ORIGINAL RESEARCH ARTICLE

Drug Safety 2007; 30 (2): 171-184
0114-5916/07/0001-0171/$44.95/0

Psychotropic Medications and the Risk of Fracture

A Meta-Analysis

Bahi Takkouche,[1] *Agustín Montes-Martínez*,[1] *Sudeep S. Gill*[2] and *Mahyar Etminan*[3]

1 Department of Preventive Medicine, Faculty of Medicine, University of Santiago de Compostela, Santiago de Compostela, Spain

2 Departments of Medicine and Community Health and Epidemiology, Queen's University, Kingston, Ontario, Canada

3 Center for Clinical Epidemiology and Evaluation, Vancouver General Hospital, Vancouver, British Columbia, Canada

Abstract

Background: Older adults throughout the developed world are at significant risk of osteoporotic fractures. Many studies have examined the relationship between the use of psychotropic medications and the risk of fractures, but these studies have reported conflicting results.

Purpose: To resolve discrepancies, we carried out a meta-analysis to assess the risk of fractures among users of several classes of psychotropic drugs.

Data sources: We retrieved studies published in any language by systematically searching MEDLINE, LILACS, EMBASE and ISI Proceedings databases and by manually examining the bibliographies of the articles retrieved electronically as well as those of recent reviews.

Study selection: We included 98 cohort and case-control studies, published in 46 different articles, that reported relative risk (RR) estimates and confidence intervals (CIs) or sufficient data to calculate these values.

Data synthesis: Study-specific RRs were weighted by the inverse of their variance to obtain fixed- and random effects pooled estimates. The random effects RR of fractures was 1.34 (95% CI 1.24, 1.45) for benzodiazepines (23 studies), 1.60 (95% CI 1.38, 1.86) for antidepressants (16 studies), 1.54 (95% CI 1.24, 1.93) for non-barbiturate antiepileptic drugs (13 studies), 2.17 (95% CI 1.35, 3.50) for barbiturate antiepileptic drugs (five studies), 1.59 (1.27, 1.98) for antipsychotics (12 studies), 1.15 (95% CI 0.94, 1.39) for hypnotics (13 studies) and 1.38 (95% CI 1.15, 1.66) for opioids (six studies). For non-specified psychotropic drugs (10 studies), the pooled RR was 1.48 (95% CI 1.41, 1.59).

Limitations: Main concerns were the potential for residual confounding and for publication bias.

Conclusion: Globally, the increase in the risk of fractures among psychotropic drug users is moderate. Further research is needed, especially to examine high-risk populations and newer medications. Future studies should be prospective and emphasise control of confounding bias.

Background

As aging populations around the world grow, osteoporotic fractures and hip fractures in particular are becoming an increasingly important public health concern. Worldwide projections estimate that the annual number of hip fractures will have swelled to 2.6 million by the year 2025 compared with 1.3 million in 1990.[1] In the US, the number of hospital admissions for hip fracture increased from 230 000 to 340 000 between 1988 and 1996.[2]

Once a fracture has occurred, it often represents a devastating milestone event in the life of an older adult, frequently leading to disability and death.[3] About a quarter of women and a third of men die within a year after a hip fracture, the worst kind of fracture that may occur in elderly people.[4] Many others are institutionalised. The total direct medical costs for osteoporotic fractures among American postmenopausal women, estimated in 1994, represent approximately $US61 billion.[5] Effective strategies to prevent fractures in older adults are clearly needed.

Although unintentional injuries (fractures) may be caused by a variety of causes including car crashes, approximately 95% of hip fractures among older adults are due to falls and some of these falls may be preventable.[6] Previous research has suggested that reducing the burden of psychotropic medications may improve the risk of falls.[7] Although fractures are related to falls, they should be considered as distinct events and should be studied separately for several reasons. First, one should bear in mind that approximately a third of adults >65 years of age fall at least once every year and, among those who fall, only 5% will experience a fracture.[8,9] Secondly, although some drugs may change the risk of fractures by changing the risk of falls, other drugs, such as diuretics, have an effect on fractures without exerting their action on falls, but rather on the calcium balance and osteoporosis.[10] Finally, in most databases, fractures are more accurately captured than simple falls and their mechanism of injury or E-codes are generally not mentioned. A diagnosis of fracture is much more accurate than that of fall, which allows a greater comparability between different studies.

Psychotropic medications are widely used. About 5.5% of adults in the US use them on a regular basis.[11] The consumption of some psychotropic drug classes, such as antidepressants, is expected to rise as only half of the cases of depressive illness receive adequate medication.[12]

Many observational studies have examined the relationship between the use of psychotropic drugs and fractures. The large majority have focused on the risk derived from the use of benzodiazepines. Although the results of some studies globally suggest that patients who are prescribed these medications have a higher risk of fractures,[3] other recent studies have failed to demonstrate a significant increase in the risk.[13,14] A meta-analysis that reviewed studies published before 1996 showed that the risk of falls was slightly increased among psychotropic drug users.[15] To date, no comprehensive meta-analysis has addressed the risk of fracture associated with the use of psychotropic medications.

Therefore, we conducted a meta-analysis with the objective of measuring this risk among users of several defined classes of psychotropic drugs: benzodiazepines, antidepressants, antiepileptic drugs, antipsychotics, hypnotics and opioids. In this work, we followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[16]

Literature Search Methodology

Study Selection

We conducted a systematic computerised MEDLINE search from 1966 to December 2005 to identify all potentially eligible studies. A study was defined as an analysis of exposure to any psychotropic medication; thus, one publication could report several studies. We applied the following algorithm using both Medical Subject Heading (MeSH) terms and free text words: (‘fracture*’ OR ‘fall*’) AND (‘Central Nervous System agent*’ OR ‘psychotropic*’ OR ‘antidepressant*’ OR ‘anticonvulsant*’ OR ‘antiepileptic*’ OR ‘barbitur*’ OR ‘neuroleptic*’ OR ‘psychotropic*’ OR ‘benzodiazepine*’ OR ‘antipsychotic*’ OR ‘hypnotic*’).

To identify as many relevant studies as possible, we performed a second search, introducing the

words from the initial search in an unstructured fashion. We used similar strategies to search EMBASE (1980–December 2005) and LILACS (Latin American and Caribbean Health Sciences Literature) databases. We searched meeting abstracts using the ISI Proceedings database from its inception in 1990 to 2005. We also examined the references of every article retrieved and those of recent reviews and monographs on the topic.[3] We included any relevant article, regardless of the language of publication. Unpublished studies were not considered. All searches were carried out independently by two epidemiologists (Dr Takkouche and Dr Montes-Martínez) and differences were settled by consensus.

Inclusion Criteria

Studies were included if they met the following criteria: (i) they presented original data from case-control or cohort studies; (ii) the outcome of interest was clearly defined as fracture (falls not followed by fractures were not included); (iii) the exposure of interest was a psychotropic medication; and (iv) they provided relative risk (RR) estimates and confidence intervals (CIs) or provided enough data to calculate them (raw data, p-value or variance estimate). If data were duplicated in more than one study, the most recent study was included in the analysis. When a study used more than one control group, we reported the average RR estimate.[17]

We excluded those studies that did not provide adjusted or crude data of RR and those studies that were cross-sectional in nature.

Data Collection

We developed a questionnaire and recorded study name, year of publication, study design, sample size (cases and controls or cohort size), type of controls for case-control studies (hospital or population controls), variables used for adjustment, matching or restriction, and association measures that compared ever users of psychotropic drugs with 'never users'.

Although the term 'hypnotics' may have referred in part to benzodiazepines, many studies did not specify the individual drugs included under this term. Therefore, studies on hypnotics were categorised separately from those focused on benzodiazepines.

Quality Assessment

Quality assessment was based on a 10-point scale that included elements of previous published scales, adapted to the needs of this meta-analysis.[18,19] Each study was scored from 0 to 10 according to five methodological characteristics. Each item was scored from 0 to 2. Specifically, for case-control studies we determined: (i) whether participation rate was at least 80% in both groups; (ii) whether cases were incident or prevalent; (iii) whether controls were taken from the general population or from one or various hospitals; (iv) whether potential confounding for sex, age and cognitive and physical impairment was corrected or prevented through matching or adjustment; and (v) whether duration of exposure to psychotropic medications was accurately presented. For cohort studies, in addition to the criteria mentioned previously that were not specific of case-control designs, we determined whether loss to follow-up was <20% of the initial cohort size and whether efforts were made to assure that no substantial change in the exposure of the cohort occurred during follow-up.

For stratification purposes, studies that scored ≥7 out of 10 were considered of high quality. The results with other cut-off points were similar and were not considered further. The complete protocol for quality scoring is available upon request.

Data Analysis

We weighted the study-specific adjusted log odds ratios (ORs) for case-control studies and log RRs for cohort studies by the inverse of their variance to compute a pooled RR and its 95% CI. We considered the OR to be an approximation of the RR. We presented both fixed and random effects pooled estimates, but preferentially used the latter when heterogeneity was present, as it represents a more conservative approach. We used the DerSimonian and Laird's Q test to check for heterogeneity.[20] To quantify this heterogeneity, we calculated the proportion of the total variance due to between-study variance (Ri statistic).[21]

To further explore the origin of heterogeneity, we restricted the analysis to subgroups of studies defined by characteristics such as case-control or cohort design, adjustment factors and source of controls (population or hospital based). We carried out separate analyses for each class of psychotropic medication. In addition, in those studies where multiple fracture sites were analysed and no overall RR or OR was given, the reported results were pooled.

We used funnel plots to assess publication bias graphically and completed this assessment by carrying out more formal testing using the asymmetry test proposed by Egger et al.[22]

When publication bias was detected by the graphical and test methods, we performed a sensitivity analysis and recalculated the pooled RR using three assumptions: (i) published case-control studies included in our meta-analysis represent only half of the studies ever conducted; (ii) the remaining unpublished studies have found no association between psychotropic medications and fractures (i.e. RR = 1) and; (iii) the unpublished studies included as many cases and controls as the average of the published ones.

We performed our analyses with the software HEpiMA version 2.1.3[23] and STATA, version 8.0 (Stata Corp, College Station, TX, USA).

Results

We identified 46 publications with 98 studies (carried out in 15 countries) that met our inclusion criteria and were included in the final analysis (table I). Two extensively cited studies were excluded from this meta-analysis,[24,25] the first one because its unexposed group (reference group) was composed of patients taking triazolam and the second because it did not present any RR estimate. We found 23 studies on benzodiazepines,[14,17,26-46] 16 studies on antidepressants,[17,26,30-32,36,41,42,44,47-53] 18 studies on antiepileptic drugs,[17,38-40,43,44,53-62] 12 studies on antipsychotics,[17,26,27,30-32,36,38,41,42,47,53] 13 studies on hypnotics[13,17,26,27,30,32,41,42,51,53,54,57,63] and 6 studies on opioids.[17,30,41,44,64,65] Ten studies dealt with unspecified psychotropic medications.[30-32,47,55,56,63,66-68]

Benzodiazepines

The 16 case-control studies[14,17,26-39] **1** and seven cohort studies[40-46] **2** that dealt with the use of benzodiazepines were published between 1987 and 2005. Ten case-control studies used population controls and six used hospital-based controls. Globally, there was a moderate but significant increase in the risk of fractures among benzodiazepine users. Compared with non-users, the random effects pooled RR of fractures among benzodiazepine users was 1.34 (95% CI 1.24, 1.45) [table II]. We did not find any evidence of a substantial difference in pooled RRs according to study design (case-control vs cohort), type of control (population-based vs hospital-based) or duration of action (long-term vs short-term benzodiazepine therapy).

Heterogeneity was moderate to large among case-control studies (Ri = 0.68) and all studies analysed together (Ri = 0.57), and low among cohort studies. This heterogeneity subsided when studies were stratified by duration of action of the medication.

The funnel plot did not show any marked asymmetry and thus did not provide evidence of publication bias (data not shown). The Egger's test of asymmetry yielded a p-value of 0.187, confirming the absence of evidence of publication bias.

Stratifying the analysis by study quality score did not reveal any substantial difference in the pooled RRs between studies with scores of ≥7 (RR = 1.32; 95% CI 1.20, 1.44) and the remainder (RR = 1.42; 95% CI 1.21, 1.67).

Limiting the analyses to hip fractures alone did not produce any change in the results.

The two studies that provided data for the newer benzodiazepine receptor agonists (zolpidem and zopiclone) yielded a pooled OR of 1.28 (95% CI 0.88, 1.85).[14,36]

1 Data from case-control studies on study-specific odds ratios (with 95% CIs) for fractures with psychotropic drugs are available as supplementary material from URL: http://drugsafety.adisonline.com (table I).
2 Data from cohort studies on study-specific relative risks (with 95% CIs) for fractures with psychotropic drugs are available as supplementary material from URL: http://drugsafety.adisonline.com (table II).

Table I. Characteristics of studies of fractures and psychotropic drugs

Study, year	Type of control	Population (y)	Type of fracture	Matching, adjustment and restriction factors	Cases/controls or cohort size
Case-control studies					
Brocklehurst et al.,[54] 1977	H	>64	Femoral neck	Age	352/61
Paganini-Hill et al.,[55] 1981	H	Women <80	Hip	Age, sex, race, date of entry in the community	91/182
Rashiq and Logan,[63] 1986	P	>60	Femoral neck	Age, sex	102/204
Sernbo et al.,[27] 1987	P	>64	Hip	Age, sex	351/445
Ray et al.,[26] 1987	P	>64	Hip	Age, sex, race, nursing home status, year	1021/5606
Taggart,[66] 1988	P	Women >73	Hip	Sex, family practice	282/145
Stevens and Mulrow,[29] 1989	H	Not specified	Hip	Age, sex, weight, cognition, stroke, diuretics, other drugs	173/134
Ray et al.,[28] 1989	P	>64	Hip	Age, sex, year, nursing home status	4501/24041
Ray,[47] 1991	P	>64	Hip	Age, sex, calendar year, nursing home residence, hospitalisation, use of specific medications	4501/24041
Jensen,[30] 1991	P	>59	Femoral neck	Age, sex, residency, number of hospital admissions within the last 2 years	200/200
Heidrich,[56] 1991	P	>49	Hip	Age, sex, alcoholism, corticosteroid use, obesity, diuretic use, disease antecedents	462/462
Jackson,[57] 1992	P	Men	Hip	Age, sex, race, living status (institution, nursing home)	28/28
Shorr,[64] 1992	P	>64	Hip	Age, sex, hospitalisation date, nursing home status, cardiovascular drugs, psychotropics	4500/24041
Cumming and Klineberg,[31] 1993	P	>64	Hip	Age, sex, type of residence	209/207
Lichtenstein et al.,[32] 1994	H	>64	Hip	Age, sex, vision impaired, ambulatory status, dementia, confusion, weight	129/234
Herings et al.,[33] 1995	P	>54	Femur	Age, sex, pharmacy, use of medications, epilepsy, Parkinson's disease, anaemia, organic brain syndrome, hypertension, osteoporosis, duration of hospitalisation	493/1311
Poor et al.,[58] 1995	P[a]	White men >35	Hip	Age, sex, race	232/232
Herings et al.,[48] 1996	P	>45	Femur	Age, sex, pharmacy, physician	386/386
Grisso et al.,[67] 1997	P	Men >44	Hip	Age, sex, BMI, height, physical activity, smoking, chronic illnesses, lower limb dysfunction	356/402

Continued next page

Table I. Contd

Study, year	Type of control	Population (y)	Type of fracture	Matching, adjustment and restriction factors	Cases/controls or cohort size
Gambassi et al.,[49] 1998	H	Elderly	Femur	Not given	8851/35086
Liu et al.,[50] 1998	P	>65	Hip	Age, sex, comorbidity, previous use of medications	8239/41195
Scane et al.,[59] 1999	H	<81	Vertebral	Age	91/91
Schwab et al.,[34] 2000	H	Community-dwelling patients	Hip	Age, sex	82/82
Sgadari et al.,[35] 2000	P	>64	Femur	Age, sex, state, falls, osteoporosis, use of medications, ADL score, cognitive score, comorbidity	9752/38564
Wang et al.,[36] 2001	P	>64	Hip	Age, sex, race, use of medications, comorbidity score, hospital days, nursing home days	1222/4888
Pierfitte et al.,[14] 2001	H	>65	Hip	Age, sex, week of admission	245/817
da Silva Freire Coutinho and Dutra Da Silva,[37] 2002	H	>59	Any type	Age, sex, education, hospital, smoking, alcohol, use of medications, falls, comorbidity	169/315
Partanen et al.,[51] 2002	P	Women 63–84	Hip	Age, sex	102/40
Bischof et al.,[60] 2002	H	Black patients with cerebral palsy, 6–29	Long bones	Age, race	20/20
Ryder et al.,[61] 2003	H	Adults with mental retardation	Appendicular	Age, sex, ambulatory status, ethnicity	23/23
Hubbard et al.,[52] 2003	P	General population	Hip	Age, sex, falls, BMI, use of medications, comorbidity, blood pressure	16341/29889
Schlienger et al.,[38] 2004	P	30–79	Any type	Age, sex, practice, calendar time, comorbidity, smoking, BMI, medical conditions, medications	30601/120819
Vestergaard et al.,[39] 2004	P	No age limits, men and women	Any type	Age, sex, comorbidity, epilepsy, previous fracture, use of antiepileptic drugs and corticosteroids, income, prior fractures, working status, marital status, contact with general practitioners	124655/373962
French et al.,[17] 2005	H	No age limits, men and women	Hip	Age, sex	2212/2212

Continued next page

Table I. Contd

Study, year	Type of control	Population (y)	Type of fracture	Matching, adjustment and restriction factors	Cases/controls or cohort size
Hugenholtz et al.,[53] 2005	H	General practice patients	Hip	Age, sex, practice	22250/22250
Cohort Studies					
Annegers et al.,[62] 1989		Patients with seizures >35	Hip	Not given	30/467
Cummings et al.,[40] 1995		White women >64	Hip	Age, sex, race, history of fractures, calcaneal bone density	
Guo et al.,[41] 1998		>74	Hip	Age, sex, education, residence, ADL limitation, cognitive impairment, history of stroke and tumours	134/1608
Jacqmin-Gadda et al.,[42] 1998		>64	Hip, Non-hip	Age, sex, BMI, smoking, alcohol consumption, profession, participation in sports, use of medication, visual or auditory impairment	306/3216
Forsén et al.,[13] 1999		Women >49	Hip	Age, sex, mental distress, use of medication, BMI, smoking, physical inactivity, impairment due to physical illness	329/18612
Vestergaard et al.,[43] 1999		Adults	Any	Age, sex, time since diagnosis, use of medication, family history of fractures, sunbathing	386/999
Bae et al.,[68] 2002		Women >65	Hip	Age, sex, BMI, alcohol consumption	56/6043
Ensrud et al.,[44] 2003		White women >64	Any non-spine, Hip	Age, sex, race, health status, walking for exercise, smoking, functional impairment, cognitive function, depression, weight change, gait speed, femoral neck bone density	1256/8127
Hasselman et al.,[45] 2003		White women >64	Foot	Age, sex, race, distal radial bone mineral density, previous fracture after the age of 50 years	301/9659
Card et al.,[65] 2004		Patients with inflammatory bowel disease	Hip	Age, sex, practice, corticosteroid use	295/99467
Wagner,[46] 2004		>64	Hip	Age, sex, race, use of medication, dementia, epilepsy, hospitalisation in the previous 6 months	2312/125203

a Population-based nested case-control study.

ADL = activity of daily living; **BMI** = body mass index; **H** = hospital-based controls; **P** = population-based controls.

Table II. Pooled relative risks (RRs) and 95% CIs of fractures and benzodiazepines

Types of studies	Number of studies	Fixed effects	Random effects	Ri	Q test p-Value
All	23	1.29 (1.24, 1.35)	1.34 (1.24, 1.45)	0.57	0.00001
Cohort only	7	1.30 (1.18, 1.43)	1.31 (1.18, 1.45)	0.10	0.36
CC only	16	1.29 (1.23, 1.35)	1.36 (1.23, 1.51)	0.68	0.0001
Population-based CC	10	1.28 (1.22, 1.34)	1.33 (1.20, 1.49)	0.73	0.0001
Hospital-based CC	6	1.47 (1.22, 1.78)	1.46 (1.09, 1.96)	0.53	0.08
Short-term benzodiazepine	9	1.24 (1.16, 1.33)	1.25 (1.14, 1.37)	0.30	0.23
Long-term benzodiazepine	10	1.29 (1.21, 1.38)	1.31 (1.20, 1.43)	0.30	0.19
Hip fracture	19	1.29 (1.23, 1.36)	1.38 (1.24, 1.54)	0.65	0.00001
Zolpidem and zopiclone	2	1.28 (0.88, 1.85)	1.34 (0.68, 2.66)	0.70	0.06

CC = case-control studies; **Ri** = proportion of the total variance due to between-study variance.

Antidepressants

Sixteen studies (13 case-control[17,26,30-32,36,47-53] and three cohort[41,42,44]) dealt with antidepressants. The random effects pooled RR from table III indicate a moderate increase in the risk of fractures (RR = 1.60; CI 1.38, 1.86). Cohort studies showed a pooled RR that was lower than that of case-control studies. Heterogeneity was large among case-control studies but absent among cohort studies. The funnel plot shows substantial asymmetry (data not shown) confirmed by statistical testing (Egger's test p-value: 0.027). These findings suggest that there is a deficit of publications showing no effect and that are relatively imprecise. However, our calculations, based on the assumption that only half of the existing case-control studies were published, show that even in this situation, the RR would still be 1.22 with 95% CI 1.11, 1.33. Publication bias, although plausible, would then explain only part of the excess pooled risk of fractures we document among antidepressants users.

Restricting the analysis to the ten studies that scored ≥7 points on the quality scale did not alter the results (RR = 1.60; 95% CI 1.31, 1.94).

Several studies have examined the risk of fractures among subclasses of antidepressants. Selective serotonin reuptake inhibitors (SSRIs) showed an increase in the pooled risk of fractures that is 33% higher than that of non-SSRI antidepressants, whereas tricyclic antidepressants showed a risk that is similar to that of all antidepressants tested. Many newer antidepressants have not yet been examined.

Antiepileptic Drugs

Globally, the five studies[39,43,54-56] examining barbiturate antiepileptic drugs show a higher increase in the risk of fractures (RR = 2.17; 95% CI 1.35, 3.50) than the 13 studies[17,38-40,43,44,53,57-61] that evaluated non-barbiturate antiepileptic drugs (RR = 1.54; 95% CI 1.24, 1.93) [table IV]. In both drug groups, heterogeneity was large among case-control studies.

Among the studies of non-barbiturate antiepileptics, the six studies that scored ≤6 on the quality scale show a pooled RR that was approximately double than that seen in the seven remaining studies

Table III. Pooled relative risks (RRs) and 95% CIs of fractures and antidepressants

Types of studies	Number of studies	Fixed effects	Random effects	Ri	Q test p-Value
All	16	1.53 (1.48, 1.58)	1.60 (1.38, 1.86)	0.93	0.00001
Cohort only	3	1.28 (1.04, 1.58)	1.28 (1.04, 1.58)	0.00	0.79
CC only	13	1.54 (1.49, 1.59)	1.66 (1.41, 1.96)	0.94	0.00001
Population-based CC	9	1.40 (1.35, 1.45)	1.54 (1.25, 1.90)	0.94	0.00001
Hospital-based CC	4	1.90 (1.79, 2.01)	1.88 (1.73, 2.04)	0.34	0.28
SSRI antidepressant	4	1.84 (1.72, 1.96)	1.91 (1.43, 2.55)	0.95	0.00001
Non-SSRI antidepressant	11	1.32 (1.26, 1.38)	1.44 (1.27, 1.63)	0.77	0.0006
Tricyclic antidepressant	4	1.31 (1.25, 1.38)	1.58 (1.24, 2.00)	0.95	0.00001
Hip fracture	16	1.54 (1.49, 1.59)	1.68 (1.44, 1.96)	0.93	0.00001

CC = case-control studies; **Ri** = proportion of the total variance due to between-study variance; **SSRI** = selective serotonin reuptake inhibitors.

(RR = 2.54; 95% CI 1.47, 4.40 and RR = 1.30; 95% CI 1.03, 1.63, respectively).

The funnel plot shows a deficit of negative or null studies with high variance (data not shown). Publication bias is confirmed by the asymmetry test, which shows a p-value of 0.025. The pooled RR from the sensitivity analysis shows that the effect of non-barbiturate antiepileptic drugs would have been neutral (RR = 1.07; 95% CI 1.02, 1.11), if the assumptions of this sensitivity analysis, explained previously, had been fulfilled.

Antipsychotics, Hypnotics and Opioids

Table V shows that, except when the analysis was restricted to the two cohort studies[41,42] (which showed no significant effect), the pooled RRs from studies on antipsychotics indicate an increase in the risk of fractures of approximately 60% (RR = 1.59; 95% CI 1.27, 1.98). The results are similar across designs (population-based vs hospital-based case-control studies), anatomic sites of the fractures (hip versus all fractures) and quality scoring (quality score of ≥7 versus the rest of studies).

Heterogeneity is large, but restricted to case-control studies. The funnel plot shows some asymmetry with a deficit of negative studies with average precision (data not shown). This asymmetry is confirmed by the borderline significance of the regression test (p-value = 0.042). The sensitivity analysis yielded a pooled RR of 1.09 with 95% CI 1.04, 1.16, which shows that, under the most conservative assumptions, the effect would be small but still significant.

When analysed together, the 13 studies[13,17,26,27,30,32,41,42,47,51,53,54,63] on hypnotic medications and fractures did not show any significant increase in the risk of fractures (random effects pooled RR = 1.15; 95% CI 0.94, 1.39). Heterogeneity was present in the overall analysis (Ri value = 0.89), but subsided when we stratified the analysis by design. Hospital-based case-control studies showed the highest pooled RR in this analysis: 1.53 with 95% CI 1.45, 1.61. In contrast, population-based studies failed to show any significant effect. The funnel plot was asymmetric, an observation that was confirmed by the regression test (p-value = 0.001). The fact that the intercept of this regression

Table IV. Pooled relative risks (RRs) and 95% CI of fractures and antiepileptic drugs

Types of studies	Number of studies	Fixed effects	Random effects	Ri	Q test p-Value
Non-barbiturate antiepileptic drugs					
All	13	1.19 (1.16, 1.23)	1.54 (1.24, 1.93)	0.96	0.00001
Cohort only	4	1.24 (0.98, 1.57)	1.34 (0.96, 1.88)	0.41	0.21
CC only	9	1.19 (1.15, 1.23)	1.64 (1.24, 2.16)	0.97	0.00001
Population-based CC	4	1.19 (1.15, 1.23)	1.49 (1.05, 2.11)	0.98	0.00001
Hospital-based CC	5	1.21 (1.06, 1.37)	2.55 (1.20, 5.42)	0.96	0.00001
Hip fracture	9	1.39 (1.30, 1.49)	1.57 (1.20, 2.05)	0.89	0.00001
Barbiturate antiepileptic drugs					
All	5	3.19 (2.29, 3.41)	2.17 (1.35, 3.50)	0.97	0.007
CC only	4	3.22 (3.02, 3.44)	2.72 (1.84, 4.02)	0.91	0.12
Hip fracture	4	1.71 (1.41, 2.08)	1.87 (1.15, 3.04)	0.77	0.06

CC = case-control studies; **Ri** = proportion of total variance due to between-study variance.

was negative (−2.308) provides evidence that small individual studies are associated with larger effects.[69] The sensitivity analysis also suggested no significant increase in the risk of fractures associated with the use of hypnotics (RR = 1.05; 95% CI 0.95, 1.17). We did not find any meaningful change in the pooled RR when the analysis was stratified by quality score.

The six studies[17,30,41,44,64,65] on opioid medications included in our meta-analysis showed a moderate but significant increase in the risk of fractures, with pooled RRs varying between 1.32 and 1.42. Heterogeneity was present among case-control studies but not among cohort studies. However the small number of studies included in this analysis does not allow firm conclusions regarding the potential of heterogeneity and publication bias.

Among the ten studies[30-32,47,55,56,63,66-68] that examined the risk of fractures associated with the use of unspecified psychotropic medications, the pooled RR was 1.48 (95% CI 1.41, 1.59) with no significant heterogeneity (Q test p-value = 0.08), and no evidence of publication bias.

Discussion

Our results indicate that a variety of commonly prescribed psychotropic medications may exert a moderate and clinically significant increase in the risk of fractures.

Barbiturates show the highest increase in the risk, whereas those psychotropic medications labelled as 'hypnotics' exert a slight effect on hip fractures only. The risk related to the use of antidepressants, antipsychotics, benzodiazepines and non-barbiturate antiepileptics is intermediate between that of barbiturates and that of hypnotics.

Within each type of medication, we observed a constant pattern: cohort studies yielded the lowest pooled RR whereas hospital-based case-control studies yielded the highest one. Results of hospital-based case-control studies should be treated with great caution because of their high potential for bias.[3]

In this meta-analysis, we were not able to study the effect of different doses of psychotropic drugs, as information was available in only a few studies.

Table V. Pooled relative risks (RR) and 95% CI of fractures and other psychotropic drugs (antipsychotics, hypnotics and opioids)

Types of studies	Number of studies	Fixed effects	Random effects	Ri	Q test p-Value
Antipsychotics					
All	12	1.46 (1.34, 1.59)	1.59 (1.27, 1.98)	0.78	0.00001
Cohort only	2	1.11 (0.70, 1.75)	1.11 (0.70, 1.75)	0.00	0.42
CC only	10	1.48 (1.35, 1.61)	1.68 (1.32, 2.14)	0.81	0.00001
Population-based CC	7	1.48 (1.31, 1.66)	1.64 (1.25, 2.16)	0.75	0.002
Hospital-based CC	3	1.47 (1.29, 1.68)	1.65 (0.80, 3.43)	0.96	0.00001
Hip fracture	11	1.57 (1.42, 1.74)	1.70 (1.32, 2.18)	0.77	0.0001
Hypnotics					
All	13	1.47 (1.40, 1.54)	1.15 (0.94, 1.39)	0.89	0.00001
Cohort only	3	1.04 (0.86, 1.25)	1.04 (0.86, 1.25)	0.00	0.49
CC only	10	1.50 (1.43, 1.58)	1.22 (0.97, 1.54)	0.89	0.008
Population-based CC	5	1.19 (0.99, 1.44)	0.87 (0.52, 1.45)	0.81	0.007
Hospital-based CC	5	1.53 (1.45, 1.61)	1.53 (1.45, 1.61)	0.00	0.84
Hip fracture	13	1.48 (1.41, 1.55)	1.20 (1.00, 1.44)	0.85	0.001
Opioids					
All	6	1.32 (1.24, 1.40)	1.38 (1.15, 1.66)	0.84	0.004
Cohort only	3	1.29 (1.08, 1.56)	1.32 (1.02, 1.70)	0.44	0.18
CC only	3	1.32 (1.24, 1.41)	1.42 (1.04, 1.93)	0.94	0.001
Hip fracture	6	1.31 (1.24, 1.40)	1.36 (1.11, 1.67)	0.86	0.004

CC = case-control studies; **Ri** = proportion of total variance due to between-study variance.

Except for benzodiazepines and unspecified psychotropic medications, there is room for publication bias in every relationship between exposure to psychotropic drug classes and fracture outcomes that we analysed (antidepressants, antiepileptics, antipsychotics and hypnotics). It is possible that studies with statistically nonsignificant results, especially those that show absence of effect, fail to be published either because they are rejected by medical journals or because the authors of those studies fail to submit them for publication.[70] Consequently, the pooled measure of effect may be overestimated. Potential for publication bias is large for anticonvulsants, antipsychotics and hypnotics, and it may contribute to part of the excess risk observed. On the contrary, the results of antidepressant medications are robust to publication bias potential, as only part of the increase in the risk of fracture would be due to it.

As is the case in any observational study of adverse events of drugs, confounding by indication may affect the results of this meta-analysis. Patients who are prescribed psychotropic drugs may be at a higher risk of falls and fractures because of the symptoms treated by these medications (anxiety, depression, agitation).[71] This would lead to an exaggeration of the effect of psychotropic drugs on fracture risk. Control of this bias may be impossible to achieve through conventional adjustment methods in non-randomised studies unless techniques such as the propensity score are implemented.[72] Furthermore, recent research has suggested that the use of some psychotropic medications (e.g. antiepileptics and opioids) may occur preferentially among patients with lower baseline bone mineral density.[73]

It is worthwhile to note that no consensus was apparent in the covariates used in risk adjustment in the various studies. However, we did not evidence substantial differences in heterogeneity between studies with extensive risk adjustment and studies with minimal adjustment.

Insufficient control of confounding is likely to occur in the individual studies of this meta-analysis. In fact, the overwhelming majority of the studies included in this meta-analysis failed to control for three known confounders: activity of daily living (ADL) score, cognitive impairment and Rosow-Breslau physical impairment scale. A recent study has shown that the net effect of SSRI antidepressants on hip fractures was considerably overestimated if the analysis failed to control for these confounders. Overestimation was as large as 21.5% in case of omission of ADL score and 10.6% for physical impairment scales.[74] However, the same study shows that, even after correcting for bias, a significant association persists. As our assessment of study quality included adjustment for known confounders, the bias due to residual confounding is partially captured in our analysis. In particular, it is remarkable that for antiepileptic drugs the pooled effect of higher quality studies is only half that of the lower quality studies.

Conclusion

In conclusion, our results show that psychotropic medications may play an important modifiable role in the development of fractures. Although the effect observed is moderate and potential for publication bias and confounding may attenuate its strength, it is clinically relevant and should be addressed seriously. As it is unlikely that randomised trials of psychotropic medications and fractures will ever exist, the scientific community should rely on observational studies to further assess the risk of fracture. This strengthens the argument that large prospective studies that minimise selection bias are needed to measure more accurately the risk of fractures associated with these medications. Clinicians caring for vulnerable older adults should carefully consider the risk of fractures associated with use of psychotropic medications, particularly when effective non-pharmacological interventions are available.

Acknowledgements

No sources of funding were used in the preparation of this manuscript. The authors have no conflicts of interest that are directly relevant to the content of this manuscript. Dr Etminan, Dr Takkouche and Dr Montes-Martínez initiated this project. Dr Montes-Martínez and Dr Takkouche screened and extracted the data. Dr Takkouche analysed the data. Dr Gill provided guidance on neurological and other clinical aspects. All authors participated in discussing the results and in writing the paper. Dr Takkouche will act as guarantor for the paper.

References

1. Gullberg B, Johnell O, Kanis JA. World-wide projections for hip fracture. Osteoporos Int 1997; 7: 407-13
2. Stevens JA, Olson S. Reducing falls and resulting hip fractures among older women. MMWR Recomm Rep 2000; 49 (RR-2): 3-12
3. Cumming RG, Le Couteur DG. Benzodiazepines and risk of hip fractures in older people: a review of the evidence. CNS drugs 2003; 17: 825-37
4. International Osteoporosis Foundation. Osteoporosis in Europe. Indicators of progress and outcomes from the European Parliament Osteoporosis Interest Group and European Union Osteoporosis Consultation Panel Meeting, 2004, p2 [online]. Available from URL: http://www.osteofound.org/advocacy_policy/eu_policy_project/pdf/indicators_of_progress.pdf. [Accessed 2006 Sep 21]
5. Chrischilles E, Shireman T, Wallace R. Costs and health effects of ostoporotic fracture. Bone 1994; 15: 377-86
6. Centers for Disease Control and Prevention. Hip fractures among older adults [online]. Available from URL: http://www.cdc.gov/ncipc/factsheets/adulthipfx.htm [Accessed 2006 Dec 2]
7. Campbell AJ, Robertson MC, Gardner MM, et al. Psychotropic medicine withdrawal and a home-based exercise program to prevent falls: a randomized controlled trial. J Am Geriatr Soc 1999; 47: 850-3
8. Tinetti ME. Preventing falls in elderly persons. N Engl J Med 2003; 348: 42-9
9. Kannus P, Sievanen H, Palvanen M, et al. Prevention of falls and consequent injuries in elderly people. Lancet 2005; 366: 1885-93
10. Schoofs M, vand der Klift M, Hofman A, et al. Thiazide diuretics and the risk for hip fracture. Ann Intern Med 2003; 139: 476-82
11. Paulose-Ram R, Jonas BS, Orwig D, et al. Prescription psychotropic medication use among the U.S. adult population: results from the third National Health and Nutrition Examination Survey, 1988-1994. J Clin Epidemiol 2004; 57: 309-17
12. Ohayon MM, Lader MH. Use of psychotropic medication in the general population of France, Germany, Italy and the United Kingdom. J Clin Psychiatry 2002; 63: 817-25
13. Forsén L, Meyer HE, Søgaard AJ, et al. Mental distress and risk of hip fracture. Do broken hearts lead to broken bones? J Epidemiol Community Health 1999; 53: 343-7
14. Pierfitte C, Macouillard G, Thicoêpe M, et al. Benzodiazepines and hip fractures in elderly people : case-control study. BMJ 2001; 322: 704-8
15. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. J Am Geriatr Soc 1999; 47: 30-9
16. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12
17. French DD, Campbell R, Spehar A, et al. Outpatient medications and hip fractures in the US. A national veterans study. Drugs aging 2005; 22: 877-85
18. Bhutta AT, Cleves MA, Casey PH, et al. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA. 2002; 288: 728-37
19. Takkouche B, Etminan M, Montes-Martínez A. Personal use of hair dyes and risk of cancer: A meta-analysis. JAMA 2005; 293: 2516-25
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trial. 1986; 7: 177-88
21. Takkouche B, Cadarso-Suarez C, Spiegelman D. Evaluation of old and new tests of heterogeneity in epidemiologic meta-analysis. Am J Epidemiol 1999; 150: 206-15
22. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-34
23. Costa-Bouzas J, Takkouche B, Cadarso-Suarez C, et al. HepiMA: software for the identification of heterogeneity in meta-analysis. Comput Methods Programs Biomed 2001; 64: 101-7
24. Wysowski DK, Baum C, Ferguson WJ, et al. Sedative-hynotic and the risk of hip fracture. J Clin Epidemiol 1996; 49: 111-3
25. Grisso JA, Kelsey JL, Strom BL, et al. Risk factors for falls as a cause of hip fracture in women. N Eng J Med 1991; 324: 1326-31
26. Ray WA, Griffin MR, Schaffner W, et al. Psychotropic drug use and the risk of hip fracture. N Eng J Med 1987; 316: 363-9
27. Sernbo I, Hansson A, Johnell O. Drug consumption in patients with hip fractures compared with controls. Compr Gerontol [A] 1987; 1: 93-6
28. Ray WA, Griffin MR, Downey W. Benzodiazepines of long and short elimination half-life and the risk of hip fracture. JAMA 1989; 262: 3303-7
29. Stevens A, Mulrow C. Drugs affecting postural stability and other risk factors in the hip fracture epidemic: case-control study. Community Med 1989; 11: 27-34
30. Jensen J, Nielsen LH, Lyhne N, et al. Drugs and femoral neck fracture: a case-control study. J Intern Med 1991; 229: 29-33
31. Cumming RG, Klineberg RJ. Psychotropics, thiazide diuretics and hip fractures in the elderly. Med J Aust 1993; 158: 414-7
32. Lichtenstein MJ, Griffin MR, Cornell JE, et al. Risk factors for hip fractures occurring in the hospital. Am J Epidemiol 1994; 140: 830-8
33. Herings R, Stricker BH, de Boer A, et al. Benzodiazepines and the risk of falling leading to femur fractures: Dosage more important than elimination half-life. Arch Intern Med 1995; 155: 1801-7
34. Schwab M, Roder F, Aleker T, et al. Psychotropic drug use, falls and hip fracture in the elderly. Aging Clin Exp Res 2000; 12: 234-9
35. Sgadari A, Lapane K, Mor V, et al. Oxidative and nonoxidative benzodiazepines and the risk of femur fracture. J Clin Psychopharmacol 2000; 20: 234-9
36. Wang PS, Bohm RL, Glynn RJ, et al. Zolpidem use and hip fractures in older people. J Am Geriatr Soc 2001; 49: 1685-90
37. da Silva Freire Coutinho E, Dutra Da Silva S. Uso de medicamentos como fator de risco para fratura grave decorrente de queda em idosos. Cad Saúde Publica 2002; 18: 1359-66
38. Schlienger RG, Kraenzlin ME, Jick SS, et al. Use of β-blockers and risk of fractures. JAMA 2004; 292: 1326-32
39. Vestergaard P, Rejmark L, Mosekilde L. Fracture associated with use of antepileptic drugs. Epilepsia 2004; 45: 1330-7
40. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. N Engl J Med 1995; 332: 767-73
41. Guo Z, Wills P, Viitanen M, et al. Cognitive impairment, drug use, and the risk of hip fracture in persons over 75 year old: a community-based prospective study. Am J Epidemiol 1998; 148: 887-92
42. Jacqmin-Gadda H, Fourrier A, Commenges D, et al. Risk factors for fractures in the elderly. Epidemiol 1998; 9: 417-23
43. Vestergaard P, Tigaran S, Rejnmark L, et al. Fracture risk is increased in epilepsy. Acta Neurol Scand 1999; 99: 269-75
44. Ensrud KE, Blackwell T, Mangione CM, et al. Central nervous system active medication and risk of fractures in older women. Arch Intern Med 2003; 163: 949-57

45. Hasselman CT, Vogt MT, Stone KL, et al. Foot and ankle fractures in elderly white women. J Bone Joint Surg 2003; 85A: 820-4

46. Wagner AK, Zhang F, Soumerai SB, et al. Benzodiazepine use and hip fractures in the elderly. Arch Intern Med 2004; 164: 1567-72

47. Ray WA, Griffin MR, Malcolm E. Cyclic antidepressants and the risk of hip fracture. Arch Intern Med 1991; 151: 754-6

48. Herings RMC, Stricker BHC, de Boer A, et al. Current use of thiazide diuretics and prevention of femur fractures. J Clin Epidemiol 1996; 49: 115-19

49. Gambassi G, Lapane KL, Sgadari A, et al. Elderly patients, use of antidepressants, and hip fracture [letter]. Lancet 1998; 352: 400

50. Liu B, Anderson G, Mittman N, et al. Use of selective serotonin-reuptake inhibitors or tricyclic antidepressants and risk of hip fractures in elderly people. Lancet 1998; 351: 1303-7

51. Partanen J, Heikkinen J, Jämsä T, et al. Characteristics of lifetime factors, bone metabolism and bone mineral density in patients with hip fracture. J Bone Miner Metab 2002; 20: 367-75

52. Hubbard R, Farrington P, Smith C, et al. Exposure to tricyclic and selective serotonin reuptake inhibitor antidepressants and the risk of hip fracture. Am J Epidemiol 2003; 158: 77-84

53. Hugenholtz GWK, Heerdink ER, van Staa TP, et al. Risk of hip/femur in patients using antipsychotics. Bone 2005; 37: 864-70

54. Brocklehurst JC, Exton-Smith AN, Lempert Barber SM, et al. Barbiturates and fractures. BMJ 1977; 2: 699-700

55. Paganini-Hill A, Ross RK, Gerkins VR, et al. Menopausal estrogen therapy and hip fractures. Ann Intern Med 1981; 95: 28-31

56. Heidrich FE, Stergachis A, Gross KM. Diuretic drug use and the risk for hip fracture. Ann Intern Med 1991; 115: 1-6

57. Jackson JA, Riggs MW, Spiekerman AM. Testosterone deficiency as a risk factor for hip fractures in men: a case-control study. Am J Med Sci 1992; 304: 4-8

58. Poor G, Atkinson EJ, O'Fallon WM, et al. Predictors of hip fractures in elderly men. J Bone Miner Res 1995; 10: 1900-7

59. Scane AC, Francis RM, Sutcliffe AM, et al. Case-control study of the pathogenesis and sequelae of symtomatica vertebral fractures in men. Osteoporos Int 1999; 9: 91-7

60. Bischof F, Basu D, Pettifor JM. Pathological long-bone fractures in residents with cerebral palsy in a long-term care facility in South Africa. Develop Med Child Neurol 2002; 44: 119-22

61. Ryder KM, Williams J, Womack C, et al. Appendicular fractures: a significant problem among institutionalized adults with developmental disabilities. Am J Ment Retard 2003; 108: 340-6

62. Annegers JF, Melton LJ, Sun C, et al. Risk of age-related fractures in patients with unprovoked seizures. Epilepsia 1989; 30: 348-55

63. Rashiq S, Logan RFA. Role of drugs in fractures of the femoral neck. BMJ 1986; 292: 861-3

64. Shorr RI, Griffin MR, Daugherty JR, et al. Opioid analgesics and the risk of hip fracture in the elderly: codeine and propoxyphene. J Gerontol 1992; 47: 111-5

65. Card T, West J, Hubbard R, et al. Hip fractures in patients with inflammatory bowel disease and their relationship to corticosteroid use: a population based cohort study. Gut 2004; 53: 251-5

66. Taggart HM. Do drugs affect the risk of hip fracture in elderly women? J Am Geriatr Soc 1988; 36: 1006-10

67. Grisso JA, Kelsey JL, O'Brien LA, et al. Risk factors for hip fracture in men. Am J Epidemiol 1997; 145: 786-93

68. Bae JM, Koo HW, Jung KO, et al. A cohort study of the association between psychotropics and hip fracture in Korean elderly women. J Korean Med Sci 2002; 17: 65-70

69. Sutton AJ, Abrams KR, Jones DR, et al. Methods for meta-analysis in medical research. Chichester: Wiley, 2000: 118

70. Coursol A, Wagner EE. Effect of positive findings on submission and acceptance rates: a note on meta-analysis bias. Prof Psychol-Res Pr 1986; 17: 136-7

71. Shorr RI. Review: psychotropic drugs increase the risk of falls in older people. Evid Based Ment Health 1999; 2: 95

72. Seeger JD, Williams PL, Walker AM. An application of propensity score matching using claims data. Pharmacoepidemiol Drug Saf 2005; 14: 465-76

73. Kinjo M, Setoguchi S, Schneeweiss S, et al. Bone mineral density in subjects using central nervous system-active medications. Am J Med 2005; 118: 1414

74. Schneeweiss S, Wang PS. Association between SSRI use and hip fractures and the effect of residual confounding bias in claims database studies. J Clin Psychopharmacol 2004; 24: 632-8

Correspondence and offprints: Dr *Bahi Takkouche*, Department of Preventive Medicine, Faculty of Medicine, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain.
E-mail: mrbahi@usc.es