Selective Serotonin Reuptake Inhibitor Use and Risk of Arrhythmia: A Nationwide, Population-Based Cohort Study

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ABSTRACT

Purpose: This study compares the risks of arrhythmia among patients with depression receiving selective serotonin reuptake inhibitors (SSRIs) and those receiving other classes of antidepressants and among patients with depression receiving citalopram-escitalopram and those receiving other SSRIs.

Methods: This retrospective cohort study used data from the 2000–2011 National Health Insurance Research Database in Taiwan. Patients with depression who were new antidepressant users were included in the study sample. Propensity score matching was used to balance the covariates between the comparison groups. Crude incidence rates were generated by Poisson regressions, and Cox proportional hazards regression models were used to assess the rates of arrhythmia among SSRI users and nonusers of SSRI antidepressants as well as between citalopram-escitalopram users and users of other SSRIs.

Findings: Neither SSRI (hazard ratio [HR] = 0.95; 95% CI, 0.83–1.08) nor citalopram-escitalopram (HR = 1.20; 95% CI, 0.95–1.51) exposure was associated with a risk of arrhythmia compared with other, newer non-SSRI antidepressants or noncitalopram SSRIs. An increase in mortality was, however, observed among citalopram-escitalopram users (HR = 1.21; 95% CI, 1.08–1.31).

Implications: Citalopram, escitalopram, and other SSRIs were not associated with an elevated risk of arrhythmia compared with each other or with non-SSRI antidepressants. Nevertheless, citalopram and escitalopram were associated with an increase in mortality risk compared with other SSRIs and deserve further investigation. (*Clin Ther.* 2019;41:1128–1138) © 2019 Published by Elsevier Inc.

Key words: arrhythmia, citalopram-escitalopram, National Health Insurance Research Database, selective serotonin reuptake inhibitors, Taiwan.

INTRODUCTION

Depression is a widely prevalent mental disorder that affects 6.7% of US adults and 4.4% of the global population, and this prevalence has been increasing significantly.[1,2] As the first-line treatment for depression, selective serotonin reuptake inhibitors (SSRIs) have long been considered to have a relatively good cardiac safety profile compared with traditional tricyclic antidepressants.[3–5] Because of this feature, SSRIs are often recommended for treating patients with cardiac conditions.[3,4,6,7] Evidence has suggested, however, that SSRIs may be associated with QT prolongation and arrhythmia, and citalopram and escitalopram seem to be the agents that cause the increased risk of QT prolongation compared with other SSRIs.[8–14]

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In August 2011, the US Food and Drug Administration (FDA) issued a warning that citalopram and escitalopram use may lead to abnormal heart rhythms.[15] This warning was based on postmarket reports and 2 clinical trials conducted by the FDA, which found that citalopram and escitalopram use was associated with QT prolongation, especially in patients taking high doses.[15,16] As a result, the FDA updated the label for citalopram in 2012 to warn of the potential cardiac risks, including QT prolongation and torsade de pointes (TdP), and recommended maximum daily doses of 40 mg for adults and 20 mg for patients >60 years of age.[16] A similar warning was also issued in the United Kingdom, which recommended maximum daily doses of 40 mg for adults and 20 mg for patients >65 years of age.[17] Two potential mechanisms may explain the QT prolongation effect: SSRIs may disrupt the expression of the hERG protein on the cell membrane and block the hERG potassium ion channels.[9] No matter the mechanism, whether this effect is clinically meaningful deserves further discussion.[18–21]

Although the potential cardiac risk found in the FDA's trials was confirmed by 2 observational studies,[8,22] different results were observed.[23–25] Using Medicaid claims data, one study found neither a dose–response relationship nor an association between citalopram exposure and sudden cardiac death or ventricular arrhythmia.[23,24] The other registry-based study found a protective effect of high-dose citalopram use.[25] In addition, some researchers have argued that the use of citalopram itself may not cause QT prolongation or arrhythmia because citalopram has previously been found to be well tolerated.[3,5,26–28] Rather, underlying diseases or other risk factors of patients may be leading to adverse cardiac events.[9,11,18,19,29–31]

Given the inconclusive evidence on the tolerability of SSRIs—especially citalopram and escitalopram—further investigation is necessary. This study evaluates the cardiac risks associated with SSRI use. To achieve this goal, 2 specific aims were set: (1) to compare the risks of arrhythmia among patients with depression receiving SSRIs and those receiving other classes of antidepressants and (2) to compare the risks of arrhythmia among patients with depression receiving citalopram-escitalopram and those receiving other SSRIs.

PATIENTS AND METHODS

Data Source

Data for this study were gathered from the 2000, 2005, and 2010 Longitudinal Health Insurance Databases (LHIDs), which are subsets of the National Health Insurance Research Database (NHIRD) in Taiwan. The NHIRD contains administrative claims data, collected since 1996, from approximately 23 million enrollees (>99.9% of the population in Taiwan) in the National Health Insurance (NHI) program in Taiwan. Each of the LHIDs is composed of 1 million beneficiaries randomly selected in the years 2000, 2005, or 2010, and the LHID samples are considered to be nationally representative.[32] All of the LHID files contain deidentified information on the beneficiaries' enrollment, inpatient and outpatient service use, and inpatient and outpatient drug prescriptions from 1995 to 2013. Information from the years 2000–2011 served as the data source. This study was reviewed and approved by the National Taiwan University Hospital Research Ethics Committee.

Study Design and Sample

This was a retrospective cohort study. Patients with at least 1 prescription of the selected antidepressants—SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), bupropion, or mirtazapine—were included in the initial sample. The first observed antidepressant prescription date served as the index date. To avoid potential health user bias, only new antidepressant users were included (ie, the new-user design).[33] Patients were identified as new users if they were free of antidepressant exposure for at least 1 year before the index date (ie, the preindex period). We then required patients to have at least 1 diagnosis of antidepressant-related indications on or within 1 year before the index date. Antidepressant-related indications were identified by the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes, including depressive disorders (ICD-9-CM codes: 296.2, 296.3, 300.4), bipolar disorders (ICD-9-CM codes: 296.0, 296.1, 296.4–296.7, 296.80, 296.89, 301.13), and anxiety disorders (ICD-9-CM codes: 300.0, 300.2, 300.3, 306.9, 308, 309.2, 309.4, 309.9).

Patients were excluded if they (1) were < 20 years of age on the index date, (2) had a diagnosis of cardiac arrhythmia (ICD-9-CM codes: 426.0, 426.13, 426.7,

426.9, 426.10, 426.12, 427.0–427.9, 785.0, 996.01, 996.04, V45.0, V53.3),[34] schizophrenia (ICD-9-CM code: 295) or dementia (ICD-9-CM codes: 290, 294, 331) during the preindex period, (3) used antipsychotics and mood stabilizers in the preindex period, or (4) used >1 antidepressant on the index date. We further excluded patients of unknown sex, those >100 years old at the index date, those having valvular disease (ICD-9-CM codes: 093.2, 394–397, 424, 746.3–746.6, V42.2, V43.3) during the preindex period, and those included more than once in the LHID 2000, 2005, and 2010 cohorts.

Dependent Variable

In this study, we measured both arrhythmia (ICD-9-CM code: 427) and ventricular arrhythmia, which included paroxysmal ventricular tachycardia (ICD-9-CM code: 427.1), ventricular fibrillation and flutter (ICD-9-CM code: 427.4), and cardiac arrest (ICD-9-CM code: 427.5).[35,36] Because arrhythmia includes a wide range of clinical outcomes with different clinical consequences, we chose to specifically measure ventricular arrhythmia in addition to overall arrhythmia because ventricular arrhythmia is more likely to be caused by QT prolongation and TdP. An arrhythmia event was defined as arrhythmia-related emergency department visits or hospitalizations. We also compared the all-cause mortality rates in different groups by defining death as withdrawal from the NHI program with no subsequent enrollment or having death as the transaction code in the NHI inpatient file.

Exposure

Two types of exposures were measured in this study. The exposure for the first aim was SSRI use (ie, fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, and escitalopram). The incidence rates of arrhythmia and ventricular arrhythmia for SSRI initiators were compared with those of patients who initiated other classes of antidepressants, including SNRIs (venlafaxine, milnacipran, and duloxetine) and other, newer antidepressants (ie, trazodone, bupropion, mirtazapine, agomelatine, and moclobemide). The exposure for the second aim was citalopram-escitalopram use versus other SSRI use. Although the existing evidence suggested that the effects of citalopram-escitalopram on the QT interval might be dose dependent, we were unable to evaluate the dose effect in this study because few patients in our study initiated their citalopram-escitalopram use at a dose higher than the FDA's recommendation.

Covariates

The covariates measured and adjusted for in this study were as follows: age on the index date, sex, baseline physical and mental comorbidities, and the use of medications that might induce TdP during the 1-year preindex period. Age was categorized as 20 to 39, 40 to 59, and ≥60 years old. The physical comorbidities measured in this study were selected from the comorbidities listed in the Gagne Index, which combines the Charlson and Elixhauser measures.[36] A dummy variable was created to indicate the use of drugs with known or possible TdP risk during the preindex period (Supplemental Table I).[25,37] Finally, year of cohort entry was controlled for.

Statistical Analysis

Baseline characteristics were balanced by propensity score weighting (standardized mortality-morbidity ratio), and absolute standardized mean difference with a value < 0.1 was considered a negligible difference in the baseline characteristics between groups. Crude incidence rates were generated by Poisson regressions. The adjusted results were generated by Cox proportional hazards regression models. Both intent-to-treat (ITT) and as-treated (AT) approaches were applied to evaluate the association between SSRI (aim 1) or citalopram-escitalopram (aim 2) exposure and the risk of arrhythmia. The ITT approach served as the primary analysis in this study. In the ITT analysis, we only considered patients' initial exposure status, regardless of subsequent switching or discontinuation of treatment. All patients were followed up until the first arrhythmia event or administrative censoring, whichever came first. In the AT analysis, patients were censored at the end of the last prescription supply or discontinuation of their index treatment. Discontinuation was defined as a gap ≥30 days between the end of the last supply and the next prescription. Patients were also censored when they added a second non-SSRI antidepressant (aim 1) or an SSRI other than citalopram-escitalopram (aim 2) to the initial therapy. Finally, given that older patients are at higher risk of adverse effects, we also conducted a subgroup analysis that

repeated the main analysis with patients ≥60 years old. A 2-sided significance level was determined a priori as $\alpha = 0.05$. All statistical procedures were performed with SAS software, version 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

After the inclusion and exclusion criteria were applied, the final sample contained 55,029 SSRI users, 41,955 non-SSRI antidepressant users, and 12,663 citalopram-escitalopram users (Figure 1). Before weighting, there were significant differences in age, sex, cohort entry year, and most of the comorbid conditions. All covariates were well balanced after propensity score weighting (Supplemental Table II to Table V).

Table I gives the crude incidence rates and the adjusted hazard ratios (HRs) of arrhythmia and ventricular arrhythmia between SSRI users and non-SSRI antidepressant users. The adjusted results from the ITT analysis suggested that SSRI use did not elevate the risk of arrhythmia (HR = 0.95; 95% CI, 0.83−1.08) or ventricular arrhythmia (HR = 0.95; 95% CI, 0.75−1.19) compared with non-SSRI antidepressants, including SNRIs, bupropion, and mirtazapine. A lower risk of mortality was found among SSRI users than non-SSRI antidepressant users (HR = 0.89; 95% CI, 0.84−0.94). Results of the AT

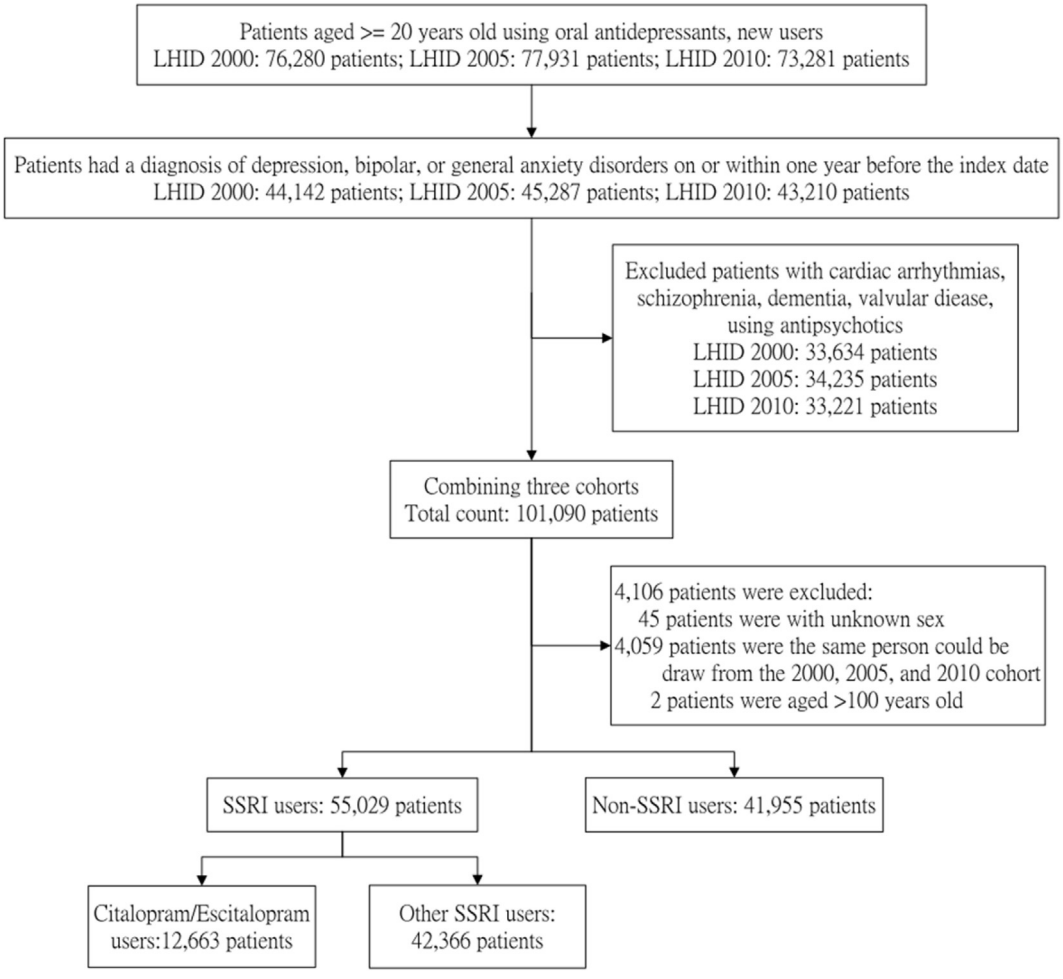

Figure 1. Sample Selection Flow Chart.

Table I. Crude incidence rates and adjusted HRs of arrhythmia and mortality between SSRI and other, non-SSRI antidepressant users among adults with depression.

Variable	Unadjusted			Adjusted	
	No. of Events	No. of Patients	Incidence Rates per 1000 Person-years (95% CI)	HR (95% CI)	*P*
Intent-to-Treat Group					
Arrhythmia					
SSRI users	510	55,029	1.41 (1.41−1.42)	0.95 (0.83−1.08)	0.43
Non-SSRI users	550	41,955	1.89 (1.89−1.90)	Reference	
Ventricular arrhythmia					
SSRI users	168	55,029	0.46 (0.46−0.47)	0.95 (0.75−1.19)	0.64
Non-SSRI users	180	41,955	0.61 (0.61−0.62)	Reference	
Mortality					
SSRI users	2936	55,029	8.33(8.32−8.34)	0.89 (0.84−0.94)	<.0001
Non-SSRI users	3314	41,955	11.79 (11.77−11.80)	Reference	
As-Treated Group					
Arrhythmia					
SSRI users	57	55,029	3.72 (3.69−3.76)	0.98 (0.66−1.46)	0.93
Non-SSRI users	52	41,955	5.10 (5.05−5.14)	Reference	
Ventricular arrhythmia					
SSRI users	13	55,029	0.85 (0.83−0.86)	1.30 (0.49−3.50)	0.60
Non-SSRI users	7	41,955	0.69 (0.67−0.70)	Reference	
Mortality					
SSRI users	155	55,029	10.07 (10.01−10.12)	0.87 (0.67−1.12)	0.28
Non-SSRI users	138	41,955	13.53 (13.46−13.60)	Reference	

HR = hazard ratio; SSRI = selective serotonin reuptake inhibitor.

analysis were generally consistent with ITT analysis, which suggested a null association between SSRI exposure and risk of arrhythmia or ventricular arrhythmia, but risk of mortality became nonsignificant (HR = 0.87; 95% CI, 0.67−1.12).

When comparing citalopram-escitalopram to other SSRIs, we found a nonsignificant increase in the risk of arrhythmia and ventricular arrhythmia (Table II). The respective HRs were 1.20 (95% CI, 0.95−1.51) and 1.08 (95% CI, 0.72−1.61) for arrhythmia and ventricular arrhythmia in the ITT analysis and 1.27 (95% CI, 0.66−2.44) and 1.52 (95% CI, 0.41−5.65) for arrhythmia and ventricular arrhythmia in the AT analysis. Interestingly, a higher risk of mortality was found among citalopram-escitalopram users compared with other non−citalopram-escitalopram SSRI users in both the ITT (HR = 1.09; 95% CI, 1.01−1.20) and AT (HR = 1.57; 95% CI, 1.07−2.30) analyses.

Tables III and IV present the results of the subgroup analyses in patients ≥60 years old. Like the main analysis, we did not find SSRI use to be associated with elevated risk of arrhythmia or ventricular arrhythmia in the ITT or AT analysis. No significant association was found between SSRI use and mortality (Table III). When comparing the outcomes between patients receiving citalopram-escitalopram and other SSRIs (Table IV), we found no increase in the risk of arrhythmia or ventricular arrhythmia in the ITT or AT analysis, but a significant increase in mortality was observed in the ITT analysis (HR = 1.21; 95% CI, 1.08−1.31).

Table II. Crude incidence rates and adjusted HRs of arrhythmia and mortality between citalopram-escitalopram and other SSRI antidepressant users among all adults with depression.

Variable	Unadjusted			Adjusted	
	No. of Events	No. of Patients	Incidence Rates per 1000 Person-years (95% CI)	HR (95% CI)	*P*
Intent-to-Treat Group					
Arrhythmia					
Citalopram-escitalopram users	99	12,663	1.69 (1.69−1.70)	1.20 (0.95−1.51)	0.13
Other SSRI users	411	42,366	1.36 (1.36−1.36)	Reference	
Ventricular arrhythmia					
Citalopram-escitalopram users	34	12,663	0.58 (0.57−0.58)	1.08 (0.72−1.61)	0.71
Other SSRI users	134	42,366	0.44 (0.43−0.44)	Reference	
Mortality					
Citalopram-escitalopram users	562	12,663	9.79 (9.76−9.81)	1.09 (1.01−1.20)	0.04
Other SSRI users	2374	42,366	8.05 (8.04−8.06)	Reference	
As-Treated Group					
Arrhythmia					
Citalopram-escitalopram users	15	12,663	4.73 (4.65−4.80)	1.27 (0.66−2.44)	0.48
Other SSRI users	40	42,366	3.94 (3.90−3.98)	Reference	
Ventricular arrhythmia					
Citalopram-escitalopram users	4	12,663	1.26 (1.22−1.30)	1.52 (0.41−5.65)	0.54
Other SSRI users	8	42,366	0.79 (0.77−0.80)	Reference	
Mortality					
Citalopram-escitalopram users	48	12,663	14.83 (14.70−14.97)	1.57 (1.07−2.30)	0.02
Other SSRI users	93	42,366	9.16 (9.10−9.22)	Reference	

HR = hazard ratio; SSRI = selective serotonin reuptake inhibitor.

Table III. Crude incidence rates and adjusted HRs of arrhythmia and mortality between SSRI and other non-SSRI antidepressant users among adults ≥60 years old.

Variable	Unadjusted			Adjusted	
	No. of Events	No. of Patients	Incidence Rates per 1000 Person-years (95% CI)	HR (95% CI)	*P*
Intent-to-Treat Group					
Arrhythmia					
SSRI users	234	7742	4.79 (4.77–4.81)	0.98 (0.91–1.06)	0.91
Non-SSRI users	294	8528	4.98 (4.96–5.00)	Reference	
Ventricular arrhythmia					
SSRI users	84	7742	1.69 (1.68–1.70)	1.01 (0.82–1.54)	0.48
Non-SSRI users	97	8528	1.61 (1.60–1.62)	Reference	
Mortality					
SSRI users	1585	7742	36.04 (35.99–36.10)	1.22 (0.83–1.29)	0.66
Non-SSRI users	1862	8528	34.73 (34.68–34.78)	Reference	
As-Treated Group					
Arrhythmia					
SSRI users	26	7742	9.39 (9.28–9.51)	0.94 (0.53–1.68)	0.83
Non-SSRI users	28	8528	11.10 (10.97–11.23)	Reference	
Ventricular arrhythmia					
SSRI users	3	7742	1.08 (1.04–1.12)	0.66 (0.13–3.36)	0.61
Non-SSRI users	4	8528	1.58 (1.53–1.63)	Reference	
Mortality					
SSRI users	89	7742	32.15 (31.94–32.36)	1.07 (0.70–1.40)	0.93
Non-SSRI users	77	8528	30.53 (30.32–30.75)	Reference	

HR = hazard ratio; SSRI = selective serotonin reuptake inhibitor.

DISCUSSION

This population-based cohort study provides additional information on associations between SSRI use and cardiac risk in an Asian population. In this study, we found that the rate of arrhythmia associated with SSRI use was similar to that associated with other, newer non-SSRI antidepressants, but the rate of mortality in adults was lower among SSRI users than users of SNRIs or other, newer antidepressants. Among different SSRIs, however, an elevated risk of mortality was observed among patients receiving citalopram-escitalopram compared with other SSRI antidepressants, with a greater difference found in adults ≥60 years old than among adults in general.

Our original hypothesis was that SSRIs, as a class, might be associated with an elevated risk of arrhythmia driven by the potential cardiac risk of citalopram-escitalopram. Nevertheless, our study results suggest that SSRIs remain tolerable and may even be better in terms of safety profile than other classes of antidepressants selected in this study, given the lower mortality rate. Previous research has also suggested that SSRIs are associated with a nondifferential or even lower risk of mortality.[38,39] The nondifferential risk of arrhythmia found in our study may be explained by the potential cardiac risk of non-SSRI antidepressants.[23,40] However, given the scarce evidence currently available, it is difficult to draw conclusions on the association between cardiac risk profiles and mortality rate for SSRIs and other, newer non-SSRI antidepressants. Further research is required to evaluate the safety profiles and clarify the potential mechanisms of these drugs that could affect heart rhythms.

Our study did not suggest an elevated risk of arrhythmia among the adults ≥60 years old receiving

Table IV. Crude incidence rates and adjusted HRs of arrhythmia and mortality between citalopram-escitalopram and other SSRI antidepressant users among adults ≥60 years old.

Variable	Unadjusted			Adjusted	
	Number of events	Number of patients	Incidence rates per 1,000 person years (95% CI)	HR (95% CI)	*P*
Intent-to-Treat Group					
Arrhythmia					
Citalopram-escitalopram users	49	1900	5.84 (5.79−5.89)	1.16 (0.81−1.66)	0.41
Other SSRI users	185	5842	4.57 (4.55−4.59)	Reference	
Ventricular arrhythmia					
Citalopram-escitalopram users	17	1900	1.99 (1.96−2.02)	1.12 (0.50−1.59)	0.70
Other SSRI users	67	5842	1.63 (1.61−1.64)	Reference	
Mortality					
Citalopram-escitalopram users	312	1900	41.00 (40.86−41.15)	1.21 (1.08−1.31)	0.04
Other SSRI users	1273	5842	35.00 (34.95−35.07)	Reference	
As-Treated Group					
Arrhythmia					
Citalopram-escitalopram users	7	1900	11.77 (11.50−12.05)	1.03 (0.28−2.23)	0.66
Other SSRI users	19	5842	10.28 (10.13−10.43)	Reference	
Ventricular arrhythmia					
Citalopram-escitalopram users	1	1900	1.69 (1.58−1.79)	1.31 (0.04−7.60)	0.67
Other SSRI users	2	5842	1.07 (1.03−1.12)	Reference	
Mortality					
Citalopram-escitalopram users	20	1900	33.67 (33.21−34.14)	1.20 (0.69−2.11)	0.51
Other SSRI users	59	5842	31.82 (31.57−32.08)	Reference	

HR = hazard ratio; SSRI = selective serotonin reuptake inhibitor.

SSRIs, which is in contrast to a prior study.[41] Because the prior study compared SSRI use to no antidepressant use, results from the prior study may be confounded by patients' underlying condition or disease severity. Our study eliminates this confounding factor by comparing SSRIs with other non-SSRI antidepressants, and we found that the safety profile of SSRIs is comparable to other, newer classes of non-SSRI antidepressants. Consistent with a prior claim-based study,[23,24] our study did not find citalopram-escitalopram use to be associated with an increased risk of arrhythmia, but a higher mortality rate was observed in adults ≥20 years old and those ≥60 old. Although previous evidence suggested an association between citalopram-escitalopram use and QT prolongation,[8,22] this abnormality in the electrocardiogram (ECG) does not necessarily develop into arrhythmia. The difference in outcome measure (ie, diagnosis codes vs QT interval in the ECG) may be a possible explanation for the discrepant results in our study and the previous studies. use of diagnosis codes to define arrhythmia may underestimate the event rate because irregular heart rhythms may be undercoded or undetected by diagnosis codes. On the other hand, use of the ECG profile to define arrhythmia may overestimate the risk of arrhythmia because a prolonged QT interval may not necessarily turn into a clinical event.

One interesting finding was that the risk of all-cause mortality might potentially be greater in adults ≥60 years old (HR = 1.21; 95% CI, 1.08−1.31) than in adults ≥20 years old (HR = 1.09; 95% CI,

1.01−1.20). Given the low absolute risk and marginal increase in mortality, the elevated risk of mortality should be of less concern for adults. With a greater underlying risk in the older population, however, the moderate increase in mortality rate found in this study may deserve further attention. Because we measured all-cause mortality instead of sudden cardiac death and patients with cardiac conditions were excluded from this study, whether the elevated mortality risk is driven by the potential cardiac risk demands further investigation.

There were several limitations in this study. One was that we were unable to measure the severity of depression in the claims database, which may have led to confounding by indication bias. We attempted to minimize this problem by using the active comparator design. Having compared 2 first-line treatments for depression—namely, SSRI and other, newer non-SSRI antidepressants—we believe we had 2 cohorts with similar baseline severities. We did not include tricyclic antidepressants for comparison because this class is known for its cardiac adverse effects.[3−5] In addition, we were unable to control for nonmeasurable risk factors for arrhythmia, such as smoking, obesity, and family history of heart disease. Another limitation was that ventricular arrhythmia might be underdiagnosed or undercoded in a claims database, which may explain the low event numbers. Because of the low number of high-dose users at the baseline or before the outcome occurred, we were unable to assess the dose−response relationship between citalopram-escitalopram use and arrhythmia risk. However, on the basis of our study, although standard dosing of citalopram-escitalopram may not increase the risk of arrhythmia, it may still be associated with an elevated risk of mortality. Finally, we were unable to evaluate cause-specific mortality because this piece of information was not available in the data source. Future research could investigate the potential dose−response relationship between citalopram-escitalopram exposure and risk of arrhythmia, and research with enriched clinical information and a validated measure of arrhythmia is needed.

CONCLUSIONS

Our study suggests that the use of SSRIs or citalopram-escitalopram does not seem to increase the risk of arrhythmia, but citalopram-escitalopram may be associated with a higher risk of mortality compared with other SSRIs, especially among patients ≥60 years old. Further investigation of the safety profiles related to citalopram-escitalopram dosage is warranted.

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CONFLICTS OF INTEREST

The funder had no role in the study design, data collection and analysis, result interpretation, publication decision, or manuscript preparation. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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eTable 1. Drugs with known and possible risks of QT prolongation

Pharmacologic Category		Generic Name
Cardiovascular System	Antihypertensive Agent	Isradipine, Moexipril/HCTZ, Nicardipine
	Antianginal Agent	Bepridil, Ranolazine
	Antiarrhythmic Agent	Amiodarone, Disopyramide, Dofetilide, Dronedarone, Flecainide, Ibutilide, Procainamide, Quinidine, Sotalol
	Antiplatelet Agent	Anagrelide
	Antihyperlipidemic Agent	Probucol
	PDE-5 Inhibitor	Vardenafil
Autonomic Nervous System	$Alpha_1$ Blocker	Alfuzosin
	$Alpha_2$ Agonist	Dexmedetomidine, Tizanidine
	$Beta_3$ Agonist	Mirabegron
	Anticholinergic	Tolterodine
Central Nervous System	Antipsychotic	Chlorpromazine, Clozapine, Haloperidol, Iloperidone, Mesoridazine, Olanzapine, Paliperidone, Pimozide, Quetiapine, Risperidone, Sulpiride, Thioridazine
	Antidepressant	Citalopram, Escitalopram Mirtazapine, Venlafaxine
	Antimanic	Lithium
	Anticonvulsant	Felbamate, Fosphenytoin
	Anti-Parkinson Agent	Apomorphine
	CNS Stimulant	Cocaine
	General Anesthetic	Sevoflurane
	Opioids	Levomethadyl, Methadone
Digestive System	Antiemetic	Dolasetron, Droperidol, Granisetron, Ondansetron, Promethazine
	H_2 Antagonist	Famotidine
	Somatostatin Analog	Pasireotide
	Prokinetic	Cisapride, Domperidone
Endocrine System	Oxytocic Agent	Oxytocin
	Cortisol Receptor Blocker	Mifepristone
Immune System	Sphingosine 1-Phosphate Receptor Modulator	Fingolimod
	Immunosuppressant	Tacrolimus
	Antihistamine	Astemizole, Terfenadine
Infectious Disease	Antimalarial	Chloroquine, Dihydroartemisinin+piperaquine, Halofantrine
	Antiviral	Foscarnet, Rilpivirine, Saquinavir, Sorafenib, Sunitinib

(*continued on next page*)

eTable 1. (*Continued*)

Pharmacologic Category		Generic Name
	Antibiotic	Azithromycin, Clarithromycin, Erythromycin, Gemifloxacin, Levofloxacin, Moxifloxacin, Norfloxacin, Ofloxacin, Pentamidine, Telavancin, Telithromycin, Sparfloxacin
	Antitubercular Agent	Bedaquiline
Oncology	Antineoplastic	Arsenic trioxide, Bortezomib, Bosutinib, Crizotinib, Dabrafenib, Dasatinib, Eribulin, Lapatinib, Nilotinib, Pazopanib, Tamoxifen, Toremifene, Vandetanib, Vemurafenib, Vorinostat
Diagnosis Agent	Contrast	Perflutren lipid microspheres

eTable 2. Patient characteristics of the SSRI users versus non-SSRI users cohort, all adults

	Propensity-Score Weighting				
	Before			After	
	SSRI Users (n=55,029)	**non-SSRI Users (n=41,955)**	**Standardized Differences**	**non-SSRI Users (n=55,610)**	**Standardized Differences**
Age, n (%)					
20-39	27,594 (50.14)	16,041 (38.23)	0.2533	28,503 (51.25)	0.0245
40-59	19,693 (35.79)	17,386 (41.44)		19,635 (35.31)	
≧60	7,742 (14.07)	8,528 (20.33)		7,472 (13.44)	
Sex, n (%)					
Male	20,543 (37.33)	18,184 (43.34)	0.1227	20,877 (37.54)	0.0044
Female	34,486 (62.67)	23,771 (56.66)		34,733 (62.46)	
Cohort entry year, n (%)					
2001	3,598 (6.54)	3,749 (8.94)	0.1286	3,383 (6.08)	0.0366
2002	4,285 (7.79)	3,869 (9.22)		4,074 (7.33)	
2003	4,528 (8.23)	3,636 (8.67)		4,506 (8.10)	
2004	4,842 (8.80)	3,914 (9.33)		4,794 (8.62)	
2005	5,206 (9.46)	3,711 (8.85)		5,155 (9.27)	
2006	4,288 (7.79)	3,162 (7.54)		4,302 (7.74)	
2007	4,236 (7.70)	3,197 (7.63)		4,309 (7.75)	
2008	4,064 (7.39)	3,025 (7.21)		4,097 (7.37)	
2009	3,946 (7.17)	2,879 (6.86)		4,030 (7.25)	
2010	3,779 (6.87)	2,790 (6.65)		3,973 (7.14)	
2011	4,081 (7.42)	2,645 (6.30)		4,327 (7.78)	
2012	4,176 (7.59)	2,582 (6.15)		4,397 (7.91)	
2013	4,000 (7.27)	2,796 (6.66)		4,262 (7.66)	

eTable 2. (*Continued*)

	Propensity-Score Weighting				
	Before			After	
	SSRI Users (n=55,029)	**non-SSRI Users (n=41,955)**	**Standardized Differences**	**non-SSRI Users (n=55,610)**	**Standardized Differences**
Comorbid condition, n (%)					
Depression	35,093 (63.77)	19,033 (45.37)	0.3762	36,150(65.01)	0.0258
Bipolar	1,309 (2.38)	608 (1.45)	0.0679	1,471 (2.65)	0.0170
General anxiety disorder	28,714 (52.18)	28,131 (67.05)	0.3066	28,434 (51.13)	0.0210
Dementia	274 (0.50)	200 (0.48)	0.0030	274 (0.49)	0.0007
Congestive heart failure	1,806 (3.28)	1,875 (4.47)	0.0615	1,751 (3.15)	0.0075
Renal failure	1,006 (1.83)	966 (2.30)	0.0334	978 (1.76)	0.0052
Hemiplegia	1,275 (2.32)	1,098 (2.62)	0.0193	1,249 (2.25)	0.0047
Alcohol abuse	661 (1.20)	805 (1.92)	0.0579	655 (1.18)	0.0021
Chronic pulmonary disease	11,453 (20.81)	9,792 (23.34)	0.0609	11,445 (20.58)	0.0057
Coagulopathy	382 (0.69)	295 (0.70)	0.0011	381 (0.68)	0.0011
Complicated diabetes	2,238 (4.07)	2,297 (5.47)	0.0661	2,178 (3.92)	0.0076
Liver disease	12,599 (22.90)	10,783 (25.70)	0.0655	12,554 (22.58)	0.0076
Peripheral vascular disorder	1,582 (2.87)	1,553 (3.70)	0.0464	1,563 (2.81)	0.0038
Psychosis	2,396 (4.35)	1,765 (4.21)	0.0073	2,502 (4.50)	0.0071
Pulmonary circulation disorders	185 (0.34)	140 (0.33)	0.0004	186 (0.34)	0.0000
Hypertension	10,831 (19.68)	10,996 (26.21)	0.1557	10,612 (19.08)	0.0152
Cancer	2,865 (5.21)	2,631 (6.27)	0.0458	2,883 (5.18)	0.0010
Drugs with known or possible TdP risk, n(%)	20,379 (37.03)	16,701 (39.81)	0.0570	20,365 (36.62)	0.0085
Mood stabilizer, n(%)	861 (1.56)	922 (2.20)	0.0466	839 (1.51)	0.0045
ER or hospitalization, n(%)	17,425 (31.67)	13,575 (32.36)	0.0148	17,669 (31.77)	0.0023
Outpatient visit times, mean(SD), frequency	17.90 (15.08)	20.27 (17.09)	0.1423	17.58(16.01)	0.0200
Hospitalization days, mean(SD), day	1.73 (9.42)	1.53 (8.65)	0.0406	1.87 (9.41)	0.0061

SSRI: Selective Serotonin Reuptake Inhibitors; SD: Standard deviation TdP: Torsade de Pointes; ER: Emergency room.

eTable 3. Patient characteristics of the citalopram/escitalopram users versus other SSRI users cohort, all adults

	Propensity-Score Weighting				
	Before			After	
	Citalopram/Escitalopram Users	**Other SSRI Users**	**Standardized Differences**	**Other SSRI Users**	**Standardized Differences**
	(n=12,663)	**(n=42,366)**		**(n=12,653)**	
Age, n (%)					
20-39	6,075 (47.97)	21,519 (50.79)	0.0579	6,049 (47.81)	0.0035
40-59	4,688 (37.02)	15,005 (35.42)		4,695 (37.11)	
≧60	1,900 (15.00)	5,842 (13.79)		1,909 (15.09)	
Sex, n (%)					
Male	4,840 (38.22)	15,703 (37.07)	0.0239	4,836 (38.22)	0.0001
Female	7,823 (61.78)	26,663 (62.93)		7,817 (61.78)	
Cohort entry year, n (%)					
2001	311 (2.46)	3,287 (7.76)	0.7213	310 (2.45)	0.0027
2002	402 (3.17)	3,883 (9.17)		402 (3.18)	
2003	457 (3.61)	4,071 (9.61)		457 (3.61)	
2004	605 (4.78)	4,237 (10.00)		603 (4.77)	
2005	753 (5.96)	4,453 (10.51)		754 (5.96)	
2006	762 (6.02)	3,526 (8.32)		763 (6.03)	
2007	876 (6.92)	3,360 (7.93)		874 (6.91)	
2008	994 (7.85)	3,070 (7.25)		993 (7.85)	
2009	1,153 (9.11)	2,793 (6.59)		1,147 (9.06)	
2010	1,296 (10.23)	2,483 (5.86)		1,291 (10.20)	
2011	1,478 (11.67)	2,603 (6.14)		1,475 (11.66)	
2012	1,763 (13.92)	2,413 (5.70)		1767 (13.97)	
2013	1,813 (14.32)	2,187 (5.16)		1,817 (14.36)	

	Propensity-Score Weighting				
	Before			After	
	Citalopram/ Escitalopram Users	**Other SSRI Users**	**Standardized Differences**	**Other SSRI Users**	**Standardized Differences**
	(n=12,663)	**(n=42,366)**		**(n=12,653)**	
Comorbid condition, n (%)					
Depression	8,359 (66.01)	26,734 (63.10)	0.0608	8,357 (66.05)	0.0008
Bipolar	211 (1.67)	1,098 (2.59)	0.0641	209 (1.65)	0.0014
General anxiety disorder	6,574 (51.92)	22,140 (52.26)	0.0069	6,583 (52.03)	0.0023
Dementia	66 (0.52)	208 (0.49)	0.0043	69 (0.55)	0.0036
Congestive heart failure	424 (3.35)	1,382 (3.26)	0.0048	423 (3.34)	0.0002
Renal failure	270 (2.13)	736 (1.74)	0.0287	267 (2.11)	0.0013
Hemiplegia	318 (2.51)	957 (2.26)	0.0165	322 (2.55)	0.0023

eTable 3. (*Continued*)

	Propensity-Score Weighting				
	Before			After	
	Citalopram/ Escitalopram Users	**Other SSRI Users**	**Standardized Differences**	**Other SSRI Users**	**Standardized Differences**
	(n=12,663)	**(n=42,366)**		**(n=12,653)**	
Alcohol abuse	165 (1.30)	497 (1.17)	0.0120	169 (1.34)	0.0030
Chronic pulmonary disease	2,912 (23.00)	8,541 (20.16)	0.0690	2,928 (23.14)	0.0035
Coagulopathy	107 (0.84)	275 (0.65)	0.0227	107 (0.84)	0.0000
Complicated diabetes	562 (4.44)	1,676 (3.96)	0.0240	560 (4.43)	0.0005
Liver disease	3,075 (24.28)	9,524 (22.48)	0.0426	3,059 (24.71)	0.0026
Peripheral vascular disorder	411 (3.25)	1,171 (2.76)	0.0282	417 (3.30)	0.0029
Psychosis	486 (3.84)	1,910 (4.51)	0.0335	482 (3.81)	0.0016
Pulmonary circulation disorders	35 (0.28)	150 (0.35)	0.0139	35 (0.28)	0.0002
Hypertension	2,645 (20.89)	8,186 (19.32)	0.0391	2,657 (21.00)	0.0028
Cancer	775 (6.12)	2,090 (4.93)	0.0520	765 (6.05)	0.0031
Drugs with known or possible TdP risk, n(%)	4,502 (35.55)	15,877 (37.48)	0.0400	4,475 (3.37)	0.0039
Mood stabilizer, n(%)	188 (1.48)	673 (1.59)	0.0084	188 (1.48)	0.0001
ER or hospitalization, n(%)	4,075 (32.18)	13,350 (31.51)	0.0144	4,097 (32.38)	0.0043
Outpatient visit times, mean(SD), frequency	17.67 (14.79)	17.96 (15.17)	0.0172	17.61 (14.88)	0.0039
Hospitalization days, mean(SD), day	1.88 (9.39)	1.68 (4.33)	0.0212	1.71 (8.96)	0.0010

SSRI: Selective Serotonin Reuptake Inhibitors; SD: Standard deviation TdP: Torsade de Pointes; ER: Emergency room.

eTable 4. Patient characteristics of the SSRI users versus non-SSRI users cohort, adults age ≥60

	Propensity-Score Weighting				
	Before			After	
	SSRI Users	**non-SSRI Users**	**Standardized Differences**	**non-SSRI Users**	**Standardized Differences**
	(n=7,742)	**(n=8,528)**		**(n=7,754)**	
Age, mean(SD), year	70.00 (7.62)	69.62 (7.41)	0.0451	69.83 (7.28)	0.0257
Sex, n (%)					
Male	3,139 (40.55)	3,810 (44.68)	0.0836	3,081 (39.73)	0.0165
Female	4,603 (59.45)	4,718 (55.32)		4.673 (60.27)	

(*continued on next page*)

eTable 4. (*Continued*)

	Propensity-Score Weighting				
	Before			After	
	SSRI Users	**non-SSRI Users**	**Standardized Differences**	**non-SSRI Users**	**Standardized Differences**
	(n=7,742)	**(n=8,528)**		**(n=7,754)**	
Cohort entry year, n (%)					
2001	483 (6.24)	931 (10.92)	0.2190	457 (5.89)	0.0429
2002	628 (8.11)	907 (10.64)		582 (7.50)	
2003	628 (8.11)	702 (8.23)		625 (8.06)	
2004	647 (8.36)	724 (8.49)		623 (8.04)	
2005	688 (8.89)	653 (7.66)		679 (8.76)	
2006	551 (7.12)	625 (7.33)		539 (6.95)	
2007	595 (7.69)	561 (6.58)		584 (7.54)	
2008	552 (7.13)	599 (7.02)		571 (7.37)	
2009	535 (6.91)	554 (6.50)		532 (6.87)	
2010	525 (6.78)	561 (6.58)		547 (7.06)	
2011	619 (8.00)	574 (6.73)		656 (8.45)	
2012	661 (8.54)	525 (6.16)		680 (8.77)	
2013	630 (8.14)	612 (7.18)		678 (8.74)	
Comorbid condition, n (%)					
Depression	4,912 (63.45)	3,165 (37.11)	0.5459	3,977 (64.18)	0.0154
Bipolar	168 (2.17)	95 (1.11)	0.0832	197 (2.54)	0.0241
General anxiety disorder	4,165 (53.80)	6,309 (73.98)	0.4298	4,123 (53.17)	0.0126
Dementia	226 (2.92)	155 (1.82)	0.0725	227 (2.93)	0.0004
Congestive heart failure	1,133 (14.63)	1,217 (14.27)	0.0199	1,081 (13.94)	0.0103
Renal failure	476 (6.15)	554 (6.50)	0.0143	466 (6.01)	0.0056
Hemiplegia	448 (5.79)	433 (5.08)	0.0313	438 (5.65)	0.0059
Alcohol abuse	62 (0.80)	87 (1.02)	0.0231	54 (0.70)	0.0115
Chronic pulmonary disease	3,152 (40.71)	3,632 (42.59)	0.0381	3,154 (40.68)	0.0007
Coagulopathy	108 (1.39)	110 (1.29)	0.0091	101 (1.30)	0.0081
Complicated diabetes	1,139 (14.71)	1,227 (14.39)	0.0092	1,144 (14.75)	0.0011
Liver disease	2,615 (33.78)	2,853 (33.45)	0.0106	2,580 (33.27)	0.0068
Peripheral vascular disorder	799 (10.32)	848 (9.94)	0.0125	810 (10.45)	0.0043
Psychosis	436 (5.63)	389 (4.56)	0.0487	4,630 (5.97)	0.0145
Pulmonary circulation disorders	88 (1.14)	78 (0.91)	0.0220	83 (1.07)	0.0065
Hypertension	5,014 (64.76)	5,569 (65.30)	0.0113	4,988 (64.33)	0.0092
Cancer	1,008 (13.02)	1,082 (12.69)	0.0099	1,028 (13.26)	0.0071
Drugs with known or possible TdP risk, n(%)	3,446 (44.51)	4,058 (47.58)	0.0617	3,418 (44.08)	0.0086
Mood stabilizer, n(%)	250 (3.23)	316 (3.71)	0.0260	243 (3.13)	0.0055
ER or hospitalization, n(%)	3,064 (39.58)	3,340 (39.17)	0.0084	3,081 (39.74)	0.0033

eTable 4. (*Continued*)

	Propensity-Score Weighting				
	Before			After	
	SSRI Users	**non-SSRI Users**	**Standardized Differences**	**non-SSRI Users**	**Standardized Differences**
	(n=7,742)	**(n=8,528)**		**(n=7,754)**	
Outpatient visit times, mean(SD), frequency	28.48 (19.48)	30.43 (20.03)	0.1083	28.14 (18.11)	0.0104
Hospitalization days, mean(SD), day	4.31 (14.93)	3.48 (10.28)	0.0290	3.54 (12.69)	0.0158

SSRI: Selective Serotonin Reuptake Inhibitors; SD: Standard deviation TdP: Torsade de Pointes; ER: Emergency room.

eTable 5. Patient characteristics of the citalopram/escitalopram users versus other SSRI users cohort, adults age ≥60

	Propensity-Score Weighting				
	Before			After	
	Citalopram/ Escitalopram Users	**Other SSRI Users**	**Standardized Differences**	**Other SSRI Users**	**Standardized Differences**
	(n = 1,900)	(n = ,5842)		(n = 1,879)	
Age, mean(SD), year	70.10 (7.91)	69.97 (4.48)	0.0131	70.18 (7.53)	0.0009
Sex, n (%)			0.0039		0.0023
Male	772 (40.63)	2,367 (40.52)		767 (40.82)	
Female	1,128 (59.37)	3,475 (59.48)		1,112 (59.18)	
Cohort entry year, n (%)			0.7309		0.0200
2001	49 (2.58)	434 (7.43)		48 (2.54)	
2002	55 (2.89)	573 (9.81)		56 (2.95)	
2003	58 (3.05)	570 (9.76)		59 (3.12)	
2004	91 (4.79)	556 (9.52)		92 (4.90)	
2005	98 (5.16)	590 (10.10)		97 (5.15)	
2006	115 (6.05)	436 (7.46)		110 (5.88)	
2007	139 (7.32)	456 (7.81)		141 (7.49)	
2008	141 (7.42)	411 (7.04)		139 (7.40)	
2009	163 (8.58)	372 (6.37)		159 (8.49)	
2010	185 (9.74)	340 (5.82)		186 (9.91)	
2011	228 (12.00)	391 (6.69)		221 (11.74)	
2012	294 (15.47)	367 (6.28)		297 (15.82)	
2013	284 (14.95)	346 (5.92)		274 (14.61)	

(*continued on next page*)

eTable 5. (*Continued*)

	Propensity-Score Weighting				
	Before			After	
	Citalopram/ Escitalopram Users	**Other SSRI Users**	**Standardized Differences**	**Other SSRI Users**	**Standardized Differences**
	(n = 1,900)	(n = ,5842)		(n = 1,879)	
Comorbid condition, n (%)					
Depression	1,225 (64.47)	3,687 (63.11)	0.0283	1,213 (64.55)	0.0016
Bipolar	37 (1.95)	131 (2.24)	0.0206	36 (1.91)	0.0028
General anxiety disorder	1,023 (53.84)	3,142 (53.78)	0.0128	1,024 (54.48)	0.0012
Dementia	51 (2.68)	175 (3.00)	0.0187	49 (2.61)	0.0045
Congestive heart failure	277 (14.58)	856 (14.65)	0.0111	267 (14.19)	0.0021
Renal failure	125 (6.58)	351 (6.01)	0.0235	117 (6.21)	0.0151
Hemiplegia	104 (5.47)	344 (5.89)	0.0179	102 (5.40)	0.0031
Alcohol abuse	18 (0.95)	44 (0.75)	0.0212	18 (0.96)	0.0012
Chronic pulmonary disease	820 (43.16)	2,332 (39.92)	0.0658	824 (43.84)	0.0138
Coagulopathy	29 (1.53)	79 (1.35)	0.0146	31 (1.67)	0.0114
Complicated diabetes	290 (15.26)	849 (14.53)	0.0205	283 (15.04)	0.0063
Liver disease	669 (35.21)	1,946 (33.31)	0.0400	651 (34.62)	0.0123
Peripheral vascular disorder	209 (11.00)	590 (10.10)	0.0293	205 (10.91)	0.0028
Psychosis	84 (4.42)	352 (6.03)	0.0722	85 (4.54)	0.0059
Pulmonary circulation disorders	14 (0.74)	74 (1.27)	0.0532	13 (0.68)	0.0068
Hypertension	1,256 (66.11)	3,758 (64.33)	0.0373	1,247 (66.36)	0.0053
Cancer	297 (15.63)	711 (12.17)	0.1002	287 (15.27)	0.0100
Drugs with known or possible TdP risk, n(%)	833 (43.84)	2,613 (44.73)	0.0178	815 (43.38)	0.0093
Mood stabilizer, n(%)	51 (2.68)	199 (3.41)	0.0420	50 (2.64)	0.0030
ER or hospitalization, n(%)	760 (40.00)	2,304 (39.44)	0.0115	757 (40.31)	0.0063
Outpatient visit times, mean(SD), frequency	27.60 (18.40)	28.76 (10.05)	0.0444	27.27 (19.83)	0.0090
Hospitalization days, mean(SD), day	4.57 (15.48)	3.53 (6.01)	0.0217	4.23 (14.74)	0.0118

SSRI: Selective Serotonin Reuptake Inhibitors; SD: Standard deviation TdP: Torsade de Pointes; ER: Emergency room.