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Risk of nonvertebral fractures among elderly postmenopausal women using antidepressants

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ABSTRACT

Objective: To examine the association between antidepressants, including TCAs, SSRIs, and miscellaneous antidepressants and the risk of nonvertebral fractures among women with osteoporosis.
Materials and methods: This study was a post-hoc analysis of pooled data from two international, phase III, randomized, placebo-controlled, double-blind studies (the Spinal Osteoporosis Therapeutic Intervention [SOTI] and TReatment Of Peripheral OSteoporosis [TROPOS]). A nested case-control study was performed in the placebo treated population. Adjusted logistic regression models were used to estimate the risk of nonvertebral fracture associated with the use of antidepressants.
Results: After 3 years of follow-up, 391 nonvertebral fractures cases were identified and matched to 1955 controls. Compared with non-users of antidepressants, antidepressants use was associated with an increased risk of nonvertebral fractures (adjusted OR = 1.64; 95%CI, 1.03–2.62]). Particularly, there was a 2-fold risk increase (95%CI, 1.07–3.79) of nonvertebral fracture for current users of SSRIs and a 2.1-fold risk increase for subjects who were current users of TCAs (95%CI, 1.02–4.30). Among patients categorized as recent or past users, none of the classes of antidepressants were statistically associated with increased risk of nonvertebral fracture.
Conclusions: Our findings confirm that both SSRIs and TCAs increase the risk of nonvertebral fracture in current users.

Introduction

The increased prevalence of depressive disorders has multiplied the prescription of antidepressant treatments whatever the countries [1,2]. The importance of the central nervous system in bone metabolism has received much interest in the last 10 years [3,4]. Several medications used to treat major depressive disorders have therefore been considered to alter bone properties [5]. Indeed, epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving selective serotonin-reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) [6–27]. Several mechanisms have been proposed to explain this adverse effect of antidepressant drug treatment, but their potential effects on bone metabolism are complex and remain incompletely understood [28–33].

Some previous studies that examined the relationship between use of these medications and risk of fractures used data from administrative databases and in consequence have been limited by their ability to control for potential confounding factors such as depressive symptoms and bone mineral density. In addition, many studies have focused only on hip fractures. Moreover, given the accumulating evidence that antidepressants are associated with increased fracture risk, further investigation in order to explore the consistency of these findings in other cohorts are warranted and would be useful steps in order to expand our understanding of the possible effects of antidepressants use on bone health.

In consequence, we planned this study in order to examine the association between antidepressants, including TCAs, SSRIs, and miscellaneous antidepressants and the risk of nonvertebral fractures among women with osteoporosis enrolled in Spinal Osteoporosis Therapeutic Intervention (SOTI) [34] and Treatment of Peripheral Osteoporosis (TROPOS) trials [35]. These datasets both contain accurate data about fractures and give the opportunity to take into account of confounding factors known to influence bone outcomes, such as depression, bone mineral density, previous fractures, lifestyle factors (smoking, alcohol), or concomitant drugs that may cause fractures.

Materials and methods

Study population

This study is a post-hoc analysis of pooled data from the Spinal Osteoporosis Therapeutic Intervention (SOTI) [34] and Treatment of

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Peripheral Osteoporosis (TROPOS) trials [35]. These randomized, double-blind, placebo-controlled clinical trials have been presented in detail previously. Briefly, SOTI investigated the anti-vertebral fracture efficacy in 1649 white postmenopausal women with osteoporosis and at least one prevalent vertebral fracture, whereas TROPOS assessed the anti-nonvertebral efficacy among 5091 white postmenopausal women with osteoporosis with femoral neck BMD $\leq$0.600 g/cm² and $\geq$74 years of age (or 70 years with one additional risk factor of osteoporotic fracture). Before inclusion either in the SOTI or in the TROPOS study, patients were subjected to a run-in study to initiate normalization of their calcium and vitamin D status. The duration of this run-in study was 2 weeks to 6 months, depending on the severity of calcium and 25-OH vitamin D deficiency. In both SOTI and TROPOS studies, patients were randomly assigned to receive 2 g/day of strontium ranelate or placebo for 5 years. Subjects were instructed to take the study drug once daily at bedtime or twice daily. Around 90% of the patients chose the once-daily regimen. Calcium and vitamin D were also prescribed throughout the study.

Study design

In order to investigate the relationship between antidepressants and the risk of nonvertebral fracture, a case-control study was performed in the placebo treated population. Using incidence density sampling, for each patient who incurred a nonvertebral fracture during the 3-year follow-up, we randomly selected 5 controls from the placebo treated population who were alive and free of fracture at the time the corresponding matched case was diagnosed. Accordingly, a patient might be selected as control before becoming a case and might be selected as a control several times for different cases [36]. The two matched criteria were age group (<60, 60–69, 70–79, >79) and the duration of follow-up in order that patients (cases or controls) were followed during the same duration. The date of the occurrence of the nonvertebral fracture was termed the index date. The index date for each control was the same as the date of fracture for the matched case.

Nonvertebral fractures were defined as fractures occurring at a nonvertebral site, with fractures of the coccyx, skull, jaw, face, ankle and phalanx (fingers and toes) not considered as related to osteoporosis and not taken into account in the analysis.

Exposure assessment

The only available data about antidepressants exposure were the start date and stop date of drug administration. Both these data were used in order to estimate the duration of antidepressants treatment.

The antidepressants were identified based on their ATC codes and classified as SSRIs, TCAs, or miscellaneous antidepressants. The miscellaneous antidepressants groups included: medifoxamine (3.6%), mianserin (38.5%), mirtazapine (3.5%), nefazodone (1.8%), tianeptine (17.5%), trazodone (35.1%). Antidepressant use was further divided into current, recent and past use of antidepressants as determined on the index date. Current use was defined as a patient using an antidepressant within 30 days before the index date, based on the start date and stop date of drug administration. Recent users were patients who were not current users, but used antidepressants within 3 months before the index date. Past use was defined as use of an antidepressant the year before the index date, not being current or recent use. Exposure to antidepressants was categorized as no use when there was no recorded use of antidepressant medication from the baseline visit till the index date or when patients used antidepressants more than 365 days prior the index date. Patients with a history of using more than one type of antidepressant 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.

Assessment of potential confounders

The following baseline patient characteristics were considered: smoking status, body mass index, alcohol consumption, the presence of previous vertebral/nonvertebral fracture (yes/no), the presence of depressive disorders and the BMD value (lumbar spine, total hip, femoral neck).

Furthermore, medication use in the 6-month period before the index date included antiepileptic drugs, antiparkinson drugs, anxiolytics/benzodiazepin drugs, neuroleptic drugs, antihypertensive drugs, antiarrhytmics drugs, antidiuretics drugs, antidiabetics drugs, glucocorticoids, hormone replacement therapy, NSAIDs, thyroid hormones. These medication covariates were selected because of their associations with falls, fractures, depression, or low BMD and have been controlled for in studies of similar design [19,21,37–42].

Statistical analysis

The case group was compared to the controls group by chi-square test for qualitative variables and by unpaired Student's *t* test for quantitative variables.

Logistic regression analysis was used to estimate the risk of nonvertebral fracture associated with the use of SSRIs, TCAs and miscellaneous antidepressants and the various confounding variables and were expressed as odds ratios (OR) with corresponding 95% confidence interval (CI). Covariates were included in the regression model if they were independently significantly associated with the outcome ($p<0.05$). Moreover, we performed subgroups analyses according to the following confounder variables: age (<70 vs $\geq$70 years), BMI (low [<25] vs high [$\geq$25]), alcohol consumption (yes vs no), smoking status (yes vs no), presence of self-reported depressive disorder at baseline (yes vs no) and history of vertebral or nonvertebral fractures (yes vs no).

Both crude and adjusted OR for nonvertebral fracture were estimated by comparing antidepressant use with no use.

All results were considered to be statistically significant if the corresponding *p* value was below 0.05.

Results

After 3 years of follow-up, 391 nonvertebral fractures cases were identified and matched to 1955 controls. The characteristics of the study population are shown in Table 1. The mean age of cases and controls was 75 years. The mean duration of follow-up (i.e. the number of days between the inclusion and the index date) was 660 days, as well as for cases as controls since they were censured at the same time. Compared to controls, cases used more medication. The most frequently prescribed drugs among cases and controls in the 6-month time window before the index date were NSAIDs, anxiolytics/benzodiazepin drugs, antidiuretics and antihypertensive drugs. 4.1% of cases and 1.9% of controls reported depressive disorders at baseline ($p<0.05$). A statistically significant association between depressive disorders and the risk of nonvertebral fracture was found (OR = 1.21; 95%CI [1.21–4.02]). The proportion of patients with depressive disorders at baseline was higher among current users of SSRI than in no users of antidepressants (15.7% vs 1.6%; $p<0.05$). Concerning the TCA users group, the proportion of patients reporting depressive disorders was higher among TCA users compared to no users of antidepressant, but this difference did not reach statistical significance (2.6% vs 1.6%; $p>0.05$).

Table 2 shows the association between use of antidepressants and risk of nonvertebral fracture. Compared with no users of antidepressants during the follow-up, antidepressants use was associated with an increased risk of nonvertebral fractures (crude OR = 1.92; 95%CI [1.4–2.97]). Particularly, there was a 2.4-fold risk increase (crude OR = 2.38; 95%CI [1.30–4.34]) of nonvertebral fracture for current users of SSRIs and a 2.1-fold risk increase for subjects who were

Table 1
Baseline characteristics of the study population.

Characteristics	Cases ($n=391$)	Controls ($n=1955$)	p Value
Age, years, mean (SD)	75.73 (6.74)	75.01 (6.71)	>0.05
<60 years, %	1.8	1.8	
60–69 years, %	11.3	11.3	>0.05
70–79 years, %	57.3	57.3	
≥80 years, %	29.6	29.6	
BMI, mean (SD)	25.59 (4.04)	25.61 (4.07)	>0.05
History of vertebral/non vertebral fractures, %	70.3	60.1	<0.001
BMD (g/cm²), mean (SD)			
Lumbar spine	0.76 (0.15)	0.78 (0.14)	<0.05
Total hip	0.64 (0.11)	0.66 (0.10)	<0.001
Femoral neck	0.57 (0.07)	0.55 (0.08)	<0.001
Smoking, %	7.9	7.4	>0.05
Alcohol, %	24.0	24.5	>0.05
Depressive disorders, %	4.1	1.9	<0.05
Drugs use before the index date, %			
Antiepileptic drugs	0	0	NA
Antiparkinson drugs	2.3	0.7	<0.01
Anxiolytics/benzodiazepin drugs	14.8	9.9	<0.01
Neuroleptic drugs	1.5	0.8	>0.05
Antihypertensive drugs	12.8	9.7	>0.05
Antiarrhytmics drugs	4.4	1.8	<0.01
Antidiuretics drugs	10.5	8.9	>0.05
Antidiabetics drugs	2.1	1.8	>0.05
Glucocorticoids	4.4	3.5	>0.05
Hormone replacement therapy	2.6	1.9	>0.05
NSAIDs	17.9	14.1	>0.05
Thyroid hormones	2.6	2.1	>0.05

NA: not applicable

current users of TCAs (crude OR = 2.11; 95%CI [1.04–4.31]). The current use of antidepressants other than SSRIs or TCAs was not statistically associated with an increased risk of fractures (crude OR = 1.52; 95%CI [0.65–3.55]).

After adjustment for possible confounders, these associations were maintained for current users of SSRIs and TCAs. Compared with non-users of antidepressants, the adjusted odds ratio for nonvertebral fractures associated with current use was 2.01 (95%CI, 1.07–3.79) for SSRIs and 2.09 (95%CI, 1.02–4.30) for TCAs. However, no statistically significant difference for risk of fractures was found between TCA users and SSRI users ($p = 0.394$). Among patients categorized as recent or past users, none of the classes of antidepressants (i.e. any antidepressants, SSRIs, TCAs and miscellaneous antidepressants) were statistically associated with increased risk of nonvertebral fracture.

In subgroups analyses, the increase in nonvertebral fracture risk among current users of antidepressants was statistically significant and more pronounced when the analyses are restricted to women aged 70 years or older, women with low BMI (i.e. <25), no smoker, without self-reported depressive disorders at baseline and no history of vertebral and/or nonvertebral fractures (Table 3). Concerning the alcohol consumption confounder variable, the increase in fracture risk was statistically significant for patients reporting alcohol consumption as well as for patients reporting no alcohol consumption. The statistically significant association disappeared in all others subgroups.

Discussion

In this case-control study, we have demonstrated an increased risk of nonvertebral fracture for current users of SSRIs and TCAs, while the increase was absent with the group of miscellaneous antidepressants. The statistically significant association between fracture risk and SSRIs or TCAs use persist even after adjusting for confounding factors implicated in fracture pathophysiology.

The magnitude of fracture increase are quite similar with those of case–control studies and other observational cohort studies [10,11,14,15,21–24,27]. Our results are also in agreement with the estimated effect sizes of a meta-analysis of the most recent data published in the literature that assessed the effect of antidepressants on the risk of fractures [43]. The results of this meta-analysis showed a significant increase in the risk of fractures of all types among antidepressant users ranging from 38% to 65%, according to the fractures site and the type of antidepressant use.

The risk of fracture has been demonstrated in several studies to be dependent on both the dose [14,15,22] and duration of exposure [10,11,15,24]. For instance, Vestergaard et al. demonstrated, among TCAs users, a limited dose-dependent increase in the risk of any fracture (from an OR of 1.1 at doses <0.15 DDD/day to 1.4 at doses >0.75 DDD/day) and spine fractures, while no increase was seen for forearm fractures and a non-dose-dependent increase was seen at doses

Table 2
Association between antidepressant exposure and nonvertebral fracture.

	Nonvertebral fracture					
	Cases ($n=391$), %	Controls ($n=1955$), %	Crude OR	95%CI	Adjusted OR[a]	95%CI
Any antidepressants[b]						
No use	88.2	92.8	Reference		Reference	
Current use	7.7	4.1	1.92	1.45–2.97	1.64	1.03–2.62
Recent use	1.3	1.1	1.18	0.44–3.14	1.06	0.39–2.90
Past use	2.8	2.0	1.43	0.72–2.82	1.22	0.61–2.48
SSRI						
No use	93.8	96.8	Reference		Reference	
Current use	4.1	1.8	2.38	1.30–4.34	2.01	1.07–3.79
Recent use	0.3	0.4	0.74	0.09–6.07	0.61	0.07–5.12
Past use	1.8	1.0	1.82	0.76–4.34	1.57	0.63–3.83
TCA						
No use	95.9	97.3	Reference		Reference	
Current use	2.8	1.4	2.11	1.04–4.31	2.09	1.02–4.30
Recent use	0.5	0.4	1.16	0.25–5.37	1.26	0.26–6.06
Past use	0.8	0.9	0.92	0.27–3.15	0.87	0.25–3.05
Miscellaneous antidepressants						
No use			Reference		Reference	
Current use	1.8	1.2	1.52	0.65–3.55	1.14	0.44–2.96
Recent use	0.5	0.4	1.49	0.31–7.19	1.25	0.25–6.32
Past use	0.3	0.2	1.3	0.14–11.68	1.05	0.11–10.00

[a] The models were adjusted for: Lumbar spine BMD, Femoral neck BMD, total hip BMD, depressive symptoms, history of vertebral/nonvertebral fracture, anxiolytics/benzodiazepin drugs, antihypertensive drugs, and antiarrhytmics drugs.
[b] This category include SSRI, TCA and miscellaneous antidepressants categories.

Table 3
Association between antidepressant exposure[a] and nonvertebral fracture according to important potential confounders.

	Crude OR	95%CI	Adjusted OR[b]	95%CI
Age				
<70	3.05	0.70–13.27	3.20	0.72–14.31
≥70	1.85	1.18–2.93	1.80	1.11–2.91
BMI				
Low (<25)	2.44	1.34–4.44	2.39	1.30–4.41
High (≥25)	1.45	0.75–2.81	1.47	0.74–2.94
Alcohol consumption				
No	1.72	1.04–2.83	1.69	1.01–2.87
Yes	2.86	1.17–6.97	2.73	1.09–6.82
Smoking				
No	1.85	1.19–2.90	1.83	1.15–2.92
Yes	4.86	0.65–36.45	4.7	0.61–36.01
Depressive disorders				
No	1.98	1.25–3.13	1.96	1.21–3.17
Yes	1.20	0.26–5.60	1.11	0.19–6.41
History of vertebral/non-vertebral fractures				
No	3.76	1.91–7.38	3.44	1.68–7.02
Yes	1.30	0.73–2.32	1.32	0.73–2.41

[a] These analyses include current users of SSRI, TCA or miscellaneous antidepressants. The reference group was the no user group.
[b] The models were adjusted for lumbar spine BMD, femoral neck BMD, total hip BMD, and for all variables in the table.

between 0.15 and 0.75 DDD/day for hip fractures. SSRIs showed increases in the relative risk of fracture across doses for all categories of fracture [14]. In the CaMOS study, Richards et al. observed a dose-dependent effect for SSRIs [22]. They also demonstrated a sustained elevation risk with prolonged use (5 years). An earlier study using data from the United Kingdom General Practice Research Database showed an increased risk of hip fractures with the use of TCAs or SSRIs, in particular within the first 15 days of use [11]. A similar pattern, i.e., a higher observed risk in the beginning of the treatment, was found by Liu et al. [10].

In our study, we did not have sufficient numbers of patients to look for evidence of a dose effect or a duration effect of antidepressants on the risk of nonvertebral fractures. Moreover, the size of the increase in risk was almost similar for SSRIs and TCAs users and we found no significant difference in the risk of nonvertebral fracture between users of SSRIs and users of TCAs, a finding consistent with previous study [10,11,21]. Lastly, in our study, the increase in risk was associated only with current use; the risk for previous users was not statistically different from that for nonusers. Some studies have investigated the relationship between antidepressants use and fractures risk in relation to current or past use and found similar results [9,10,15,24]. For instance, Liu et al. found that the current but not former use of SSRIs was associated with a higher risk [10]. The risk was more pronounced early in treatment, as was also observed by Hubbard et al. [11]. This would suggest that the association is not related to a long-term detrimental effect of SSRIs on BMD, but some other effect, perhaps related to an increased risk of falling. Moreover, in our study, the number of fractures among the recent or past users was very small. As a result, the adjusted OR was not significant and the confidence intervals were wide.

The consistency of these results provides strong evidence that the use of antidepressants is associated with increased risk of fractures in older individuals. Several mechanisms have been proposed to explain this adverse effect of antidepressant drug treatment. One explanation is that the increased fracture risk is mediated simply by falling. Dizziness, drowsiness, ataxia, blurred vision, cardiac conduction disturbances and orthostatic hypotension are all possible side effects of antidepressant therapy that may increase one's fall risk [21,22,44–48]. Tricyclic antidepressants, which have anticholinergic, antihistamine and α-blocking effects are most likely to contribute to falls [7,49,50].

Another explanation lies in the potential for antidepressants to affect the micro-architecture of bone. Recent research have documented functional serotonin (5-hydroxytryptamine [5-HT]) receptors and transporters (5-HTT) in osteoblasts, osteoclasts and osteocytes in animal models, raising the possibility that inhibition of these transporter systems may have effects on bone metabolism [28–33]. This could signal a reduction in BMD also in humans with the use of SSRIs and thus perhaps an increased fracture risk. Several studies in varied populations have demonstrated an effect of SSRIs on BMD. Cross-sectional studies support an association between SSRIs and lower BMD in men and women [22,51,52]. Adjusted differences in BMD between SSRI users and nonusers range from 2.4% to 6.2% across anatomic sites [22,52]. In contrast, results from the National Health and Nutrition Examination Survey and the Women's Health Initiative do not support an association between antidepressant use and BMD changes [23,53]. The WHI observational study did not show a decrease in BMD in antidepressant treated patients over 3 years, despite showing an increased risk for fractures. A further point is that not only SSRIs block the 5-HTT, some of the TCAs may also affect serotonin reuptake in the same way as SSRI. For instance, clomipramine has more pharmacological similarities with SSRIs than with other TCAs. Imipramine has a high affinity for the 5-HTT as well. Recently, two studies evaluated the risk of hip/femur fractures and any fracture according the degree of 5-HTT inhibition [13,18]. In both studies, fracture risk increased with an increasing degree of affinity for the 5-HTT. No studies are available showing a direct effect of TCAs on bone metabolism; however, recent studies have failed to show an effect on cross-sectional BMD and rate of BMD loss [51,54], thus indicating that TCAs may be safe in terms of BMD. However, TCAs are frequently used for indications other than depression, such as pain. The doses used for the management of pain are usually lower than doses used for depression; possibly underestimating the effects of TCAs on bone strength.

Underlying diseases such as depression or depressive symptomatology treated with antidepressants could also explain the increase in risk. Indeed, a major limitation of the observational studies evaluating the association between antidepressants and fractures or bone loss is confounding by indication, which can exist if a disease and the treatment both have potential to be associated with the outcome of interest. Depression and its consequences (e.g., weight loss, inactivity and overconsumption of alcohol) are potentially associated with both the outcome of interest (BMD and fracture) and the exposure (antidepressants) [21,23,51–60]. In addition, individuals using SSRIs or TCAs may have poorer health status and therefore be more likely to fall. Indeed, patients with depression may be more likely to fall and thus suffer fractures. The mechanisms responsible for the falls may be related to reduced physical function both as a result of reduced physical activity with decreased muscle strength and from poorer nutrition, leading to poorer physical condition. In our study, we observed an increased risk of nonvertebral fractures associated with depressive symptoms. Moreover, we found that the proportion of patients reporting depressive disorders at baseline is higher among current users of SSRI than in no users of antidepressants ($p<0.05$). Concerning the TCA users group, the proportion of patients reporting depressive disorders was higher among TCA users compared to no users of antidepressant, but this difference did not reached statistical significance. Additionally, in our subgroup analyses, restricting analysis to patients stating no depressive disorders at baseline did not alter the results. The statistically significant association between current use of any antidepressants and the risk of fracture disappeared when the analysis is limited to patients with depressive disorders at baseline.

We dealt with confounding by indication by including, among other confounding factors such as BMD, depressive state at baseline into the model. However, a rigorous measure of depression was not used. Indeed, we used a measure of self-reported depressive symptoms, as this is the case in most studies using various methods for assessing depression and not a clinical diagnosis of depression. To

our knowledge, only one study of SSRIs and bone health assessed participants with a more rigorous research measure, the structured clinical interview, and adjusted for the presence of either past or current depression that met DSM-IV diagnostic criteria [52].

The major methodological strengths of our study is the accuracy of data about fractures and other confounding factors, such as BMD, since these data come from randomized clinical trials. Moreover, for the same reason, we have access to a great number of variables. Unlike some studies reported in the literature, we were able to take into account for many confounding variables such as depression, bone mineral density, previous fractures, lifestyle factors (smoking, alcohol), or concomitant drugs that may cause fractures. Indeed, some previous work examining use of antidepressant medications and risk of fracture utilized claims databases and did not reliably control for many confounding variables that may affect the relationship between the use of these medications and fractures. However, in our analysis, although we controlled for many confounding variables and drugs that are associated with an increased risk of fracture, we cannot rule out the possibility that residual confounding occurred or that alternative causes for our findings exist. Other strengths include long-term follow-up and updated information regarding antidepressants and concomitant medications use and covariates at several examinations. Nonetheless, several limitations should be considered. As already mentioned, an indication bias may also overinflate the odds ratios in our case-control study because depression per se may be a risk factor for fracture. However, we adjusted all analyses for the presence of depressive symptoms at baseline. In addition to the lack of accurate diagnostic of depressive symptoms in our population, as in most of the studies, measures of depression severity were also not available. In addition, as in some studies, we report a small number of patients taking antidepressants compared with the number of fracture cases, yielding low-powered analyses. In addition, we cannot extrapolate our findings to other populations. Although the age of the participants has been limited to 65 years or over in the majority of previous studies, many surveys have also included younger participants [14,22]. Therefore, the results of such studies are not entirely comparable with those of ours, since our cohort consists of elderly women. Many studies have focused on hip fractures, and their results cannot be generalized to all fractures [9,10,12,18]. Moreover, in our study, as in many previous studies, patients were invited to self-report use of antidepressants. In some cases, patients may forget to report use of antidepressants or report to consume them without being actually consumed or to be used but with low compliance; all these facts may lead to potential misclassification of exposure. Lastly, it would be interesting to study the relationship between the use of antidepressants and vertebral fractures since there are very few data on this topic in the literature. However, in this study, we could not perform such analyses since no accurate data on the occurrence of vertebral fracture were available (only the year of its occurrence was available).

In summary, this study provides further evidence that tricyclic antidepressants and selective serotonin reuptake inhibitors are both associated with an increased risk of fracture in elderly people. Together with existing literature, our findings have a potentially important public health impact and have important clinical implications in the medical management of older adults, given the high prevalence of antidepressants use among the general population and in particular, among the frail older population. This underscores the need to consider the potential for increased risk of fracture and other serious fall-related injuries when these drugs are used in geriatric practice. The consistency of the findings in the literature suggests that changes are needed in the way doctors manage psychological problems in elderly patients or at least that these patients should be aware of this increased risk so that they can take appropriate precautions. Moreover, further studies, including controlled prospective trials, are needed to evaluate the relative contribution of treatment-related and disease-related effects to the increased risk of falls and fractures and to elucidate the underlying mechanism.

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