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Risk of Hip Fracture in Older People Using Selective Serotonin Reuptake Inhibitors and Other Psychoactive Medicines Concurrently: A Matched Case–Control Study in Australia

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Abstract

Background Few studies have assessed the risk of hip fracture following concurrent use of psychoactive medicines, and none has investigated combinations with selective serotonin reuptake inhibitors.

Objectives To assess the risk of hip fracture in older people as a result of concurrent use of selective serotonin reuptake inhibitors and other psychoactive medicines.

Methods A matched case–control design was employed. Cases were Australian Government Department of Veterans' Affairs beneficiaries aged over 65 years who experienced a hip fracture between 2009 and 2012. Each case was matched with up to four randomly selected controls of the same age ($\pm$2 years) and sex. Medicine-hip fracture associations were estimated via conditional logistic regression. The relative excess risk due to interaction (RERI) was calculated to determine whether combined effects differed from the sum of individual effects.

Results There were 8828 cases and 35,310 controls. The median age of subjects was 88 years and 63% were women. The risk of hip fracture was elevated for all medicines assessed individually, most notably selective serotonin reuptake inhibitors (initiation: odds ratio [OR] = 2.7, 95% confidence interval [CI] 2.1, 3.6) and opioids (initiation: OR = 2.3, 95% CI 1.9, 2.9). Combinations associated with an increased odds of hip fracture included addition of benzodiazepines to selective serotonin reuptake inhibitor therapy (OR = 3.0, 95% CI 1.9, 4.8; RERI = 0.9, 95% CI −0.5, 2.3), concurrent use of both opioids and selective serotonin reuptake inhibitors (OR = 2.2, 95% CI 1.9, 2.6; RERI = 0.1, 95% CI −0.3, 0.5), addition of opioids to selective serotonin reuptake inhibitor therapy (OR = 3.2, 95% CI 1.8, 5.5; RERI = −0.1, 95% CI −2.0, 1.7), and initiation of both benzodiazepines and selective serotonin reuptake inhibitors (OR = 4.7, 95% CI 1.7, 13; RERI = 1.3, 95% CI −3.8, 6.3). The RERI results suggested that the effect of each of these medicine combinations equalled the sum of the effects of individual medicine use.

Conclusions In older people, the concurrent use of selective serotonin reuptake inhibitors and other psychoactive medicines increased the risk of hip fracture as much as the sum of the risks owing to individual medicine use. Our results highlight the need for prescribers to consider the sedative burden of medicines in each older patient as well as the potential for an additive risk of hip fracture when initiating additional psychoactive therapy.

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Key Points

Little is known about the risk of hip fracture as a result of concurrent use of psychoactive medicines.

The concurrent use of selective serotonin reuptake inhibitors and other psychoactive medicines was associated with an increased risk of hip fracture among older people, with the risk being as high as the sum of the risks owing to use of the medicines individually.

When deciding whether to treat older people with combinations of selective serotonin reuptake inhibitors and other psychoactive medicines, prescribers ought to consider the overall sedative burden and limit concurrent exposure.

1 Introduction

Psychoactive medicines are established risk factors for hip fracture [1]. A meta-analysis of observational studies identified that, relative to the non-use of medicines, many different types of psychoactive medicine use were associated with an increased risk of hip fracture. The psychoactive medicines included antidepressants, non-barbiturate anti-epileptic drugs, barbiturate anti-epileptic drugs, antipsychotics, hypnotics, benzodiazepines and opioids [1]. For most of these medicines, there was between a 1.5- and 2-fold increased risk of hip fracture [1].

Although a single psychoactive medicine may contribute to the risk of hip fracture, multiple medicine use may also be problematic. Multiple medicine use, which can lead to interactions, is common. In a cross-sectional study, half of all older Australians admitted to hospital for hip fracture used at least two medicines associated with falls or hip fracture during the 6 weeks before hospital admission [2]. The concurrent use of multiple psychoactive medicines could increase a patient's risk owing to the potential for pharmacodynamic or pharmacokinetic interactions between the medicines [3]. For example, an antidepressant can add to the sedative effect of a benzodiazepine [4]. This is an example of a pharmacodynamic interaction whereby two medicines share a pharmacological effect. By comparison, the selective serotonin reuptake inhibitor (SSRI) antidepressants fluoxetine and fluvoxamine may inhibit the metabolism of the benzodiazepine alprazolam, leading to increased alprazolam concentrations and enhanced sedation [4]. These are examples of pharmacokinetic interactions. Age-related changes in pharmacodynamics and pharmacokinetics, as well as multi-morbidity and

polypharmacy, predispose older people to medicine interactions [5]. A case–control study found a dose-response relationship between the number of medicines and the risk of hip fracture in older people aged ≥65 years [6]. For example, older people taking two to four medicines had a 64% greater risk of hip fracture than older people taking zero to one medicine [6].

Four case–control or cohort studies have assessed the risk of hip or hip/femur fracture as a result of concurrent use of psychoactive medicines defined in terms of current exposure [7–10]. An increased risk of hip or hip/femur fracture was found for current use of opioids with psychotropic medicines, current use of anxiolytics with hypnotics, and current use of benzodiazepines or zolpidem with potentially interacting medicines identified in drug information sources [7, 8, 10]. For each combination of a benzodiazepine or zolpidem with interacting medicines, an assessment of additive interaction found that the risk estimate as a result of concurrent exposure was similar to the sum of the risk estimates due to individual exposures [8]. In one case–control study, the association between dopaminergic agents and hip/femur fracture was stronger among antidepressant users than among non-users of antidepressants [9]. This study assessed the interaction in terms of subgroup effects using a multiplicative scale rather than in terms of joint effects using an additive scale. The former is less relevant to clinical practice [11–13]. Two of the four studies of concurrent use of psychoactive medicines and the risk of hip or hip/femur fracture did not assess interaction [7, 10]. Three past studies [7–9] of the risk of hip or hip/femur fracture as a result of concurrent use of psychoactive medicines were limited by the potential for survivor bias, as new medicine use was not assessed separately to continuous medicine use [14]. Continuous users of psychoactive medicines are likely to be less vulnerable to adverse effects, falls and hip fractures than new users of psychoactive medicines. This is because tolerance to sedative effects can develop over time [14]. Only one of the four past studies, which assessed the risk of hip/femur fracture as a result of concurrent use of anxiolytics and hypnotics, defined concurrent use in terms of new exposure [10].

No published studies have assessed the risk of hip fracture as a result of concurrent use of psychoactive medicines defined in terms of new and continuous exposure, such as adding a new psychoactive medicine to an antidepressant used continuously. Such clinically relevant information could help medical practitioners weigh up the risks and potential benefits of combining psychoactive medicines in older patients with depression or anxiety.

As SSRIs are commonly used to treat depression and anxiety, they may be the antidepressant class with the greatest potential for co-prescribing alongside other

psychoactive medicines. Selective serotonin reuptake inhibitors have been associated with a significantly increased risk of hip fracture [15–19]. A meta-analysis of seven case–control or cohort studies found SSRIs were associated with a 70% increased risk of hip fracture [15]. When cohort and case–control studies were conducted with a common study protocol across three different primary care databases, current use of SSRIs was consistently associated with at least a 61% greater risk of hip/femur fracture [16]. A further case–control study found a duration-dependent effect of SSRIs on hip fracture, with cumulative durations of ≥6 and <6 months associated with two times and 3.9 times greater risk of hip fracture, respectively [17]. In terms of within-person study designs, short-term use of SSRIs has been associated with a 98% increased risk of hip fracture in a self-controlled case series analysis [18] and a 54% increased risk of hip fracture in a case–crossover study [19]. The risk of hip fracture as a result of combining SSRIs with other psychoactive medicines has not been previously reported in the literature. The aim of this study was to assess the risk of hip fracture in older people as a result of concurrent use of SSRIs and other psychoactive medicines.

2 Methods

2.1 Setting

This study was undertaken using data from the Australian Government Department of Veterans' Affairs (DVA) healthcare claims database. This is an administrative database of dispensing claims made on behalf of Australian war veterans, as well as war widows and dependents, for prescription medicines subsidised nationally under the Pharmaceutical Benefits Scheme and the Repatriation Pharmaceutical Benefits Scheme. The DVA healthcare claims database also includes data on hospital admissions as well as claims made for medical services and allied health visits. In December 2010, this database contained records for more than 250,000 beneficiaries from all Australian States and Territories [20].

2.2 Study Design

A matched case–control study design was used to ascertain cases and controls for assessment of medicine use and the risk of hip fracture [21]. The source population comprised people who were aged over 65 years on 1 January 2008 and were eligible to receive all health services subsidised by DVA. De-identified data on hospital admissions, patient demographics and medicines were obtained for this source population between 1 January 2008 and 31 December 2012.

The cases were all people in the population who were admitted to hospital with a hip fracture as a primary diagnosis between 1 January 2009 and 31 December 2012. Hip fracture was identified by the *International Classification of Diseases and Related Health Problems-10-Australian Modification* codes S72.0 and S72.1 [22]. Where multiple hip fractures per patient were evident in the data, only the first case was included. The date of each case's hospital admission for hip fracture was recorded as the index date.

Risk set sampling was used in the matched case–control study design [21]. Risk sets were created by matching each case with up to four randomly selected, eligible controls. For a given case, the controls eligible for matching were source population members of the same sex and age (±2 years) who had not been admitted to hospital for hip fracture up to the case's index date. As this is a population-based case–control study, controls included both hospitalised and non-hospitalised patients. The controls in a given risk set were assigned the same index date as the corresponding case. The controls in all but the final risk set remained eligible for inclusion in future risk sets. This meant that a patient in the source population could potentially be a control more than once, and subsequently become a case.

2.3 Patient Characteristics

Patients' age, sex, number of co-morbidities, socioeconomic status and residential status were assessed. The number of co-morbidities was measured over the year before the index date using the Australian version of the Rx-Risk-V [23], which is a medication-based co-morbidity index. Those morbidities treated by the psychoactive medicines under study were excluded to prevent adjusting for a variable that included the exposures of interest. Socioeconomic status was measured using the Australian Bureau of Statistics' quintiles of the socioeconomic indexes for areas [24]. This measure was based on patients' residential postcodes, which were determined on 1 January 2008. Patient age and residential aged care status were determined on the index date.

2.4 Medicines Assessed

Four groups of psychoactive medicines were assessed alone and in combination with SSRIs: opioids, antiepileptic drugs, antipsychotics and benzodiazepines. SSRIs were also assessed alone. Effect estimates in statistical models were adjusted for anti-Parkinson medicines, benzodiazepine-related medicines, tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors, other antidepressants (mirtazapine, moclobemide, mianserin,

reboxetine and agomelatine) and anticholinesterases, as well as the psychoactive medicines opioids, anti-epileptic drugs, antipsychotics and benzodiazepines when they were not the subject of the case–control analysis. All medicine groups were defined using Anatomic Therapeutic Chemical classification codes [25] (see the Appendix).

2.5 Medicine Exposure Status

Prescription supply dates and duration of supply estimates were employed to categorise patients' medicine use. Because information on dose was unavailable, duration of supply estimates were calculated from the data based on the period within which 75% of patients returned for a repeat medicine dispensing [26]. Two pharmacists independently reviewed all duration of supply estimates and made any necessary adjustments on the basis of clinical knowledge. For example, the duration of use of medicines that tend to be used intermittently, including analgesics, were adjusted because dispending data are unlikely to reflect actual exposure. The exposure window for current use was defined as the period equivalent to one duration of use estimate before the index date. Each person was classified as a new user, continuous user or non-user of each medicine group. This gave rise to main effects variables. A patient was classified as a new user if there was a dispensing for a medicine during the exposure window, but no supply of any medicine in the same group up to 180 days prior. A patient was classified as a continuous user if there was a dispensing for a medicine during the exposure window as well as one or more supplies of any medicine in the same group up to 180 days prior. A patient was classified as a non-user of a medicine group if there was no dispensing for any medicine in the given group during the exposure window.

Following the classification of patients into categories of individual medicine use, patients were further classified into categories of concurrent medicine use. Concurrent use was also determined based on the dispensing date and estimated duration of supply. Concurrent use was defined where the duration of supply of one medicine overlapped with the supply duration of the second medicine by any number of days. A single categorical variable was created for the joint effects of each medicine pair under investigation. The variable featured mutually exclusive categories of medicine exposure corresponding to the use of two medicine groups together and alone. Each psychoactive medicine pair was assessed in terms of the following categories: initiation of both medicines, addition of one medicine to another medicine, continuous use of both medicines, initiation of one medicine without another medicine, continuous use of one medicine without another medicine and no use of either medicine.

2.6 Data Analysis

Initially, the risk of hip fracture associated with each of the individual medicine groups was assessed. A single, conditional logistic regression model was used to estimate main effects, with no use of the particular medicine as the reference category. Subsequently, conditional logistic regression was used to determine joint effects of SSRIs with each of the four groups of psychoactive medicines. Each pair of medicines was assessed in a separate model, with no use of either medicine as the reference category.

Conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for all groups of medicine use. As risk set sampling was employed, each OR provided an estimate of relative risk [27]. If the 95% CI around a risk estimate excluded one, then there was said to be a statistically significant association between medicine use and hip fracture. All conditional logistic regression models were adjusted for the number of co-morbidities, socioeconomic status and all other medicines assessed. The variance inflation factor was calculated to check for multicollinearity among all explanatory variables in the multivariate models. A variance inflation factor less than ten was considered to be acceptable. The power of each risk estimate was calculated a posteriori using a formula applicable to case–control designs [28]. Power less than 80% was highlighted.

The risk of hip fracture as a result of concurrent use of two medicines may be assessed in terms of joint effects [13]. This involves estimating the risk of hip fracture in patients who use both medicines (i.e. concurrent users) and patients who use each medicine without the other (i.e. individual users), relative to non-users of either medicine. The effect for concurrent users can then be compared with the effect for individual users.

For each medicine combination, the extent to which the combined effect differed from the sum of the corresponding independent effects (i.e. additive interaction) was assessed using the relative excess risk due to interaction (RERI): $RERI = OR_{11} - OR_{10} - OR_{01} + 1$ [29]. In this formula, OR_{11}, OR_{10} and OR_{01} are the risk estimates for use of a psychoactive medicine with an SSRI, use of the psychoactive medicine without the SSRI and use of the SSRI without the psychoactive medicine, respectively. Negative, zero and positive RERI values indicate sub-additivity, additivity and super-additivity, respectively [11]. The Hosmer–Lemeshow delta method was employed to compute a 95% CI for each RERI value [30]. If the upper limit of the 95% CI around a RERI was less than 0, then the combined effect was considered to be sub-additive (i.e. negative interaction or antagonism). If the 95% CI around a RERI included 0, then the combined effect was considered to be additive (i.e. additivity of independent effects). If the

lower limit of the 95% CI around a RERI exceeded 0, then the combined effect was considered to be super-additive (i.e. positive interaction or synergism).

All analyses were conducted using SAS Version 9.4 (SAS Institute, Inc., Cary, NC, USA).

3 Results

3.1 Subject Characteristics

Overall, 8828 cases of hip fracture were matched by age and sex with 35,310 controls. Characteristics were similar between cases and controls (Table 1).

3.2 Individual Medicines

Case–control study results for the effects of SSRIs on the risk of hip fracture are shown in Table 2. Relative to no use of SSRIs, the initiation of SSRIs and the continuous use of SSRIs increased the odds of hip fracture by 2.7-fold and 1.8-fold, respectively.

Case–control study results for the effects of psychoactive medicines on the risk of hip fracture are also shown in Table 2. The odds of hip fracture were increased 2.3-fold and 1.3-fold for initiation and continuous use of opioids, respectively. Initiation of anti-epileptic drugs was associated with a 41% increased odds of hip fracture, whereas continuous use of anti-epileptic drugs was unrelated to hip fracture. The odds of hip fracture were elevated by 29% and 28% for initiation and continuous use of

antipsychotics, respectively, as well as 34% and 19% for initiation and continuous use of benzodiazepines, respectively.

3.3 Medicine Combinations

Case–control study results for the risk of hip fracture as a result of concurrent use of SSRIs and psychoactive medicines are shown in Table 3. Significant associations were observed for 11 of the 16 combinations assessed. The initiation of both SSRIs and each of benzodiazepines and opioids increased the odds of hip fracture by 4.7-fold and 4-fold, respectively. The addition of SSRIs to continuous opioid therapy was associated with a 3.5-fold greater odds of hip fracture. The addition of opioids, anti-epileptic drugs, antipsychotics and benzodiazepines to continuous SSRI therapy increased the odds of hip fracture by 3.2, 2.4, 2.3 and three times, respectively. The continuous use of both SSRIs and each of opioids, anti-epileptic drugs, antipsychotics and benzodiazepines increased the odds of hip fracture by 2.2, 1.3, 1.4 and 1.8 times, respectively.

The results in Table 4 build on the results in Table 3 by providing an interaction measure calculated from the effect estimates for concurrent medicine use, namely the RERI. Additivity of effects was observed for the initiation of both SSRIs and each of opioids and benzodiazepines, the addition of SSRIs to continuous opioid therapy, the addition of each of the four psychoactive medicines to continuous SSRI therapy, and the continuous use of both SSRIs and opioids (Table 4). Sub-additivity of effects was observed for the continuous use of both SSRIs and each of the anti-epileptic drugs, antipsychotics and benzodiazepines, as well as the addition of SSRIs to continuous antipsychotic therapy (Table 4). There was no evidence of multi-collinearity in any of the multivariate conditional logistic regression models. All variance inflation factor values were less than 10 (data not shown).

4 Discussion

In this case–control study, 11 of the 16 combinations of SSRIs and psychoactive medicines under investigation were associated with a significantly increased risk of hip fracture among older people. All combinations of opioids and SSRIs elevated the risk of hip fracture, consistent with the risk observed for opioids and SSRIs individually. Combinations that significantly increased the risk of hip fracture included the addition of benzodiazepines to SSRI therapy, concurrent use of both opioids and SSRIs, the addition of opioids to SSRI therapy, initiation of both benzodiazepines and SSRIs, and the addition of SSRIs to opioid therapy. Exposure to each of these medicine

Table 1 Characteristics of hip fracture cases and age- and sex-matched controls

Characteristic	No. of case patients (%), $n = 8828$	No. of control patients (%), $n = 35,310$
Female sex	5592 (63)	22,368 (63)
Age (years)[a]	88 (85–91)	88 (85–91)
Number of co-morbidities[a]	4 (2–6)	3 (0–6)
Socioeconomic status		
Upper	2537 (29)	9493 (27)
Middle-upper	1559 (18)	6263 (18)
Middle	1664 (19)	6941 (20)
Lower-middle	1737 (20)	6925 (20)
Unknown	11 (0.1)	80 (0.2)
Lower	1320 (15)	5608 (16)
Residential status		
Community	5668 (64)	23,170 (66)
Residential aged care	3160 (36)	12,140 (34)

[a] Median (interquartile range)

Table 2 Case–control study results for associations between individual use of medicines and the risk of hip fracture

Medicine use	No. of case patients (%), n = 8828	No. of control patients (%), n = 35,310	Adjusted OR (95% CI)
Antidepressants			
SSRIs			
New (initiation)	98 (1.1)	122 (0.4)	2.73 (2.07, 3.58)
Continuous	1232 (14)	2598 (7.4)	1.77 (1.64, 1.91)
None	7498 (85)	32,590 (92)	1.00 [reference]
Psychoactive medicines			
Opioids			
New (initiation)	140 (1.6)	210 (0.6)	2.34 (1.87, 2.92)
Continuous	1064 (12)	2633 (7.5)	1.31 (1.21, 1.42)
None	7624 (86)	32,467 (92)	1.00 [reference]
Anti-epileptic drugs			
New (initiation)	102 (1.2)	217 (0.6)	1.41 (1.10, 1.80)
Continuous	404 (4.6)	1188 (3.4)	1.04 (0.93, 1.18)
None	8322 (94)	33,905 (96)	1.00 [reference]
Antipsychotics			
New (initiation)	111 (1.3)	269 (0.8)	1.29 (1.02, 1.62)
Continuous	608 (6.9)	1599 (4.5)	1.28 (1.16, 1.42)
None	8109 (92)	33,442 (95)	1.00 [reference]
Benzodiazepines			
New (initiation)	151 (1.7)	360 (1.0)	1.34 (1.10, 1.63)
Continuous	1389 (16)	3729 (11)	1.19 (1.10, 1.27)
None	7288 (83)	31,221 (88)	1.00 [reference]

CI confidence interval, *OR* odds ratio, *SSRIs* selective serotonin reuptake inhibitors

combinations increased the risk of hip fracture as much as the sum of the effects for individual medicine use.

Eight combinations of SSRIs and psychoactive medicines increased the risk of hip fracture as much as the sum of the effects for individual medicine use. These combinations were the initiation of both SSRIs and each of opioids and benzodiazepines, the addition of SSRIs to continuous opioid therapy, the addition of each of the four psychoactive medicines to continuous SSRI therapy, and the continuous use of both SSRIs and opioids. Combinations of SSRIs and psychoactive medicines that increased the risk of hip fracture, but to a lesser extent than the sum of the effects for individual medicine use, were continuous use of both SSRIs and each of the anti-epileptic drugs, antipsychotics and benzodiazepines.

The increased risk of hip fracture as a result of the initiation of a medicine alone or in combination may be explained by the greater potential for adverse effects during the early stages of treatment. Patients tend to be more vulnerable to adverse effects earlier in a course of treatment than later on, as tolerance may develop with time [14]. Nevertheless, increased risk of hip fracture was observed for continuous use of medicines alone and in combination. This suggests that patients remain vulnerable to the adverse effects of SSRIs and other psychoactive

medicines over extended periods. The sustained increase in risk may also be related to the potential for SSRIs, antipsychotics and anti-epileptic drugs to reduce bone mineral density in the long term [31–34].

The findings of an increased risk of hip fracture in individuals taking both benzodiazepines and SSRIs are consistent with a case–control study conducted among 17,198 hip fracture cases and 85,990 controls aged 65 years or over [8]. This case–control study, which used data from a US administrative claims database, assessed the risk of hip fracture following use of specific benzodiazepines with any interacting medicines [8]. The interacting medicines were those known to be moderate or strong inhibitors of the isoenzyme cytochrome P450 3A4 as well as interactions listed in DRUGDEX, Stockley's and summaries of product characteristics [8]. In this study, relative to no use of either medicine, the risk of hip fracture was increased for use of alprazolam with interacting medicines (RR = 1.51, 95% CI 1.34, 1.69) and use of interacting medicines without alprazolam (relative risk [RR] = 1.40, 95% CI 1.35, 1.46). There was no association for use of alprazolam without interacting medicines (RR = 0.90, 95% CI 0.77, 1.07). In the same case–control study, a significantly increased risk of hip fracture was found for use of lorazepam with interacting medicines (RR = 1.94,

Table 3 Case–control study results for the joint effects of selective serotonin reuptake inhibitors (SSRIs) with each of the four psychoactive (PA) medicine groups

SSRI use	PA use	PA medicine group											
		Opioid			Antiepileptic drug			Antipsychotic			Benzodiazepine		
		Cases N = 8828	Controls N = 35,310	Adjusted OR (95% CI)	Cases N = 8828	Controls N = 35,310	Adjusted OR (95% CI)	Cases N = 8828	Controls N = 35,310	Adjusted OR (95% CI)	Cases N = 8828	Controls N = 35,310	Adjusted OR (95% CI)
New New (Initiate SSRI and PA)		5 (0.1%)	5 (0.01%)	4.0 (1.1, 14)	2 (0.02%)	2 (0.01%)	3.1 (0.4, 22)[a]	4 (0.05%)	6 (0.02%)	2.5 (0.7, 9.1)[a]	8 (0.1%)	7 (0.02%)	4.7 (1.7, 13)
New Cont. (Add SSRI to PA)		14 (0.2%)	13 (0.04%)	3.5 (1.6, 7.6)	3 (0.03%)	3 (0.01%)	3.9 (0.8, 20)[a]	5 (0.1%)	12 (0.03%)	1.5 (0.5, 4.2)[a]	16 (0.2%)	29 (0.1%)	1.8 (0.9, 3.3)
Cont. New (Add PA to SSRI)		23 (0.3%)	29 (0.1%)	3.2 (1.8, 5.5)	19 (0.2%)	27 (0.1%)	2.4 (1.3, 4.3)	24 (0.3%)	40 (0.1%)	2.3 (1.4, 3.9)	35 (0.4%)	42 (0.1%)	3.0 (1.9, 4.8)
Cont. Cont. (Cont. SSRI and PA)		238 (2.7%)	407 (1.2%)	2.2 (1.9, 2.6)	74 (0.8%)	199 (0.6%)	1.3 (1.0, 1.7)	119 (1.3%)	340 (1.0%)	1.4 (1.2, 1.8)	283 (3.2%)	592 (1.7%)	1.8 (1.5, 2.1)
New No (Initiate SSRI only)		79 (1.3%)	104 (0.9%)	2.8 (2.1, 3.8)	93 (1.1%)	117 (0.3%)	2.7 (2.1, 3.6)	89 (1.0%)	104 (0.3%)	3.0 (2.3, 4.0)	74 (0.8%)	86 (0.2%)	3.2 (2.3, 4.4)
No New (Initiate PA only)		112 (0.9%)	176 (1.3%)	2.5 (2.0, 3.2)	81 (0.9%)	188 (0.5%)	1.4 (1.1, 1.9)	83 (0.9%)	223 (0.6%)	1.3 (1.0, 1.7)	108 (1.2%)	311 (0.9%)	1.3 (1.0, 1.6)
Cont. No (Cont. SSRI only)		971 (9.2%)	2162 (11%)	1.8 (1.7, 2.0)	1139 (13%)	2372 (6.7%)	1.8 (1.7, 2.0)	1089 (12%)	2218 (6.3%)	1.9 (1.8, 2.1)	914 (10%)	1964 (5.6%)	1.9 (1.7, 2.0)
No Cont. (Cont. PA only)		812 (9.2%)	2213 (6.3%)	1.3 (1.2, 1.4)	327 (3.7%)	986 (2.8%)	1.1 (0.99, 1.3)	484 (5.5%)	1247 (3.5%)	1.5 (1.3, 1.7)	1090 (12%)	3108 (8.8%)	1.3 (1.2, 1.4)
No No (No SSRI or PA)		6574 (74%)	30,201 (86%)	1.00 (reference)	7090 (80%)	31,416 (89%)	1.00 (reference)	6931 (79%)	31,120 (88%)	1.00 (reference)	6300 (71%)	29,171 (83%)	1.00 (reference)

CI confidence interval, Cont. continuous, OR odds ratio, PAs psychoactives, SSRIs selective serotonin reuptake inhibitors

[a] Power <80% found a posteriori

Table 4 Additive interaction assessment for concurrent use of selective serotonin reuptake inhibitors (SSRIs) and psychoactive (PA) medicine groups

Medicine use		RERI (95% CI)			
SSRIs	PA	Opioids	Anti-epileptic drugs	Antipsychotics	Benzodiazepines
New (Initiation of SSRIs with PAs)	New	−0.4 (−5.5, 4.7)	−0.1 (−6.2, 6.1)	−0.8 (−4.2, 2.5)	1.3 (−3.8, 6.3)
New (Addition of SSRIs to PAs)	Cont.	0.4 (−2.5, 3.2)	1.0 (−5.3, 7.3)	−2.1 (−3.8, −0.3)	−1.7 (−3.2, −0.2)
Cont. (Addition of PAs to SSRIs)	New	−0.1 (−2.0, 1.7)	0.03 (−1.4, 1.5)	0.1 (−1.2, 1.3)	0.9 (−0.5, 2.3)
Cont. (Cont. SSRIs with PAs)	Cont.	0.1 (−0.3, 0.5)	−0.7 (−1.1, −0.3)	−1.0 (−1.4, −0.6)	−0.3 (−0.7, −0.02)

CI confidence interval, *Cont.* continuous, *RERI* relative excess risk due to interaction, *PAs* psychoactives, *SSRIs* selective serotonin reuptake inhibitors

95% CI 1.74, 2.17), use of lorazepam without interacting medicines (RR = 1.32, 95% CI = 1.18, 1.48) and use of interacting medicines without lorazepam (RR = 1.57, 95% CI = 1.50, 1.64). Consistent with the case–control study presented here, the increased risk of hip fracture as a result of the use of alprazolam or lorazepam with interacting medicines equalled the sum of the risks for individual medicine use [8].

The concurrent use of SSRIs and other psychoactive medicines in older people is potentially modifiable. As some of these medicines are second-line treatments for particular conditions, there may be scope to reduce doses, cease therapy or employ safer treatment alternatives [4]. SSRIs prescribed for mild depression or anxiety disorders could be substituted or supplemented with psychotherapy [4]. Exposure to benzodiazepine anxiolytics could also be reduced through psychotherapy, whereas exposure to benzodiazepine hypnotics could be minimised through behavioural, cognitive or light therapy [4]. Antipsychotics prescribed for mild behavioural symptoms of dementia could be substituted or supplemented with non-pharmacological therapies such as environmental modifications [35]. The overall sedative burden should be considered. In patients who take psychoactive medicines and have been symptom free for a period of time, the psychoactive medicines may be gradually withdrawn or given at lower doses [4]. For instance, the use of opioids in pain management should be regularly reviewed, with a view towards dosage reduction, cessation or substitution with non-opioid analgesics [4].

The case–control study presented here has four main strengths. First, current use of medicines was broken down into new and continuous exposure. This will have removed survivor bias from the new user estimates [14]. Second, joint effects and a measure of additive interaction were employed to assess concurrent medicine use in a clinically relevant manner. Third, because data were sourced from an administrative claims database, there was no opportunity for recall bias to influence subject's exposure status. Fourth, because the median age of our subjects was 88 years and half of geriatric hip fractures occur in those aged over 85 years, our results can be generalised from the study population to other older Australians aged over 65 years [36].

There are also several limitations of this research. There was less than 80% power to detect significant results for 4 of the 16 combinations assessed. There were small counts for concurrent medicine use and some of the calculated 95% CIs were wide, denoting imprecision in estimates of both risk and RERI. This may explain why no super-additive effects were found. Additionally, residual confounding by a range of unmeasured factors may have biased the observed associations between medicine use and the risk of hip fracture. Confounding by indication may be a factor influencing the results for individual medicines. Depression may have confounded the observed associations between SSRI use and hip fracture because, in a case–control study conducted among older people aged ≥65 years, depression was independently associated with an increased risk of hip fracture [37]. As new diagnoses of each of Alzheimer's disease and schizophrenia have been associated with an increased risk of hip fracture in observational studies [38, 39], these diseases may have confounded the observed associations between antipsychotic use and hip fracture. However, the independent contribution of each of Alzheimer's disease and schizophrenia to the risk of hip fracture is unclear owing to a lack of adjustment for medicine use in the past studies [38, 39]. It is unlikely that residual confounding accounted for the significance of the results for SSRIs, opioids and antipsychotics because, in a case–crossover study among the same cases that controlled for patient-specific time-invariant

confounders, SSRIs, opioids and antipsychotics were associated with an increased risk of hip fracture [19].

We adjusted for comorbidity using the Rx-Risk-V co-morbidity score, a measure that counts the subjects' number of co-morbidities but does not indicate the severity of illness. There were likely discrepancies between the Rx-Risk-V scores and subjects' actual numbers of co-morbidities. In particular, a number of people with co-morbidities may not have been detected, as the Rx-Risk-V only has low-to-moderate sensitivity compared with self-report in the older Australian population [23].

A further limitation was the assessment of only the simplest type of combined medicine use, exposure to two medicines, among older people who may have been taking more than two medicines concurrently. Exposure misclassification likely occurred because medicine dispensing acted as a proxy for medicine use, without any accounting for secondary non-adherence. As there was no information in the DVA database pertaining to the use of non-prescription medicines, data on certain low-dose codeine products that were purchased over the counter may not have been captured. This could have resulted in misclassification of some opioid users as non-users. There is, however, no reason to believe that this misclassification would have been differential between cases and controls.

5 Conclusion

This case–control study found that, for the majority of SSRI and psychoactive medicine pairs assessed, the increased risk of hip fracture equalled the sum of the risks due to individual medicine use. Our results highlight the need for prescribers to consider the underlying sedative burden of each older patient, as well as the potential for risk of hip fracture when initiating additional psychoactive therapy. The risk estimates presented here could help medical practitioners to weigh up the risks and benefits of combining SSRIs with other groups of psychoactive medicines. In instances where the risks outweigh the benefits, alternative treatment options may be available. Limiting concurrent exposure to psychoactive medicines wherever possible may minimise the risk of hip fracture among older people.

Appendix

See Table 5.

Table 5 Anatomical therapeutic chemical (ATC) codes used to define medicine groups

Medicine group	ATC code(s)
Opioids	N02A
Anti-epileptic drugs	N03A except N02AE01 (clonazepam)
Anticholinergic agents	N04A
Anti-Parkinson medicines	N04
Antipsychotics	N05A except N05AN01 (lithium) and N05AB04 (prochlorperazine)
Benzodiazepines	N03AE, N05BA and N05CD
Benzodiazepine-related medicines	N05CF
TCAs	N06AA
SSRIs	N06AB
Other antidepressants	N06AG02, N06AX03, N06AX11, N06AX18 and N06AX22
SNRIs	N06AX16, N06AX21 and N06AX23
Anticholinesterases	N06DA

SNRIs serotonin and noradrenaline reuptake inhibitors, *SSRIs* selective serotonin reuptake inhibitors, *TCAs* tricyclic antidepressants

References

1. Takkouche B, Montes-Martínez A, Gill SS, et al. Psychotropic medications and the risk of fracture: a meta-analysis. Drug Saf. 2007;30:171–84.

2. Leach MJ, Pratt NL, Roughead EE. Medicine use among older Australians before and after hip fracture. J Pharm Pract Res. 2013;43:265–8.

3. Chadwick B, Waller DG, Edwards JG. Potentially hazardous drug interactions with psychotropics. Adv Psychiatr Treat. 2005;11:440–9.

4. Rossi S, editor. Australian medicines handbook 2016. Adelaide: Australian Medicines Handbook Pty Ltd; 2016.

5. Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. Lancet. 2007;370:185–91.

6. Lai S, Liao KF, Liao CC, et al. Polypharmacy correlates with increased risk of hip fracture in the elderly: a population-based study. Medicine. 2010;89:295–9.

7. 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:M111–5.

8. Zint K, Haefeli WE, Glynn RJ, et al. Impact of drug interactions, dosage, and duration of therapy on the risk of hip fracture associated with benzodiazpine use in older adults. Pharmacoepidemiol Drug Saf. 2010;19:1248–55.

9. Arbouw ME, Movig KL, van Staa TP, et al. Dopaminergic drugs and the risk of hip or femur fracture: a population-based case–control study. Osteoporos Int. 2011;22:2197–204.

10. Requena G, Huerta C, Gardasdottir H, et al. Hip/femur fractures associated with the use of benzodiazepines (anxiolytics, hypnotics and related drugs): a methodological approach to assess consistencies across databases from the PROTECT-EU project. Pharmacoepidemiol Drug Saf. 2016;25(Suppl. 1):66–78.

11. Greenland S, Lash TL, Rothman KJ. Concepts of interaction. In: Rothman K, Greenland S, Lash TL, editors. Modern epidemiology. Philadelphia: Lippincott Williams & Wilkins; 2008.

12. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on methodological standards in pharmacoepidemiology (revision 5). EMA/95098/2010. 2016. http://www.encepp.eu/standards_and_guidances. Accessed 12 Dec 2016.

13. Szklo M, Nieto F. Defining and assessing heterogeneity of effects. In: Szklo M, Nieto F, editors. Interaction: beyond the basics. Boston: Jones and Bartlett Publishers; 2007.

14. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol. 2003;158:915–20.

15. Wu Q, Bencaz AF, Hentz JG, et al. Selective serotonin reuptake inhibitor treatment and risk of fractures: a meta-analysis of cohort and case–control studies. Osteoporos Int. 2012;23:365–75.

16. Souverein P, Abbing-Karahagopian V, Martin E, et al. Understanding inconsistency in the results from observational pharmacoepidemiological studies: the case of antidepressant use and risk of hip/femur fractures. Pharmacoepidemiol Drug Saf. 2016;25(Suppl. 1):88–102.

17. Hung SC, Lin CH, Hung HC, et al. Use of selective serotonin reuptake inhibitors and risk of hip fracture in the elderly: a case–control study in Taiwan. J Am Med Dir Assoc. 2017;18:350–4.

18. 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.

19. Leach MJ, Pratt NL, Roughead EE. Psychoactive medicine use and the risk of hip fracture in older people: a case–crossover study. Pharmacoepidemiol Drug Saf. 2015;24:576–82.

20. Australian Government Department of Veterans' Affairs. Treatment population statistics. 2010. http://www.dva.gov.au/sites/default/files/files/publications/datastatistical/treatmentpop/TpopDec2010.pdf. Accessed 3 June 2014.

21. Rothman K, Greenland S, Lash TL. Case–control studies. In: Rothman K, Greenland S, Lash TL, editors. Modern epidemiology. Philadelphia: Lippincott Williams & Wilkins; 2008.

22. National Centre for Classification in Health. International statistical classification of diseases and related health problems, tenth revision, Australian Modification (ICD-10-AM). Sydney: National Centre for Classification in Health, Faculty of Health Sciences, University of Sydney; 2005.

23. Vitry A, Wong SA, Roughead EE, et al. Validity of medication-based co-morbidity indices in the Australian elderly population. Aust N Z J Public Health. 2009;33:126–30.

24. Australian Bureau of Statistics. Census of population and housing: Socio-Economic Indexes for Areas (SEIFA), Australia, 2011. 2013. http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/2033.0.55.001Main+Features12011?OpenDocument. Accessed 24 Feb 2014.

25. World Health Organization Collaborating Centre for Drug Statistics Methodology. ATC/DDD index. 2014. http://www.whocc.no/atc_ddd_index/. Accessed 7 March 2014.

26. Pottegård A, Hallas J. Assigning exposure duration to single prescriptions by use of the waiting time distribution. Pharmacoepidemiol Drug Saf. 2013;22:803–9.

27. Knol MJ, Vanderbroucke JP, Scott P, et al. What do case–control studies estimate? Survey of methods and assumptions in published case–control research. Am J Epidemiol. 2008;168:1073–81.

28. Newman S. Sample size and power. In: Newman S, editor. Biostatistical methods in epidemiology. New York: Wiley; 2001. p. 293.

29. Rothman K. Modern epidemiology. 1st ed. Boston: Little, Brown and Company; 1986.

30. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. Epidemiology. 1992;3:452–6.

31. Diem SJ, Blackwell TL, Stone KL, et al. Use of antidepressants and rates of hip bone loss in older women: the study of osteoporotic fractures. Arch Intern Med. 2007;167:1240–5.

32. Crews MP, Howes OD. Is antipsychotic treatment linked to low bone mineral density and osteoporosis? A review of the evidence and the clinical implications. Hum Psychopharmacol. 2012;27:15–23.

33. Ensrud KE, Walczak TS, Blackwell T, et al. Antiepileptic drug use increases rates of bone loss in older women: a prospective study. Neurology. 2004;62:2051–7.

34. Ensrud KE, Walczak TS, Blackwell TL, et al. Antiepileptic drug use and rates of hip bone loss in older men: a prospective study. Neurology. 2008;71:723–30.

35. Turner S. Behavioural symptoms of dementia in residential settings: a selective review of non-pharmacological interventions. Aging Ment Health. 2005;9:93–104.

36. Australian Institute of Health and Welfare. Separation statistics by principal diagnosis in ICD-10-AM, Australia, 2008-09 to 2009-10. 2013. https://reporting.aihw.gov.au/Reports/openRVUrl.do?rsRID=SBIP%3A%2F%2FMETASERVER%2FAIHW%2FReleasedPublic%2FHospitals%2FReports%2FHDU_Principal+Diagnosis%2C+2008-09+to+2009-10.srx%28Report%29. Accessed 25 Jan 2017.

37. Lai SW, Lin CL, Chen WC, et al. Correlation between use of zopiclone and risk of hip fracture in elderly adults: a case–control study in Taiwan. J Am Geriatr Soc. 2015;63:2534–7.

38. Lai SW, Chen YL, Lin CL, et al. Alzheimer's disease correlates with greater risk of hip fracture in older people: a cohort in Taiwan. J Am Geriatr Soc. 2013;61:1231–2.

39. Lai SW, Lin CL, Liao KF. Higher incdence of hip fracture in newly diagnosed schizophrenic patients in Taiwan. Libyan J Med. 2013;8:1–2.