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Comparative safety of antidepressants on fracture risk in older adults

JJ Gagne¹, AR Patrick¹, H Mogun¹, and DH Solomon^{1,2}

¹Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

²Division of Rheumatology, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Abstract

We examined variation in fracture rates among antidepressant initiators identified from Medicare data in two US states and assessed whether observed variation was explained by affinity for serotonin transport receptors. We used Cox-proportional hazards models to compare fracture rates of the hip, humerus, pelvis, wrist, and a composite of these, among propensity-score matched cohorts of users of secondary amine tricyclics (2° TCAs), tertiary amine tricyclics (3° TCAs), selective serotonin reuptake inhibitors (SSRIs), and atypical antidepressants. As compared to 2° TCA initiators, SSRIs initiators had the highest composite fracture rate (hazard ratio [HR], 1.30; 95% confidence interval [CI] 1.12–1.52) followed by atypical antidepressants (HR, 1.12; 95% CI 0.96–1.31) and 3° TCAs (HR, 1.01; 95% CI 0.87–1.18). Results were robust to sensitivity analyses. While SSRI use was associated with the highest rate of fractures, variation in fracture risk across specific antidepressant medications did not depend on affinity for serotonin transport receptors.

Keywords

pharmacoepidemiology; adverse event; psychiatry; serotonin; elderly

INTRODUCTION

Antidepressants were the most commonly prescribed therapeutic class in the US in 2005 (1). The discovery that gut-derived serotonin can bind to serotonin receptors on preosteoblasts to suppress osteoblast proliferation (2) has heightened concern about the safety of antidepressant medications and selective serotonin reuptake inhibitors (SSRIs), in particular

Corresponding author and for reprint requests: Joshua Gagne, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, 1620 Tremont Street, Suite 3030, Boston, MA 02120, T: 617-278-0930, F: 617-232-8602, jgagne1@partners.org.

CONFLICT OF INTEREST/DISCLOSURE

Dr. Gagne participated in a research fellowship administered by Jefferson Medical College and sponsored by Ortho-McNeil Janssen Scientific Affairs, L.L.C., which ended in 2007. Dr. Solomon has received research support from Amgen and Abbott, neither project involved osteoporosis. He also serves as an unpaid member of two Pfizer-sponsored trial's organizing committees; neither trial tests osteoporosis drugs.

(3,4). The potential relations between use of antidepressant medications and bone metabolism are complex and incompletely understood (5). In contrast to the inhibitory effects of gut-derived serotonin on bone formation, brain-derived serotonin indirectly promotes bone mass accrual by enhancing bone formation and limiting bone resorption (6).

Multiple epidemiologic studies have demonstrated that antidepressant users have reduced bone mineral density and a greater fracture risk than non-users (7–9). However, antidepressant users and non-users differ in important ways, particularly with respect to osteoporotic risk factors (7). The role of the underlying depression, and coexisting psychiatric illnesses, in the potential association between antidepressants and fracture, is not well understood (10,11). Other pharmacological properties of these drugs may affect fracture risk via mechanisms that are independent of potential serotonin-mediated paths. For example, certain antidepressant medications (e.g. trazodone) are particularly sedating, while others may induce orthostatic hypotension, both of which might increase patients' risk of falls and subsequent fracture (12–15).

While estimating the risk of serious adverse events among users versus non-users of a particular drug or drug class is important, comparing users of one member of a drug class to another better mirrors clinical decision-making. In addition, defining users of a drug with a similar indication as the reference group has the benefit that all subjects have a common underlying indication, i.e., depression. While prior studies have examined fracture risk with a variety of antidepressant medications, they have typically compared users with non-users. Since there are many antidepressant options, it is critical to estimate the comparative safety of these drugs with respect to fracture risk and to use an active comparator group to limit confounding from the underlying depression.

We studied a very large cohort of older adults to compare fracture rates across patients initiating different antidepressant medication classes and explored whether variation in rates could be explained by affinity for serotonin transport receptors (5-HTT), and whether short-versus long-term effects were evident.

RESULTS

We identified a total of 73,072 antidepressant initiators (2,916 secondary amines, 4,701 tertiary amines, 56,941 SSRIs, and 8,514 atypicals) between 1994 and 2004 (Table 1). A large portion of secondary amine initiators (2,711 or 93%) was matched by propensity score to users of each of the other three antidepressant classes. Overall, good balance was achieved on variables that entered the propensity score since the largest pair-wise standardized difference was <0.10 (Table 2). The mean age among those in the propensity score matched cohorts was 77 years and 84% were female, reflecting the underlying demographics of the source population.

Among the 10,844 propensity score matched patients, 1,303 experienced at least one fracture of the hip, humerus, pelvis, or wrist during a total of 33,908 person-years of follow-up (Table 3). Users of SSRIs had the highest composite fracture outcome rate (46.6 per 1,000 person-years; 95% CI, 42.0–51.6), which was approximately 30% greater than that

among users of secondary amine tricyclics (HR, 1.30; 95% CI, 1.12–1.52). The corresponding incidence rate difference was 12 events per 1,000 exposed person-years. Users of tertiary amine tricyclics (34.5 per 1,000 person-years; 95% CI, 30.8–38.5) and atypical antidepressants (39.9 per 1,000 person-years; 95% CI, 35.6–44.6) had rates that were more similar to that of secondary amine users (34.4 per 1,000 person-years; 95% CI, 30.7–38.5). Figure 1 displays the fracture-free probability curves over the first two years of follow-up. Similar patterns were observed for each fracture subtype, except for fractures of the radius, for which the rate among users of secondary amine tricyclics was slightly higher than the rates among users of tertiary amine tricyclics and atypical antidepressants (Table 3).

Results of sensitivity analyses (Figure 2) were qualitatively similar to those of the primary analysis (Figure 2A). Slightly stronger associations were observed for the ‘as treated’ analysis (Figure 2B) and the ‘as matched’ analysis truncated at 90 days follow-up (Figure 2C). Slightly smaller associations were observed when the analysis was restricted to those remaining on treatment at 90 days (Figure 2D) and when the propensity score matching was broken and all antidepressant initiators were included with confounding adjustment in an outcome model (Figure 2E). Additional adjustment for variables that displayed slight imbalances in the primary analysis made little difference (Figure 2F).

When we stratified by sedating potential and affinity for 5-HTT, the highest incidence of fracture was observed in the low sedation, high 5-HTT-affinity stratum, corresponding to the SSRIs (Table 4). No discernible pattern was observed across the other strata.

DISCUSSION

In a cohort of older adults with diagnoses of depression, we observed variation in fracture rates following the initiation of different antidepressant classes. Initiators of SSRIs had the highest rate of fracture, which was substantially greater than that observed among users of secondary amine tricyclics. We observed approximately 12 additional composite fractures for every 1,000 person-years among patients exposed to SSRIs versus secondary amines tricyclics. We observed no substantial differences in composite fracture rates among users of atypical antidepressants or tertiary amine tricyclics as compared to secondary amine tricyclic users.

Several lines of research support the hypothesis that SSRIs may have adverse effects on bone health. In the central nervous system, serotonin reuptake inhibitors increase perisynaptic serotonin by binding to and blocking the serotonin transporter, 5-HTT. These drugs may also inhibit 5-HTT at other sites, including the platelets and bone, which may increase local concentrations of serotonin (5). Gut derived serotonin, which comprises approximately 95% of serotonin in the body (5), regulates bone formation via the low-density lipoprotein receptor-related protein 5 (Lrp5) (2). Mice lacking global 5-HTT exhibit reduced bone mass (16) and a recent epidemiologic study observed a correlation between fracture risk and affinity for 5-HTT (17). On the other hand, brain-derived serotonin appears to have bone mass accrual effects by both promoting bone formation and by suppressing resorption through a putative effect on sympathetic tone (5). Further, some animal studies offer evidence that conflicts with the prevailing notion that SSRIs have a deleterious effect

on bone mass. In one study, mice treated for six weeks with fluoxetine exhibited beneficial effects on bone formation (18).

We observed the highest rate of fracture in the stratum defined by low sedating potential and high 5-HTT affinity, which comprised all SSRIs. However, we observed no discernible patterns in variation of risk across the other strata. Furthermore, we hypothesized that if the variation in risk were mediated by serotonin, then outcomes resulting from this mechanism would manifest in the long-term, particularly after continued exposure to the drugs; however, long-term results were similar to the primary results. More importantly, fracture-free survival probabilities began to diverge early in follow-up. We observed a 43% increase in fracture rate among users of SSRIs as compared to users of secondary amine tricyclics within the first 90 days following initiation. Bone mineral density (BMD) reductions of one standard deviation correlate with roughly a 20% to 50% increase in fracture risk (19). Diem and colleagues observed annualized BMD reductions of between 0.32% and 0.47% among users of tricyclic antidepressants and between 0.60% and 0.93% for users of SSRIs (7). For a 75-year-old white woman with a BMD of 740, a 1% BMD reduction would correspond to approximately a 0.06 standard deviation change. Thus, these relatively small differences in BMD suggest it is unlikely that changes in BMD that may occur in the first 90 days of treatment can fully explain the observed increase in fracture rates during this period. Hubbard et al. also observed high increases in fracture risk shortly after initiation of antidepressants, including a doubling of risk observed in the first 14 days following SSRI initiation (20); results that cannot plausibly be attributed to decrease in bone mass leading to fracture. This suggests that another explanation may account for observed increases in fracture rates shortly after SSRI initiation.

In the absence of known causal mechanisms for effects immediately after treatment initiation, as observed in this study and in other epidemiologic studies, one must consider the possibility of differences due to baseline risk factors (21). Depression severity may be correlated with bone resorption (22) and fracture risk may increase with increasing number of depression symptoms (11). If prescribers chose SSRIs for patients with the most severe depression or for those with the most symptoms, then confounding can occur that cannot be easily excised in a study using claims data. Another possible explanation for our findings concerns risk of falls. Whooley et al found that the association between depression and fracture may be mediated by a greater frequency of falls among those with depression as compared to those without it (11). Confounding can occur if those treated with SSRIs are more likely to fall as a result of more severe underlying depression. Although we required diagnoses of depression for all patients, measures of depression severity are not available in typical administrative claims data. Even self-controlled designs can suffer from confounding by depression severity since this can change over time and is likely to be at its peak around the time of antidepressant initiation. Furthermore, although we required all patients to have evidence of depression around the time of antidepressant initiation based on an algorithm with a positive predictive value of 86% (23), some patients included in the study likely did not have depression and it is possible that this misclassification may have occurred differentially across exposure groups.

While our results are not entirely consistent with the hypothesis that antidepressants increase fracture risk through effects on serotonin, we cannot rule out subtle effects due to serotonin. It may be the case that the potential detrimental effect of antidepressants on bone has clinical implication only for drugs with extremely high affinity for 5-HTT. Although certain non-SSRI antidepressants have generally high affinity for 5-HTT, such as imipramine (1.41), duloxetine (1.55), and amitriptyline (4.33), many SSRIs have much greater affinity – e.g. paroxetine (0.13), sertraline (0.29), fluoxetine (0.81) (24). However, antidepressants act on several neurotransmitter systems including norepinephrine and dopamine, which could play a role in explaining the observed association. Given that we observed an increase in fracture rate among SSRIs shortly after initiation, a synthesis of randomized clinical trials would provide an opportunity to explore whether this association may have a causal basis.

We observed little variation in results across multiple sensitivity analyses. In our primary ‘as matched’ analysis we classified patients’ exposure status according to their index prescription and regardless of whether they continued taking the medication during follow-up or whether they switched to another antidepressant class. This approach preserves balance on baseline covariates achieved by propensity score matching, similar to the intention to treat principle in randomized clinical trials. However, this approach is subject to a potentially large amount of exposure misclassification. As a result, this approach generally, but not always, leads to bias toward the null. In the ‘as-treated’ sensitivity analysis, we censored patients when they discontinued their index drug (which could lead to informative censoring) and when they switched to an agent in another class (which can introduce time-varying confounding). However, this approach is less susceptible to exposure misclassification as compared to the ‘as-matched’ approach and, accordingly, yielded results that were slightly larger than the results of the primary analysis. We observed slightly larger rate ratios in analyses restricted to the first 90 days of follow-up as compared to analyses of those on treatment at 90 days, suggesting a lack of increase in effect with longer duration of exposure. However, a greater degree of exposure misclassification in the latter may also explain this difference. Finally, analyses among all eligible initiators, with confounder adjustment via conventional outcome models, yielded the smallest rate ratios. However, we urge caution in comparing these results to the results of the other analyses in which we used propensity score matching, since the distributions of effect measure modifiers among all new users of each antidepressant class may differ from distributions among samples standardized to the common reference group through the propensity score matching.

Our results are not likely attributable to confounding by other risk factors that are not related to depression. Restricting analyses to new users of medications (25), use of active comparators as controls (26), and propensity score techniques helps mitigate confounding bias (27). Adjustment for risk factors that are not typically measured in claims data, including body mass index, smoking, activities of daily living score, cognitive impairment, and physical impairment, did not substantially change estimates in a study of hip fracture among those treated with SSRIs compared to those untreated (28). Since a risk factor’s ability to confound an association is a function of both its correlation with the outcome and its differential distribution among exposure groups, we expect that the potential for these unmeasured confounders to bias the results of this study are minimal, particularly since we

compared only patients exposed to some antidepressant, rather than comparing exposed with truly unexposed patients (29).

We did not observe a clear association between fracture rates and potential to cause sedation. However, another important limitation of administrative claims data is that they lack precise information regarding timing of drug use. This may play an important role in influencing whether a sedating drug causes fracture. For example, highly sedating antidepressants, such as trazodone, may be consumed at night, a time during which patients are less likely to ambulate, whereas less sedating drugs may be taken during the day. While large administrative claims databases are useful for identifying and quantifying potentially causal links between medical products and health outcomes, this lack of granularity limits their use in mechanistic research. Another limitation is that fracture outcomes were not adjudicated, but validation studies have shown that their ascertainment from claims data is highly accurate (positive predictive values in a Medicare population: hip, 98%; humerus, 95%; pelvis, 93%; radius, 96%) (30). Furthermore, claims data provide records that medications were dispensed but not that they were actually consumed, which can result in misclassification of exposure. We expect any misclassification of exposure to be nondifferential among groups, thus any resulting bias would be towards the null. Finally, the algorithm used to identify depression among patients initiating antidepressant medications has a negative predictive value of 70% (23), which may have resulted in the inadvertent exclusion of many eligible patients from the study cohorts.

In summary, after accounting for confounding through use of propensity scores in an incident-user cohort design, differences in fracture risk among antidepressant classes could not be explained by affinity for serotonin transport receptors. A higher risk was found among users of SSRIs as compared to users of other antidepressant classes, but this risk was not substantially higher than that among users of atypical antidepressants. Together with existing literature, our results suggest that there may be an important explanation for observed increases in fracture among users of SSRIs other than, or in addition to, a serotonin-mediated effect. The role of underlying depression severity cannot be ruled out, particularly as an explanation for the early increase in fracture risk.

METHODS

Patients and data source

We conducted a cohort study among Medicare beneficiaries enrolled in pharmaceutical assistance programs in New Jersey and Pennsylvania who initiated use of an antidepressant medication between July 1, 1994 and December 31, 2004. Initiation was defined as filling an antidepressant prescription without having filled one in the preceding 180 days. To ensure complete ascertainment of baseline conditions and prior drug use, we required that individuals be enrolled in both Medicare and the drug benefit program during the 6 months prior to antidepressant initiation. We considered only the first treatment episode during the study period for each patient in the analysis. We required evidence of depression as indicated by a diagnosis of depression (ICD-9-CM code 296.2X, 296.3X, 309.0X, 309.1X, or 311.XX) recorded during an office visit or as a hospital discharge diagnosis during the 6

months prior to through two months after the initiation date (23). The study was approved by the Partners Healthcare Institutional Review Board.

Antidepressant medication exposure

We classified antidepressant medications into the following four groups, according to a standard reference (24): SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine), secondary amine tricyclics (amoxapine, desipramine, maprotiline, nortriptyline, protriptyline), tertiary amine tricyclics (amitriptyline, clomipramine, doxepin, imipramine, trimipramine), and atypical antidepressants (duloxetine, mirtazapine, nefazodone, trazodone). We excluded bupropion because of its potential for use in smoking cessation and monoamine oxidase inhibitors because few patients meeting eligibility criteria ($n = 35$) initiated these drugs during our study timeframe.

Fracture outcomes and follow-up

The primary study endpoint was a composite fracture outcome, comprising fractures at four anatomic sites typical for fragility fractures: hip, humerus, pelvis, and wrist. We used previously validated algorithms for claims data to identify fractures (30). These involved combinations of diagnoses and procedures specific for a given fracture, but they cannot identify low-energy from high-energy trauma.

In the primary 'as matched' analysis, we considered patients exposed to one of the four classes of antidepressants from the day after the first dispensing through the duration of follow-up. For each fracture subtype outcome, we followed patients in their initial treatment class until they experienced the fracture subtype, died, or were censored because of loss of coverage or end of the study period. For the composite fracture outcome, we censored patients at the first occurrence of any of the fracture subtypes. In an 'as treated' sensitivity analysis, we also censored patients when they initiated another antidepressant medication class or when 14 days elapsed between the last available dose of a prescription and the dispensing of a subsequent prescription.

Patient characteristics

Baseline patient characteristics were defined using medical claims during the 6 months preceding treatment initiation. These included sociodemographic characteristics such as age, sex, and race and health service utilization information such as number of hospitalizations, Charlson Comorbidity Index score (31), and number of distinct molecular entities prescribed. Psychiatric disorders, which may determine treatment selection, were defined as the presence of two outpatient diagnoses or one inpatient diagnosis and included anxiety or sleep disorders, mania and bipolar disorder, attention-deficit/hyperactivity disorder, substance abuse, psychotic disorder, delirium, personality disorders, and other mental disorders (hysteria, acute reactions to stress, sexual deviations, and disturbance of emotions specific to childhood or adolescence). We also identified risk factors for fracture, including history of fracture, emergency room visit for fall, use of oral steroids or agents for osteoporosis (alendronate, calcitonin, etidronate, ibandronate, estrogen replacement therapy, raloxifene, risendronate, and teriparatide), and diagnosis of osteoporosis, rheumatoid arthritis, or hyperparathyroidism.

Statistical analysis

The primary analysis used propensity score matching to control for confounding by indication. A propensity score is the estimated probability of receiving one treatment versus another based on observed covariate information (27). We constructed three separate propensity score models using multivariable logistic regression. The first model predicted exposure to tertiary amines versus secondary amine tricyclics, the second predicted exposure to SSRIs versus secondary amines, and the third predicted exposure to atypical antidepressants versus secondary amines. We chose secondary amine tricyclics as the reference group since drugs in this class are generally less sedating and less serotonergic than drugs in other classes. We used a greedy algorithm to match initiators of secondary amine tricyclics to initiators of each of the other three drugs classes in a 1:1 ratio, using their respective propensity scores. Initiators of secondary amines who were matched to users of each of the other three classes were retained, along with their three matches. This resulted in four cohorts of equal size and with similar distributions of observed covariates (32). All potential confounders described above (i.e. all sociodemographic variables, health services utilization information, observed psychiatric conditions, and risk factors for fracture) were included in each propensity score model. Success in achieving balance on propensity score was assessed using the standardized difference (33).

We plotted Kaplan-Meier event-free survival curves for the primary composite fracture outcome and for each fracture subtype. We computed incidence rates, incidence rate differences, and used Cox proportional hazards models to estimate incidence rate ratios to compare fracture rates among the four antidepressant classes. We estimated separate models for each fracture subtype and for the composite fracture outcome.

We performed a range of sensitivity analyses. First, we used the original 'as matched' analysis but truncated follow-up at a maximum of 90 days for all patients, to explore short-term effects. Second, to examine long-term effects, we conducted a separate analysis among only patients who remained on their initial treatment at day 90 following initiation. Patients who discontinued treatment, experienced a fracture, died, or were censored because of loss of coverage or end of the study period, within 90 days of initiation, were excluded from this analysis. We repeated the propensity score matching procedure described above among those eligible for this analysis, again using the baseline covariates. We began follow-up for these patients at day 91. Third, all sociodemographic variables and fracture risk factors were adjusted in a Cox proportional hazards model, rather than in a propensity score analysis. All initiators of the antidepressants of interest were eligible for this analysis, even those who were not matched in the primary analysis. Fourth, in a separate analysis, we again used the original propensity score-matched cohorts but further adjusted the Cox outcome model for variables with residual imbalance after propensity score matching. Standardized differences of 0.10 are commonly used to define imbalance. Since all variables exhibited good balance (i.e. no standardized differences > 0.10), we used a stricter threshold, by including variables for which the largest pair-wise standardized difference between any two cohorts was > 0.05. Finally, we also explored fracture rates stratified by pharmacological properties thought to mediate a potential association. Each antidepressant was cross-classified as having low receptor affinity ($K_i > 100$ nM), medium receptor affinity (K_i 10–100 nM) or high receptor

affinity ($K_i < 10$ nM) for 5-HTT and as having low, medium, or high sedating potential, based on a standard reference (24).

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Figure 1.
Probability of remaining free of fracture by antidepressant class within the first two years following antidepressant initiation.

Figure 2.

Incidence rates ratios for the composite fracture outcome according to antidepressant exposure in the primary analysis (A) and in sensitivity analyses: (B) 'as treated' analysis; (C) 'as matched' analysis with follow-up truncated at 90 days post-initiation; (D) among those continuing treatment 90 days post-initiation; (E) among all (i.e. unmatched) antidepressant initiators, adjusted for covariates in Table 2; (F) 'as matched' analyses adjusted for covariates with residual imbalance (standardized difference ≤ 0.05): age, comorbidity score, prior psychiatric hospitalization, diagnosis of dementia, prior fracture, and diagnosis of Alzheimer disease. Note: secondary amine tricyclics are the reference group in each analysis.

Table 1

Baseline patient characteristics of all new antidepressant initiators eligible for analysis

Characteristic	Secondary amine tricyclics (n = 2,916)	Tertiary amine tricyclics (n = 4,701)	Selective serotonin reuptake inhibitors (n = 56,941)	Atypical antidepressants (n = 8,514)
Sociodemographic				
Age in years, mean ± SD	76.8 (10.8)	74.2 (12.0)	77.7 (10.8)	77.7 (12.3)
Sex, female, n (%)	2,463 (84.5)	3,755 (79.9)	45,935 (80.7)	6,701 (78.7)
Race, white, n (%)	2,672 (91.6)	4,253 (90.5)	52,611 (92.4)	7,835 (92.0)
Health services use intensity				
Distinct generic medications prescribed, mean ± SD	7.2 (4.9)	7.8 (5.2)	7.5 (4.8)	7.8 (5.0)
Comorbidity score, mean ± SD	2.3 (2.2)	2.1 (2.2)	2.5 (2.3)	2.7 (2.5)
Psychiatric hospitalization, n (%)	287 (9.8)	201 (4.3)	3,527 (6.2)	1,070 (12.6)
Use of 1 additional psychiatric medication, n (%)	1,465 (50.2)	2,267 (48.2)	24,074 (42.3)	4,340 (51.0)
Mental health-related comorbidities				
Attention deficit hyperactivity disorder, n (%)	3 (0.1)	5 (0.1)	105 (0.2)	56 (0.5)
Anxiety or sleep disorder, n (%)	323 (11.1)	507 (10.8)	5,592 (9.8)	1,112 (13.1)
Dementia, n (%)	286 (9.8)	218 (4.6)	6,923 (12.2)	1,707 (20.1)
Mania, n (%)	71 (2.4)	113 (2.4)	914 (1.6)	322 (3.8)
Psychotic disorder, n (%)	180 (6.2)	158 (3.4)	2,655 (4.7)	778 (9.1)
Substance abuse, n (%)	74 (2.5)	112 (2.4)	1,134 (2.0)	320 (3.8)
Osteoporosis-related factors				
Osteoporosis diagnosis, n (%)	495 (17.0)	712 (15.2)	9,709 (17.1)	1,643 (19.3)
Prior bone mineral density test, n (%)	40 (1.4)	87 (1.9)	1,227 (2.2)	177 (2.1)
Prior fracture, n (%)	156 (5.4)	163 (3.5)	2,647 (4.7)	533 (6.3)
Prior emergency visit for fall, n (%)	13 (0.5)	36 (0.8)	280 (0.5)	50 (0.6)
Hyperparathyroidism, n (%)	17 (0.6)	32 (0.7)	298 (0.5)	54 (0.6)
Rheumatoid arthritis, n (%)	103 (3.5)	199 (4.2)	1,965 (3.5)	291 (3.4)
Osteoporosis medication use, n (%)	166 (5.7)	345 (7.3)	5,449 (9.6)	888 (10.4)
Use of other medications that may modify fracture risk				
Benzodiazepine use, n (%)	1,183 (40.5)	1,891 (40.2)	19,466 (34.2)	3,237 (38.0)
Oral glucocorticoid use, n (%)	164 (5.6)	309 (6.6)	3,715 (6.5)	537 (6.3)
Thiazolidinedione use, n (%)	21 (0.7)	79 (1.7)	1,402 (2.5)	192 (2.3)
Anticonvulsant use, n (%)	235 (8.1)	385 (8.2)	3,843 (6.8)	830 (9.8)
Proton-pump inhibitor use, n (%)	432 (14.8)	848 (18.0)	11,330 (19.9)	1,872 (22.0)
Exogenous estrogen use, n (%)	149 (5.1)	287 (6.1)	2,487 (4.4)	376 (4.4)
Other comorbidities				
Parkinson disease diagnosis, n (%)	107 (3.7)	115 (2.5)	1,879 (3.3)	346 (4.1)
Alzheimer disease diagnosis, n (%)	90 (3.1)	72 (1.5)	2,704 (4.8)	737 (8.7)

SD, standard deviation

Table 2

Baseline patient characteristics of propensity score-matched cohorts

Characteristic	Secondary amine tricyclics (n = 2,711)	Tertiary amine tricyclics (n = 2,711)	Selective serotonin reuptake inhibitors (n = 2,711)	Atypical antidepressants (n = 2,711)	Largest pair-wise standardized difference
Sociodemographic					
Age in years, mean ± SD	76.4 (10.9)	76.3 (10.9)	77.2 (11.2)	76.6 (12.5)	0.0814
Sex, female, n (%)	2,273 (83.8)	2,272 (83.8)	2,290 (84.5)	2,297 (84.7)	0.0179
Race, white, n (%)	2,486 (91.7)	2,474 (91.3)	2,506 (92.4)	2,480 (91.5)	0.0305
Health services use intensity					
Distinct generic medications prescribed, mean ± SD	7.2 (4.9)	7.2 (4.8)	7.2 (4.6)	7.2 (4.8)	0.0000
Comorbidity score, mean ± SD	2.2 (2.2)	2.1 (2.2)	2.3 (2.3)	2.2 (2.3)	0.0889
Psychiatric hospitalization, n (%)	198 (7.3)	154 (5.7)	196 (7.2)	252 (9.3)	0.0973
Use of 1 additional psychiatric medication, n (%)	1,353 (49.9)	1,338 (49.4)	1,350 (49.8)	1,345 (49.6)	0.0078
Mental health-related comorbidities					
Attention deficit hyperactivity disorder, n (%)	2 (0.1)	4 (0.2)	3 (0.1)	1 (0.0)	0.0258
Anxiety or sleep disorder, n (%)	300 (11.1)	287 (10.6)	295 (10.9)	304 (11.2)	0.0142
Dementia, n (%)	186 (6.9)	190 (7.0)	271 (10.0)	262 (9.7)	0.0799
Mania, n (%)	64 (2.4)	68 (2.5)	57 (2.1)	48 (1.8)	0.0361
Psychotic disorder, n (%)	113 (4.2)	120 (4.4)	141 (5.2)	184 (6.8)	0.0815
Substance abuse, n (%)	65 (2.4)	68 (2.5)	63 (2.3)	73 (2.7)	0.0167
Osteoporosis-related factors					
Osteoporosis diagnosis, n (%)	434 (16.0)	405 (14.9)	459 (16.9)	446 (16.5)	0.0385
Prior bone mineral density test, n (%)	39 (1.4)	40 (1.5)	37 (1.4)	42 (1.6)	0.0109
Prior fracture, n (%)	103 (3.8)	106 (3.9)	130 (4.8)	148 (5.5)	0.0559
Prior emergency visit for fall, n (%)	13 (0.5)	16 (0.6)	12 (0.4)	11 (0.4)	0.0185
Hyperparathyroidism, n (%)	15 (0.5)	17 (0.6)	21 (0.8)	20 (0.7)	0.0193
Rheumatoid arthritis, n (%)	97 (3.6)	100 (3.7)	94 (3.5)	81 (3.0)	0.0276
Osteoporosis medication use, n (%)	159 (5.9)	143 (5.3)	158 (5.8)	164 (6.1)	0.0237
Use of other medications that may modify fracture risk					
Benzodiazepine use, n (%)	1,106 (40.8)	1,110 (40.9)	1,090 (40.2)	1,079 (39.8)	0.0165
Oral glucocorticoid use, n (%)	160 (5.9)	163 (6.0)	157 (5.8)	134 (4.9)	0.0333

Characteristic	Secondary amine tricyclics (n = 2,711)	Tertiary amine tricyclics (n = 2,711)	Selective serotonin reuptake inhibitors (n = 2,711)	Atypical antidepressants (n = 2,711)	Largest pair-wise standardized difference
Thiazolidinedione use, n (%)	21 (0.8)	19 (0.7)	21 (0.8)	15 (0.6)	0.0193
Anticonvulsant use, n (%)	212 (7.8)	198 (7.3)	203 (7.5)	230 (8.5)	0.0310
Proton-pump inhibitor use, n (%)	415 (15.3)	418 (15.4)	408 (15.1)	387 (14.3)	0.0227
Exogenous estrogen use, n (%)	143 (5.3)	137 (5.1)	122 (4.5)	155 (5.7)	0.0391
Other comorbidities					
Parkinson disease diagnosis, n (%)	76 (2.8)	81 (3.0)	99 (3.7)	95 (3.5)	0.0340
Alzheimer disease diagnosis, n (%)	55 (2.0)	56 (2.1)	86 (3.2)	75 (2.8)	0.0508

SD, standard deviation

Table 3

Incidence rates, incidence rate ratios, and incidence rate differences for fracture type according to antidepressant exposure in primary “as matched” analysis

	Secondary amine tricyclics	Tertiary amine tricyclics	Selective serotonin reuptake inhibitors	Atypical antidepressants
Total no. in cohort	2,711	2,711	2,711	2,711
Composite				
Events	310	323	361	309
Person-years	9,011.5	9,363.0	7,784.1	7,749.4
Incidence rate (95% CI) ^a	34.4 (30.7, 38.5)	34.5 (30.8, 38.5)	46.4 (41.7, 51.4)	39.9 (35.6, 44.6)
IRR (95% CI) ^b	Reference	1.01 (0.87, 1.18)	1.30 (1.12, 1.52)	1.12 (0.96, 1.31)
IRD (95% CI) ^a	Reference	0.10 (−5.27, 5.47)	11.98 (5.85, 18.10)	5.47 (−0.39, 11.34)
Hip				
Events	144	155	170	164
Person-years	9,453.9	9,739.9	8,181.5	8,052.1
Incidence rate (95% CI) ^a	15.2 (13.5, 18.6)	15.9 (13.5, 18.6)	20.8 (17.8, 24.2)	20.4 (17.4, 23.7)
IRR (95% CI) ^b	Reference	1.05 (0.84, 1.32)	1.33 (1.06, 1.66)	1.29 (1.03, 1.62)
IRD (95% CI) ^a	Reference	0.68 (−2.85, 4.21)	5.55 (1.55, 9.54)	5.14 (1.15, 9.12)
Humerus				
Events	49	54	50	52
Person-years	9,602.5	9,922.3	8,351.3	8,253.0
Incidence rate (95% CI) ^a	5.1 (3.8, 6.7)	5.4 (4.1, 7.1)	6.0 (4.4, 7.9)	6.3 (4.7, 8.3)
IRR (95% CI) ^b	Reference	1.07 (0.73, 1.57)	1.15 (0.77, 1.71)	1.21 (0.82, 1.79)
IRD (95% CI) ^a	Reference	0.34 (−1.70, 2.38)	0.88 (−1.31, 3.07)	1.20 (−1.03, 3.43)
Pelvis				
Events	95	103	124	105
Person-years	9,544.0	9,869.5	8,246.0	8,159.8
Incidence rate (95% CI) ^a	10.0 (8.1, 12.2)	10.4 (8.5, 12.7)	15.0 (12.5, 17.9)	12.9 (10.5, 15.6)
IRR (95% CI) ^b	Reference	1.06 (0.80, 1.40)	1.46 (1.11, 1.90)	1.24 (0.94, 1.64)
IRD (95% CI) ^a	Reference	0.48 (−2.36, 3.32)	5.08 (1.77, 8.40)	2.91 (−0.26, 6.09)
Radius				
Events	85	73	83	53
Person-years	9,470.6	9,849.0	8,244.0	8,190.5
Incidence rate (95% CI) ^a	9.0 (7.2, 11.1)	7.4 (5.8, 9.3)	10.1 (8.0, 12.5)	6.5 (4.8, 8.5)
IRR (95% CI) ^b	Reference	0.83 (0.61, 1.13)	1.10 (0.81, 1.49)	0.71 (0.50, 1.00)
IRD (95% CI) ^a	Reference	−1.56 (−4.12, 0.99)	1.09 (−1.79, 3.98)	−2.50 (−5.09, 0.08)

CI, confidence interval; IRD, incidence rate difference; IRR, incidence rate ratio

^a Rates and rate differences are per 1,000 person-years

^b Incidence rate ratios estimated with a Cox proportional-hazards model

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Table 4

Incidence rates (95% confidence intervals) for the composite fracture outcome according to affinity for the serotonin transport receptor and sedating potential of index antidepressant

Sedating potential	Affinity for 5-HTT			Summary for row
	Low (Ki>100 nM)	Medium (Ki 10–100 nM)	High (Ki<10 nM)	
Low	–	31.22 (21.58–43.77)	46.57 (41.96–51.55)	44.86 (40.59–49.46)
Medium	8.02 (0.40–39.54)	35.22 (31.26–39.55)	36.88 (27.31–48.76)	35.10 (31.43–39.07)
High	39.32 (35.10–43.90)	37.28 (29.88–45.98)	33.33 (28.88–38.28)	36.86 (33.96–39.94)
Summary for column	38.85 (34.69–43.38)	35.30 (31.93–38.92)	40.60 (37.45–43.94)	38.45 (36.41–40.58)

Rates are per 1,000 person-years