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ORIGINAL ARTICLE

Serotonergic antidepressant use and the risk of fracture: a population-based nested case–control study

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Abstract
Summary This is the first study to investigate the association between the use of selective serotonin reuptake inhibitor (SSRI)/serotonin–norepinephrine reuptake inhibitor (SNRI) and the risk of fractures using a nationwide representative cohort of ethnic Chinese. Current use of SSRI/SNRI and the co-morbidity, especially osteoporosis and history of falling, play an important role in the increased risk of fractures.
Introduction This nested case–control study examines the association between the timing, intensity, and individual components of serotonergic antidepressant (including SSRIs and SNRIs) use and the risk of all-cause fracture.
Methods Using the 2002–2011 Taiwan National Health Insurance Research Database, we identified patients who received at least three prescriptions of antidepressants between January 1st 2002 and December 31st 2010 as our study cohort. In the study cohort, we identify 8250 patients who had first admission for fracture and 33,000 matched controls (1:4, matched by age, sex, and cohort entry date). Multivariate conditional logistic regression was used to estimate the association between the use of serotonergic antidepressants and the risk of fracture.
Results Current users of serotonergic antidepressants were associated with an increased risk of fracture (adjusted odds ratio (aOR) 1.16 [95 % confidence interval 1.07–1.25]). Furthermore, a higher risk of fractures was found in patients with osteoporosis (aOR 3.05 [2.73–3.42]) or a history of falling (aOR 6.13 [3.41–11.0]). The risks of fracture between SSRI and SNRI users were comparable.
Conclusion Current use of SSRI/SNRI is associated with an increased risk of all caused fractures. Additionally, the co-morbidity, especially osteoporosis and a history of falling, plays an important role in the risk of fractures.

Keywords Falling · Fracture · Osteoporosis · Serotonergic antidepressants

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Introduction

The use of antidepressant has been steadily increasing, not only in the elderly but also in the young and middle-aged populations [1–3]. Among all antidepressants, selective serotonin reuptake inhibitors (SSRIs) are the most frequently used, because of their favorable adverse effect profile [3, 4]. However, some studies demonstrated that the use of SSRIs is associated with decreased bone mineral density (BMD) and increased risk of fracture [5–11]. A systematic review and meta-analysis of 12 studies showed that SSRI use is associated with an increased risk of fractures (adjusted odds ratio [aOR] 1.69, 95 % confidence interval (CI) 1.51–1.90) [12]. Recently, a meta-analysis of 34 studies further reported a significant

increased risk of fractures associated with the SSRI use (risk ratio [RR] 1.39, 95 % CI 1.32–1.47) [13].

A possible mechanism for the increased risk of fracture associated with SSRI is that SSRIs influence the serotonin transporter system in bone tissue [14]. There are several serotonin receptors that have been identified in osteocytes [15–17]. Nevertheless, most studies have focused on SSRI's impact on bone metabolism. Very few studies have assessed the effect on the risk of fractures of serotonin–norepinephrine reuptake inhibitors (SNRIs), a frequently used class of antidepressants with similar serotonergic properties like SSRIs. Shea et al. examined the effect of SNRIs on biomarkers of bone turnover and suggested that venlafaxine (a commonly used SNRI) was associated with increased bone resorption [18]. Additional studies are therefore needed to assess the impact of this potential effect on the risk of clinically meaningful fractures. Furthermore, almost all the studies used Western subjects, and therefore, the findings cannot be easily generalized to non-Western populations.

In order to gather more clinical information on this important drug safety issue, we conducted a nested case–control study and assessed the association between the timing and the intensity of serotonergic antidepressant use (including SSRIs and SNRIs) and the risk of fracture in an Asian population. In order to enhance the application of our study findings to clinical settings, we included in the study all frequently used individual SSRIs and SNRIs.

Method

Data source

The National Health Insurance Research Database (NHIRD) is population-based claims data of Taiwan's mandatory National Health Insurance (NHI) program. The NHI program was launched in 1995 and covers over 99 % of Taiwan's population (approximately 23 million residents). The database provides abundant data including ambulatory care, inpatient care, prescriptions, and medications and has been commonly used for pharmacoepidemiology research in Taiwan [19]. Our study includes the subset of the NHIRD, the Longitudinal Health Insurance Database (LHID), which contains approximately 3 million individuals, randomly sampled from the Registry for Beneficiaries of the NHIRD.

Study cohort

We identified in the LHID all patients who were 20 years old and older and who were given at least three prescriptions of antidepressants (at least one prescription of SSRI or SNRI) between January 1st 2002 and December 31st 2010. The date of the first prescription of the SSRI or SNRI was assigned as the cohort entry date. To ensure a new user design, patients who received antidepressants 2 years prior their cohort entry date were excluded.

Cases and controls

Among our study cohort, we identified patients who were firstly diagnosed with fracture (ICD-9-CM codes 800-829) between 2002 and 2010. Only the first visit for fracture was included in our study. The date of first visit for fracture was defined as the index date. Using incidence-density sampling, cases were matched with four controls by age (±2 year), sex, and cohort entry date (±30 day). The index date of the control

Table 1 Baseline characteristic of the study cohort

	Case (n=8250)	Control (n=33,000)	p value
Age, means (SD)	46.14 (15.99)	46.07 (15.91)	0.739
Gender, male (%)	3327 (40.32)	13,308 (40.32)	1.000
Co-morbidities (%)			
Hypertension	1989 (24.11)	7171 (21.73)	<0.001
Diabetes mellitus	1159 (14.05)	3741 (11.30)	<0.001
Osteoporosis	668 (8.10)	896 (2.72)	<0.001
Fall history	32 (0.39)	20 (0.06)	<0.001
Cardiac disorder	514 (6.23)	1864 (5.65)	<0.001
COLD	217 (2.63)	595 (1.80)	<0.001
Urinary incontinence	85 (1.03)	196 (0.59)	<0.001
Parkinson disease	243 (2.95)	607 (1.84)	<0.001
CMD	138 (1.67)	267 (0.81)	<0.001
Dementia	338 (4.10)	1092 (3.31)	<0.001
Depression	2417 (29.30)	8285 (25.11)	<0.001
Liver disease	1059 (12.84)	3162 (9.58)	<0.001
PVD	91 (1.10)	241 (0.73)	<0.001
CVD	363 (4.40)	1097 (3.32)	<0.001
Arthritis	772 (9.36)	1721 (5.22)	<0.001
CKD	191 (2.32)	574 (1.74)	<0.001
Glaucoma	176 (2.13)	698 (2.12)	<0.001
Co-medications (%)			
Opiates	289 (3.50)	377 (1.14)	<0.001
Non-opioid analgesic	5217 (63.20)	16,896 (51.20)	<0.001
Antipsychotics	2103 (25.49)	6190 (18.75)	<0.001
Anxiolytics	5166 (62.62)	17,259 (52.30)	<0.001
Sedatives	4343 (52.64)	13,524 (40.98)	<0.001
Corticosteroid	1480 (17.94)	4308 (13.05)	<0.001
Diuretic	740 (8.97)	2246 (6.81)	<0.001
HRT	529 (6.41)	1902 (5.76)	<0.001
Antiepileptic drugs	2096 (25.41)	5630 (17.06)	<0.001
TCA	538 (6.52)	1589 (4.82)	<0.001

PVD peripheral vascular disease, *COLD* chronic obstructive lung disease, *CVD* cerebrovascular disease, *CMD* chronic mental disorder, *HRT* hormone replace therapy, *CKD* chronic kidney disease, *TCA* tricyclic antidepressants

is the index date of the corresponding case. All patients were followed from the cohort entry date to the index date, and this period is the observational period.

Exposure to SSRIs and SNRIs

All antidepressant prescriptions received within the observational period by our cases and controls were retrieved from the LHID. In the primary analysis, different types of antidepressants were considered as one group, including SSRIs (fluoxetine, paroxetine, sertraline, citalopram, escitalopram, and fluvoxamine) and SNRIs (venlafaxine, duloxetine, and milnacipran). We assessed the association of timing (current, former, and non-user), intensity of antidepressant use, and the individual component use, with the risk of fracture.

A current user was defined as one whose last day of using antidepressants was within 30 days before the index date. A former user was one whose last day of using prescribed antidepressants was between 31 and 365 days before the index date. A non-user was one with no prescriptions of antidepressants within 365 days before the index date. Pre-planned sensitivity analyses were conducted by varying the definition of current user of SSRI/SNRI as patients whose last day of using SSRI/SNRI was within 60 and 90 days before the index date.

The intensity of exposure to antidepressants was calculated by the medication possession ratio (MPR) during the follow-up period as the total antidepressant prescribing days divided

Table 2 Crude and adjusted risks for fractures and exposure to SSRI/SNRIs

	Crude OR	95 % CI	*p* value	Adjusted OR	95 % CI	*p* value
Exposure to SSRI/SNRIs (reference: non-users)						
Current user	1.55	1.45–1.66	<0.001	1.16	1.07–1.25	<0.001
Past user	1.23	1.15–1.36	<0.001	0.97	0.90–1.05	0.4385
Co-morbidities						
Hypertension	1.18	1.11–1.26	<0.001	0.99	0.93–1.07	0.8568
Diabetes mellitus	1.31	1.22–1.42	<0.001	1.16	1.08–1.26	<0.001
Osteoporosis	3.44	3.08–3.83	<0.001	3.05	2.73–3.42	<0.001
Fall history	6.62	3.75–11.7	<0.001	6.13	3.41–11.00	<0.001
Cardiac disorder	1.11	1.00–1.23	0.0408	0.91	0.82–1.02	0.1093
COLD	1.51	1.28–1.77	<0.001	1.18	0.99–1.40	0.0661
Urinary incontinence	1.75	1.35–2.26	<0.001	1.40	1.06–1.83	0.0158
Parkinson disease	1.60	1.42–1.94	<0.001	1.36	1.15–1.61	<0.001
CMD	2.09	1.70–2.57	<0.001	1.61	1.30–2.00	<0.001
Dementia	1.31	1.14–1.50	<0.001	1.26	1.08–1.46	0.0028
Depression	1.25	1.19–1.33	<0.001	1.05	0.99–1.11	0.1306
Liver disease	1.40	1.30–1.51	<0.001	1.21	1.12–1.31	<0.001
PVD	1.52	1.20–1.93	<0.001	1.16	0.90–1.45	0.2568
CVD	1.36	1.20–1.54	<0.001	1.16	1.06–1.33	0.025
Arthritis	1.90	1.74–2.08	<0.001	1.58	1.43–1.73	<0.001
CKD	1.35	1.14–1.59	<0.001	1.11	0.93–1.32	0.2711
Glaucoma	1.00	0.85–1.20	0.9173	0.93	0.78–1.12	0.4561
Co-medications						
Opiates	3.13	2.68–3.66	<0.001	2.20	1.87–2.60	<0.001
Non-opioid	1.65	1.58–1.74	<0.001	1.42	1.35–1.50	<0.001
Antipsychotics	1.50	1.41–1.58	<0.001	1.14	1.07–1.21	<0.001
Anxiolytics	1.60	1.51–1.68	<0.001	1.81	1.11–1.25	<0.001
Sedatives	1.64	1.56–1.73	<0.001	1.32	1.24–1.40	<0.001
Corticosteroid	1.46	1.37–1.56	<0.001	1.15	1.08–1.24	<0.001
Diuretic	1.38	1.26–1.51	<0.001	1.08	0.99–1.20	0.093
HRT	1.13	1.02–1.25	0.0218	0.93	0.84–1.04	0.1822
Antiepileptic	1.67	1.57–1.76	<0.001	1.30	1.22–1.39	<0.001
TCA	1.38	1.25–1.53	<0.001	1.04	0.93–1.16	0.4963

PVD peripheral vascular disease, *COLD* chronic obstructive lung disease, *CVD* cerebrovascular disease, *CMD* chronic mental disorder, *HRT* hormone replace therapy, *CKD* chronic kidney disease, *TCA* tricyclic antidepressant

by the total number of days of the follow-up period [20]. Patients were classified into three intensity level based on their MPR: low (MPR <0.2), intermediate (MPR ≥0.2 to MPR <0.8), and high (MPR ≥0.8). Furthermore, we assess the use of individual component of SSRI/SNRI with the risk of fracture.

Co-morbidities and co-medications

As many diseases and drugs other than serotonergic antidepressants may affect the fracture risk [21, 22], we retrieved these information using claims data 1 year before the index date for our cases and controls. The co-morbidities taken into consideration included hypertension, diabetes mellitus, osteoporosis, history of falling, cardiac disorders, chronic obstructive lung disease (COLD), urinary incontinence (UI), Parkinson disease, chronic mental disease (CMD), dementia, depression, liver disease, peripheral vascular disease (PVD), cerebrovascular disease (CVD), arthritis, chronic kidney disease (CKD), and glaucoma. The co-medications consisted of opiate, non-opioid analgesics, antipsychotics, anxiolytics, sedatives, corticosteroid, diuretic, hormone replacement therapy (HRT), antiepileptics, and tricyclic antidepressants (TCAs).

Statistical analysis

McNemar tests were used to compare categorical variables between cases and controls. Multivariate conditional logistic regressions were used to evaluate the associations between the exposure to antidepressants and risk of fracture. All models were adjusted for co-morbidities and co-medications. The associations were presented as adjusted odds ratios (aORs) and 95 % confidence intervals (CIs). The p values were two sided, with $p<0.05$ considered statistically significant. All data management and analyses were performed using SAS 9.3 for Windows (SAS Institute, Cary, NC, USA).

Results

We identified 8250 cases and 33,000 matched controls by age, sex, and cohort entry date. Overall, the distribution of age, sex, and cohort entry year in cases and controls were well matched. Cases were more likely to have co-morbid conditions and co-medications than controls (Table 1).

After adjusting for all co-morbidities and co-medications, only current users were associated with an increased risk of fractures (current; aOR 1.16 [95 % CI 1.07–1.25], $p<0.001$). However, higher risks of fracture was found in patients with osteoporosis (aOR 3.05 [2.73–3.42], $p<0.001$), history of falling (aOR 6.13 [3.41–11.0], $p<0.001$), chronic mental disease (aOR 1.61 [1.30–2.00], $p<0.001$), and arthritis (aOR 1.58 [1.43–1.73], $p<0.001$). Patients who were exposed to drugs that are potentially associated with fractures within 1 year before the index date also had a higher risk of fracture, especially those exposed to opiate analgesics (aOR 2.20 [1.87–2.60], $p<0.001$) (Table 2).

Among current users, we found a temporal relationship between use of SSRI/SNRI and risk of fracture. The risk of fracture appeared to decrease as the MPR increase (MPR <0.2: aOR 1.19 [1.01–1.41], $p=0.031$; 0.2≤MPR<0.8: aOR 1.15 [1.02–1.29], $p=0.0217$; MPR ≥0.8: aOR 1.10 [0.98–1.22], $p=0.893$). The risk of fracture was greater for patients who used combination of SSRI and SNRI (with aOR of 1.16 [95 % CI 1.05–1.28], $p=0.0025$), but not in patients who used SSRI or SNRI alone (Table 3). Separate ORs were estimated for exposure to each SSRIs or SNRIs. Compared to non-users, there were no differences in the risk of fractures found for individual SSRIs or SNRIs (Table 4).

Table 3 Crude and adjusted risks for fractures and intensity or types of antidepressant; current users of antidepressant

	Total	Case	Control	Crude OR		Adjusted OR	
	n	*n*	*n*	95 % CI	*p* value	95 % CI	*p* value
Non-users	17,989	3259	14,730	1.00 (Reference)		1.00 (Reference)	
Intensity of antidepressant							
MPR <0.2	3759	816	2943	1.50 (1.27–1.75)	<0.001	1.19 (1.01–1.41)	0.0331
0.8>MPR≥0.2	4750	1119	3631	1.48 (1.33–1.66)	<0.001	1.15 (1.02–1.29)	0.0217
MPR ≥0.8	3420	828	2592	1.38 (1.25–1.53)	<0.001	1.10 (0.98–1.22)	0.0893
Types of antidepressant							
SSRI alone	6197	1303	4894	1.32 (1.18–1.47)	<0.001	1.10 (0.98–1.24)	0.1018
SNRI alone	901	205	696	1.52 (1.26–1.85)	<0.001	1.16 (0.95–1.42)	0.1536
Combination	4738	1255	3483	1.68 (1.54–1.82)	<0.001	1.16 (1.05–1.28)	0.0025

MPR medication possession ratio

Table 4 Adjusted risks for fracture among each SSRI or SNRI

	Case	Control	Adjusted OR	95 % CI	*p* value
Non-user	3259	14,730	1.00 (Reference)		
SSRI					
Fluoxetine	1782	7442	1.03	0.96–1.10	0.3794
Sertraline	1144	4823	1.02	0.94–1.10	0.6529
Citalopram	492	1928	1.05	0.94–1.18	0.3551
Fluvoxamine	189	896	0.89	0.75–1.05	0.1567
Paroxetine	824	3422	1.06	0.97–1.54	0.2260
Escitalopram	332	1301	1.09	0.95–1.25	0.2448
SNRI					
Venlafaxine	522	2102	1.02	0.92–1.14	0.7058
Duloxetine	113	415	1.12	0.89–1.41	0.3361
Milnacipran	24	121	0.84	0.54–1.33	0.4615

We also performed a sensitivity analysis by varying the cut-off for *current* and *past* user of SSRI/SNRI. We found that only current users of SSRI/SNRI were associated with increased risks of fracture (cut-off=60 days, current user: aOR 1.14 [1.06–1.20], p=0.001, and cut-off=90 days, current user: aOR 1.12 [1.04–1.21], p=0.0023) (Table 5).

Discussion

To our knowledge, this is the first study investigating the association between the use of SSRIs and SNRIs and the risk of fracture using a nested matched case–control design in a nationwide representative cohort of ethnic Chinese. We found that current use of SSRI/SNRIs increased fracture risk by 16 %. Our sensitivity analyses by varying the definition of *current users* yield similar results. These findings are consistent with several previous studies. Brand et al. found that the risk of hip/femur fractures is increased in current users of antidepressant and declines rapidly after discontinuation of use [9]. Liu et al. and Rabenda et al. also showed that current users of antidepressants are associated with a higher risk of hip fractures and non-vertebral fractures [23, 24]. In addition, the prescription prevalence of antidepressants rose significantly after hip fractures and are known to have a negative effect on bone and on the risk of falling, and finally on re-fracturing [25].

Our study is also the first study to use MPR for exploring the association between intensity of SSRI/SNRI use and risk of fracture. Recently, Zucker et al. used proportion of days covered (PDC) as an indicator of adherence to investigate the association between adherence to SSRI treatment and risk of bone loss-related events [15]. They suggest that a higher adherence to SSRI treatment is significantly associated with an increased risk of bone loss-related events. In contrast, we found the risk of fracture decreased as the MPR increased. The differences can be explained by the following: First, this temporal association may be supported by the study done by Brand et al. They found that the risk of hip and femur fractures is increased in current users of antidepressant and declines rapidly after discontinuation of use [9]. Furthermore, patients may discontinue their SSRI/SNRI due to drug-associated adverse events (such as fracture) and resulting in a lower MPR of drug exposure. However, more researches are warranted to clarify such findings.

Secondly, the confounding factors included for adjustment may further explain this discrepancy. Our study included 17 co-morbidities and 10 co-medications associated with the risk of fracture. However, the study done by Zucker et al. included only 10 associated confounding factors [15]. Our study produced similar results when we only included co-morbidities for adjustments. However, when all the confounding factors are included for adjustments, the relationship of intensity and the outcome become not statistically significant. In addition to timing of SSRI/SNRI use, our findings were consistent with existing evidence that underlying diseases and co-medications are influential on the risk of fracture. For example, Hubbard R. et al. found that history of falling has an important impact on the association between SSRIs and hip fracture [26].

Table 5 Sensitivity analyses: different cut-off points of current and past users of SSRI/SNRI and risk of fracture

Exposure to SSRI/SNRI	Case (n=8250)	Control (n=33,000)	aOR	95 % CI	*p* value
30 days					
Current user	2763	9166	1.16	1.07–1.25	<0.001
Past user	2228	9104	0.97	0.90–1.05	0.4385
60 days					
Current user	3182	10,803	1.14	1.06–1.2	0.0010
Past user	1809	7467	0.97	0.89–1.05	0.3701
90 days					
Current user	3469	11,957	1.12	1.04–1.21	0.0023
Past user	1522	6313	0.96	0.88–1.04	0.3476

Reference group: non-users

Our results extend the current evidence by evaluating the association between SNRI and risk of fracture. No study has addressed this issue before even SNRIs have similar serotonergic properties like SSRIs. We found that the risks of fracture were comparable in patients who used SSRI or SNRI alone. Furthermore, the risk of fractures was not significantly different among each SSRIs or SNRIs. However, we found that combined use of SSRIs and SNRIs was associated with an increased risk of fracture. Such association could be explained by the severity of depressive symptoms. According to clinical guidelines, patients who do not respond to one antidepressant may use a combination of two different kinds of antidepressants to control their disease [27]. As depression itself has been reported to be associated with increased risks of fall-related events, such as fractures, those who used a combination of SSRI and SNRI may represent a group of patients vulnerable to fracture [28].

Our study has some limitations. First, as this is a claims-based database, we cannot retrieve information not routinely collected in claims database such as smoking, body mass index (BMI), and severity of depressions. In particular, depressions were also suggested to increase the risk of fall-related events [28]. Our study thus includes those who received at least three prescriptions of antidepressants to minimize the variation of underlying clinical situations. Secondly, our study endpoint was all fracture instead of fractures more likely to be osteoporosis related. Therefore, the results may not be specific to SSRI-related bone resorption-induced fractures. The reason that we included all fractures is because there are two possible mechanisms of action regarding SSRI-related fractures. One possible mechanism concerns SSRI/SNRI-mediated osteoporosis events. This pathway takes time to develop the osteoporosis-related fracture risk. Existing evidence suggests that it takes about three or more months [29]. However, there are also some studies that show that the fracture is more likely to happen within the first 15 days after initiation of SSRI treatment [26]. The cause of this early effect on fracture may be associated with the SSRI-related syncope, postural hypotension, or dizziness [9, 30, 31]. Therefore, in order to catch all possible causes of SSRI-related fractures, we did not limit our study endpoint to "osteoporosis-related fractures." However, we have done a subgroup analysis focusing on the association between the use of serotonergic antidepressant in postmenopausal women (age ≥55) and risk of fragility fracture (including hip, spine, wrist, and femoral fractures) and yielded similar results.

There are certain strengths to our study. To our knowledge, this study is the first to investigate the association between the use of SSRI/SNRI and the risk of fracture using a nested matched case–control study design in a nationwide representative cohort of ethnic Chinese. In an aging society, the problems of osteoporosis-related disabilities create both medical economic burdens seen in many Asian countries which make these studies clinically significant [32, 33]. In particular, a higher risk of fracture associated with current use of serotonergic antidepressant was found in the elderly when stratifying our study cohort into two age groups (aOR; ≥65 years old 1.45 vs. <65 years old 1.11). Secondly, the use of antidepressants is increasing among the younger generation. Therefore, our study population was not limited to the elderly and the results can be adapted to broad-range age groups. Thirdly, to enhance the application of our study results to clinical settings, we examine the fracture risk among individual SSRIs or SNRIs. Finally, we included many clinical-related confounding factors to evaluate the relationship between SSRI/SNRI use and the risk of fracture. By doing so, we have found that several important diseases potentially increase the risk of fractures. These results convey the need for more studies to be done on those high-risk populations.

Conclusion

The current use of SSRI/SNRI is associated with risk of fractures. Furthermore, patients with osteoporosis and history of falling have increased risk of fractures.

Screening of bone mineral density and supplementation with calcium and vitamin D are recommended during the SSRI/SNRI treatment period in high-risk patients.

Conflicts of interest None.

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