# Multinational Investigation of Fracture Risk with Antidepressant Use by Class, Drug, and Indication

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**OBJECTIVES:** Antidepressants increase the risk of falls and fracture in older adults. However, risk estimates vary considerably even in comparable populations, limiting the usefulness of current evidence for clinical decision making. Our aim was to apply a common protocol to cohorts of older antidepressant users in multiple jurisdictions to estimate fracture risk associated with different antidepressant classes, drugs, doses, and potential treatment indications.

**DESIGN:** Retrospective (2009–2014) cohort study.

**SETTING:** Five jurisdictions in the United States, Canada, United Kingdom, and Taiwan.

**PARTICIPANTS:** Older antidepressant users—subjects were followed from first antidepressant prescription or dispensation to first fracture or until the end of follow-up.

**MEASUREMENTS:** The risk of fractures with antidepressants was estimated by multivariable Cox proportional hazards models using time-varying measures of antidepressant dose and use vs nonuse, adjusting for patient characteristics.

**RESULTS:** Between 42.9% and 55.6% of study cohorts were 75 years and older, and 29.3% to 45.4% were men. Selective serotonin reuptake inhibitors (SSRIs) (48.4%-60.0%) were the predominant class used in North America compared with tricyclic antidepressants (TCAs) in the United Kingdom and Taiwan (49.6%-53.6%). Fracture rates varied from 37.67 to 107.18 per 1,000. The SSRIs citalopram (hazard ratio [HR] = 1.23; 95% confidence interval [CI] = 1.11-1.36 to HR = 1.43; 95% CI = 1.11-1.84) and sertraline (HR = 1.36; 95% CI = 1.10-1.68), the SNRI duloxetine (HR = 1.41; 95% CI = 1.06-1.88), TCAs doxepin (HR = 1.36; 95% CI = 1.00-1.86) and imipramine (HR = 1.16; 95% CI = 1.05-1.28), and atypicals (HR = 1.34; 95% CI = 1.14-1.58) increased fracture risk in some but not all jurisdictions. In the United States and the United Kingdom, fracture risk with all classes was higher when prescribed for depression than chronic pain, a trend that is likely explained by drug choice.

**CONCLUSION:** The fracture risk for patients may be reduced by selecting paroxetine, an SSRI with lower risk than citalopram, the SNRI venlafaxine over duloxetine, and the TCA amitriptyline over imipramine or doxepin. There is uncertainty about the risk associated with the atypical antidepressants. **J Am Geriatr Soc 68:1494-1503, 2020.**

**Keywords: antidepressant; fracture; older adults; multinational**

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In the past decade, many countries have reported a two- to threefold increase in antidepressant medication use.[1] Antidepressants now represent one of the most commonly prescribed medications,[2,3] especially among older adults, where annual prevalence varies from 10.3% to 23.4%.[4] Increasing use of antidepressants may reflect better recognition and treatment of depression,[5,6] but antidepressants are



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also known to increase the risk of falls and fractures in older adults.[7-15]

There are several challenges in using current evidence of antidepressant risks in clinical decision making. First, risk estimates vary considerably in comparable populations and settings[14] from a fourfold[12] increase in fall and fracture risk to no significant risk increase.[11,15] The therapeutic class of antidepressants appears to be an important determinant of risk. Although selective serotonin reuptake inhibitors (SSRIs) are considered safer drugs in older adults because they lack the anticholinergic effects of tricyclic antidepressants (TCAs),[16-18] SSRIs are systematically associated with a higher risk of falls and fractures. In a 2018 meta-analysis, the pooled odds ratio (OR) for SSRIs was 2.0 (95% confidence interval [CI] = 1.9-2.2) compared with 1.4 (95% CI = 1.1-1.9) for TCAs.[11] Moreover, few studies have evaluated risks associated with newer, increasingly popular choices[4] such as selective noradrenaline reuptake inhibitors (SNRIs) trazodone, bupropion, and mirtazapine.[11] When assessed, the risk of falls and fractures appears to be equivalent to or less than that observed for SSRIs.[11]

Dose also represents a potentially important risk determinant. Although few studies have estimated dose-related antidepressant effects, they have shown that the risk of fractures is limited to higher doses of antidepressants but not necessarily for all antidepressant classes.[19] There is a substantial difference in prescribed dose in different jurisdictions and by treatment indication.[4] Higher doses of antidepressants are prescribed for patients with depression than those with chronic pain, and depression is an independent risk factor for falls and fractures.[10,20] Chronic pain, the most common potential indication for antidepressant use in older adults, is more likely to be treated by SSRIs in North America compared with TCAs in the United Kingdom.[4] Thus heterogeneity in risks associated with antidepressant use in different studies may be confounded by differences in therapy choice for different treatment indications, treatment aggressiveness, and study methods.

In an attempt to disentangle heterogeneity in risk estimates, Souverein et al applied a common protocol to three European electronic health record databases.[21] Although there was a systematic trend for fracture risks to be higher with SSRIs than TCAs, the magnitude of risk with SSRIs was substantially higher in the Netherlands (hazard ratio [HR] = 3.13; 95% CI 1.87-5.22) than in Spain (HR = 1.67; 95% CI = 1.49-1.87). Variations in dose, drug choice within class, and modification of risk by treatment indication were not evaluated. In this study, we addressed these gaps in evidence by applying a common study protocol to cohorts of older antidepressant users in four countries and five jurisdictions. We estimated the dose-related risk of fracture with commonly used (SSRI, TCAs) and newer antidepressants, for individual drugs within a class, and by potential treatment indication.

## METHODS

### Design and Data Sources

Equivalent cohorts of older antidepressant users were created in each jurisdiction composed of individuals who were prescribed or dispensed an antidepressant between 2009 and 2014, and were 65 years of age or older at the time of their first prescription. Persons were followed from the date of their first prescription to the date of the first fracture or until the end of 2014 if there was no fracture. Antidepressant use was treated as a time-dependent exposure during follow-up, whereby the fracture risk during periods of antidepressant use was compared with periods of nonuse. Data sources for the five jurisdictions (Quebec, Montreal, Boston, United Kingdom, Taiwan) were described previously[4] and are detailed in Supplementary Appendix S1.

### Time-Varying Measurement of Antidepressant Use

#### *Episodes of Antidepressant Use*

To account for the time-varying nature of antidepressant use, we defined treatment episodes as starting with the first prescription/dispensation and ending when there was a gap of 30 days or longer in prescribed duration or dispensed supply. Antidepressant prescription/dispensing after a 30-day gap was considered a new treatment episode. Changes in antidepressant drug and/or dose during a treatment episode were accounted for by creating a new record to reflect the new exposure on the date of the therapy change. Antidepressant users were classified as new or continued based on whether they had a prescription for an antidepressant in the 2 years before their first prescription. For the look-back period, data were also retrieved for 2007 and 2008.

#### *Therapeutic Class*

Any drug with an indication for depression was included in this analysis. The Anatomic Therapeutic Classification (ATC) system[22] was used to map national drug names and identification numbers to a common nomenclature. Therapeutic classes included TCAs, SSRIs, SNRIs, and atypical antidepressants.

#### *Antidepressant Dose*

To allow comparisons among antidepressants, we created a standardized dose for each drug by dividing the prescribed dose by the World Health Organization defined daily dose[23] that represents the proportion of the average daily adult maintenance dose that was prescribed. When more than one antidepressant was prescribed concurrently, we summed the standardized doses of each drug.

#### *Potential Treatment Indications*

Potential treatment indications for antidepressant use[24,25] included *depression with or without other mental health conditions* and *chronic pain*, measured using diagnostic codes from the electronic medical record (EMR), medical service claims, and hospitalizations in the 2 years preceding the first antidepressant prescription. *Depression* included mild, moderate, or major single or recurrent depressive disorder with or without psychotic symptoms, adjustment reaction, and mixed anxiety and depression. *Other mental health conditions* included anxiety, alcohol abuse, illicit drug use, attempted suicide, psychosis, schizophrenia, and bipolar disorder. To measure *chronic pain*, a common use of antidepressants,[4,24,25] we used a previously validated *International Classification of Diseases* (ICD)-9/ICD-10 code set for noncancer pain[26] and mapped these to READ

codes (Supplementary Appendix S2). If a patient had both chronic pain and depression, they were classified as having depression.

## Measurement of Fractures during Baseline and Follow-Up

The primary outcome was fractures, most of which are fall related,[27] likely related to central nervous system side effects of antidepressants,[28] although there is some evidence that SSRIs directly affect osteoporosis.[29] Fractures of the skull, face, vertebral column, ribs, pelvis, hip, and upper and lower extremity were included. Three data sources were used to measure fractures: (1) ICD-9, ICD-10, or READ code diagnosis of a fracture from hospitalization databases; (2) a medical service procedure for fracture treatment; or (3) ICD-9 or READ diagnostic code of a medical visit for a fracture (Supplementary Appendix S2). Because individuals could have multiple fracture events, we identified the most likely date of each event by ordering all fracture records by date in the 2 years before the first prescription and during follow-up. We selected, in order of priority, the dates of hospital admission for a fracture, a fracture procedure, and a medical visit for a fracture as the most likely date of the event. To distinguish a new fracture from follow-up care, we required 6 months to elapse after the first fracture for a new fracture to be recorded.[30] Each fracture was defined as occurring before (fracture history) and/or after the first prescription.

## Demographics, Concurrent Drug Use, and Comorbidities

### *Demographics*

Age and sex at the date of the first prescription were retrieved from EMR or insurance beneficiary files. To protect confidentiality, age was grouped in two intervals: 65 to 74 years and 75 years and older.

### *Concurrent Drugs*

Drugs known to increase the fall/fracture risk (antipsychotics, benzodiazepines, anxiolytics, opioids) were measured as time-dependent covariates.[31] The ATC system[32] was used to identify and map local drug names within these classes to a common data structure. Four binary variables designated the presence of a prescription for these therapeutic classes during follow-up.

**Table 1. Characteristics of Antidepressant Users in Each Jurisdiction**

| | Canada | | | | United States | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Montreal | | Quebec City/Montreal | | Boston | | United Kingdom | | Taiwan | |
| | N | % | N | % | N | % | N | % | N | % |
| Older adults, N | 23,422 | | 4,448 | | 17,359 | | 24,858 | | 24,225 | |
| Demographic characteristics | | | | | | | | | | |
| 65-74 y at index | 10,395 | 44.4 | 2,323 | 52.2 | 9,918 | 57.1 | 11,381 | 45.8 | 12,084 | 49.9 |
| ≥75 y at index | 13,027 | 55.6 | 2,125 | 47.8 | 7,441 | 42.9 | 13,477 | 54.2 | 12,141 | 50.1 |
| Female | 16,570 | 70.7 | 3,110 | 69.9 | 10,645 | 61.3 | 16,405 | 66 | 13,218 | 54.6 |
| Male | 6,852 | 29.3 | 1,338 | 30.1 | 6,714 | 38.7 | 8,453 | 34 | 11,007 | 45.4 |
| Potential indications for antidepressants | | | | | | | | | | |
| Depression | 4,846 | 20.7 | 1970 | 44.3 | 6,423 | 37.0 | 5,496 | 22.1 | 3,223 | 13.3 |
| Anxiety | 6,945 | 29.7 | 1,601 | 36 | 3,829 | 22.1 | 3,797 | 15.3 | 9,928 | 41.0 |
| Other mental health issues | 2,120 | 9.1 | 372 | 8.4 | 1,553 | 8.9 | 13,652 | 54.9 | 1,437 | 5.9 |
| Pain | 11,121 | 47.5 | 1983 | 44.6 | 9,685 | 55.8 | 6,835 | 27.5 | 8,481 | 35.0 |
| Conditions that increase the risk of falls | | | | | | | | | | |
| Dementia | 2,642 | 11.3 | 370 | 8.3 | 404 | 2.3 | 2096 | 8.4 | 3,826 | 15.8 |
| Parkinson's disease | 446 | 1.9 | 61 | 1.4 | 92 | .5 | 449 | 1.8 | 1,579 | 6.5 |
| Epilepsy | 252 | 1.1 | 49 | 1.1 | 204 | 1.2 | 262 | 1.1 | 339 | 1.4 |
| Hypertension | 10,952 | 46.8 | 2,432 | 54.7 | 4,897 | 28.2 | 10,987 | 44.2 | 16,890 | 69.7 |
| Peripheral vascular disease | 1849 | 7.9 | 167 | 3.8 | 681 | 3.9 | 1,044 | 4.2 | 1,764 | 7.3 |
| Obesity | 764 | 3.3 | 34 | .8 | 2,200 | 12.7 | 1,154 | 4.6 | 90 | .4 |
| Conditions that increase the risk of fractures | | | | | | | | | | |
| Cardiac problems | 7,956 | 33.9 | 1,327 | 29.8 | 2,530 | 14.6 | 6,023 | 24.2 | 14,239 | 58.8 |
| Stroke | 1,585 | 6.8 | 157 | 3.5 | 492 | 2.8 | 2,164 | 8.7 | 4,120 | 17.0 |
| Renal disease | 1,302 | 5.6 | 74 | 1.7 | 281 | 1.6 | 4,739 | 19.1 | 3 | 0 |
| Cancer | 5,075 | 21.7 | 824 | 18.5 | 1,589 | 9.2 | 3,140 | 12.6 | 2,955 | 12.2 |
| Osteoporosis | 3,878 | 16.6 | 846 | 19.0 | 1886 | 10.9 | 1857 | 7.5 | 3,468 | 14.3 |
| History of fractures | 1,689 | 7.2 | 322 | 7.2 | 1,118 | 6.4 | 1,730 | 7 | 4,700 | 19.4 |
| Drugs that increase the risk of falls | | | | | | | | | | |
| Benzodiazepines/Anxiolytics | 11,787 | 50.3 | 1,647 | 37 | 6,215 | 35.8 | 4,696 | 18.9 | 17,024 | 70.3 |
| Antipsychotics | 2,119 | 9 | 189 | 4.2 | 2,138 | 12.3 | 3,038 | 12.2 | 5,213 | 21.5 |
| Opioids | 6,854 | 29.3 | 552 | 12.4 | 6,539 | 37.7 | 12,408 | 49.9 | 2,527 | 10.4 |

### *Comorbidities*

Health problems that could increase the risk of falls and fractures were measured before the first antidepressant using diagnostic codes (ICD-9, ICD-10, READ) from EMR and administrative databases (Supplementary Appendix S2). These included depression, cardiovascular and cerebrovascular problems, osteoporosis, Parkinson's disease, dementia, epilepsy, hypertension, peripheral vascular disease, cancer, renal disease, and obesity.[10,20,33-39]

## Analysis

Descriptive statistics summarized the characteristics of each cohort, antidepressant use, and fracture rates. Fracture rates during follow-up were estimated by dividing the number of patients with a fracture by the number of months of follow-up. Cox proportional hazards models, with time-varying measures of exposure to antidepressants and concurrent drugs, estimated the association between antidepressants and fractures, adjusting for patient age, sex, type of user (new, continuing), potential treatment indication, concurrent drug use, fracture history, and preexisting comorbidities.

We first modeled fracture risk with the use of any antidepressant, represented as a binary variable, and compared fracture risk during periods of antidepressant use with periods of nonuse. In a second model, we estimated fracture risk by class (SSRIs, TCAs, SNRIs, other antidepressants, and multiple concurrent classes). In these models, fracture risk for each class is compared with pooled periods of nonuse across all classes. In a third model, we estimated fracture risk for each drug within a class. Each drug is represented as a binary variable, reflecting periods of use and nonuse. The estimated HRs for each drug represent the fracture risk during periods of use compared with periods of nonuse pooled across all drugs.

To assess dose effects, we repeated the three models but replaced the binary indicator representing antidepressant use with the standardized dose, and modeled it as a continuous variable, assuming a linear risk increase. The

**Table 2. Characteristics of First Antidepressant Prescribed during Follow-Up by Drug Class, Standardized Dose, and Jurisdiction**

| | Canada | | | | United States | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Montreal | | Quebec City/Montreal | | Boston | | United Kingdom | | Taiwan | |
| | N | % | N | % | N | % | N | % | N | % |
| Older adults, N | 23,422 | | 4,448 | | 17,359 | | 24,858 | | 24,225 | |
| Antidepressant use status | | | | | | | | | | |
| Continuing user | 10,119 | 43.2 | 3,140 | 70.6 | 7,228 | 41.6 | 8,990 | 36.2 | 6,667 | 27.5 |
| New user | 13,303 | 56.8 | 1,308 | 29.4 | 10,131 | 58.4 | 15,868 | 63.8 | 17,558 | 72.5 |
| SSRI | | | | | | | | | | |
| Citalopram | 6,784 | 29.0 | 1,215 | 27.3 | 3,427 | 19.7 | 6,226 | 25.0 | 498 | 2.1 |
| Escitalopram | 2 | .0 | 109 | 2.5 | 700 | 4.0 | 351 | 1.4 | 1,058 | 4.4 |
| Fluoxetine | 306 | 1.3 | 63 | 1.4 | 2040 | 11.8 | 1,691 | 6.8 | 1,173 | 4.8 |
| Fluvoxamine | 119 | .5 | 39 | .9 | 41 | .2 | 5 | .0 | 163 | .7 |
| Paroxetine | 1,658 | 7.1 | 290 | 6.5 | 829 | 4.8 | 466 | 1.9 | 686 | 2.8 |
| Sertraline | 1,149 | 4.9 | 315 | 7.1 | 2,151 | 12.4 | 1,431 | 5.8 | 1,621 | 6.7 |
| SNRI | | | | | | | | | | |
| Duloxetine | 174 | .7 | 73 | 1.6 | 434 | 2.5 | 225 | .9 | 327 | 1.3 |
| Venlafaxine | 2,874 | 12.3 | 549 | 12.3 | 752 | 4.3 | 421 | 1.7 | 368 | 1.5 |
| Other | 1 | .0 | 6 | .1 | 37 | .2 | 0 | .0 | 37 | .2 |
| TCA | | | | | | | | | | |
| Amitriptyline | 4,155 | 17.7 | 444 | 10.0 | 1,274 | 7.3 | 9,764 | 39.3 | 1,490 | 6.2 |
| Doxepin | 261 | 1.1 | 55 | 1.2 | 111 | .6 | 41 | .2 | 959 | 4.0 |
| Imipramine | 146 | .6 | 17 | .4 | 54 | .3 | 130 | .5 | 9,333 | 38.5 |
| Nortriptyline | 131 | .6 | 48 | 1.1 | 791 | 4.6 | 306 | 1.2 | 0 | 0 |
| Other | 249 | 1.1 | 51 | 1.1 | 80 | .5 | 1,094 | 4.4 | 63 | .2 |
| Atypical antidepressants | | | | | | | | | | |
| Bupropion | 460 | 2.0 | 127 | 2.9 | 1,591 | 9.2 | 38 | .2 | 287 | 1.2 |
| Mirtazapine | 1,304 | 5.6 | 271 | 6.1 | 476 | 2.7 | 1,688 | 6.8 | 772 | 3.2 |
| Trazodone | 2,901 | 12.4 | 462 | 10.4 | 1,591 | 9.2 | 549 | 2.2 | 4,809 | 19.9 |
| Other | 0 | .0 | 2 | .0 | 16 | .1 | 13 | .0 | 56 | .2 |
| Multiple antidepressants | 748 | 3.2 | 312 | 7.0 | 964 | 5.6 | 419 | 1.7 | 525 | 2.2 |
| Mean standardized dose | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Continuing user | .86 | .64 | .9 | .65 | 1.13 | .9 | .81 | .57 | .53 | .46 |
| New user | .52 | .41 | .64 | .4 | .86 | .73 | .52 | .42 | .4 | .34 |

Abbreviations: SD, standard deviation; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

estimated HR represented the risk associated with a one-unit increase in the average adult dose. Because trabecular fractures may be more sensitive to the effects of medication, we conducted a sensitivity analysis with the Montreal sample using only hip fracture as the outcome. All analyses were conducted using SAS software v.9.4.

## RESULTS

Overall, between 42.9% (United States) and 55.6% (Montreal) of the study populations were 75 years of age or older, and 29.3% (Montreal) to 45.4% (Taiwan) were men (Table 1). Between 13.3% (Taiwan) and 44.3% (Quebec) of patients had a diagnosis of depression, 15.3% (United Kingdom) to 41.0% (Taiwan) had anxiety, 5.9% (Taiwan) to 54.9% (United Kingdom) had other mental health problems, and 27.5% (United Kingdom) to 47.5% (Montreal) had chronic pain. In the United Kingdom, alcohol and substance abuse disorders (53.6% vs 1.3%-2.8% elsewhere) were the main source of other mental health problems. Hypertension, dementia, cardiac problems, cancer, and osteoporosis were the most prevalent comorbidities, along with stroke in Taiwan (17.0% vs 2.8%-8.7%) and obesity in the United States (12.7% vs .4%-4.6%). A substantial proportion of patients were prescribed benzodiazepines (35.8%-70.3%) or opioids (10.4%-49.9%) before their first antidepressant prescription.

New users represented 29.4% (Quebec City) to 72.5% (Taiwan) of all antidepressant users (Table 2). Antidepressant choice varied by jurisdiction. In the United Kingdom, amitriptyline (39.3%) was the most commonly prescribed antidepressant, and imipramine (38.5%) was the most common in Taiwan. In North American jurisdictions, SSRIs, specifically citalopram (19.7%-29.0%), were most commonly prescribed.

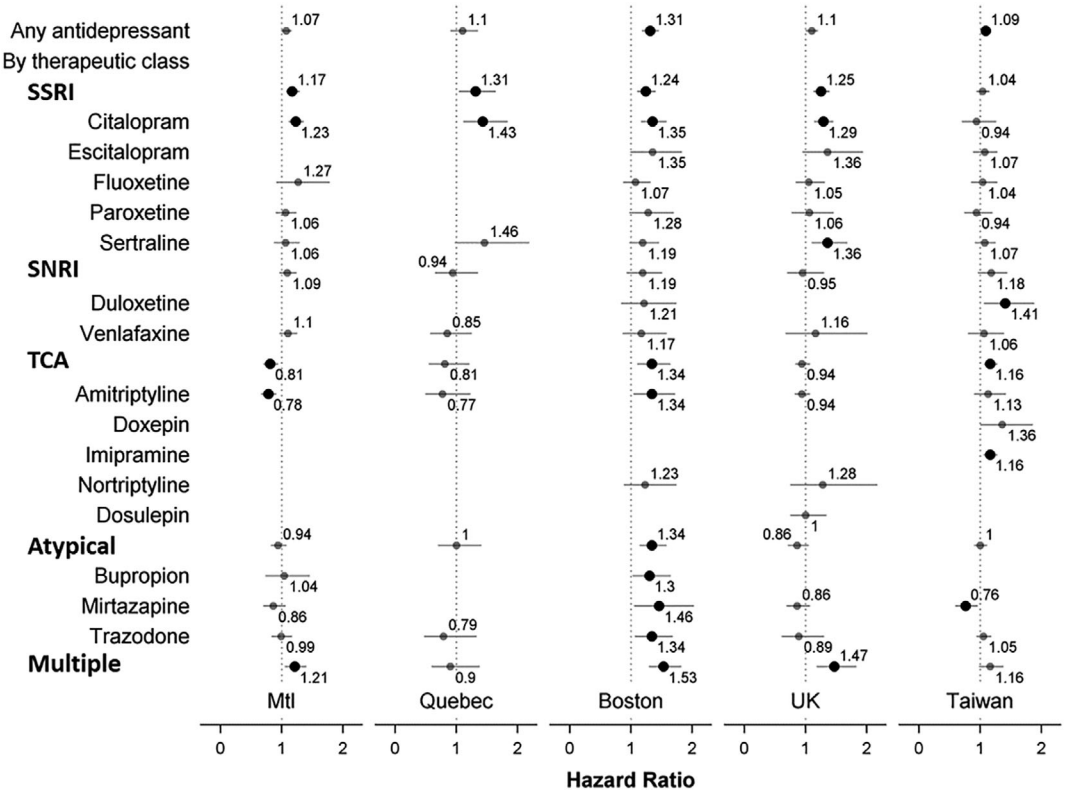


**Figure 1.** Association between antidepressant use and the risk of fractures overall, by therapeutic class, and by drug. Any antidepressant use: In each jurisdiction, we first modeled periods of any antidepressant use vs periods of nonuse using time-dependent measures of exposure, and adjusted for age, sex, potential treatment indications (depression, anxiety, other mental health issues, pain), conditions that increase the risk of falls (dementia, Parkinson's disease, epilepsy, hypertension, peripheral vascular disease, obesity) and fractures (cardiac problems, stroke, renal disease, cancer, osteoporosis, history of fracture), and concurrent drugs (as time-dependent exposures, benzodiazepines, antipsychotics, opioids). By class: In each jurisdiction, we estimated a second model, where antidepressant exposure was measured as a time-varying covariate by therapeutic class (SSRI [selective serotonin uptake inhibitor], SNRI [serotonin norepinephrine reuptake inhibitor], TCA [tricyclic antidepressant], atypical, multiple classes), using binary on (1)-off(0) indicators to represent periods of use for each of the five mutually exclusive therapeutic classes. Periods of use were compared with pooled periods of nonuse across all classes. Models were adjusted for the same potential confounders listed for the any antidepressant model. By drug: In each jurisdiction, we estimated a third model, where antidepressant exposure was measured as a time-varying exposure by individual drug. All drugs were included in the model, and binary on (1)-off(0) indicators were used to represent periods of use. The estimated hazard ratios (HRs) represent risk during periods of use compared with pooled period of nonuse across all drugs. Models were adjusted for the same potential confounders listed for the any antidepressant model. HRs are shown when there were at least 300 or more users of a given drug within the respective jurisdiction. The error bars represent the 95% confidence intervals around the HRs. Mtl, Montreal; UK, United Kingdom.

Venlafaxine was the most commonly prescribed SNRI, and among other antidepressants, bupropion, mirtazapine, and trazodone were the most common. Only a small proportion of patients were started on multiple antidepressants. The standardized dose was highest in the United States and was systematically higher for continuing compared with new users across jurisdictions.

During follow-up, SSRIs (48.4%-60.0%) were the predominant class used in North America, followed by other antidepressants (23.1%-23.6%) (Supplementary Appendix S3). In the United Kingdom and Taiwan, TCAs were the predominant class (49.6%-53.6%), with increasing use of SSRIs in the United Kingdom (46.7%) and other antidepressants (31.1%) in Taiwan. Mean standardized doses tended to be higher for SSRIs (.8-1.3) and SNRIs (.7-1.1), lower for TCAs (.3-.6) and other antidepressants (.4-.8), and systematically lower in Taiwan (.2-.4) than other jurisdictions (.4-1.3). Across jurisdictions, adding or switching antidepressants occurred less frequently with TCAs (11.6%-24.3%) than other classes, and most often with SNRIs, particularly in Taiwan. Multiple antidepressant use was higher during follow-up than at start of therapy, with 13.6% (United Kingdom, Taiwan) to 22.0% (United States) using multiple antidepressants.

During follow-up, fracture rates were similar in all jurisdictions (37.7-47.2 per 1,000) except Taiwan (107.2 per 1,000), where the rate was substantially higher, particularly for spine-skull fractures, most (92.3%) of which were

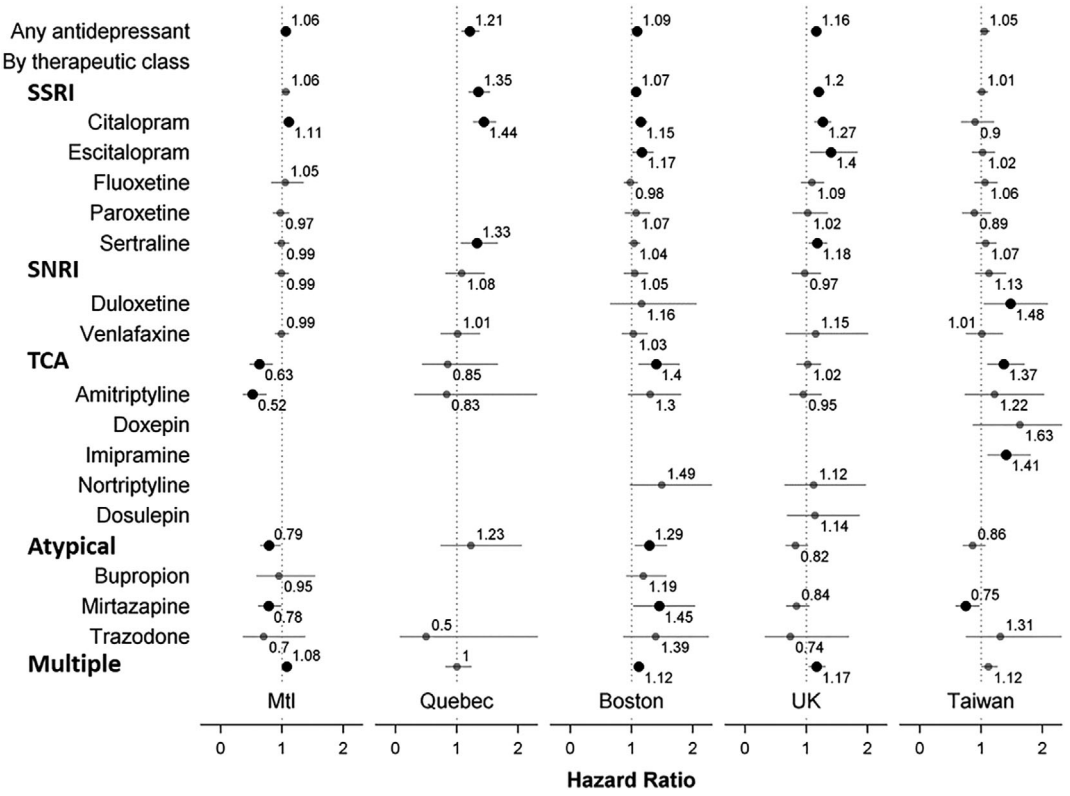


**Figure 2.** Association between antidepressant dose and the risk of fractures overall, by therapeutic class, and by drug. Any antidepressant dose: In each jurisdiction, we first modeled use of any antidepressant, where use was represented by a continuous measure of antidepressant dose, and the estimated hazard ratio (HR) represents the risk associated with a one-unit increase in the standardized adult dose. During periods of nonuse of antidepressants, dose would be represented as zero. Models were adjusted for age, sex, potential treatment indications (depression, anxiety, other mental health issues, pain), conditions that increase the risk of falls (dementia, Parkinson's disease, epilepsy, hypertension, peripheral vascular disease, obesity), and fractures (cardiac problems, stroke, renal disease, cancer, osteoporosis, history of fracture), and concurrent drugs (as time-dependent exposures, benzodiazepines, antipsychotics, opioids). By class: In each jurisdiction, we estimated a second model, where antidepressant exposure was measured as a time-varying covariate by therapeutic class (SSRI [selective serotonin uptake inhibitor], SNRI [serotonin norepinephrine reuptake inhibitor], TCA [tricyclic antidepressant], atypical, multiple classes). Antidepressant use in each class was represented by a continuous measure of antidepressant dose, and the estimated HR represents the risk associated with a one-unit increase in the standardized adult dose for a given therapeutic class. During periods of nonuse of antidepressants, dose would be represented as zero. Models were adjusted for the same potential confounders listed for the any antidepressant model. By drug: In each jurisdiction, we estimated a third model, where antidepressant exposure was measured as a time-varying exposure by individual drug. All drugs were included in the model and use was represented as a continuous measure of antidepressant dose, and the estimated HR represents the risk associated with a one-unit increase in the standardized adult dose for a given drug. During periods of nonuse of antidepressants, dose would be represented as zero. Models were adjusted for the same potential confounders listed for the any antidepressant model. HRs are shown when there were at least 300 or more users of a given drug within the respective jurisdiction. The error bars represent the 95% confidence intervals around the HRs. Mtl, Montreal; UK, United Kingdom.

osteoporotic vertebral fractures (Supplementary Appendix S4). In all jurisdictions, fracture rates were similar for continuing and new users. The most common type of fracture was of the hip or lower extremity (27%-39.3%), followed by upper extremity fractures (19.6%-30.3%), except in Taiwan where fractures of the skull and thorax were the most common (33.3%).

Antidepressant use was associated with a 7% (Montreal, HR = 1.07) to 10% (United Kingdom, HR = 1.10) increase in fracture risk, which was statistically significant in some jurisdictions (Figure 1 and Supplementary Appendix S5). The United States was the exception with an estimated 31% increase in fracture risk with antidepressant use. The most likely explanation is that clinicians in the United States prescribed antidepressants at systematically higher doses (mean 1.13 of the standard adult dose compared with .53-.9 elsewhere). When current dose was modeled rather than use vs nonuse, the United States was similar to other jurisdictions: a 9% risk increase per one-unit increase in standardized dose (Figure 2 and Supplementary Appendix S6).

In all jurisdictions except Taiwan, there was a statistically significant increase in fracture risk with the use of SSRIs, varying from a 17% (Montreal) to 31% (Quebec) increase. Citalopram, the most commonly prescribed SSRI, was associated with a significant 23% to 43% increase in fracture risk in all jurisdictions except Taiwan, where it was rarely prescribed (Table 2). Except for sertraline in the United Kingdom, no other SSRI was associated with a statistically significant risk increase. SNRIs were not associated with an increased fracture risk in any jurisdiction (Figures 1 and 2 and Supplementary Appendixes S5 and S6). However, at the individual drug level, duloxetine, a drug rarely prescribed in any jurisdiction, was associated with a 41% (use) and 48% (dose) increase in fracture risk in Taiwan.

The fracture risk with TCAs varied substantially by jurisdiction. It was significantly protective in Montreal, with similar protective but nonsignificant point estimates in Quebec and the United Kingdom, and significantly increased fracture risk in the United States and Taiwan. These differences were primarily related to higher doses in the United States and differences in drug choice in Taiwan, as there was a significantly increased fracture risk with doxepin (HR = 1.36) and imipramine (HR = 1.36).

The fracture risk with newer atypical antidepressants varied by jurisdiction with a 29% (dose) to 34% (use) increase in fracture risk in the United States (Figure 1 and Supplementary Appendixes S5 and S6). In contrast, there was no significant association in other jurisdictions, with the exception of Montreal, where the effect was protective (Figure 2 and Supplementary Appendix S6; HR = .79). Drug choice accounts for some of these differences as bupropion was almost exclusively prescribed in the United States and was associated with a 30% increase in fracture risk. However, a similar difference in effect across jurisdictions existed in fracture risks for mirtazapine and trazadone. Multiple antidepressant use was associated with a significant increase in fracture risk in all jurisdictions. In sensitivity analysis, the association between antidepressant use and hip fracture showed similar associations.

Between 48.3% (Taiwan) and 69.5% (Quebec) of antidepressant use occurred in persons with a diagnosis of depression or chronic pain (Table 3). In the United

**Table 3. Association between Antidepressant Use and the Risk of Fractures by Treatment Indication and Therapeutic Class**

| | Canada | | | | United States | | United Kingdom | | Taiwan | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Montreal | | Quebec City/Montreal | | Boston | | | | | |
| Treatment indication | HR | 95% CI (*P* value) | HR | 95% CI (*P* value) | HR | 95% CI (*P* value) | HR | 95% CI (*P* value) | HR | 95% CI (*P* value) |
| Depression | N = 4,846 | | N = 1,970 | | N = 4,949 | | N = 5,496 | | N = 3,223 | |
| SSRI | 1.13 | .94-1.37 (.19) | 1.27 | .93-1.74 (.13) | 1.16 | .98-1.38 (.08) | 1.32 | 1.09-1.60 (<.01) | .92 | .76-1.12 (.41) |
| SNRI | 1.23 | .96-1.56 (.10) | 1.02 | .64-1.62 (.94) | 1.08 | .78-1.51 (.64) | 1.36 | .90-2.06 (.14) | 1.01 | .72-1.41 (.96) |
| TCA | .94 | .61-1.45 (.78) | .48 | .18-1.33 (.16) | 1.50 | 1.09-2.06 (.01) | 1.23 | .91-1.66 (.19) | 1.25 | .89-1.76 (.19) |
| Atypical | 1.00 | .76-1.31 (.98) | .88 | .50-1.54 (.65) | 1.27 | 1.01-1.59 (.04) | .89 | .64-1.25 (.50) | 1.04 | .84-1.30 (.71) |
| Multiple | 1.41 | 1.10-1.80 (<.01) | .70 | .38-1.26 (.23) | 1.42 | 1.15-1.76 (<.01) | 1.87 | 1.34-2.60 (<.01) | .96 | .71-1.30 (.81) |
| Chronic pain | N = 8,704 | | N = 1,122 | | N = 6,348 | | N = 6,835 | | N = 8,481 | |
| SSRI | 1.19 | 1.03-1.37 (.02) | 1.32 | .83-2.11 (.24) | 1.37 | 1.11-1.69 (<.01) | 1.06 | .85-1.33 (.59) | 1.14 | .89-1.45 (.32) |
| SNRI | .96 | .78-1.19 (.72) | 1.24 | .59-2.60 (.58) | 1.47 | .98-2.19 (.06) | .54 | .22-1.30 (.17) | 1.90 | 1.27-2.85 (<.01) |
| TCA | .77 | .62-.94 (.01) | .85 | .46-1.59 (.62) | 1.25 | .93-1.67 (.13) | .82 | .68-1.00 (.06) | 1.17 | 1.02-1.35 (.03) |
| Atypical | 1.08 | .88-1.32 (.48) | .82 | .41-1.63 (.57) | 1.34 | 1.00-1.80 (.05) | .97 | .64-1.49 (.90) | .91 | .73-1.13 (.39) |
| Multiple | 1.18 | .92-1.51 (.19) | 1.41 | .65-3.06 (.38) | 1.88 | 1.33-2.66 (<.01) | 1.08 | .65-1.79 (.77) | 1.10 | .69-1.74 (.69) |

Abbreviations: CI, confidence interval; HR, hazard ratio; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Kingdom and United States, fracture risk tended to be higher for all classes when antidepressants were used by persons with depression (Table 3). In the United States, there was a 50% increase in fracture risk for TCAs when prescribed for depression compared with a 25% increase when prescribed for chronic pain, a phenomenon likely explained by drug choice. Doxepin, which was associated with a threefold risk increase in the United States, was prescribed for 8.5% of persons with depression compared with 3.0% of persons with chronic pain. Similarly, in Taiwan, the 90% risk increase with SNRIs prescribed for chronic pain compared with a 1% increase among persons with depression was related to different drug choices for each indication. Duloxetine, associated with a 41% risk increase, was prescribed to 54.8% of persons with chronic pain compared with 35.3% of persons with depression, whereas venlafaxine, associated with a 6% risk increase, was prescribed to 61.4% of persons with depression and 39.7% of those with chronic pain.

## DISCUSSION

In this multi-jurisdictional study of antidepressant use in older adults, we used a common protocol and harmonized data to create equivalent measures of antidepressant use, fractures, and potential confounders. We found considerable variation in antidepressant choice and dose between jurisdictions with the United Kingdom and Taiwan prescribing TCAs and North American jurisdictions prescribing SSRIs. The US jurisdiction prescribed the highest doses and Taiwan the lowest. In all jurisdictions, use of any antidepressant was associated with a modest but significant increase in the risk of fracture. Except in Taiwan, SSRIs were associated with a significant increase in fracture risk. Differences in risk were noted for SNRIs in Taiwan, TCAs in the US and Taiwan jurisdictions, and newer atypical antidepressants in the United States. These differences in risk were predominantly attributable to differences in drug choice within a therapeutic class for different treatment indications and differences in dose.

Consistent with previous studies, SSRIs were associated with a higher fracture risk compared with TCAs in all jurisdictions except Taiwan, but only for two antidepressants: citalopram and sertraline. The magnitude of the risk was lower in this study, 17% to 31%, compared with a twofold risk increase estimated by systematic reviews (OR = 2.02),[11] likely because this study compared periods of use with nonuse among persons prescribed antidepressants. By estimating risk only among antidepressant users, we eliminated the possibility of unmeasured confounders that differ between patients who do and do not receive antidepressants. As previously illustrated,[21] increasing the number of confounders in the model consistently attenuates the magnitude of risk between antidepressant use and fractures. The absence of a relationship between SSRI use and fractures in Taiwan was noted in a previous cohort study,[32] and risk estimates were similar to what was found in this study (HR = 1.02). Known ethnic differences in genetic variants that influence treatment response to SSRIs, both efficacy and adverse events, may explain the lack of an association between SSRI use and fractures in Taiwan.[40] Also, there are documented differences in bone microstructure in Asians that explain the higher rates of osteoporotic fractures and lower rates of other fractures, noted in this study.[41]

The finding that TCAs were protective in some jurisdictions but harmful in others was predominantly related to differences in risk among drugs within the same class, which has important therapeutic implications. Both doxepin and imipramine, TCAs used in Taiwan, increased the risk of fracture, whereas amitriptyline, the most commonly used TCA, was either protective or not significantly associated with fractures. The exception was in the United States, where higher doses were prescribed. Higher doses of TCAs were associated with a much greater increase in fracture risk in older adults.[19] The apparent protective effect of TCAs may be due to physicians selectively prescribing them to lower risk patients[42] because TCAs have established benefits in treating chronic pain, the most common treatment indication in older adults,[4] but are contraindicated because of their potent anticholinergic effects.[16-18] The possibility that chronic pain was the indication for much TCA prescribing is supported by the observed lower dosages.

There is less evidence about the potential fracture risk with SNRIs and newer atypical antidepressants.[11,43] Although we found no significant risk with SNRI use in any jurisdiction, we did find differences in risk among drugs within this class, a significantly higher risk with duloxetine than venlafaxine, both in magnitude and statistical significance, a finding also noted in a recent review.[44] For atypicals, we also found that risk varied substantially by drug. However, the findings were more complex because the significantly increased risk with mirtazapine in the United States was not seen in other jurisdictions, possibly attributable to differences in unmeasured treatment indications such as smoking cessation and insomnia. Few other studies have assessed the risk associated with atypical antidepressants, and even fewer have assessed the risk of individual drugs within this class. Results suggest a trend of increased risk, with some reporting statistically significant increased risks with trazodone,[9,45] mirtazapine,[9] and others reporting statistically insignificant increased risks with "other antidepressants."[46-48]

This is the first study we are aware of to examine fracture risk by potential treatment indication. Our findings suggest that the risk is higher when antidepressants are used for the treatment of depression than chronic pain. However, this was not a systematic trend in all jurisdictions, possibly because of differences in the way in which depression and chronic pain are diagnosed. Future studies are needed to confirm these initial results.

There are limitations to consider in interpreting study results. We did not measure whether antidepressants were used by patients, only whether they were prescribed or dispensed, a limitation that will likely underestimate antidepressant risk because up to 50% of patients who are nonadherent to treatment[49-53] will be misclassified as exposed. Even though efforts were made to harmonize data from different sources, measurement and reporting issues may nevertheless result in arbitrary differences between countries and jurisdictions. Montreal and Taiwan cohorts comprised entire populations or representative samples, whereas US, UK, and Quebec cohorts were created based on clinical practices supported by certain information technology systems. However, antidepressant use observed in these more selected populations is similar to that reported for older adults in these countries.[3,54-59] Some potentially important confounders that increase the risk of

fracture could not be measured such as smoking, use of proton pump inhibitors, Z hypnotics, and glucocorticoids.

In conclusion, this multijurisdictional investigation confirmed an increased fracture risk with individual antidepressants within the same therapeutic class and for different treatment indications. The fracture risk for patients may be reduced by selecting paroxetine, an SSRI with lower risk than citalopram, the SNRI venlafaxine over duloxetine, and the TCA amitriptyline over imipramine or doxepin. There is uncertainty about the risk associated with the atypical antidepressants. Future studies should focus on risks associated with individual drugs and for different treatment indications to refine the clinical implications of our findings.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

**Supplementary Appendix S1:** Data sources

**Supplementary Appendix S2:** Diagnostic codes

**Supplementary Appendix S3:** Characteristics of antidepressant use during the follow-up period (2009-2014)

**Supplementary Appendix S4:** Fracture rate during follow-up (2009-2014), overall and by type of antidepressant user, fracture type, and jurisdiction

**Supplementary Appendix S5:** Association between antidepressant use and the risk of fractures: overall, by therapeutic class, and by drug

**Supplementary Appendix S6:** Association between antidepressant dose[1] and the risk of fractures: overall, by therapeutic class, and by drug