

The Risk of Hip Fracture Due to Mirtazapine Exposure When Switching Antidepressants or Using Other Antidepressants as Add-On Therapy

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Abstract

Background Antidepressants are associated with adverse effects such as sedation and hypotension, which can result in falls and fractures. Few studies have assessed the risk of hip fracture due to mirtazapine, and no known studies have assessed whether the risk of hip fracture is higher in patients taking other antidepressant medicines in combination with mirtazapine.

Objectives This study aimed to examine the risk of hip fracture in older people due to mirtazapine use as well as switching between or concurrently using mirtazapine and other antidepressants.

Method A matched case–control study was conducted. Cases were people aged over 65 years who were eligible for Australian Government Department of Veterans' Affairs (DVA) benefits and who sustained a hip fracture between 2009 and 2012. Each case was matched with up to

four randomly selected controls of the same gender and age (± 2 years). Multivariable conditional logistic regression was used to estimate associations between antidepressant use and hip fracture. In order to assess whether combined antidepressant effects differed from the sum of individual effects, the relative excess risk due to interaction (RERI) was calculated.

Results The study population comprised 8828 cases and 35,310 controls. The median age of these participants was 88 years and 63% were women. The risk of hip fracture was increased for mirtazapine (continuous use: odds ratio [OR] 1.27, 95% confidence interval [CI] 1.12–1.44). The combinations associated with increased odds of hip fracture were addition of selective serotonin reuptake inhibitors (SSRIs) to mirtazapine (OR 11, 95% CI 2.2–51; RERI 7.7, 95% CI –9.0 to 24), addition of tricyclic antidepressants (TCAs) to mirtazapine (OR 14, 95% CI 1.4–132; RERI 12, 95% CI –19 to 43) and continuous use of both SSRIs and mirtazapine (OR 2.4, 95% CI 1.4–4.2; RERI 0.4, 95% CI –0.9 to 1.7). RERIs indicated that the effect of each antidepressant pair equalled the sum of the effects of individual antidepressant use. There was no evidence of dispensing of lower strength mirtazapine upon introducing TCAs and SSRIs.

Conclusions Our results show elevated risk of hip fracture following use of mirtazapine alone and in combination with other antidepressants. The overlapping use of antidepressants may reflect the treatment of comorbidities (e.g. anxiety), switching from mirtazapine to other antidepressants, or add-on therapy. Our results highlight the risks of employing add-on therapy or switching antidepressants in older people, providing further evidence to support cautious cross-tapering where switching between antidepressants is required.

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Key Points

We have not identified any studies that assessed whether the risk of hip fracture is higher in people switching between mirtazapine and other antidepressants or using mirtazapine with antidepressants as add-on therapy.

This case-control study found that adding a selective serotonin reuptake inhibitor (SSRI) or tricyclic antidepressant to mirtazapine therapy or continuously using both an SSRI and mirtazapine significantly increased the risk of hip fracture among older people.

Our results highlight the risks of switching antidepressants in older people, supporting cautious cross-tapering where switching between antidepressants is required.

1 Introduction

Mirtazapine is a second-generation antidepressant that acts as an antagonist of α_2 -adrenergic autoreceptors and serotonin (5-HT₂ and 5-HT₃) receptors, resulting in an antidepressant effect [1]. Mirtazapine also acts as a potent antagonist of histamine (H₁) receptors, leading to predictable adverse effects such as sedation [1]. Rates of sedation are greater for mirtazapine than all other second-generation antidepressants, including selective serotonin reuptake inhibitors (SSRIs) [2]. Although mirtazapine may be useful in depression characterised by insomnia [3], it can lead to unwanted daytime sedation [4].

A meta-analysis of observational studies found that the risk of hip fracture is increased by use of antidepressants [5], while another meta-analysis of observational studies found that the risk of hip fracture is increased by SSRIs and by tricyclic antidepressants (TCAs) [6]. Subsequent studies have confirmed these findings across multiple observational study designs and databases [7, 8]. Mirtazapine, which was first marketed in Australia in 2001, has been less well studied. One study of mirtazapine use and the risk of hip fracture was a cohort study conducted among 439,317 new users of antidepressants aged ≥ 65 years [9]. This cohort study found that initiating mirtazapine was associated with a 34% lower rate of hip fracture than initiating the SSRI citalopram [9]. No studies were located investigating mirtazapine use and the risk of hip fracture compared with no mirtazapine use. Mirtazapine use is increasing in Australia; the defined daily dose (DDD)/1000 people/day was 0.17 during 2010 and 0.24 during 2015 [10–13].

In addition to studies which suggest an increased risk of hip fracture with antidepressants, pharmacological theory suggests that concomitant use of more than one antidepressant could elevate the risk of hip fracture beyond that of antidepressant monotherapy, potentially through pharmacodynamic or pharmacokinetic interactions [14]. There are two main ways in which antidepressants are combined in clinical practice: switching and add-on therapy. It may be necessary to switch from an initial antidepressant to a new antidepressant when the initial antidepressant causes adverse effects or is ineffective [15]. In the process of switching, medicines may be administered concurrently as one medicine is tapered and the other is introduced. Alternatively, multiple antidepressants can be used concurrently as add-on therapy when patients are resistant to treatment with antidepressant monotherapy [15, 16].

In practice, the use of multiple antidepressants is infrequent [17–19]. Two studies set in Australia estimated that two or more antidepressants were used by 5 and 3% of patients, respectively [17, 18]. A Canadian study identified that, of 17,622 adults prescribed at least one antidepressant, 3842 (22%) were co-prescribed multiple antidepressants [19]. Of the 3842 adults who were co-prescribed multiple antidepressants, 92% used agents from different classes and 46% used another antidepressant in combination with an SSRI [19].

When switching from one antidepressant to another, there may be short-term overlap in use or effects of the two different antidepressants [3]. This occurs because, in order to prevent withdrawal symptoms and serotonin syndrome, the dose of the initial antidepressant is gradually tapered [3]. The new antidepressant may be added during or after the tapering period [15]. The most appropriate approach to switching depends on the types of antidepressants involved in the switch and the reason for switching [15]. The gradual introduction of a new antidepressant while tapering the initial antidepressant is referred to as cross-tapering [15]. Cross-tapering needs to be performed cautiously due to the possibility of withdrawal symptoms as well as pharmacodynamic and pharmacokinetic interactions [3, 15]. The dose of the initial antidepressant should be gradually reduced while a low dose of the new antidepressant is slowly titrated upwards [15]. The Maudsley Prescribing Guidelines in Psychiatry and the Australian Medicines Handbook recommend the use of cross-tapering when switching between mirtazapine and TCAs, SSRIs, or serotonin and noradrenaline reuptake inhibitors (SNRIs) [3, 15].

The second type of combined antidepressant exposure, namely add-on therapy, refers to the concurrent use of two antidepressants in the treatment of either refractory depression [15, 20] or depression with comorbidities for which antidepressants are indicated (e.g. anxiety) [19]. The

two antidepressants used in add-on therapy typically have distinct yet complementary mechanisms of action [16], with an example being the mirtazapine-SSRI combination [15, 21]. In the treatment of refractory depression, one agent is employed to augment the effect of the other. While some international guidelines advocate antidepressant add-on therapy [2, 15], the Australian Medicines Handbook and Australian Therapeutic Guidelines: Psychotropic caution against it due to a lack of supporting evidence and the potential for interactions between antidepressants [3, 22]. Despite this guidance, psychiatrists prescribe antidepressant combinations in practice. In 2004, 76% of 1107 Australian psychiatrists who responded to a postal survey reported prescribing combination antidepressant therapy at some stage during their medical careers [23]. Furthermore, 37% of respondents reported that they had combined mirtazapine with SSRIs sometime in the past [23].

Patients who are prescribed two antidepressants for switching or add-on therapy may experience adverse drug interactions, including additive sedative or hypotensive effects, which in turn may lead to falls and fractures. No studies were located that assessed the risk of hip fracture due to concurrent use of multiple antidepressants related to switching or add-on therapy.

This study aimed to investigate the risk of hip fracture associated with mirtazapine use and to examine the risk of hip fracture in older people after switching between or concurrently using mirtazapine and other antidepressants.

2 Methods

2.1 Setting

This case-control study was undertaken using data obtained from the Australian Government Department of Veterans' Affairs (DVA) health care claims database [24]. Data included demographics, information on hospital admissions and details of medicines reimbursed through the Pharmaceutical Benefits Scheme (PBS) and the Repatriation Pharmaceutical Benefits Scheme (RPBS). In December 2010, records for more than 250,000 DVA beneficiaries from all Australian states and territories were held in the database [24].

2.2 Study Design

In much the same way as in our past study [25], a matched case-control study design was employed to determine the associations between psychoactive medicines and hip fracture [26]. This design was chosen over a cohort design because it is suitable for assessing the impact of multiple exposures on a relatively uncommon outcome. The source

population consisted of DVA beneficiaries who were aged over 65 years between 1 January 2009 and 31 December 2012. Cases were members of the source population who were admitted to hospital for a hip fracture (International Classification of Diseases and Related Health Problems-10-Australian Modification codes S72.0 and S72.1) as a primary diagnosis between 1 January 2009 and 31 December 2012 [27]. Where multiple hip fractures were present in the data, only the first event was included. Each case's hospitalisation date was defined as the index date. Using risk set sampling [26], each case of hip fracture was matched with up to four randomly selected controls who were the same gender and age (± 2 years) as the case and who had not been hospitalised for hip fracture up to the case's index date. For each risk set of one case and up to four controls, the controls were assigned the same index date as the case. Both cases and controls needed to have at least 1 year of dispensing history prior to the index date.

2.3 Patient Characteristics

The following patient characteristics were assessed: age on the index date, gender, number of comorbidities during the year before the index date, socio-economic status and residential status on the index date. The number of comorbidities was assessed in terms of the Australian version of the Rx-Risk-V [28], which has been validated in Australians [28]. Morbidities treated by the psychoactive medicines under investigation were excluded so as to avoid adjusting for a variable containing exposures that were already in the statistical model. Socioeconomic status was measured using residential postcodes and the Australian Bureau of Statistics (ABS) quintiles of the socioeconomic indexes for areas (SEIFA) [29].

2.4 Medicine Codes

The following antidepressants were assessed: mirtazapine, TCAs, SSRIs and SNRIs. All effect estimates were adjusted for use of opioids, antiepileptics, anti-Parkinson medicines, antipsychotics, benzodiazepine-related medicines and anticholinesterases, as well as the antidepressants TCAs, SSRIs and SNRIs when these were not the subject of the analysis. Anatomic Therapeutic Chemical (ATC) classification codes were employed to define all medicines (Appendix 1, see electronic supplementary material [ESM]) [30].

2.5 Medicine Exposure Status

Prescription dispensing data were used to determine medicine exposure. As the number of days supplied was not available in the data set, a duration of use estimate was

determined for each specific medicine as the period within which 75% of patients returned for a repeat dispensing of that medicine [31]. All duration of use estimates were then reviewed independently by two pharmacists. For the majority of antidepressants, one prescription corresponded to 35 days of exposure. The duration of the current exposure window was set at one duration of use estimate before the index date. Every patient was classified as a new user, continuous user or non-user of each medicine. A patient was classified as a new user of a medicine if there was a dispensing for that medicine during the current exposure window, but no supply of the medicine up to 180 days before the dispensing date. A patient was classified as a continuous user of a medicine if there was one dispensing for that medicine during the current exposure window as well as one or more supplies of the medicine up to 180 days before the dispensing date. A patient was classified as a non-user of a medicine if there was no dispensing for that medicine during the current exposure window. The joint effects of mirtazapine and each of TCAs, SSRIs and SNRIs were then expressed by three separate variables with mutually exclusive categories of antidepressant exposure. These categories corresponded to use of two antidepressants together and use of each antidepressant without the other. Thus, patients were classified into the following mirtazapine/other antidepressant categories: initiation of both antidepressants, addition of one antidepressant to the other (probable switching or add-on therapy), continuous use of both antidepressants (concurrent use), initiation of one antidepressant without the other, continuous use of one antidepressant without the other, and no use of either antidepressant.

2.6 Data Analysis

Conditional logistic regression was employed to estimate the risk of hip fracture due to use of antidepressants alone, as expressed in the main effects variables, and mirtazapine in combination with other antidepressants, as expressed in the joint effects variables. For each individual antidepressant, no current use of that particular antidepressant was defined as the reference category. For each joint effect, no current use of either mirtazapine or the other antidepressant was defined as the reference category. Effects were estimated by fitting a multivariable conditional logistic regression model adjusting for potential confounding factors that were independently associated with hip fracture: number of co-morbidities, socio-economic status and use of other psychoactive medicines [25]. Where probable switching or add-on therapy occurred, the product strengths were examined to assess appropriateness. The potential for multicollinearity was assessed using the variance inflation factor, with values less than ten deemed acceptable. For

each effect estimate, power was calculated *a posteriori* using a formula applicable to case-control designs [32]. Power was deemed to be insufficient if it was < 80%.

With respect to combinations, the degrees to which combined effects differed from independent effects were examined using Rothman's relative excess risk due to interaction (RERI): $RERI = OR_{11} - OR_{10} - OR_{01} + 1$ [33]. OR_{11} denotes the effect estimates for concurrent use of mirtazapine and a given other antidepressant, OR_{10} denotes use of mirtazapine without the other antidepressant, and OR_{01} denotes use of the other antidepressant without mirtazapine. The 95% confidence interval (CI) surrounding each RERI was calculated using the Hosmer-Lemeshow delta method [34]. The Hosmer-Lemeshow delta method was chosen because, unlike alternative methods, it is less computationally intensive, is well established in the literature, and provides confidence intervals that are uniquely determined by case-control data [35, 36]. The effect of concurrent antidepressant use was considered to be sub-additive if the upper limit of the 95% CI for RERI was < 0, additive if the 95% CI included 0, or super-additive if the lower limit of the 95% CI exceeded 0 [33, 34].

All data analysis was performed in SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

3 Results

Overall, 8828 cases and 35,310 controls were included in this analysis. Cases and controls were similar for all baseline characteristics (Table 1).

There were insufficient mirtazapine initiators to assess the effect, as the power was below 80%. Compared with non-users of mirtazapine, existing users of mirtazapine had 27% greater odds of hip fracture (Table 2). Initiation of TCAs was not found to be associated with hip fracture; however, existing users of TCAs had 38% greater odds of hip fracture (Table 2). The odds of hip fracture were increased by factors of 2.73 and 2.38 for new use of SSRIs and SNRIs, respectively, and by factors of 1.77 and 1.51 for continuous use of SSRIs and SNRIs, respectively (Table 2).

In the assessment of mirtazapine-antidepressant combinations, the odds of hip fracture were elevated by a factor of 11 when an SSRI was added to continuous mirtazapine therapy, relative to no current use of either medicine (Table 3). The odds of hip fracture were also increased by a factor of 14 when a new TCA was added to continuous mirtazapine therapy (Table 3). Additive effects were identified for all antidepressant combinations that were used by both cases and controls (Table 4).

Table 1 Characteristics of cases and controls

Characteristic	No. of case patients <i>n</i> = 8828	No. of control patients <i>n</i> = 35,310
Female gender	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%)
Lower	1320 (15%)	5608 (16%)
Unknown	11 (0.1%)	80 (0.2%)
Residential status		
Community	5668 (64%)	23,170 (66%)
Residential aged care	3160 (36%)	12,140 (34%)

^aMedian (interquartile range)

When SSRIs were added to mirtazapine therapy in seven cases, the strength of mirtazapine dispensed before the SSRI did not appear to be subsequently reduced (Appendix 2, see ESM). The strength of mirtazapine appeared to be increased in three of the seven cases (Appendix 2). Similarly, when TCAs were added to mirtazapine therapy in all

four cases and in one control, the strength of mirtazapine dispensed before the TCA was not subsequently reduced (Appendix 3, see ESM).

4 Discussion

This study found that continuous use of mirtazapine was associated with increased risk of hip fracture among older people. When SSRIs and TCAs were added to mirtazapine, the risk of hip fracture in older people relative to no current use of these antidepressants was increased by a factor of 11 and 14, respectively. The overlapping use of these medicines may reflect three situations in clinical practice: switching from mirtazapine to other antidepressants, add-on therapy, or the addition of other antidepressants to treat comorbidities (e.g. an SSRI for anxiety or a TCA for neuropathic pain) [3]. The RERI did not reach significance, however, suggesting that combined use was not necessarily greater than the sum of the risk estimates for use of the antidepressants individually. The risk of hip fracture associated with continuously using both mirtazapine and an SSRI was also significant, although the magnitude of the risk estimate was lower than for the addition of an SSRI to mirtazapine therapy. This may be due to the greater potential for sedation and hypotension when antidepressants are initiated. Dosage may also play a role; however, a

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

Medicine use	No. of case patients (%) <i>n</i> = 8828	No. of control patients (%) <i>n</i> = 35,310	Unadjusted OR (95% CI)	Adjusted ^a OR (95% CI)
Mirtazapine				
New	35 (0.4)	90 (0.3)	1.59 (1.08–2.36)	1.11 (0.74–1.66) ^b
Continuous	375 (4.2)	1026 (2.9)	1.49 (1.32–1.68)	1.27 (1.12–1.44)
No	8418 (95)	34,194 (97)	1.00 [Reference]	1.00 [Reference]
TCAs				
New (initiation)	47 (0.5)	109 (0.3)	1.76 (1.25–2.48)	1.40 (0.98–1.99)
Continuous	434 (4.9)	1126 (3.2)	1.58 (1.41–1.77)	1.38 (1.23–1.55)
No	8347 (95)	34,075 (97)	1.00 [Reference]	1.00 [Reference]
SSRIs				
New (initiation)	98 (1.1)	122 (0.4)	3.45 (2.64–4.50)	2.73 (2.07–3.58)
Continuous	1232 (14)	2598 (7.4)	2.06 (1.92–2.22)	1.77 (1.64–1.91)
No	7498 (85)	32,590 (92)	1.00 [Reference]	1.00 [Reference]
SNRIs				
New (initiation)	27 (0.3)	37 (0.1)	2.99 (1.82–4.91)	2.38 (1.43–3.96)
Continuous	256 (2.9)	603 (1.7)	1.72 (1.49–2.00)	1.51 (1.29–1.75)
No	8545 (97)	34,670 (98)	1.00 [Reference]	1.00 [Reference]

CI confidence interval, OR odds ratio, SNRI serotonin and noradrenaline reuptake inhibitor, SSRI selective serotonin reuptake inhibitor, TCA tricyclic antidepressant

^aAdjusted for number of comorbidities, socio-economic status and all other psychoactive medicines assessed

^bPower < 80% found *a posteriori*

Table 3 Case-control study results for the joint effects of mirtazapine with each of three antidepressant groups

Use	AD group												
	TCAs						SNRIs						
	Cases <i>n</i> = 8828	AD	Controls <i>n</i> = 35,310	Adjusted ^a OR (95% CI)	Cases <i>n</i> = 8828	Controls <i>n</i> = 35,310	Adjusted ^a OR (95% CI)	Cases <i>n</i> = 8828	Controls <i>n</i> = 35,310	Adjusted ^a OR (95% CI)	Cases <i>n</i> = 8828	Controls <i>n</i> = 35,310	Adjusted ^a OR (95% CI)
New	0	New	1	-	4	2	4.8 (0.9-27) ^b	1	0	-	1	0	-
(Initiate mirtazapine and AD)	(0%)	(0.003%)	(0.003%)		(0.05%)	(0.01%)		(0.01%)	(0%)		(0.01%)	(0%)	
New	2	Continuous	2	2.4 (0.3-19) ^b	2	7	0.9 (0.2-4.4) ^b	0	3	-	0	3	-
(Add mirtazapine to AD)	(0.02%)	(0.01%)	(0.01%)		(0.02%)	(0.02%)		(0%)	(0.008%)		(0%)	(0.008%)	
Continuous	4	New	1	14 (1.4-132) ^b	7	2	11 (2.2-51)	1	2	1.7 (0.1-19) ^b	1	2	1.7 (0.1-19) ^b
(Add AD to mirtazapine)	(0.05%)	(0.003%)	(0.003%)		(0.1%)	(0.01%)		(0.01%)	(0.005%)		(0.01%)	(0.005%)	
Continuous	8	Continuous	17	1.5 (0.6-3.5) ^b	22	33	2.4 (1.4-4.2)	12	22	1.9 (0.95-4.0) ^b	12	22	1.9 (0.95-4.0) ^b
(Cont. mirtazapine and AD)	(0.1%)	(0.05%)	(0.05%)		(0.2%)	(0.1%)		(0.1%)	(0.06%)		(0.1%)	(0.06%)	
New	33	No	87	1.1 (0.7-1.7) ^b	29	81	1.2 (0.7-1.8) ^b	34	87	1.1 (0.8-1.7) ^b	34	87	1.1 (0.8-1.7) ^b
(Initiate mirtazapine alone)	(0.4%)	(0.2%)	(0.2%)		(0.3%)	(0.2%)		(0.4%)	(0.2%)		(0.4%)	(0.2%)	
No	43	New	107	1.3 (0.9-1.9) ^b	87	118	2.6 (1.9-3.4)	25	35	2.4 (1.4-4.0)	25	35	2.4 (1.4-4.0)
(Initiate AD alone)	(0.5%)	(0.3%)	(0.3%)		(1.0%)	(0.3%)		(0.3%)	(0.1%)		(0.3%)	(0.1%)	
Continuous	363	No	1008	1.3 (1.1-1.43)	346	991	1.3 (1.1-1.4)	362	1002	1.3 (1.1-1.4)	362	1002	1.3 (1.1-1.4)
(Cont. mirtazapine alone)	(4.1%)	(2.9%)	(2.9%)		(3.9%)	(2.8%)		(4.1%)	(2.8%)		(4.1%)	(2.8%)	
No	424	Continuous	1107	1.4 (1.2-1.6)	1208	2558	1.8 (1.6-1.9)	244	578	1.5 (1.3-1.8)	244	578	1.5 (1.3-1.8)
(Cont. AD alone)	(4.8%)	(3.1%)	(3.1%)		(14%)	(7.2%)		(2.8%)	(1.6%)		(2.8%)	(1.6%)	
No	7951	No	32,980	1.00 [Ref]	7123	31,518	1.00 [Ref]	8149	33,581	1.00 [Ref]	8149	33,581	1.00 [Ref]
(No mirtazapine or AD)	(90%)	(93%)	(93%)		(81%)	(89%)		(92%)	(95%)		(92%)	(95%)	

AD antidepressant, CI confidence interval, OR odds ratio, SNRI serotonin and noradrenaline reuptake inhibitor, SSRI selective serotonin reuptake inhibitor, TCA tricyclic antidepressant

^aAdjusted for number of comorbidities, socio-economic status and all other psychoactive medicines assessed

^bPower < 80% found *a posteriori*

Table 4 Additive interaction assessment for concurrent use of mirtazapine and antidepressant groups

Medicine use		RERI (95% CI)		
Mirtazapine	AD	TCA's	SSRIs	SNRIs
New	New	–	2.1 (–6.3 to 11)	–
(Initiation of mirtazapine with AD)				
New	Continuous	1.0 (–4.1 to 6.0)	–1.0 (–2.5 to 0.5)	–
(Addition of mirtazapine to AD)				
Continuous	New	12 (–19 to 43)	7.7 (–9.0 to 24)	–1.0 (–5.3 to 3.3)
(Addition of AD to mirtazapine)				
Continuous	Continuous	–0.2 (–1.4 to 1.1)	0.4 (–0.9 to 1.7)	0.2 (–1.3 to 1.6)
(Continuous mirtazapine with AD)				

AD antidepressant, CI confidence interval, RERI relative excess risk due to interaction, SNRI serotonin and noradrenaline reuptake inhibitor, SSRI selective serotonin reuptake inhibitor, TCA tricyclic antidepressant

limitation of the study was inability to assess dosage as it was not available in the data source.

Despite clinical recommendations to gradually reduce mirtazapine dose when initiating a new antidepressant at a low dose [3, 15], the strengths of mirtazapine in this study did not appear to be reduced upon introducing TCAs and SSRIs. Our study was limited by a lack of dose information in the dataset, so it was not possible to tell whether the mirtazapine 30-mg scored tablets were halved before use. Use of mirtazapine at strengths of 30–45 mg is not consistent with current clinical guidelines to switch between antidepressants via cross-tapering [15].

Rather than switching from mirtazapine to the other antidepressants, patients may have been using mirtazapine together with SSRIs or TCAs in the treatment of refractory depression or comorbidities. Antidepressant add-on therapy in the treatment of refractory depression is controversial and potentially inappropriate [22, 37]. The Maudsley Prescribing Guidelines in Psychiatry state that the concurrent use of an SSRI with mirtazapine (30–45 mg/day) is one of the first-choice drug treatments for refractory depression [15]. The observed addition of an SSRI to mirtazapine is consistent with these guidelines because mirtazapine was used at strengths of 30–45 mg. However, this study was conducted in an older population and the Australian Medicines Handbook Drug Choice Companion: Aged Care suggests that prescribers should initiate mirtazapine in older patients at a dose of 15 mg/day and, due to a lack of evidence supporting a therapeutic benefit and the potential for interactions, avoid all antidepressant combinations [37]. The results of this case–control study suggest that prescribers may not always be following the recommendations in the Australian Medicines Handbook Drug Choice Companion: Aged Care [37].

To the best of our knowledge, this is the first study to investigate the risk of hip fracture due to concurrent use of mirtazapine with other antidepressants. The results of this

study may help general practitioners and psychiatrists to weigh up the risks and benefits of prescribing add-on therapy in older populations and to be more cautious when switching therapies and tapering doses. A strength of this study was the classification of patients as new and continuous medicine users. This prevented the survivor bias that would have otherwise affected estimates of current medicine use [38]. The use of administrative claims data precluded recall bias. Furthermore, as the median age of our subjects was 88 years and half of hip fractures among the elderly occur in those aged over 85 years, our results can be generalised from the study population to other older Australians over 65 years of age [39].

This case–control study has several limitations. There was inadequate power to assess new use of mirtazapine individually as well as in combination with other antidepressants, mainly due to the low use of mirtazapine in the study population. This led to uncertainty in our conclusions of no effect. Larger datasets are required to further study the risk of hip fracture in older people following concurrent use of mirtazapine with other antidepressants. As in any observational study, unmeasured confounding factors could have biased the effect estimates towards or away from the null. In this case–control study, potential unmeasured confounders of the associations between antidepressant use and hip fracture include the severity of depression symptoms and ability to undertake activities of daily living (ADLs) [40]. Since case-crossover studies have reported associations between antidepressants and hip fracture, it is likely that antidepressant use does indeed increase the risk of hip fracture independently of patient-specific, time-invariant confounders [8, 41]. Since medicine use was inferred from dispensing records, a further limitation of this study is the potential misclassification of non-users of medicines as current users of medicines, and vice versa. However, a sensitivity analysis in which duration of use estimates were shortened by 50% found no impact of

duration of exposure on effect estimates (results not shown). The use of the reference group of never users and past users is conservative and biases the result to the null. Thus, our study may have under-estimated risk. Furthermore, the lack of information on dosage prevented a rigorous assessment of the appropriateness of potential add-on therapy, switching or tapering.

5 Conclusions

Overall, adding an SSRI or TCA to mirtazapine therapy or continuously using both an SSRI and mirtazapine significantly increased the risk of hip fracture among older people. The risk of hip fracture for each of these antidepressant combinations was similar to the sum of the corresponding effects of the individual medicines. The results of this study highlight the risks of employing add-on therapy or switching antidepressants in older people, providing further evidence to support cautious cross-tapering where switching between antidepressants is required.

Compliance with Ethical Standards

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Conflict of interest Michael Leach, Nicole Pratt and Libby Roughead have no conflicts of interest directly relevant to the content of this manuscript.

Consent to participate Informed consent was not required for the purpose of this study.

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