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Rabenda, V.; Nicolet, D.; Beaudart, C.; Bruyère, O.; Reginster, J. Y.

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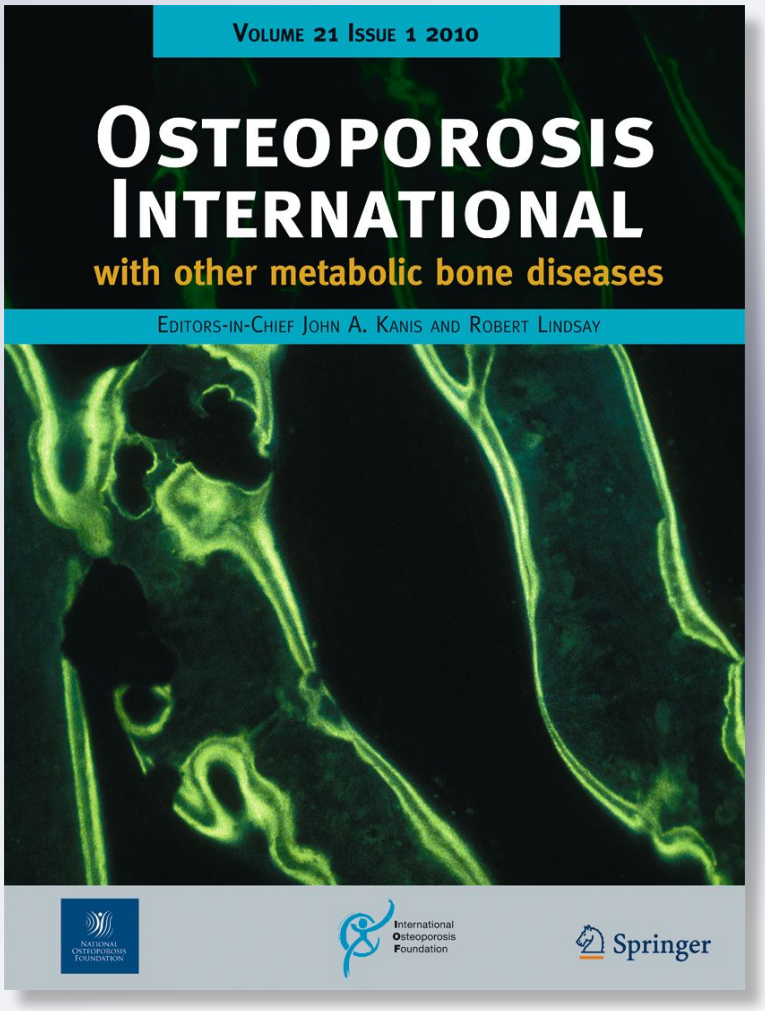

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ORIGINAL ARTICLE

Relationship between use of antidepressants and risk of fractures: a meta-analysis

V. Rabenda · D. Nicolet · C. Beaudart · O. Bruyère · J.-Y. Reginster

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Abstract
Summary It has been shown that antidepressants would have a direct action on bone metabolism and would be associated with increased fracture risk. Results from this large meta-analysis show that both SSRIs and TCAs are associated with a moderate and clinically significant increase in the risk of fractures of all types.
Introduction This study seeks to investigate the relationship between use of antidepressants and the risk of fracture.
Methods An exhaustive systematic research of case–control and cohort studies published or performed between 1966 and April 2011 that reported risk estimates of fracture associated with use of antidepressants was performed using MEDLINE, PsycINFO, and the Cochrane Systematic Review Database, manual review of the literature, and congressional abstracts. Inclusion, quality scoring, and data abstraction were performed systematically by three independent reviewers.
Results A total of 34 studies (n=1,217,464 individuals) were identified. Compared with non-users, the random effects pooled RR of fractures of all types, among antidepressant users, were 1.39 (95%CI 1.32–1.47). Use of antidepressants were associated with a 42 %, 47 %, and 38 % risk increase in non-vertebral, hip, and spine fractures, respectively ([For non-vertebral fractures: RR=1.42, 95%CI 1.34–1.51]; [For hip fractures: RR=1.47, 95%CI 1.36–1.58]; [For spine fractures: RR=1.38, 95%CI 1.19–1.61]). Studies examining SSRI use showed systematically a higher increase in the risk of fractures of all types, non-vertebral, and hip fractures than studies evaluating TCA use.
Conclusions Results from this large meta-analysis show that both SSRIs and TCAs are associated with a moderate and clinically significant increase in the risk of fractures of all types.

Keywords Antidepressants · Fractures · Meta-analysis · Selective serotonin-reuptake inhibitor · Tricyclic antidepressants

Introduction

Antidepressants are a class of drugs widely used around the world, with selective serotonin-reuptake inhibitors (SSRI) considered as first-line therapy for the treatment of depressive symptoms among older adults because of their presumed favourable adverse effect profile [1–3]. It has been shown that these treatments would be associated with a higher risk of falls [4–8] but would also have a direct action on bone metabolism [9–11]. Evidence from longitudinal, cross-sectional, and prospective cohort studies suggests that the use of antidepressants at therapeutic doses is associated with decreased bone mineral density (BMD) and increased fracture risk [10, 12–17]. These associations have been demonstrated in several distinct populations, using various study designs and with bone density, bone loss or fractures as outcomes, and are consistent after adjustment for confounding variables such as age, body mass index, lifestyle factors (alcohol, tobacco use), and history of fractures.

However, at present, the mechanism of action of antidepressants in the regulation of bone tissue is not fully understood. Whether antidepressants have the ability to increase the risk of falls, to reduce BMD, or both, has been a matter

V. Rabenda (✉) · D. Nicolet · C. Beaudart · O. Bruyère · J.-Y. Reginster
Department of Public Health, Epidemiology and Health Economics, University of Liège,
CHU—Bât. B23,
4000 Liège, Belgium
e-mail: veronique.rabenda@ulg.ac.be

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of scientific debate for years, and this topic has been the subject of many studies. In 2005, Takkouche et al. published a meta-analysis showing that the pooled relative risk for fracture was 33 % higher for those exposed to an SSRI as compared to those exposed to a non-SSRI antidepressant [18]. However, this meta-analysis focused only on fractures at any site and on hip fractures. Moreover, since then, many studies aiming to investigate the relationship between the use of antidepressants and fractures have been published. To date, no comprehensive meta-analysis including these most recent data published in the literature has addressed the risk of fractures associated with the use of antidepressants. Moreover, to our knowledge, no pooled relative risk for non-vertebral and spine fractures has never been published.

In order to obtain an update of these data and a comprehensive overview of this field, we conducted a meta-analysis to quantitatively assess all available case–control and cohort studies that assessed the effect of antidepressants on the risk of fractures, which allowed us to gather more precise and accurate information on the relationship between the use of antidepressants and the risk of fractures.

Material and methods

Search strategy and data extraction

The Preferred Reporting Items for Systematic Reviews and Meta-analyses statement was followed [19]. A protocol was developed in advance to specify the research objective, search strategy, study eligibility criteria, and the methods of data extraction and statistical analysis. Sensitivity analysis was also prespecified.

We conducted a systematic literature search of MEDLINE from 1966 to April 2011, PsycINFO from 1967 to April 2011, and the Cochrane Systematic Review Database from 2005 to April 2011. The search terms were “antidepressant”, “antidepressive agents”, “selective serotonin-reuptake inhibitor”, “tricyclic antidepressant”, “monoamine oxidase inhibitors”, “psychotropic drugs”, “fractures”, “falls”, “bone density”, and “osteoporosis” (Appendix).

The computerized searches were supplemented by a manual search of relevant references of retrieved articles and of abstracts from major meetings of bone research or psychiatrics societies.

Eligible study and quality assessment

For the initial screening stage, two investigators (DN and CB) independently reviewed each title to exclude only the obviously irrelevant citations. After this first step, the two investigators independently reviewed each abstract of articles not excluded during the initial screening stage. In both screening stages, the following simple relevant criteria were used: (1) human participants, (2) any antidepressants, SSRI or TCA, and (3) fractures of any type. Their disagreements were resolved by consensus (VR). This first study selection stage resulted in a total of 54 articles for eligibility for a full-text articles assessment. All potentially relevant articles were reviewed independently by three investigators (DN, CB, VR).

We included both case–control and cohort studies that reported the HR or the RR or the OR of fracture associated with use of antidepressants. Studies that did not provide risk estimates and confidence intervals but provided enough data to calculate them were included. Moreover, to be included, the outcome of interest must have been clearly defined as fracture. In other words, falls not followed by fractures were not included.

The quality of the studies was appraised with the Newcastle-Ottawa Scale, which is designed for observational studies [20]. The New Castle-Ottawa Scale is a nine-point scale that assigns points on the basis of the process of selection of the cohorts or of the case and of the controls (0–4 points), of the comparability of the cohorts or of the case and of the controls (0–2 points), and of the identification of the exposure and of the outcomes of study participants (0–3 points). Studies that achieved seven or more points were considered to be of high quality.

Data extraction

Data were independently extracted by three authors (DN, CB, VR) according to data extraction forms and checked for accuracy. The following study characteristics were recorded: (1) name of first author, (2) publishing year, (3) country in which the study was conducted, (4) study setting and design, (5) study population and baseline characteristics, (6) measures of outcomes and exposure, and (7) matching and adjustment factors. In addition to the descriptive information, all data needed for the statistical analysis, including relative risk (RR) estimates (in terms of odds ratio, OR; hazard ratio, HR), relative 95 % confidence intervals (95%CI), standard error (SE), or p value for each exposed group (or data useful to derive such estimates), were extracted from published reports.

Statistical analysis

Potential publication bias was explored by drawing a funnel plot. Publication bias was analysed using the Begg and Mazumdar [21] and Eger et al. tests [22]. If publication bias was detected, the effect of such bias was assessed with the fail-safe number method [23, 24]. The fail–safe number was the number of unpublished studies that would be needed to nullify the observed result to statistical non-significance at

the α=0.05 level. Publication bias is generally regarded as a concern if the fail–safe number is less than $5n+10$, where n is the number of studies included in the meta-analysis. The results were examined for heterogeneity by using formal statistical tests for heterogeneity and trial inconsistency. Heterogeneity was assessed with Cochran's Q statistic ($p \leq 0.10$ indicating significance) and quantified using the I^2 statistic, which indicated the proportion of variability across studies that was due to heterogeneity rather than sampling error [25].

We assumed the presence of heterogeneity a priori, and we used random effects models. The odds ratio from case–control studies and the hazard ratios were assumed to provide a valid estimate of the relative risk, and consequently, were considered as an approximation of the relative risk. When available, adjusted estimates have been used in this meta-analysis. If a paper reported the results of different multivariate models, the most stringently controlled estimates (those from the model adjusting for more factors) were extracted.

We carried out separate analyses for each class of antidepressants (i.e. all antidepressants, SSRIs and TCAs) and for each type of fracture (i.e. all fractures, non-vertebral fractures, spine fractures, and hip fractures). In studies where multiple fracture sites or several classes of antidepressants were analysed and no overall RR or OR was given, the reported results were pooled. For the "non-vertebral fractures" analyses, we included studies reporting at least one of the following non-vertebral fractures data: hip, femur, femoral neck, non-spine fracture, humeral fracture, pelvic fracture, wrist, Colle's fracture, and lower limb.

To evaluate the impact of individual studies on the overall results, we performed a one-way sensitivity analysis by omitting one study at a time, and repeating the analysis. We were not able to perform meta-regression analysis to examine the variation in antidepressant effect attributable to prespecified variables. In fact, some important variables were not available in the original studies, limiting the number of studies that would be included in the meta-regression analysis. However, to explore the origin of heterogeneity, analyses were stratified by study quality score (NOS score <7 vs ≥7), study design (case–control vs cohort studies) and by the adjustment or not of the RR (crude RR vs adjusted RR). In addition, to assess whether the effect of antidepressants on fracture risk was modified by demographic or clinical variables, a list of subgroup analysis was specified. These variables were chosen on the basis of known risk factors or biological plausibility, such as gender, age, ethnicity, study location, adjustment or not for BMD, or depression. We were not able to conduct subgroup analysis for ethnicity since some studies used multi-ethnic groups and others did not specify the variable. For the analysis of the risk of factor of age, we conducted one post hoc analysis by including studies with participants aged of 50 years or more only. Other potential sources of the variation, such as type of drug, dose of drug, duration of exposure, and time since last use, were available in a limited number of studies and categories used were mixed, so that we could not calculate a summary estimate.

Results were regarded as statistically significant if $p<0.05$. All analyses were done with Comprehensive Meta-Analysis software.

Results

A total of 34 studies (n=1217464 individuals) were identified that satisfied the inclusion criteria (Fig. 1) [26–59]. Results of Vestergaard et al. were reported in two papers [40, 41] but were considered as one study in the analyses and, in consequence, analyses included 33 studies. Characteristics of the 33 studies included in the meta-analysis are presented in Table 1. Twenty studies were case–controls studies [26–46] and 13 studies were cohort studies [47–59]. A total of 26 studies reported data on non-vertebral fractures (including wrist, Colle's, femur, hip, femoral neck…) [26–40, 44, 45, 47–50, 54, 55, 57–59], 19 studies on hip fractures [26, 28–30, 33–36, 38–40, 44, 45, 47–49, 54, 58, 59], and 3 studies reported data on spine fractures [40, 44, 54]. Sixteen and fourteen studies reported data specifically on SSRI [32, 33, 36, 38, 41, 42, 44–46, 49–51, 54, 55, 58, 59] or TCA use [26, 28, 33, 36, 38, 41, 45, 46, 49–51, 55, 58, 59], respectively.

In seven studies, the antidepressant use was divided into categories of user (current user, recent user, past user…) [26, 28, 30, 42, 45, 46, 55]. In this case, only the results of the current users' category were taken into account. In the Ray et al. study [28], the authors reported results for cyclic antidepressants, without distinguishing tricyclic antidepressants and tetracyclic antidepressants. In our analyses, we considered these results as being tricyclic antidepressants. In the study conducted by Perreault et al. [43], the authors performed two nested case–control analysis using two sub-cohorts of women; a sub-cohort of women with a diagnosis of osteoporosis and a sub-cohort of women with a prior fracture. In our analyses, we used data coming from the sub-cohort of women with a diagnosis of osteoporosis. In one study [57], the referent group was an "atypical antipsychotics users" group, and not a "non-users" group, as it is the case in most of the studies. In other study [59], the referent group was a "secondary amine tricyclics users" group.

Most of the studies (73 %) achieved seven or more points in the NOS scale and were considered to be of high quality (Table 2). Egger's regression analysis showed that publication bias was not present (p=0.06; Fig. 2).

Globally, there was a moderate but significant increase in the risk of fractures of all types among antidepressant users. Compared with non-users, the random effects pooled RR of

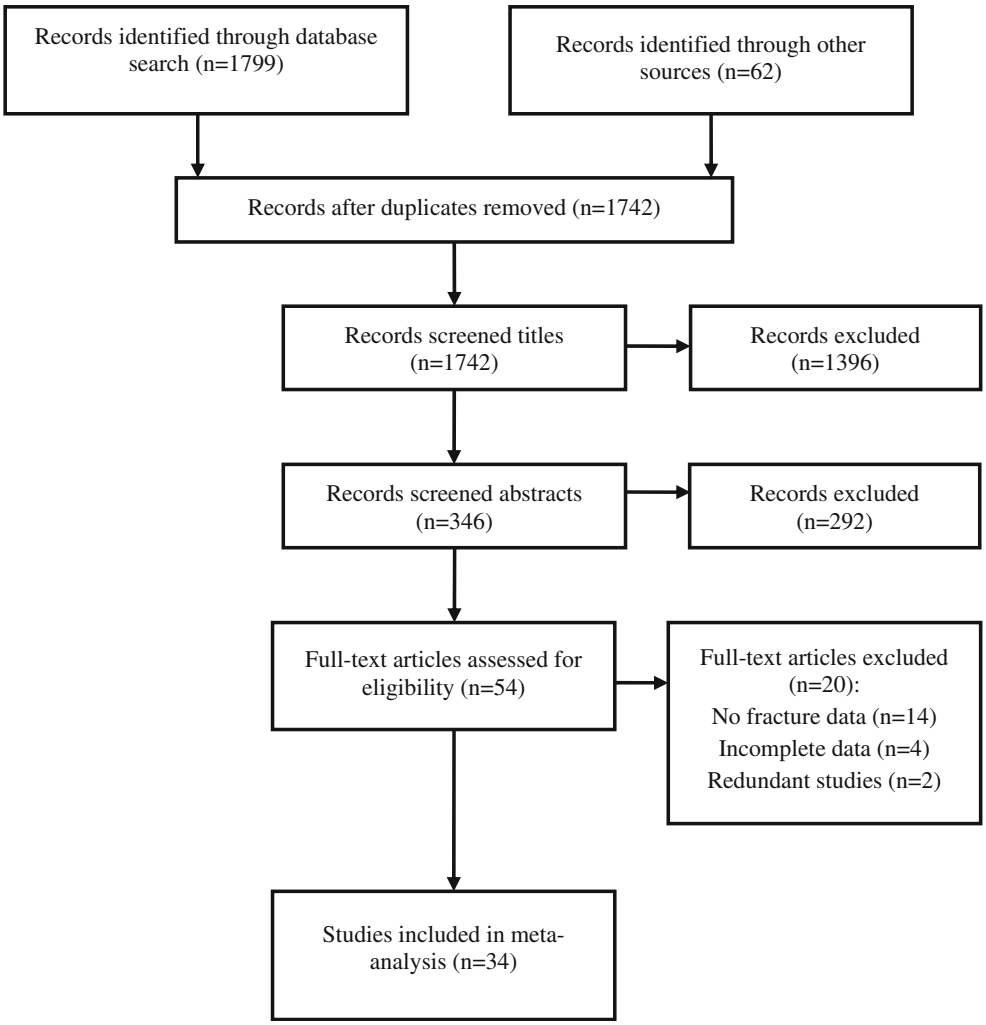

Fig. 1 Flowchart of study selection

fractures of all types, among antidepressant users, were 1.39 (95%CI 1.32–1.47; Table 2). The results were unchanged when individual trials were removed singly (yielding 33 sensitivity models, one model for each trial that was dropped). The Q statistic for heterogeneity was significant ($p<0.0001$), with the I^2 value of 84.5 %. Heterogeneity subsided when we stratified the analysis by study design (case–control vs cohort studies) and we did not find any evidence of substantial difference in pooled RRs according to study design ([For case–control studies: RR=1.40, 95%CI 1.31–1.49]; [For cohort studies: RR=1.37, 95%CI 1.23–1.52]; Table 2). Restricting the analysis to the studies that scored ≥7 on the quality score, to the studies reporting adjusted RR or to the studies including persons aged ≥50 years did not alter the results ([For studies with NOS score ≥7: RR=1.38; 95%CI 1.31–1.47]; [For studies with adjusted RR: RR=1.38, 95%CI 1.29–1.48]; [For studies with persons ≥50 years: RR=1.37, 95%CI 1.27–1.47]; Table 2). A less pronounced increase in fracture risk was observed in studies with adjustment for depression or BMD and for studies including only women (Table 2).

Limiting the analysis to non-vertebral, hip, or spine fractures did not produce any substantial change in the results. Use of antidepressants was associated with a 42 %, 47 %, and 38 % risk increase in non-vertebral, hip, and spine fractures, respectively ([For non-vertebral fractures: RR=1.42, 95%CI 1.34–1.51]; [For hip fractures: RR=1.47, 95%CI 1.36–1.58]; [For spine fractures: RR=1.38, 95%CI 1.19–1.61]; Table 2).

Studies examining SSRI use showed systematically a higher increase in the risk of fractures of all types, non-vertebral, and hip fractures than studies evaluating TCA use. Use of SSRI was associated with a 61 %, 65 % , 64 %, and 22 % risk increase in fractures of all types, non-vertebral, hip, and spine fractures, respectively ([For fractures at any site: RR=1.61, 95%CI 1.49–1.74]; [For non-vertebral fractures: RR=1.65, 95%CI 1.44–1.89]; [For hip fractures: RR=1.64, 95%CI 1.42–1.89]; [For spine fractures: RR=1.22, 95%CI 1.05–1.42]; Table 3). The pooled RRs from studies on TCA indicated an increase of 40 %, 42 %, and 43 % in the risk of fractures of all types, non-vertebral and hip fractures, respectively ([For fractures at any site: RR=

Table 1 Characteristics of the included studies

References	Design study	Population	Exposure	Outcome	Cases/ controls or cohort size	Matching and adjustment factors
Ray et al. [26], USA	CC	Elderly population(65 years of age or older) enrolled in Medicaid	TCA	Hip	1021/5606	Matching: Age/sex/race/index year/ home status
Jensen et al. [27], Denmark	CC	Persons over 59 years old	AD	Femoral neck	200/200	Matching: Age/sex/nursing home residency/number of admissions within the last 2 years
Ray et al. [28], Canada	CC	Elderly population (65 years and over) dwelling in the community	TCA (tri- and tetra-cyclic)	Hip	4501/24041	Matching: Birth year/sex/index date Adjustment: Age/sex/calendar year/ nursing home residence on the index date/hospitalization and use of specific medication in the year preceding the index date
Cummings et al. [29], Australia	CC	Elderly population (65 years and over) living in a defined area in western Sydney	AD	Hip	209/207	Adjustment: Age/sex/type of residence
Lichtenstein et al. [30], Canada	CC	Elderly population (65 years of age or older) identified from a previously reported population-based case–control study of hip fracture	AD	Hip	129/234	Matching: Age/sex Adjustment: Age/sex/vision impaired/ ambulatory status/dementia/ confusion/weight
Herings et al. [31], the Netherlands	CC	General population (45 years and older) data from the PHARMO record linkage system	AD	Femur	386/386	Matching: Age/sex/pharmacy/general practitioner
Gambassi et al. [32], USA	CC	Elderly population living in a nursing home of 5 US states	SSRI	Femur	8851/35086	Matching and adjustment not given
Liu et al. [33], Canada	CC	Elderly population (66 years and older)	SSRI, TCA	Hip	8239/41195	Matching: Age/sex Adjustment: Comorbidity/previous drug exposure
Wang et al. [34], USA	CC	Individuals (65 years and older) enrolled in Medicare and in Medicaid or the pharmaceutical assistance to the Aged and Disabled program of New Jersey	AD	Hip	1222/4888	Matching: Year of birth/sex Adjustment: Age/sex/race/comorbidity illness severity/prior use of other psychoactive medications/prior hospitalization/prior nursing home use
Partanen et al. [35], Finland	CC	Post-menopausal women (age range:53–84 years)	AD	Hip	74/40	Matching: Age/sex/geographical area
Hubbard et al. [36], UK	CC	Patients data from the GPRD	TCA, SSRI	Hip	16341/29889	Matching: Age/sex/general practice/ duration of available GPRD data Adjustment: History of falls/prescription for hypnotics and antipsychotics
Kaye et al. [37], UK	CC	General population data from the GPRD	AD	Lower limb	32827/65295	

Table 1 (continued)

References	Design study	Population	Exposure	Outcome	Cases/ controls or cohort size	Matching and adjustment factors
						Matching: Year of birth/sex/general practice/index date/duration of follow-up time in the GPRD Adjustment: Diagnoses (Osteoporosis, Parkinsonism, Alcoholism, Cataract, Dementia, Epilepsy, Cancer, Obesity, Rheumatoid arthritis, Osteoarthritis, Road collision)/corticosteroids use/ antipsychotics use/hypnotics and sedatives use/smoking status, BMI
French et al. [38], USA	CC	Patients (age range:30–101 years) admitted to VHA hospitals	AD, TCA, SSRI, Other	Hip	2212/4424	Matching: Age/sex
Hugenholtz et al. [39], UK	CC	General population (≥18 years) data from the GPRD	AD	Hip	22250/22250	Matching: Year of birth/sex/ medical practice
Vestergaard et al. [40, 41], Denmark	CC	Danish population (all ages)	AD, TCA, SSRI, Other	Any site, Hip, Colle's, Spine	124655/ 373962	Matching: Age/sex Adjustment: Use of anxiolytics, sedatives, neuroleptics/schizophrenia/ manic-depressive states/other psychoses/use of corticosteroids and antiepileptic/number of bed days in 1999/number of contacts to general practitioners or specialists in 1999/ Charlson index/working or not/ income in 1999/living with another person vs. alone
Bolton et al. [42], Canada	CC	General population (50 years and older) data from administrative health database	SSRI, Other	Any site	15792/47289	Matching: Age/sex/ethnicity/ comorbidity index Adjustment: Demographic variables (income quintile, region of residence, interaction of income quintile and region of residence)/medications/ physical conditions/mental disorders
Perreault et al. [43], Canada	CC	Elderly women (70 years and older) with a diagnosis of osteoporosis form the Quebec health databases	AD	Any site	1824/18240	Matching: Age/time period/BMD testing/diagnosis of osteoporosis in the 5 year period before the index Adjustment: Time since the diagnosis of osteoporosis/site of residency/ number of medical visits/number of physician prescribers/risk of fall/use of long acting benzodiazepines,

Table 1 (continued)

References	Design study	Population	Exposure	Outcome	Cases/ controls or cohort size	Matching and adjustment factors
						antidepressants, anticonvulsants, narcotics/diagnosis of diabetes
Abrahamsen et al. [44], Denmark	CC	Men (50 years and older) data from the Danish National Hospital Discharge Register and the National Prescriptions Database	AD, SSRI	Any site, Hip, Spine	15716/47149	Matching: Age/sex Adjustment: Fracture history/age/ Charlson comorbidity index
van den Brand et al. [45], the Netherlands	CC	General population (≥18 years) data from Dutch PHARMO Record Linkage System database	SSRI, TCA	Hip	6763/26341	Matching: Age/sex/geographical region Adjustment: Current use of an AD other than SSRI or TCA/use of benzodiazepine,oral corticosteroids, hormone replacement therapy, antipsychotics,beta-blockers,opioids, anticonvulsivants,drugs for diabetes, ≥2 NSAIDs, DMARDs and metoclopramide/a history of malignant neoplasms, mental disorders, cerebrovascular diseases, obstructive airway diseases or inflammatory bowel diseases
Verdel et al. [46], the Netherlands	CC	General population (≥18 years) data from Dutch PHARMO Record Linkage System database	AD, SSRI, TCA, Other	Any site	9943/36359	Matching: Year of birth/gender/ geographical area/index date Adjustment: Cancer/cardiovascular disease/cerebrovascular disease/ inflammatory bowel disease/ mental disorders/obstructive airway disease/use of antidiabetics, antiepileptics, antiparkinson drugs, benzodiazepines,beta-blocking agents,DMARDs,hormone replacement therapy,NSAIDs, oral glucocorticoids and opioids
Guo et al. [47], Sweden	CH	Inhabitants (75 years and older) of the Kungsholmen district of Stockholm	AD	Hip	1608	Adjustment: Age/sex/education/ institution as residence/limitation in ADL/visual problem/history of stroke/history of a tumor/cognitive impairment
Jacqmin-Gadda et al. [48], France	CH	Elderly population (65 years and older) from 2 areas in south-western France, selected from the Paquid	AD	Hip; non-hip	3216	Adjustment: Age/BMI/sex/tobacco consumption/spirits consumption/ profession/use of psychotropic drugs/administrative area/presence

Table 1 (continued)

References	Design study	Population	Exposure	Outcome	Cases/ controls or cohort size	Matching and adjustment factors
		cohort study on mental and physical aging				of dementia/design variables (interview vs postal questionnaire)
Ensrud et al. [49], USA	CH	Elderly (at least 65 years) community-dwelling women from 4 areas of the US	AD, SSRI, TCA	Non-spine; hip	8127	Adjustment: Age/health status/ medical conditions/walking for exercise/functional impairment/fall in previously year/cognitive function/weight change/gait speed/ inability to rise from a chair/ smoking/depression
Lewis et al. [50], USA	CH	Elderly men (65 years and older) from 6 communities in the US	SSRI, TCA	Non-spine	5876	Adjustment: Age/BMD
Richards et al. [51], Canada	CH	Community-dwelling adults (50 years and older)	SSRI, TCA	Any site	5008	Adjustment: Age/total hip BMD/ modified Charlson index/prevalent vertebral deformity/prevalent fragility fractures at baseline/ cumulative lifetime oestrogen use in women
Spector et al. [52], USA	CH	Nursing home residents (65 years and older) enrolled in the MEPS	AD	Any site	2711	Adjustment: Resident characteristics/ prescribed medications/facility characteristics
Cooper et al. [53], European countries	CH	Postmenopausal women enrolled in the OSSO	AD	Any site	1885	Not applicable
Spangler et al. [54], USA	CH	Postmenopausal women (50–79 years old) enrolled in the WHI study	AD, SSRI	Any site Hip Spine Wrist Other	93676	Adjustment: Age/weight/height/ ethnicity/years since menopause/ physical function/exercise/ current smoking/CVD/use of analgesic or narcotic/previous fracture
Ziere et al. [55], the Netherlands	CH	All persons (55 years and older) enrolled in the Rotterdam study	SSRI, TCA, Other	Non-vertebral	7983	Adjustment: Age/sex/depression during follow up period/disability category/lower-limb disability
Nurminen et al. [56], Finland	CH	Elderly population (65 years and older) living in the municipality of Lieto, South-Western Finland	AD	Any site	1177	Adjustment: Age
Huyberchts et al. [57], Canada	CH	Elderly patients (65 years and older) newly admitted in a nursing home in the province of British Columbia	AD	Femur	10900	Adjustment: Age/sex/calendar year/level of care assigned at the time of admission to a nursing home/clinical conditions/psychiatric comorbidity/other comorbidity condition/Charlson comorbidity index/number of physician visits

Table 1 (continued)

References	Design study	Population	Exposure	Outcome	Cases/ controls or cohort size	Matching and adjustment factors
						for any reason/number of hospital admissions for any reason and of any length/number of prescription drugs/prior specialist care
Diem et al. [58], USA	CH	Community-dwelling women (65 years and older) from 4 US clinical centers recruited for participation in the SOF	SSRI, TCA	Non-vertebral; hip; wrist	8217	Adjustment: Age/Health status/IADLs/ ability to rise from a chair/m-MMSE/ smoking/ alcohol use/estrogen use/ bisphosphonate use/ benzodiazepine use/thiazide use/proton pump inhibitor use/oral steroid use/weight/GDS score/ walks for exercise/history of prior fracture/total-hip BMD
Gagne et al. [59], USA	CH	Elderly (mean age: 76 years) Medicare beneficiaries from 2 US states	SSRI, TCA, Other	Non-vertebral; hip; humerus; pelvis; radius	10844	Adjustment: Age/sex/race/health service-utilization information/ Charlson comorbidity index score/psychiatric disorders/risk factors for fracture

CC case–control study, *CH* cohort study, *AD* antidepressant, *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant, *GPRD* General Practice Research Database, *IADL* independent activities of daily living, *m-MMSE* modified Mini-Mental State Examination, *GDS* geriatric depression scale, *BMD* bone mineral density, *SOF* Study of Osteoporotic Fractures, *BMI* body mass index, *NSAIDs* non-steroidal anti-inflammatory drugs, *DMARDs* disease-modifying anti-rheumatic drugs, *VHA* Veterans Health Administration, *ADL* activities of daily living, *CVD* cardiovascular disease, *MEPS* Medical Expenditure Panel Survey, *OSSO* Observational Study of Severe Osteoporosis, *WHI* Women's Health Initiative Observational Study

Table 2 Summary of the results of the meta-analysis: relative risk of fracture associated with use of any antidepressants in overall and in subgroups defined by characteristics of study design, quality score, confounder adjustment, age, sex, study location, and fracture site

Analyses	Number of studies	Random effects	I^2 statistics (Heterogeneity)	Q test p value
Overall	33	1.39 (1.32–1.47)	84.47	<0.0001
Study design				
CC study	20	1.40 (1.31–1.49)	89.10	<0.0001
CH study	13	1.37 (1.23–1.52)	57.17	<0.01
Quality score				
NOS score <7	8	1.45 (1.23–1.70)	66.44	<0.01
NOS score ≥7	25	1.38 (1.31–1.47)	87.04	<0.0001
Confounder adjustment				
Crude RR	7	1.47 (1.29–1.69)	62.38	<0.05
Adjusted RR	26	1.38 (1.29–1.48)	86.57	<0.0001
Adjusted for BMD				
Yes	4	1.22 (1.04–1.42)	73.69	<0.05
No	28	1.41 (1.33–1.49)	84.98	<0.001
Adjusted for depression				
Yes	6	1.30 (1.15–1.47)	18.82	0.29
No	26	1.41 (1.33–1.50)	87.04	<0.001
Population ≥50 years[a]	32	1.37 (1.27–1.47)	82.31	<0.001
Gender				
Women	6	1.29 (1.16–1.45)	81.60	<0.001
Men	2	1.40 (1.14–1.73)	70.42	0.07
Men and women	24	1.42 (1.33–1.52)	85.75	<0.001
Study location				
USA	10	1.36 (1.23–1.50)	59.55	<0.01
International	23	1.41 (1.32–1.51)	87.97	<0.001
Fracture site				
Non-vertebral fractures	26	1.42 (1.34–1.51)	80.42	<0.0001
Hip fractures	19	1.47 (1.36–1.58)	85.80	<0.0001
Spine fractures	3	1.38 (1.19–1.61)	64.09	0.062

[a] This analysis included studies that included persons aged ≥50 years

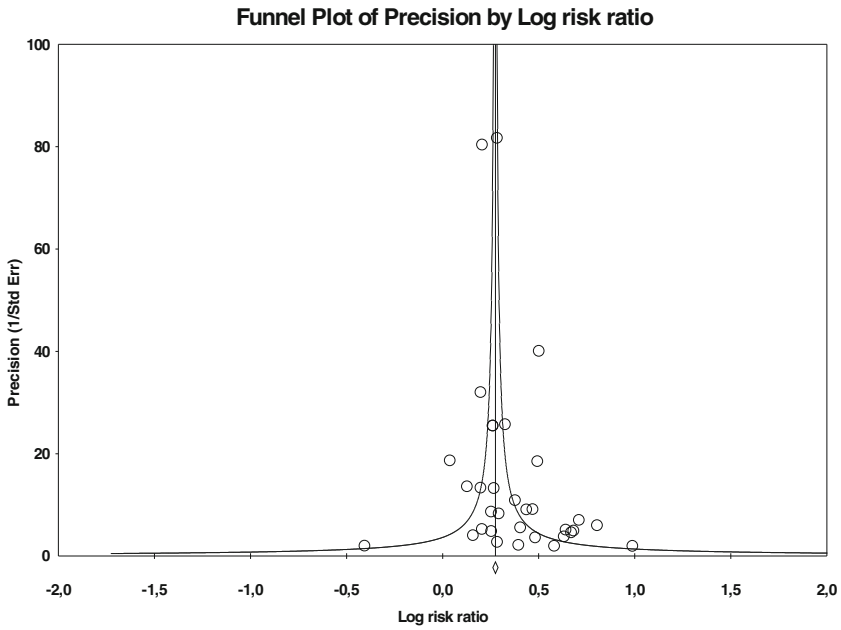

Fig. 2 Funnel plot to assess publication bias. *Circles* indicate individual studies. *Diamond* indicates summary estimates

Table 3 Summary of the results of the meta-analysis: relative risk of fracture associated with use of SSRI in overall and in subgroups defined by characteristics of study design, quality score, confounder adjustment, age, sex, study location, and fracture site

Analyses	Number of studies	Random effects	I^2 statistics (Heterogeneity)	Q test p value
Overall	16	1.61 (1.49–1.74)	89.54	<0.0001
Study design				
CC study	9	1.70 (1.55–1.87)	93.20	<0.0001
CH study	7	1.42 (1.23–1.64)	28.45	0.211
Quality score				
NOS score <7	3	1.44 (1.13–1.83)	11.64	0.322
NOS score ≥7	13	1.63 (1.50–1.78)	91.33	<0.0001
Confounder adjustment				
Crude RR	1	1.54 (1.16–2.03)	NA	NA
Adjusted RR	15	1.62 (1.49–1.77)	90.23	<0.0001
Adjusted for BMD				
Yes	3	1.51 (1.17–1.96)	41.10	0.18
No	12	1.62 (1.49–1.76)	92.08	<0.001
Adjusted for depression				
Yes	5	1.41 (1.21–1.65)	40.55	0.15
No	10	1.69 (1.54–1.87)	92.61	<0.001
Population ≥50 years[a]	10	1.56 (1.38–1.77)	90.5	<0.001
Gender				
Women	3	1.33 (1.08–1.63)	0	0.86
Men	2	1.69 (1.30–2.20)	0	0.92
Men and women	10	1.68 (1.51–1.86)	92	<0.001
Study location				
USA	7	1.41 (1.23–1.61)	45.68	0.09
International	9	1.75 (1.58–1.94)	93.37	<0.001
Fracture site				
Non-vertebral fractures	12	1.65 (1.44–1.89)	92.87	<0.0001
Hip fractures	9	1.64 (1.42–1.89)	91.23	<0.0001
Spine fractures	2	1.22 (1.05–1.42)	0	0.805

NA not applicable

[a] This analysis included studies that included persons aged ≥50 years

1.40, 95%CI 1.29–1.51]; [For non-vertebral fractures: RR= 1.42, 95%CI 1.27–1.58]; [For hip fractures: RR=1.43, 95%CI 1.28–1.61]; Table 4). As well as for studies reporting specifically data on SSRI use than for studies reporting data on TCA use, heterogeneity was large. Restricting the analysis to the studies that scored ≥7 on the quality score or to the studies reporting adjusted RR or to the studies including persons aged ≥50 years did not alter the results (Tables 3 and 4). In addition, a less pronounced increase in fracture risk associated with SSRI or TCA use was observed in all subgroups, particularly in studies with cohort design, adjustment for depression or BMD, including women only, and conducted in USA. Moreover, the results were unchanged when individual trials were removed singly as well as for studies reporting specifically data on SSRI use than for studies reporting data on TCA use (yielding 16 sensitivity models for studies reporting data on SSRI use and 14 sensitivity models for studies reporting data on TCA use).

Discussion

This meta-analysis is a comprehensive examination of the effect of antidepressants, including TCAs and SSRIs, on fracture risk at any site, and also specifically on non-vertebral, hip, and spine fractures, based on all available cases–controls and cohort studies that were conducted in a wide range of populations and geographic regions. Our results indicate that antidepressants use is associated with a moderate and clinically significant increase in the risk of fractures of any type. The increase in risk was consistent in

Table 4 Summary of the results of the meta-analysis: relative risk of fracture associated with use of TCA in overall and in subgroups defined by characteristics of study design, quality score, confounder adjustment, age, sex, study location, and fracture site

Analyses	Number of studies	Random effects	I^2 statistics (Heterogeneity)	Q test p value
Overall	14	1.40 (1.29–1.51)	81.21	<0.0001
Study design				
CC study	8	1.46 (1.34–1.58)	83.16	<0.0001
CH study	6	1.21 (1.05–1.40)	57.79	<0.05
Quality score				
NOS score <7	2	1.12 (0.89–1.40)	85.15	<0.01
NOS score ≥7	12	1.43 (1.33–1.54)	76.46	<0.0001
Confounder adjustment				
Crude RR	2	1.57 (1.25–1.97)	33.39	0.22
Adjusted RR	12	1.38 (1.27–1.50)	83.54	<0.0001
Adjusted for BMD				
Yes	3	1.28 (1.01–1.63)	56.35	0.10
No	11	1.41 (1.30–1.53)	83.88	<0.001
Adjusted for depression				
Yes	3	1.31 (1.06–1.61)	18.14	0.30
No	11	1.41 (1.30–1.54)	84.52	<0.001
Population ≥50 years[a]	9	1.39 (1.22–1.57)	75.01	<0.001
Gender				
Women	2	1.26 (1.004–1.57)	23.75	0.25
Men	1	2.39 (1.23–4.65)	NA	NA
Men and women	11	1.41 (1.30–1.53)	84	<0.001
Study location				
USA	6	1.32 (1.15–1.50)	76.98	<0.01
International	8	1.44 (1.31–1.59)	82.57	<0.001
Fracture site				
Non-vertebral fractures	11	1.42 (1.27–1.58)	81.89	<0.0001
Hip fractures	9	1.43 (1.28–1.61)	80.62	<0.0001
Spine fractures	0	–	–	–

NA not applicable

[a] This analysis included studies that included persons aged ≥50 years

sensitivity analyses, in which studies were included on the basis of different criteria.

The exact mechanism by which antidepressant drugs increase the risk of fracture in the elderly has not yet been elucidated, and the mechanism may differ across the classes of antidepressants. TCAs have been postulated to increase the risk of fractures due to an increased risk of falls, attributed to sedation, orthostatic hypotension, and/or confusion [4, 5]. SSRIs have also been associated with an increased risk of fractures, due to an increased tendency to falls [5, 6]. In addition, the recent description of functional serotonin transporters in osteoblasts, osteoclasts, and osteocytes raises the possibility that serotonin transporters may play a role in bone metabolism and that medications that affect these transporter systems may also affect bone metabolism [9–11, 60].

Despite emerging evidence suggesting antidepressant medications as potential risk factors for osteoporotic fractures, significant limitations persist in the literature. As is the case in any observational study of adverse events of drugs, even when controlling for a large number of risk factors, the possibility of confounding due to unmeasured risk factors remains. A particular concern is confounding by indication which may affect the results of this meta-analysis. In fact, confounding by indication may be an important cause of the observed association since the medications are often prescribed for depressive symptom which have been associated with lower BMD, increased risk of falls, and increased risk of fractures in some studies [61–71]. A decrease in BMD during a depression may be the consequence of immobilization during the disease rather than an effect of the prescribed antidepressants per se. The disease or its

complications rather than the drug may therefore be responsible for the increased fracture risk. This would lead to an exaggeration of the effect of antidepressants on fracture risk. In our subgroup analysis, the increase in fracture risk associated with any antidepressant, SSRI, and TCA persist when the analysis was confined to the studies that adjusted for depression, although it was less pronounced to that observed in the overall analysis. This result suggests that antidepressants may exert an increased risk of fracture independent of depression. In addition, we observed a less pronounced increase in fracture risk in the studies that adjusted for BMD.

Moreover, although confounding variables were adjusted in most of the studies included in this meta-analysis, the types of confounders varied among the trials. It seems that no consensus exist in the covariates used in risk adjustment. Many investigations have been performed using administrative [26, 28, 31, 33, 36, 37, 45, 46] that do not contain objective measures of variables that may confound or modify the relationships between medication use and risks for fracture, such as cognition, depressive symptoms, physical function, and bone mineral density [33, 36, 40, 45]. In addition, medical conditions associated with increased loss of BMD, such as chronic obstructive pulmonary disease, liver disease, and diabetes mellitus may predispose to depression and subsequent prescription of antidepressants [72–80]. Although controlling for such factors is possible, it is difficult to control for their severity. However, as our assessment of study quality included adjustment for known confounders, the bias due to residual confounding may be partially captured in our analysis.

Another concern about studies in the literature pertains to the assessment of medication use. Indeed, many studies have been performed using administrative databases providing records that medications were dispensed but not that they were actually consumed, thereby may lead to potential misclassification of exposure. Moreover, others have relied on participating subjects' self-report of medication use. In addition, various methods for assessing depression were used in the studies published and some studies may not account for chronicity and severity of prior depression. Most population-based studies have relied on measures of depressive symptoms rather than actual diagnosis of depression made with diagnostic interviews. This may have introduced bias in the results published.

Our study has some potential limitations. First, the studies included in this meta-analysis mainly focused on evaluating the risk of fracture with use of TCAs or SSRIs, the two most widely prescribed classes of antidepressant medications. Few studies looked at other classes of antidepressants, so that we limited our analyses to these two classes of antidepressants. In this meta-analysis, strong evidence of heterogeneity was present. Indeed, the studies included in our analysis were conducted among participants with different ethnicities, sexes, ages, durations of antidepressants use, and in different settings with different study designs. Therefore, we used the random effects model instead of the fixed effects. As already mentioned, meta-regression analysis was not performed because of the unavailability of some important variables in the original studies. However, to investigate sources of heterogeneity, subgroup analyses were performed according to demographic or clinical variables such as sex, age, adjustment for BMD or depression, study design, study location, and quality score. However, in most of the subgroups analyses, heterogeneity persisted, except when analyses were restricted for studies which adjusted for depression. This was observed for analyses of risk associated with use of antidepressants as well as for analyses of risk associated with use SSRI or TCA. Moreover, for the analyses of risk of fracture associated with use of SSRI, no evidence of heterogeneity was found when the analyses were restricted to cohort studies, to studies which adjusted for BMD, and to studies limiting to either women or men only. For the analyses of risk of fracture associated with use of TCA, no statistically significant heterogeneity was observed when the analyses were restricted to studies adjusting for BMD and to studies limiting to women only.

Furthermore, we were not able to study the effect of other important sources of heterogeneity such as different doses of psychotropic drugs and duration of use, as information was available in only a few studies. In addition, when there were available, we were unable to assess the effect of these variables because trials reporting this information used mixed categories of defined daily doses or of duration. Lastly, some medications may affect bone strength, such as glucocorticoids. Indeed, the evidence suggests that glucocorticoid-induced osteoporosis is the most common form of secondary osteoporosis and that these drugs are associated with increased risk of fracture [81, 82]. In our meta-analysis, some studies did not control for these drugs, and consequently, we cannot rule out the possibility that the association observed was confounded by these medications, as well as by other concomitant medications, particularly drugs acting on the central nervous system.

Our study has also strength. To our knowledge, this meta-analysis is the first to date to study the effects of both SSRIs and TCAs according to different types of fractures. Moreover, our results are robust and consistent, as shown by our subgroups and sensitivity analysis

Given the high prevalence of antidepressants use among the general population, our findings have a potentially important public health impact. Physicians treating elderly depressive patients should be aware of unfavourable long-term effects associated with these drugs. Our results add to the growing list of problems associated with the use of psychotropic medications in elderly people and suggest that

changes are needed in how doctors manage psychological problems in elderly patients. This study provides further evidence that the sedative and autonomic effects of the two most frequently prescribed antidepressants increase the older patient's risk of falling and subsequent fracture. 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 clinical implication is that older patients starting treatment with either tricyclic antidepressants or selective serotonin reuptake inhibitors will have an increased risk of fracture and that patients should be aware of this increased risk so that they can take appropriate precautions.

A major challenge in future studies addressing the influence of antidepressants on fracture risk is to deal with confounding by indication or severity, a factor which was not adequately controlled for in earlier studies. Further exploration of the role of the confounders, notably targeting the separation of the effects of treatment from the effects of depression, is necessary. More rigorous evaluation of the influence of antidepressants use on fracture adjusting for depressive symptoms, diagnoses of major depression, and other variables that could explain this association is warranted. Further studies are needed to evaluate the relative contribution of disease-related and treatment-related effects to the increased risk of falls and fractures. Additional clinical studies including longitudinal studies of antidepressants, BMD, bone turnover markers, and fracture outcomes would be useful future steps in order to expand our understanding of the possible effects of antidepressants use on bone health.

Conclusion

We conclude from the present meta-analysis that both SSRIs and TCAs are associated with a moderate and clinically significant increase in the risk of fractures of all types. These results are clinically relevant and should be addressed seriously given the high prevalence of use of antidepressants among the general population, and in particular, among the frail older population.

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Appendix

Search strategy for MEDLINE (OVID)

1 exp antidepressive agents/
2 antidepressive agent$.tw.
3 antidepressant$.tw.
4 anti-depressant$.tw.
5 selective serotonin-reuptake inhibitor$.tw.
6 tricyclic antidepressant$.tw.
7 monoamine oxidase inhibitor$.tw.
8 psychotropic drug$.tw.
9 or/1-8
10 exp fractures,bone/
11 fracture$.tw.
12 10 or 11
13 exp osteoporosis/
14 osteoporosis.tw
15 13 or 14
16 fall$.tw.
17 exp bone density/
18 bone density.mp.
19 bone loss.mp.
20 bone mass.mp.
21 17 or 18 or 19 or 20
22 9 and 12
23 9 and 15
24 9 and 16
25 9 and 21
26 22 or 23 or 24 or 25

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