. These unmeasured types of confounding as well as selection bias (e.g. healthy user bias), which can change over time, may be alternative explanations for our observed associations between fracture risk and duration of anti-depressant use or discontinuation of anti-depressants. In Figs. 1 and 2, data beyond 4 years are sparse, which makes extrapolation uncertain. Lastly, the PAR calculation showed that 4.4% of hip fractures in The Netherlands might be attributed to current use of SSRI; however, given the previous limitations and the susceptibility of our study for unmeasured distortions, this figure should be interpreted with great care.

Table 5 Risk of hip/femur fracture by degree of serotonin (5-HT) transporter inhibition

	Cases (n=6,763)	Controls (n=26,341)	Adjusted OR[a]	95% CI
Never exposed	5,677	23,698	Referent	–
Past use (>90 days before the index date)	506	1,514	1.19	1.76–2.29
Recent use (31–90 days before the index date)	158	404	1.32	1.09–1.61
Current use (1–30 days before the index date)	422	725	2.01	1.76–1.29
Low 5-HT transporter inhibition	46	102	1.64	1.14–2.35
Medium 5-HT transporter inhibition	132	241	1.92	1.53–2.40
High 5-HT transporter inhibition	234	358	2.31	1.94–2.76
Not classified	10	24	1.44	0.67–3.04

[a] Adjustments were made for the confounders listed in the footnote of Table 3

One of the strengths of this study is size of the population available and the reliability of information on prescribing and hospitalisations. Furthermore, the longitudinal nature of recording has two advantages. First, to our knowledge, this is the only study where duration of use analysis has allowed speculation on the effects of anti-depressants on bone. Second, this is the second study to evaluate the effect of 5-HTT inhibition on fracture risk estimates.

In summary, our findings demonstrate that both SSRIs and TCAs increase the risk of hip/femur fracture in current users and that the risk increases with the degree of 5-HTT inhibition afforded by different anti-depressants. We did not find convincing evidence for a dose effect. The pathophysiology can be fall-related and/or bone-related. Further studies, including controlled prospective trials, are needed to evaluate the relative contribution of disease-related and treatment-related effects to the increased risk of falls and hip/femur fractures and to elucidate the pathophysiology. Until then, physicians prescribing anti-depressants should consider the elevated risk for fractures in elderly, possibly frail, people using anti-depressants and value the rule: "start low, go slow".

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