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Serotonin-Norepinephrine Reuptake Inhibitor and Selective Serotonin Reuptake Inhibitor Use and Risk of Fractures: A new-user cohort study among US adults aged 50 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 vs. SSRI initiation on fracture rates.

Data source—Data came 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 for fractures by antidepressant class.

Results—In weighted analyses, the fracture rates were approximately equal in SNRI and SSRI initiators: hazard ratios for the first one and five-year periods following initiation were,

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respectively, 1.11 (95% CI: 0.92–1.36) and 1.06 (95% CI: 0.90–1.26). For the sub-group 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, hazard ratio = 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.

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have become the mainstream pharmacological treatments for patients with depressive disorders since the late 1990s [1, 2], due in part to the perception that SSRIs and SNRIs have more favorable side-effect profiles than do 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 [8, 4]; 2) serotonin-affecting drugs, such as SSRIs, down regulate osteoblast activity and thereby, in time, decrease bone mineral density, increasing the risk of sustaining a fracture after a fall or other impact [8, 3, 9, 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 [8, 13, 3, 14, 15]. SSRIs have been weakly linked with an increased risk of fracture when compared to both TCAs and MAOIs [8, 14]. Excess fracture risk has been shown in users of SSRIs and SNRIs when compared to non-users [9, 3, 4, 16].

SSRIs' risk profile has been studied extensively, but SNRIs' safety concerns are currently less well-studied, especially as the drugs relate to risk of fractures and bone fragility [8, 13, 3, 14, 4]. 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 United States. 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 Health Care 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, gender, 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 50 years of age or older who initiated use of SSRIs or SNRIs between January 1, 1998 and December 31, 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 below) 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 end of the old prescription. 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 use 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 health care 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 do 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 *International Classification of Diseases, Ninth Revision* (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 sub-categorized 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 patients exposed to SNRI vs. SSRI over the entire exposure period using weighted Poisson regression. Robust methods were used to calculate 95% confidence intervals. We also used weighted Cox proportional hazard models to estimate hazard ratios of medication class on fracture stratified by 1 and 5-year time periods.

3. Results

3. 1 Description of cohort

Between January 1, 1998 and December 31, 2010, 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 health care 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 1,000 person-years, 95% CI: 6.2–9.0; SSRI: 6.7 per 1,000 person-years, 95% CI: 6.3–7.1). Follow up through 5-years (1800 days) after initiation (Table 2) also showed that patients filling prescriptions for SNRIs showed a fracture rate of 6.9 per 1,000 person-years (95% CI: 5.9–8.2) while patients filling prescriptions for SSRIs showed a very similar fracture rate of 6.5 per 1,000 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 (hazard ratio = 1.11, 95% CI: 0.92–1.36) (Table 3). A similarly null finding was observed over the first five years after beginning therapy (hazard ratio = 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, though not statistically significantly elevated, rate of fracture (hazard ratio = 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 SSRI (hazard ratio = 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 SNRI compared to SSRI among subjects aged 50 years or older. In our study, there was no statistically significant differential in fracture risk between initiators of SNRIs vs. initiators of SSRIs during our 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, though related pathways. It is possible, for example, that the extent to which serotonin-affecting drugs down regulate osteoblast activity and, in time, decrease bone mineral density[8, 3, 9, 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 point 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 been reported in the previous literature to our knowledge. Nevertheless, our findings are similar for grace periods from 7 days 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 numbers of subjects and events, we did not have sufficient statistical power to report findings that are stratified under specific risk factors, for example, age of the subjects, or to parse fractures by type. Finally, we did not perform dose-response analyses as our study was not powered to do so; further, doses across drug classes (SNRI vs. SSRI) are not directly comparable.

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 do 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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Key Points

- There is no statistically significant difference in rate of fracture among patients who initiate SNRIs versus those who initiate SSRIs.
- 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.

Table 1

Characteristics of the Study Cohort, SNRI vs SSRI Primary Analysis: 1 Rx Fill, Ages 50+

Characteristic	SSRI N=335,146	SNRI N=61,612	SNRI Weighted to SSRI
Age			
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%)	7,810 (12.7%)	14.5%
75–84	33,072 (9.9%)	3,739 (6.1%)	9.7%
85–99	15,935 (4.8%)	1,185 (1.9%)	5.2%
Sex, M	119,950 (35.8%)	18,379 (29.8%)	36.3%
Attention deficit hyperactivity disorder (ADHD)	1,407 (0.4%)	422 (0.7%)	0.4%
Antipsychotics	14,004 (4.2%)	3,044 (4.9%)	4.4%
Anxiety	59,467 (17.7%)	7,897 (12.8%)	18.4%
Cardiac Arrhythmias	37,519 (11.2%)	5,239 (8.5%)	11.5%
Rheumatoid Arthritis	6,481 (1.9%)	1,786 (2.9%)	1.9%
Barbiturate	406 (0.1%)	62 (0.1%)	0.1%
Beta Blockers	71,810 (21.4%)	11,040 (17.9%)	21.6%
Benzodiazepine	82,224 (24.5%)	13,580 (22.0%)	25.0%
Bipolar Disorder	2,669 (0.8%)	816 (1.3%)	0.9%
History of Falls, Syncope or Gait Abnormality	41,229 (12.3%)	7,211 (11.7%)	12.6%
Suicidal Ideation	498 (0.1%)	106 (0.2%)	0.2%
Bone Mineral Density Scan	30,770 (9.2%)	6,956 (11.3%)	8.9%
Cataracts	36,208 (10.8%)	6,038 (9.8%)	10.8%
Myocardial Infarction	9,544 (2.8%)	1,199 (1.9%)	3.0%
Paraplegia and Hemiplegia	1,429 (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%)	3,772 (6.1%)	6.5%
Peptic Ulcer Disease	4,014 (1.2%)	688 (1.1%)	1.3%
Congestive Heart Failure	19,523 (5.8%)	2,531 (4.1%)	6.1%
Asthma/Chronic Obstructive Pulmonary Disease (COPD)	51,384 (15.3%)	8,866 (14.4%)	15.7%
Cox-2 Inhibitors	20,816 (6.2%)	4,768 (7.7%)	6.3%
Crohn Disease/Gastroenteritis	11,037 (3.3%)	2,096 (3.4%)	3.4%
Alzheimer or Other Dementia	15,570 (4.6%)	1,586 (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%

Characteristic	SSRI N=335,146	SNRI N=61,612	SNRI Weighted to SSRI
T3: Non-Primary Inpatient Diagnosis <=360 Days Pre-Index Date	5,968 (1.8%)	971 (1.6%)	1.9%
T4: 2+ Outpatient Diagnosis <=360 Days Pre-Index Date	48,163 (14.4%)	8,869 (14.4%)	15.1%
T5: 1 Outpatient Diagnosis <=360 Days Pre-Index Date	45,774 (13.7%)	5,902 (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%)	2,306 (3.7%)	4.8%
Hip Fracture	2,253 (0.7%)	279 (0.5%)	0.7%
Humerus Fracture	1,360 (0.4%)	242 (0.4%)	0.4%
Hyperparathyroidism	1,313 (0.4%)	257 (0.4%)	0.4%
Hyperthyroidism	4,095 (1.2%)	783 (1.3%)	1.2%
Kyphosis	2,862 (0.9%)	786 (1.3%)	0.9%
Liver Disease	12,701 (3.8%)	2,405 (3.9%)	3.9%
Malignant Neoplasm	39,968 (11.9%)	8,485 (13.8%)	11.5%
Other nonsteroidal anti-inflammatory drug (NSAIDs)	62,762 (18.7%)	13,904 (22.6%)	18.7%
# of Prescription Drugs			
1 (antidepressant only)	16,279 (4.9%)	3,083 (5.0%)	4.9%
2–3	49,631 (14.8%)	8,304 (13.5%)	14.7%
4–5	55,563 (16.6%)	8,988 (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%
# of Hospitalizations, 1+	60,258 (18.0%)	9,892 (16.1%)	18.3%
Number of Outpatient Visits			
<5	53,861 (16.1%)	8,823 (14.3%)	16.1%
5–9	61,093 (18.2%)	9,572 (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%)	3,007 (4.9%)	4.0%
Osteoporosis	20,431 (6.1%)	3,828 (6.2%)	6.0%
Other Fracture	12,291 (3.7%)	2,345 (3.8%)	3.8%
Antiparkinson Drug	7,281 (2.2%)	1,643 (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	1,889 (0.6%)	351 (0.6%)	0.6%
Renal Disease	4,728 (1.4%)	664 (1.1%)	1.4%
Schizophrenic Disorder	908 (0.3%)	150 (0.2%)	0.3%
Ischemic Stroke	12,595 (3.8%)	1,631 (2.6%)	4.1%
Suicide Attempt	184 (0.1%)	34 (0.1%)	0.1%
Thiazides	31,528 (9.4%)	5,271 (8.6%)	9.3%

Characteristic	SSRI N=335,146	SNRI N=61,612	SNRI Weighted to SSRI
Thyroid	43,939 (13.1%)	8,504 (13.8%)	13.1%
Urinary Incontinence	7,974 (2.4%)	1,553 (2.5%)	2.4%
Vertebral Fracture	3,328 (1.0%)	648 (1.1%)	1.1%

SSRI = selective serotonin reuptake inhibitor; **SNRI** = serotonin norepinephrine reuptake inhibitor

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 1,000 person-years
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	1,223.6	164,996.80	7.5 (6.2–9.0)
	SSRI	335,146.0	1,072.0	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)
721–1080 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)
1081–1440 Days	SNRI	8,857.7	11.9	6,010.73	2.0 (0.6–6.6)
	SSRI	9,292.0	35.0	6,437.72	5.5 (3.9–7.6)
1441–1800 Days	SNRI	3,956.2	4.2	2,429.55	1.7 (0.2–12.4)
	SSRI	4,333.0	9.0	2,744.35	3.3 (1.7–6.3)
>1800 Days	SNRI	1,260.3	4.8	1,026.95	4.7 (0.6–34.3)
	SSRI	1,460.0	7.0	1,435.70	4.9 (2.3–10.4)
0–1800 Days	SNRI	336,949.7	1,589.5	232,165.67	6.9 (5.9–8.2)
	SSRI	335,146.0	1,458.0	226,548.00	6.5 (6.2–6.8)

SSRI = selective serotonin reuptake inhibitor; **SNRI** = serotonin norepinephrine reuptake inhibitor

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Table 3

SNRI vs. 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

Table 4

SNRI vs. SSRI Fracture Hazard Ratios, with vs. without depression diagnoses

	With Depression, Excluding Bipolar and Schizophrenic Disorders		Without Depression	
Analysis	**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