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ORIGINAL RESEARCH ARTICLE

Serotonin–Norepinephrine Reuptake Inhibitor and Selective Serotonin Reuptake Inhibitor Use and Risk of Fractures: A New-User Cohort Study Among US Adults Aged 50 Years and Older

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Abstract

Background Antidepressants may increase the risk of fractures by disrupting sensory-motor function, thereby increasing the risk of falls, and by decreasing bone mineral density and consequently increasing the fall- or impact-related risk of fracture. Selective serotonin reuptake inhibitor (SSRI) antidepressants appear to increase fracture risk relative to no treatment, while less is known about the effect of serotonin–norepinephrine reuptake inhibitor (SNRI) antidepressants, despite SNRIs being prescribed with increasing frequency. No prior study has directly examined how fracture risk differs among patients initiating SNRIs versus those initiating SSRIs.

Objective The objective of this study was to assess the effect of SNRI versus SSRI initiation on fracture rates.

Data Source Data were derived from a PharMetrics claims database, 1998–2010, which is comprised of commercial health plan information obtained from managed care plans throughout the US.

Methods We constructed a cohort of patients aged 50 years or older initiating either of the two drug classes (SSRI, $N = 335{,}146$; SNRI, $N = 61{,}612$). Standardized mortality weighting and Cox proportional hazards regression were used to estimate hazard ratios (HRs) for fractures by antidepressant class.

Results In weighted analyses, the fracture rates were approximately equal in SNRI and SSRI initiators: HRs for the first 1- and 5-year periods following initiation were 1.11 [95 % confidence interval (CI) 0.92–1.36] and 1.06 (95 % CI 0.90–1.26), respectively. For the subgroup of patients with depression who initiated on either SNRIs or SSRIs, those initiating SNRIs had a modestly, but not significantly, elevated fracture risk compared with those who initiated on SSRIs [HR 1.31 (95 % CI 0.95–1.79)].

Conclusions We found no evidence that initiating SNRIs rather than SSRIs materially influenced fracture risk among a cohort of middle-aged and older adults.

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Key Points

There is no statistically significant difference in the rate of fracture among patients who initiate serotonin–norepinephrine reuptake inhibitors (SNRIs) versus those who initiate selective serotonin reuptake inhibitors.

Future studies should examine whether the elevated fracture-risk trend we observe among patients with depression who initiate on SNRIs is present among high fracture-risk populations.

1 Introduction

Since the late 1990s, selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) have become the mainstream pharmacological treatments for patients with depressive disorders [1, 2] (due in part to the perception that SSRIs and SNRIs have more favorable side-effect profiles than older drugs such as tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs] [3–6]), with the possible exception of fracture risk, which is of particular concern among older adults [7]. Antidepressants have been hypothesized to increase fracture risk among older adults through three mechanisms: (1) antidepressants can cause dizziness at initiation of the drug, increasing the risk of falls and resulting fractures [4, 8]; (2) serotonin-affecting drugs, such as SSRIs, downregulate osteoblast activity and thereby, in time, decrease bone mineral density, increasing the risk of sustaining a fracture after a fall or other impact [3, 8–10]; and (3) norepinephrine-affecting drugs, such as SNRIs, may play a role in osteoblast activity and may result in reduced bone density by increasing bone resorption [11, 12].

Existing literature examining the link between antidepressant use and fractures largely focuses on three antidepressants classes—SSRIs, TCAs, and MAOIs [3, 8, 13–15]. SSRIs have been weakly linked with an increased risk of fracture when compared with both TCAs and MAOIs [8, 14]. Excess fracture risk has been shown in users of SSRIs and SNRIs when compared with non-users [3, 4, 9, 16].

The risk profile of SSRIs has been studied extensively but the safety concerns of SNRIs are currently less well-studied, especially as the drugs relate to risk of fractures and bone fragility [3, 4, 8, 13, 14]. To our knowledge, the current study is the first to directly compare the risk of fractures between SSRIs and SNRIs.

2 Methods

2.1 Data Source and Patients

The PharMetrics Claims Database used in this study was purchased from IMS Health and is comprised of commercial health plan information obtained from managed care plans throughout the US. The database includes medical and pharmaceutical claims for over 61 million unique patients from over 98 health plans (approximately 16 million covered lives per year). The database includes inpatient and outpatient diagnoses [in International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) format] and procedures [in Current Procedure Terminology (CPT-4) and Healthcare Common Procedure Coding System (HCPCS) formats], as well as both retail and mail order records of all reimbursed dispensed prescriptions. Available data on prescriptions include the National Drug Code (NDC), as well as the quantity, number of days supplied, and the date of dispensing. Additional data elements include demographic variables (age, sex, geographic region), provider specialty, and start and stop dates of health-plan enrollment. Only health plans that submit data for all members are included in the database.

The current cohort study involves commercially-insured US patients aged 50 years or older who initiated use of SSRIs or SNRIs between 1 January 1998 and 31 December 2010 (the most recent data set available from the PharMetrics Claims Database). Initiation was defined as filling an SSRI or SNRI antidepressant prescription without evidence of having filled a prescription for any class of antidepressants in the preceding 12 months. Such initiators are referred to throughout as ‘new users’. Primary analyses focused on the first treatment episode initiated during the study period. Subjects were required to be actively enrolled in a health plan with prescription benefits that contributed data to our claims database (see Sect. 2.3) during the 15 months prior to initiation (i.e. 12 months for baseline covariate assessment and an additional 3 months to allow uniform assessment of all patients based on a 60-day grace period and a usual antidepressant supply of 30 days).

2.2 Medication Exposure

Medications were classified as SSRIs or SNRIs. SSRIs studied were citalopram hydrobromide, fluoxetine hydrochloride, fluvoxamine maleate, paroxetine hydrochloride, and sertraline hydrochloride; SNRIs studied were venlafaxine hydrochloride and duloxetine hydrochloride. Patients initiating more than one antidepressant agent on the same day were excluded.

2.3 Follow-Up

Exposure status was assigned based on the initiated medication, and carried forward. Study follow-up began on the day after initiation of the first antidepressant therapy. For each patient we created a record of drug coverage by listing consecutive prescription fills, based on dispensing dates and reported days' supply. When a dispensing occurred before the previous prescription should have run out, use of the new prescription is assumed to begin the day after the old prescription ended. Since users of any prescription medicine, especially chronic users, may experience relatively brief episodes without a supply of medicine, or may skip taking the medicine some days, our primary analyses allowed for up to 60 extra days to elapse beyond the provided days' supply before censoring (i.e. we used a 60-day grace period—twice the most common days' supply). Note, a person contributes information, and is thus included in the number of patients contributing to any post-initiation interval, if they are eligible to contribute time for the given analysis. Therefore, for the as treated analysis, the person must still be on their initial treatment at the start of the time period; for the first treatment carried forward analysis, the person must only continue to be enrolled in the healthcare plan at the start of the time period.

Patients were also censored at the date they switched agents (including when switching occurred within antidepressant class), added other antidepressant agents to the initiated regimen (i.e. treatment augmentation), ended enrollment in their health insurance plan, or the end of the study period, whichever came first. Our rationale for censoring was based on the knowledge that because more SSRI drugs exist than SNRI drugs, switching agents even within classes had the potential to introduce differential bias and thus introduce asymmetry into our analyses. New users were not allowed to become new users again; patients who were prevalent users at the start of their enrollment were allowed to become new users later during the study period.

2.4 Outcome

The occurrence of hip, humerus, radius, and ulna fractures during follow-up was our outcome of interest. These fractures were defined as a medical claim with an ICD-9 external cause of injury code (E-code) of hip (733.14 or 820.xx), humerus (733.11 or 812.xx), or radius/ulna (733.12 or 813.xx) fracture diagnosis.

2.5 Patient Characteristics

Patient characteristics considered as potential confounders were age, sex, and several indicators of past year medical comorbidity based on inpatient, outpatient, and pharmacy claims, including the number of acute hospitalizations for non-psychiatric reasons, number of outpatient visits, constituents of the Charlson Comorbidity Index score, and number of distinct generic drugs filled. Psychiatric risk factors studied were the number of acute psychiatric hospitalizations, the number of acute hospitalizations for substance abuse, psychiatric comorbidity, and suicide ideation/attempts. Drug initiators were also subcategorized as having or not having a depression diagnosis in order to parse out any potential effect modification on fracture risk. For drug initiators with a depression diagnosis, a hierarchy of depression severity was constructed for each patient as a function of the proximity of the most recent depression diagnosis to antidepressant initiation (i.e. within 30 days of antidepressant initiation vs. within 31–360 days of initiation) and whether the diagnosis was an inpatient or outpatient diagnosis. For inpatient diagnoses, depression diagnosis was further characterized as to whether the diagnosis was the primary or secondary diagnosis of record. For outpatient diagnoses, persons with a single depression diagnosis were distinguished from those with multiple depression diagnoses in the year prior to initiation of antidepressant therapy. Other psychiatric disorders were defined as the presence of at least one inpatient or outpatient diagnostic code. The disorders studied were anxiety or sleep disorders, substance abuse, attention deficit hyperactivity disorder, cognitive impairment or dementia, bipolar disorder, schizophrenic disorder, and personality disorders. In addition to psychiatric comorbidities, we measured a number of general medical comorbidities, including malignant neoplasms, opiate use, stroke and transient ischemic attack, and Parkinson disease, all of which are listed in Table 1. Risk factors for the outcome of interest were diagnostic codes for fractures or medical procedures performed on the hip, humerus, and/or radius/ulna.

2.6 Statistical Analyses

We estimated the propensity for initiating SNRIs versus SSRIs using multivariable logistic regression including all of the covariates outlined above. Standardized mortality weighting [17] was applied to weight the SNRI cohort by the propensity score odds to achieve a similar distribution of patient characteristics in SNRI initiators as in SSRI initiators. We chose to weight SNRI patients to SSRI patients because, by current prescribing patterns, individuals are most commonly prescribed SSRIs as first-line antidepressant medications. Thus, our study examines what the fracture risk differential would be among patients who started on SNRIs (the less common practice) as opposed to SSRIs, and if this would be beneficial in terms of alleviating fracture risk. Fracture rates were calculated for

Table 1 Characteristics of the study cohort, SNRI versus SSRI primary analysis: 1 Rx fill, ages 50+ years

Characteristic	SSRI ($N = 335,146$) (%)	SNRI ($N = 61,612$) (%)	SNRI weighted to SSRI (%)
Age, years			
50–54	95,920 (28.6)	20,786 (33.7)	28.2
55–59	80,093 (23.9)	16,779 (27.2)	24.4
60–64	59,918 (17.9)	11,313 (18.4)	18.0
65–74	50,208 (15.0)	7810 (12.7)	14.5
75–84	33,072 (9.9)	3739 (6.1)	9.7
85–99	15,935 (4.8)	1185 (1.9)	5.2
Sex, male	119,950 (35.8)	18,379 (29.8)	36.3
ADHD	1407 (0.4)	422 (0.7)	0.4
Antipsychotics	14,004 (4.2)	3044 (4.9)	4.4
Anxiety	59,467 (17.7)	7897 (12.8)	18.4
Cardiac arrhythmias	37,519 (11.2)	5239 (8.5)	11.5
Rheumatoid arthritis	6481 (1.9)	1786 (2.9)	1.9
Barbiturate	406 (0.1)	62 (0.1)	0.1
β-Blockers	71,810 (21.4)	11,040 (17.9)	21.6
Benzodiazepine	82,224 (24.5)	13,580 (22.0)	25.0
Bipolar disorder	2669 (0.8)	816 (1.3)	0.9
History of falls, syncope or gait abnormality	41,229 (12.3)	7211 (11.7)	12.6
Suicidal ideation	498 (0.1)	106 (0.2)	0.2
Bone mineral density scan	30,770 (9.2)	6956 (11.3)	8.9
Cataracts	36,208 (10.8)	6038 (9.8)	10.8
Myocardial infarction	9544 (2.8)	1199 (1.9)	3.0
Paraplegia and hemiplegia	1429 (0.4)	315 (0.5)	0.5
Moderate or severe liver disease	902 (0.3)	129 (0.2)	0.3
AIDS/HIV	431 (0.1)	88 (0.1)	0.1
Peripheral vascular disease	21,215 (6.3)	3772 (6.1)	6.5
Peptic ulcer disease	4014 (1.2)	688 (1.1)	1.3
Congestive heart failure	19,523 (5.8)	2531 (4.1)	6.1
Asthma/COPD	51,384 (15.3)	8866 (14.4)	15.7
COX-2 inhibitors	20,816 (6.2)	4768 (7.7)	6.3
Crohn's disease/gastroenteritis	11,037 (3.3)	2096 (3.4)	3.4
Alzheimer's or other dementia	15,570 (4.6)	1586 (2.6)	5.0
Diabetes	58,086 (17.3)	11,721 (19.0)	17.7
Severity level of depression diagnosis			
T1: primary inpatient diagnosis ≤30 days pre-index date	866 (0.3)	180 (0.3)	0.3
T2: primary inpatient diagnosis 31–360 days pre-index date	254 (0.1)	91 (0.1)	0.1
T3: non-primary inpatient diagnosis ≤360 days pre-index date	5968 (1.8)	971 (1.6)	1.9
T4: Two or more outpatient diagnoses ≤360 days pre-index date	48,163 (14.4)	8869 (14.4)	15.1
T5: One outpatient diagnosis ≤360 days pre-index date	45,774 (13.7)	5902 (9.6)	14.2
T6: no diagnosis	234,121 (69.9)	45,599 (74.0)	68.4
Glucocorticosteroids	47,435 (14.2)	10,357 (16.8)	14.2
H_2 antagonists	16,146 (4.8)	2306 (3.7)	4.8
Hip fracture	2253 (0.7)	279 (0.5)	0.7
Humerus fracture	1360 (0.4)	242 (0.4)	0.4
Hyperparathyroidism	1313 (0.4)	257 (0.4)	0.4
Hyperthyroidism	4095 (1.2)	783 (1.3)	1.2
Kyphosis	2862 (0.9)	786 (1.3)	0.9
Liver disease	12,701 (3.8)	2405 (3.9)	3.9

Table 1 continued

Characteristic	SSRI ($N = 335,146$) (%)	SNRI ($N = 61,612$) (%)	SNRI weighted to SSRI (%)
Malignant neoplasm	39,968 (11.9)	8485 (13.8)	11.5
Other NSAIDs	62,762 (18.7)	13,904 (22.6)	18.7
No. of prescription drugs			
1 (antidepressant only)	16,279 (4.9)	3083 (5.0)	4.9
2–3	49,631 (14.8)	8304 (13.5)	14.7
4–5	55,563 (16.6)	8988 (14.6)	16.5
6–9	94,994 (28.3)	16,521 (26.8)	28.3
10+	118,679 (35.4)	24,716 (40.1)	35.7
No. of hospitalizations (one or more)	60,258 (18.0)	9892 (16.1)	18.3
No. of outpatient visits			
<5	53,861 (16.1)	8823 (14.3)	16.1
5–9	61,093 (18.2)	9572 (15.5)	18.1
10–19	92,445 (27.6)	15,845 (25.7)	27.6
20–39	81,406 (24.3)	16,196 (26.3)	24.4
40+	46,341 (13.8)	11,176 (18.1)	13.9
Overweight or obese	13,570 (4.0)	3007 (4.9)	4.0
Osteoporosis	20,431 (6.1)	3828 (6.2)	6.0
Other fracture	12,291 (3.7)	2345 (3.8)	3.8
Antiparkinson drug	7281 (2.2)	1643 (2.7)	2.2
Personality disorder	968 (0.3)	211 (0.3)	0.3
PPI	54,090 (23.1)	10,896 (23.9)	23.6
Radius/ulna fracture	1889 (0.6)	351 (0.6)	0.6
Renal disease	4728 (1.4)	664 (1.1)	1.4
Schizophrenic disorder	908 (0.3)	150 (0.2)	0.3
Ischemic stroke	12,595 (3.8)	1631 (2.6)	4.1
Suicide attempt	184 (0.1)	34 (0.1)	0.1
Thiazides	31,528 (9.4)	5271 (8.6)	9.3
Thyroid	43,939 (13.1)	8504 (13.8)	13.1
Urinary incontinence	7974 (2.4)	1553 (2.5)	2.4
Vertebral fracture	3328 (1.0)	648 (1.1)	1.1

SSRI selective serotonin reuptake inhibitor, *SNRI* serotonin–norepinephrine reuptake inhibitor, *Rx* prescription, *ADHD* attention-deficit hyperactivity disorder, *COPD* chronic obstructive pulmonary disease, *NSAID* non-steroidal anti-inflammatory drug, *AIDS* acquired immune deficiency syndrome, *HIV* human immunodeficiency virus, *COX* cyclooxygenase, *PPI* proton pump inhibitor

patients exposed to SNRI versus SSRI over the entire exposure period using weighted Poisson regression. Robust methods were used to calculate 95 % confidence intervals (CIs). We also used weighted Cox proportional hazard models to estimate hazard ratios (HRs) of medication class on fracture stratified by 1- and 5-year time periods.

3 Results

3.1 Description of Cohort

Between 1 January 1998 and 31 December 2010, a total of 335,146 patients initiated SSRI antidepressants and 61,612 patients initiated SNRI antidepressants. As shown in Table 1, baseline characteristics, including comorbidities, severity level of depression diagnosis (if a diagnosis existed at all), and measures of healthcare utilization, largely reflect the characteristics of the original SSRI cohort, which indicates a well-matched SNRI-weighted cohort.

3.2 Risk of Fractures

In our primary (as-treated, 60-day grace period, 360 days follow-up) analysis (Table 2), the rate of fractures was approximately equal in both the SSRI and SNRI cohorts (SNRI: 7.5 per 1000 person-years, 95 % CI 6.2–9.0; SSRI: 6.7 per 1000 person-years, 95 % CI 6.3–7.1). Follow-up

Table 2 Weighted fracture event rates by antidepressant class and time of follow-up

Period	Drug	Number contributing	Number of events	Total person time (years)	Rate per 1000 person-years (95 % CI)
0–30 days	SNRI	336,949.7	193.9	26,758.35	7.3 (4.4–12.0)
	SSRI	335,146.0	192.0	26,596.29	7.2 (6.3–8.3)
31–90 days	SNRI	313,478.2	284.7	47,917.74	5.9 (4.1–8.7)
	SSRI	310,930.0	297.0	47,471.80	6.3 (5.6–7.0)
91–360 days	SNRI	267,612.6	745.0	90,320.71	8.3 (6.5–10.5)
	SSRI	266,836.0	583.0	87,228.48	6.7 (6.2–7.3)
0–360 days	SNRI	336,949.7	1223.6	164,996.80	7.5 (6.2–9.0)
	SSRI	335,146.0	1072.0	161,296.57	6.7 (6.3–7.1)
361–720 days	SNRI	71,874.7	296.5	43,580.68	6.8 (4.7–10.0)
	SSRI	67,855.0	261.0	40,979.64	6.4 (5.7–7.2)
721–1,080 days	SNRI	24,781.3	53.4	15,147.92	3.5 (1.9–6.4)
	SSRI	23,874.0	81.0	15,089.71	5.4 (4.3–6.7)
1,081–1,440 days	SNRI	8857.7	11.9	6010.73	2.0 (0.6–6.6)
	SSRI	9292.0	35.0	6437.72	5.5 (3.9–7.6)
1,441–1,800 days	SNRI	3956.2	4.2	2429.55	1.7 (0.2–12.4)
	SSRI	4333.0	9.0	2744.35	3.3 (1.7–6.3)
>1,800 days	SNRI	1260.3	4.8	1026.95	4.7 (0.6–34.3)
	SSRI	1460.0	7.0	1435.70	4.9 (2.3–10.4)
0–1,800 days	SNRI	336,949.7	1589.5	232,165.67	6.9 (5.9–8.2)
	SSRI	335,146.0	1458.0	226,548.00	6.5 (6.2–6.8)

SSRI selective serotonin reuptake inhibitor, *SNRI* serotonin–norepinephrine reuptake inhibitor, *CI* confidence interval

Table 3 SNRI versus SSRI fracture hazard ratios

Analysis	1-year HR (95 % CI)	5-year HR (95 % CI)
7-day GP	1.01 (0.78–1.30)	1.03 (0.82–1.30)
14-day GP	0.98 (0.78–1.25)	1.01 (0.82–1.24)
30-day GP	1.02 (0.83–1.26)	1.02 (0.85–1.23)
60-day GP	1.11 (0.92–1.36)	1.06 (0.90–1.26)
90-day GP	1.12 (0.93–1.36)	1.06 (0.90–1.26)
180-day GP	1.09 (0.90–1.31)	1.04 (0.88–1.22)
360-day GP	1.03 (0.86–1.24)	1.01 (0.87–1.18)
First treatment carried forward	1.02 (0.87–1.21)	0.98 (0.87–1.10)

SSRI selective serotonin reuptake inhibitor, *SNRI* serotonin–norepinephrine reuptake inhibitor, *GP* grace period, *HR* hazard ratio, *CI* confidence interval

through 5 years (1,800 days) after initiation (Table 2) also showed that patients filling prescriptions for SNRIs showed a fracture rate of 6.9 per 1000 person-years (95 % CI 5.9–8.2), while patients filling prescriptions for SSRIs showed a very similar fracture rate of 6.5 per 1000 person-years (95 % CI 6.2–6.8). Over the first year after initiating therapy, those starting SNRIs, relative to those initiating with SSRIs, were not significantly more likely to suffer a fracture (HR 1.11, 95 % CI 0.92–1.36) (Table 3). A similarly null finding was observed over the first 5 years after beginning therapy (HR 1.06, 95 % CI 0.90–1.26). Additionally, for a cohort of patients with a depression diagnosis who initiated on either SNRIs or SSRIs, those initiating on SNRIs had a slightly elevated, although not statistically significantly elevated, rate of fracture (HR 1.31, 95 % CI 0.95–1.79) (Table 4). For a cohort of patients without a depression diagnosis who initiated on either SNRIs or SSRIs, those initiating on SNRIs had essentially the same rate of fracture as those initiating on SSRIs (HR 1.04, 95 % CI 0.80–1.34) (Table 4).

4 Discussion

Our study is the first of which we are aware to directly examine the differences in the risk of fracture associated with initiating SNRIs compared with SSRIs among subjects aged 50 years or older. In our study, there was no statistically significant differential in fracture risk between initiators of SNRIs versus initiators of SSRIs during our

Table 4 SNRI versus SSRI fracture hazard ratios—with versus without depression diagnoses

Analysis	With depression, excluding bipolar and schizophrenic disorders		Without depression	
	1-year HR (95 % CI)	5-year HR (95 % CI)	1-year HR (95 % CI)	5-year HR (95 % CI)
7-day GP	1.34 (0.91–1.96)	1.35 (0.95–1.92)	0.83 (0.59–1.17)	0.84 (0.62–1.15)
14-day GP	1.27 (0.88–1.84)	1.26 (0.90–1.76)	0.84 (0.62–1.15)	0.87 (0.66–1.13)
30-day GP	1.22 (0.86–1.72)	1.19 (0.88–1.62)	0.92 (0.70–1.21)	0.91 (0.72–1.15)
60-day GP	1.31 (0.95–1.79)	1.22 (0.92–1.60)	1.04 (0.80–1.34)	0.98 (0.78–1.22)
90-day GP	1.30 (0.95–1.77)	1.21 (0.92–1.58)	1.05 (0.82–1.34)	0.98 (0.79–1.22)
180-day GP	1.23 (0.91–1.66)	1.15 (0.88–1.50)	1.03 (0.81–1.30)	0.97 (0.79–1.19)
360-day GP	1.17 (0.87–1.57)	1.12 (0.87–1.45)	0.98 (0.78–1.23)	0.95 (0.78–1.15)
First treatment carried forward	1.12 (0.86–1.46)	1.06 (0.88–1.29)	1.01 (0.82–1.25)	0.94 (0.81–1.09)

SSRI selective serotonin reuptake inhibitor, *SNRI* serotonin–norepinephrine reuptake inhibitor, *GP* grace period, *HR* hazard ratio, *CI* confidence interval

follow-up period. Our finding that, on balance, SSRIs and SNRIs are correlated with similar fracture rates is consistent with the notion that both SSRIs and SNRIs may contribute to fracture risk through different, although related, pathways. It is possible, for example, that the extent to which serotonin-affecting drugs downregulate osteoblast activity and, in time, decrease bone mineral density [3, 8–10], is similar to the effect of norepinephrine-affecting drugs, such as SNRIs [11, 12, 18].

Although depression is known to be an independent risk factor for fracture, no prior work of which we are aware points to effect modification by depression status. Future work is needed to examine whether our secondary finding of a non-significant and modest increase in fracture risk among depressed patients initiating SNRIs, compared with those initiating SSRIs, can be replicated, or whether our finding in this regard is due to chance or residual confounding that is attenuated in our larger cohort of initiators both with and without depression.

There are several methodological issues to be considered regarding the current study. First, as depression itself has been shown to be a risk factor of osteoporosis [19–22], incomplete elimination of the impact of disease severity (or other potential confounders) during the matching process could affect our findings, especially in our cohort with depression diagnoses. Another limitation comes from our assessment of medication exposure. While we used the best-available data to define duration of exposure to the drug (longitudinal information on prescription refills), this may not accurately reflect the reality of drug adherence among SSRI and SNRI patients. It has been shown that non-adherence to antidepressants is a prevalent phenomenon [23, 24], but whether there are differences in adherence between SSRIs and SNRIs has not, to our knowledge, been reported in the previous literature. Nevertheless, our findings are similar for grace periods from 7 to 60 days, suggesting that, to the extent that antidepressant persistence is a reasonable proxy for antidepressant adherence, our findings may not be largely affected by differential adherence. Because there are many reasons people stop antidepressant therapy, including some side effects that would not be measured in administrative data but might be related to underlying fracture risk, we did not perform analyses on the effects of drug discontinuation as this would have opened up our findings to more unmeasured confounding. We do not have information on the magnitude of patients obtaining prescriptions outside of the PharMetrics Claims Database, but we have no reason to believe that SSRI initiators are any more likely or less likely to purchase medication out-of-plan than are SNRI initiators. Due to limitation in the numbers of subjects and events, we did not have sufficient statistical power to report findings that are stratified under specific risk factors, e.g. age of subjects, or to parse fractures by type. Finally, we did not perform dose-response analyses as our study was not powered to do so. Furthermore, doses across drug classes (SNRI vs. SSRI) are not directly comparable.

5 Conclusions

Despite the stated limitations, our null findings with respect to fracture rates comparing SNRI and SSRI antidepressant initiators suggest that, although mechanically plausible, SSRIs do not materially increase fracture risk any more than SNRIs, the class of antidepressants next most likely to be prescribed today. Given the frequency with which antidepressant medications are prescribed, more research is needed to fully understand the relative risks and benefits of prescribing these classes of antidepressants.

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References

1. Uchida N, Chong MY, Tan CH, Nagai H, Tanaka M, Lee MS, et al. International study on antidepressant prescription pattern at 20 teaching hospitals and major psychiatric institutions in East Asia: analysis of 1898 cases from China, Japan, Korea, Singapore and Taiwan. Psychiatry Clin Neurosci. 2007;61(5):522–8.
2. Bauer M, Monz BU, Montejo AL, Quail D, Dantchev N, Demyttenaere K, et al. Prescribing patterns of antidepressants in Europe: results from the Factors Influencing Depression Endpoints Research (FINDER) study. Eur Psychiatry. 2008;23(1):66–73.
3. Bakken MS, Engeland A, Engesæter LB, Ranhoff AH, Hunskaar S, Ruths S. Increased risk of hip fracture among older people using antidepressant drugs: data from the Norwegian Prescription Database and the Norwegian Hip Fracture Registry. Age Ageing. 2013;42(4):514–20.
4. Eom CS, Lee HK, Ye S, Park SM, Cho KH. Use of selective serotonin reuptake inhibitors and risk of fracture: a systematic review and meta-analysis. J Bone Miner Res. 2012;27(5):1186–95.
5. Gorman JM, Kent JM. SSRIs and SNRIs: broad spectrum of efficacy beyond major depression. J Clin Psychiatry. 1999;60:33–9.
6. Artigas F. Selective serotonin/noradrenaline reuptake inhibitors (SNRIs): pharmacology and therapeutic potential in the treatment of depressive-disorders. CNS Drugs. 1995;4(2):79–89.
7. Cummings SR, Kelsey JL, Nevitt MC, O'Dowd KJ. Epidemiology of osteoporosis and osteoporotic fractures. Epidemiol Rev. 1985;7:178–208.
8. Vestergaard P, Rejnmark L, Mosekilde L. Anxiolytics, sedatives, antidepressants, neuroleptics and the risk of fracture. Osteoporos Int. 2006;17(6):807–16.
9. Richards JB, Papaioannou A, Adachi JD, Joseph L, Whitson HE, Prior JC, et al. Effect of selective serotonin reuptake inhibitors on the risk of fracture. Arch Intern Med. 2007;167(2):188–94.
10. Haney EM, Chan BK, Diem SJ, Ensrud KE, Cauley JA, Barrett-Connor E, et al. Association of low bone mineral density with selective serotonin reuptake inhibitor use by older men. Arch Intern Med. 2007;167(12):1246–51.
11. Hanyu R, Wehbi VL, Hayata T, Moriya S, Feinstein TN, Ezura Y, et al. Anabolic action of parathyroid hormone regulated by the β(2)-adrenergic receptor. Proc Natl Acad Sci USA. 2012;109(19):7433–8.
12. Ma Y, Krueger JJ, Redmon SN, Uppuganti S, Nyman JS, Hahn MK, et al. Extracellular norepinephrine clearance by the norepinephrine transporter is required for skeletal homeostasis. J Biol Chem. 2013;288(42):30105–13.
13. Vestergaard P, Rejnmark L, Mosekilde L. Selective serotonin reuptake inhibitors and other antidepressants and risk of fracture. Calcif Tissue Int. 2008;82(2):92–101.
14. Bolton JM, Metge C, Lix L, Prior H, Sareen J, Leslie WD. Fracture risk from psychotropic medications: a population-based analysis. J Clin Psychopharmacol. 2008;28(4):384–91.
15. Schneeweiss S, Wang PS. Association between SSRI use and hip fractures and the effect of residual confounding bias in claims database studies. J Clin Psychopharmacol. 2004;24(6):632–8.
16. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ. 2011;343:d4551.
17. Sturmer T, Rothman KJ, Glynn RJ. Insights into different results from different causal contrasts in the presence of effect-measure modification. Pharmacoepidemiol Drug Saf. 2006;15(10):698–709.
18. Shelton RC. Serotonin norepinephrine reuptake inhibitors: similarities and differences. Prim Psychiatry. 2009;16:25–35.
19. Wu Q, Magnus JH, Liu J, Bencaz AF, Hentz JG. Depression and low bone mineral density: a meta-analysis of epidemiologic studies. Osteoporos Int. 2009;20(8):1309–20.
20. Erez HB, Weller A, Vaisman N, Kreitler S. The relationship of depression, anxiety and stress with low bone mineral density in post-menopausal women. Arch Osteoporos. 2012;7(1–2):247–55.
21. Bab I, Yirmiya R. Depression, selective serotonin reuptake inhibitors, and osteoporosis. Curr Osteoporos Rep. 2010;8(4):185–91.
22. Williams LJ, Pasco JA, Jacka FN, Henry MJ, Dodd S, Berk M. Depression and bone metabolism: a review. Psychother Psychosom. 2009;78(1):16–25.
23. Demyttenaere K, Enzlin P, Dewe W, Boulanger B, De Bie J, De Troyer W, et al. Compliance with antidepressants in a primary care setting, 1: beyond lack of efficacy and adverse events. J Clin Psychiatry. 2001;62(Suppl 22):30–3.
24. Sansone RA, Sansone LA. Antidepressant adherence: are patients taking their medications? Innov Clin Neurosci. 2012;9(5–6):41–6.