The use of antidepressants and the risk of chronic atrial fibrillation

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Running head: antidepressants and atrial fibrillation

Keywords: antidepressants, serotonin, chronic atrial fibrillation, nested case-control study

Word count: 2921

Abstract word count: 196

Number of figures: 1

Number of tables: 3

Number of references: 42

Financial Disclosures and Conflicts of Interest

Dr. Suissa has received research grants from AstraZeneca, Boehringer Ingelheim and GlaxoSmithKline, and has participated in advisory board meetings and as speaker in conferences for AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Pfizer and Merck. Dr. Lapi provided consultancies in protocol preparation for epidemiological studies for Menarini, Abbvie, IBSA, Angelini, and Servier. Dr. Azoulay, Dr. Benisty, Dr. Kezouh, Dr. Matok and Dr. Mugelli do not have any conflicts of interest to disclose.

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Abstract

Serotonin stimulation of the 5HT4 receptor might be responsible for an increased risk of atrial fibrillation (AF). Thus, we assessed whether the use of antidepressants (ADs) is associated with an increased risk of chronic AF (cAF). Using the UK Clinical Practice Research Datalink, a nested case-control analysis was conducted within a cohort of new AD users having a diagnosis of depression and/or anxiety. Cases of cAF occurring during follow-up were individually matched with up to 10 controls on age, sex, year of cohort entry, and duration of follow-up. Conditional logistic regression was used to estimate rate ratios (RRs) and 95% confidence intervals (CIs) of cAF associated with current and recent use of ADs, when compared to past use. The cohort included 116,125 new AD users, of whom 1271 were diagnosed with cAF during follow-up (incidence rate: 1.6 per 1000 person-years). The adjusted RR of cAF associated with current and recent use of ADs was 0.98 (95% CI: 0.86-1.12) and 1.02 (95% CI: 0.86-1.30), respectively. No association was observed when ADs were classified according to their potency in reducing serotonin reuptake. These findings suggest that exposure to ADs is not associated with an increased risk of cAF.

INTRODUCTION

Chronic atrial fibrillation (cAF) is the most common disease among the cardiac rhythm disorders. This condition has been associated with increased morbidity and mortality.[1, 2] Pre-clinical evidence has suggested a role for serotonin 5HT4 receptors in atrial arrhythmias.[3] Indeed, serotonin promotes intracellular calcium overload and increases the amplitude of the pacemaker current I_f in atrial myocytes. These alterations are potentially arrhythmogenic and might trigger AF.[4, 5] Furthermore, a greater concentration of mRNA coding 5HT4 receptors has been identified in patients with cAF.[6]

Antidepressants (ADs) exert their therapeutic effect by increasing the endogenic levels of serotonin. Given this mechanism, long-term exposure to ADs might be associated to a higher risk of cAF. The association between the use of these drugs and other arrhythmogenic disorders [7, 8], as well as ischemic stroke (the most common cardiovascular consequence of cAF) have been already investigated.[9, 10] However, no studies have examined the electrophysiological hypothesis to date. The objective of this study was therefore to determine whether the use of ADs is associated with an increased risk of cAF.

METHODS

Data source

We used the United Kingdom (UK) Clinical Practice Research Datalink (CPRD), formerly known as the General Practice Research Database. This is the world's largest computerized database of primary care, which contains the complete medical records for more than 13 million people (corresponding to approximately 8.4% of the UK population) enrolled in more than 680 general practices. The geographic distribution of the practices participating in the CPRD has been shown to be representative of the UK population, and age and sex distributions of patients in the CPRD are similar to those reported by the National Population Census.[11] The data recorded in the CPRD since 1987 include demographic information, prescription details, clinical events, specialist referrals, along with lifestyle variables comprising body mass index (BMI), smoking habits and alcohol use.[11] A recent review found that medical data in the CPRD are of high quality.[12, 13] Read codes are used to enter medical diagnoses and procedures, which is the standard clinical terminology system used in general practice in the UK, and a coded drug dictionary based on the UK Prescription Pricing Authority Dictionary is used for recording prescriptions.

The study protocol was approved by the Independent Scientific Committee of the CPRD and the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

Study population

We identified a cohort of patients, at least 18 years of age, newly-prescribed ADs (agomelatine, amitriptyline, amoxapine, bupropion, butriptyline, citalopram, clomipramine, desipramine, dosulepin, doxepin, duloxetine, escitalopram, fluoxetine, flupentixol, fluphenazine/fluvoxamine, imipramine, iprindole, iproniazid, isocarboxazid, lofepramine,

maprotiline, mianserin, mirtazapine, moclobemide, nefazodone, nortriptyline, paroxetine, phenelzine/protriptyline, reboxetine, sertraline, tranylcypromine, trazodone, trifluoperazine, trimipramine, tryptophan, venlafaxine, viloxazine) with a prior diagnosis of depression and/or anxiety, registered with an *up-to-standard* practice between January 1, 1993 and December, 31, 2010. To be eligible, patients were required to have at least one year of medical history in the CPRD prior to cohort entry (date of the first AD prescription), and at least 6 months of follow-up. The latter criterion was applied in order to ensure that all ADs users were exposed for a sufficiently long period necessary to induce cAF.[14] We also excluded patients with a previous history of AF (both paroxysmal and persistent form), valvular disease or mitral or aortic valve repair or replacement, life-threatening ventricular tachyarrhythmia, cardioversion, implantation of a cardiac defibrillator or pacemaker for AF, cardiac arrest, congenital conduction disorder or advanced cardiomyopathy, stroke, heart infarction, hyperthyroidism, use of anticoagulants and/or antiarrhythmic medications at any time prior to cohort entry.

All patients were followed from the first AD prescription until the first of the following events: an incident diagnosis of cAF (cases), death from any cause, occurrence of one of the exclusion criteria (except the procedures of implantation of a cardiac defibrillator or pacemaker or those to monitor AF, paroxysmal AF and use of anticoagulants and/or antiarrhythmic drugs and stroke, because of their clinical relationship with AF diagnosis), end of registration with the general practice, or end of the study period (December, 31, 2011).

Case and control definition

All cases of cAF occurring during follow-up were identified, using the Read codes used in previous CPRD studies.[1, 15, 16] All codes related to paroxysmal AF and other acute forms of arrhythmia were not considered as part of the case definition. Cases were then coupled with

specific cardiac surgical or monitoring procedures and interventions (i.e., AF monitoring, ECG confirming a diagnosis of AF or flutter, pacemaker implantation, percutaneous transluminal ablation, chemical or external cardioversion) as well as pharmacological treatments (i.e., anticoagulants or antiarrhythmic drugs). Codes pertaining to cardiac interventions to treat rhythm disorders (±3 months from the date of diagnosis) and all prescriptions for an antiarrhythmic drug (±1 months from the date of diagnosis), were examined with respect to each cAF event The index date was then defined as the earlier date from either the diagnosis of cAF or the occurrence of a cAF-related surgical/interventional procedures or pharmacological treatment.

For each case of cAF, up to 10 controls were randomly selected from the case's risk set, matching on year of birth, sex, year of cohort entry, and duration of follow-up. The index date of the cases was assigned to the matched controls.

Exposure assessment

For all cases and matched controls, we obtained all ADs prescribed between cohort entry and index date. For the primary analysis, the exposure was defined according to three timing of use categories: current use, defined as the last prescription in the 6 months before the index date; recent use, defined as the last prescription in the 6-12 months before the index date; and past use, defined as the last prescription more than 12 months before the index date.

For secondary analyses, exposure was redefined in three ways. First, we evaluated the risk of developing the event among patients currently exposed according to AD class: tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRIs), mono-amino oxidase (MAO) inhibitors, and other ADs or combinations. Second, current exposure was also sub-classified into three mutually-exclusive groups based on inhibitory potency to serotonin reuptake: high-potency (dissociation constant (Kd)<1 nmol/L), intermediate-potency (Kd=1-10

nmol/L), and low-potency (Kd>10 nmol/L).[17, 18] Third, we investigated duration of use, degree of adherence, and individual molecules among current users of high-potency ADs. The duration of each prescription was calculated from the number of prescribed tablets combined with dosing instructions. A duration of 28 days was assumed (the mode), when it was not possible to derive exposure duration from the available information. For unusually low or high values of prescription duration we assigned a minimum of 7 or a maximum of 90 days to the prescription duration.[7] Additionally, continuous use was defined as when the duration of one prescription overlapped the date of the next prescription, allowing for a 28-day "grace period" between prescriptions.[19-23] Among overlapping prescriptions, individuals were assumed to have refilled early and not completed the first prescription before starting the second prescription. Thus, duration of use was calculated by summing up the total number of prescribed days. Adherence was expressed as proportion of days covered (PDC), which is derived from dividing the cumulative days of medication use by the length of follow-up. The degree of adherence was categorized as a PDC <80 or ≥80%.[19, 20, 24]

Potential confounders

Covariates used for adjustment were identified from factors known to be associated with cAF that could also influence the choice of AD therapy. These included the indications of use (depression, anxiety or both) at cohort entry, heart failure, hypertension, diabetes, chronic obstructive pulmonary disease (COPD) and asthma,[15] all measured at any time before the index date. Excessive alcohol use, smoking status and obesity (BMI > 30 kg/m^2) were defined as the last record before the index date. Covariates also included medications prescribed within a 2-year time-window before the index date. These included antihypertensive drugs (i.e., alpha-blockers, beta-blockers, calcium channel blockers, angiotensin converting-enzyme inhibitors,

angiotensin receptor blockers, diuretics), statins, anti-inflammatory drugs, acetaminophen, beta2 agonists, corticosteroids, and other respiratory medications.

Statistical analysis

Given that all cohort members had at least 6 months of follow-up (and thus no events), person-time at risk was calculated starting 6 months after the first AD prescription. The crude incidence rate of cAF was calculated by dividing the number of cases by the total person-years of follow-up.

Conditional logistic regression was used to compute odds ratios of cAF which, which in the context of a nested case-control analysis, are unbiased estimators of the incidence rate ratio (RR) with 95% confidence intervals (CI).[25] In addition to age, sex, year of cohort entry, and duration of follow-up on which the logistic regression was conditioned, the models were adjusted for the aforementioned potential confounders. Confounding by indication[26] was minimized because the reference category for all analyses consisted of past users, a group of patients likely sharing several characteristics of current and recent users.

In the primary analysis, we compared the risk of cAF associated with current and recent use with past use of ADs. In a secondary analysis, we estimated the RRs of cAF among current users of ADs according to chemical class and potency in reducing serotonin reuptake. Furthermore, among current users of high-potency ADs, we assessed whether the risk of cAF varied according to the duration of use, degree of adherence, and individual molecule.

Finally, two sensitivity analyses were conducted. The first sensitivity analysis addressed issues related to possible misclassification of the outcome. Thus, cases of cAF were restricted to those requiring surgical or monitoring procedures/interventions or pharmacological therapy. In a

second sensitivity analysis, we varied the current exposure time-window to 2 and 3 months. All analyses were conducted with SAS version 9.2 (SAS Instititute, Cary, NC).

RESULTS

A total of 116,125 new users of ADs previously diagnosed with depression and/or anxiety met the study inclusion criteria (Figure 1). At cohort entry, mean age was 43.5 years (SD: 16.2), and most of the patients were female (67.5%). The cohort members received ADs because of depression (55%), anxiety (44.6%) or both (0.4%). During follow-up, 1270 cases of cAF were identified, generating an overall incidence rate of 1.6/1,000 person-years.

Table 1 depicts the demographic and clinical characteristics of cases and their matched controls. Mean age at cAF was 72.4 (SD: 12.8) and 72.0 (SD: 12.0) in cases and their respective controls; 63.5% of cases and controls were women (age and sex were matching factors). Moreover, more than half of cases and controls received ADs to treat anxiety. Excessive alcohol use was slightly higher among cases than controls, and cases were more likely to be obese than controls, while no differences were observed in terms of smoking between the two groups.

Cases were more likely to have cardiovascular diseases such as heart failure, hypertension and diabetes, as well as chronic respiratory conditions such as asthma and COPD. Consequently, cases were also more likely to have been using antihypertensives, antiarrhythmics, antithrombotics, lipid-lowering drugs as well as oral corticosteroids and respiratory medications. The use of non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen was also greater among cases than controls (Table 1).

Table 2 presents the results of the primary analysis. Compared to past use, the risk of cAF was not increased with either current (RR=0.98; 95% CI=0.86-1.12) or recent use of ADs (RR=1.02; 95% CI=0.86-1.30). When current use was further categorized according to chemical class, no association with cAF was observed among SSRIs users (RR=1.06; 95% CI=0.89-1.24) as well as for TCA (RR=0.93; 95% CI=0.76-1.13) and others ADs (RR=0.80; 95% CI=0.59-1.10). Similarly, there was no association with potency of ADs.

Table 3 shows the results of the secondary analyses. Although not statistically significant, current use of high-potency ADs tended to be associated with slightly higher risks with shorter durations of use (<12 months: RR=1.26; 95% CI=0.86-1.83; 12 to 24 months: RR=1.22; 95% CI=0.80-1.86; >24 months: RR=0.88; 95% CI=0.67-1.15). Similarly, non-adherent patients showed a non-significant higher risk of cAF (RR=1.23; 95% CI=0.97-1.57) than the adherents (RR=0.73; 95% CI=0.51-1.02). No substantial difference was observed among individual AD molecules (Table 3).

In sensitivity analyses, varying the length of the current time-window to 2 and 3 months produced results similar to the ones observed in the primary analyses (see supplemental Tables 1 and 2). In addition, using a stricter case definition (i.e., limiting cases to those that had surgical procedures/interventions or a pharmacological therapy) generated results consistent with those of the primary analyses (see supplemental Table 3).

DISCUSSION

In this first population-based study examining the association between ADs and the risk of cAF, we found that the use of ADs does not appear to be associated with an increased risk of cAF, even when the agents were categorized according to their potency in reducing serotonin reuptake.

Several reasons might explain our results. Although some preclinical evidence has correlated the electrophysiological role of 5HT4 serotonin receptors in inducing AF,[4, 5, 27-29] other biological pathways might be more involved in the development of serotonin-related cardiac disease. Specifically, cardiac valvulopathy, which is a leading risk factor for cAF, is one of the major complications in patients with carcinoid syndrome because of serotonin overproduction.[30] Nevertheless, through the stimulation of 5HT2B receptors, as recently demonstrated by some of us,[31] ADs seem unable to act on this pathway.

We adopted a minimum time of 6 months of follow-up because a long-term exposure to high serum serotonin concentration is hypothesized to induce cAF.[14] Nevertheless, the lack of an association for both duration of use and degree of AD adherence indicate that the increased concentration of serotonin resulting from the pharmacological effect of ADs might not be sufficient to increase the risk of cAF. This is consistent with the fact that ADs seem unable to further increase serotonin levels even in patients already with serotonin overproduction, such as those with carcinoid syndrome [32].

Given that an indirect stimulation of 5HT4 receptors was the biological rationale of our study, the direct binding of ADs to 5HT4 receptors could be more likely to have a causal association with cAF. However, there is no evidence of relevant affinity towards 5HT4 for any ADs, and also the new medications acting as highly selective 5HT4 agonists (i.e., prucalopride) showed a good cardiovascular safety profile according to recent clinical trials.[33]

Trifirò and colleagues[34] observed an increased risk of ischemic stroke among users of SSRIs (adjusted OR=1.39, 95% CI=1.03-1.86). Given that cAF is a major risk factor for stroke,[35] our study excludes an indirect effect due ADs-related cAF. On the other hand, our results show a non-significant trend of risk reduction of cAF moving from a short to a longer duration of use as well as from a low to a greater degree of adherence to ADs. Possible explanations supporting these results might concern a protective effect of ADs[36-38] towards cAF as well as a "healthy adherer" effect (i.e., better general lifestyle) among adherent patients.[39]

This study has a number of strengths. First, we used a large source population and study size that allowed us to adjust for a number of potential confounders including medical histories and lifestyle information such as smoking, alcohol use and BMI measurements. Second, by assembling a cohort of ADs users, we effectively minimized confounding by indication. Third, both exposure and covariates definitions were time-dependent given the nested case-control design. Fourth, the exposure to ADs was prospectively recorded in the CPRD, thus eliminating the possibility of recall bias. Finally, we performed several sensitivity analyses whose results were consistent with those of the primary analysis.

This study also has some limitations. First, cases of cAF have not been formally validated. Nevertheless, the incidence rate of cAF produced in this analysis was in line with the data from literature (incidence rate: 1.2 per 1000 person-years [40]). In addition, when the analyses were restricted to cases requiring monitoring or surgical procedure/intervention or pharmacological therapy, the results remained consistent with those of the primary analysis. Secondly, although the 6-month 'current' exposure time-window was biologically consistent with the expected timeframe of cAF occurrence, there are no conclusive data on this regard. However, we obtained similar results when repeated the analysis by using shorter exposure time

windows of 2 and 3 months. Thirdly, given that dosage was not consistently entered in the CPRD, we did not conduct a dose analysis, which would have been subject to important exposure misclassifications. Reassuringly, we performed several complementary analyses by potency, duration, and class which confirmed the absence of risk for cAF due to ADs. Finally, ADs use was assessed on the basis of prescription records, thus assuming that patients actually took these medications. While this might be problematic for medications used for acute conditions, it is reasonable to assume that patients regularly renewing prescriptions for ADs are in fact using them.

In summary, our study indicates that the use of ADs is not associated with an increased risk of cAF. In order to significantly reduce the risk of depression recurrences, an effective pharmacotherapy based on ADs might need to reach a duration of use of 48 months.[41] Thus, the absence of an association with cAF in the duration-response analysis was demonstrated by accounting for the potential adverse effects being expected in the chronic course of therapy. These findings confirm that ADs generally possess a good cardiovascular safety profile. As already demonstrated, they appear unable to reduce platelets aggregation [34] or induce cellular fibrosis [31] with clinical consequences, and we showed they do not seem to impair the electrophysiology of atrial myocytes. All this information sounds reassuring particularly against the backdrop in the increasing use of ADs in western countries.[42] Although our findings need to be confirmed, such information could bear clinical relevance in terms of ADs safety profile.

Acknowledgements

This study was funded in part by the Canadian Institutes of Health Research (CIHR). Dr. Samy Suissa is the recipient of the James McGill Chair.

All authors participated in the study design. SS acquired the data. FL, LA and AK performed the statistical analyses. FL wrote the initial draft, and all authors critically revised the manuscript. SS had full access to all statistical reports and tables in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. SS is the guarantor for the paper.

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Table 1 Characteristics of cases of chronic atrial fibrillation and their matched controls*

Characteristic	Cases (n=1271)	Controls (n=12,710)
Age, mean (SD), y	72.4 (12.8)	72.0 (12.5)
Follow-up, mean (SD), y	5.8 (3.8)	5.8 (3.8)
Gender, female	36.5	36.5
Excessive alcohol use	11.0	9.0
Smoking status		
Current	13.9	13.9
Former	26.4	22.5
Never	50.8	53.7
Unknown	8.9	9.9
BMI		
<30	74.3	83.3
≥30	25.7	16.7
Unknown	11.9	15.0
Indication of AD use		
Anxiety	53.9	54.1
Depression	45.8	45.6
Both	0.3	0.3
Comorbidities		
Heart failure	12.3	3.0
Hypertension	49.2	39.8
Diabetes	11.2	8.5
COPD	23.1	16.6
Asthma	16.6	12.5
Co-medications		
Antihypertensives	62.9	44.7
Antiarrhythmics	12.8	6.9
Antithrombotics	49.7	21.7
Lipid lowering drugs	20.8	18.0
NSAIDs	7.4	6.6
Paracetamol	58.0	49.7
Oral corticosteroids	21.4	14.9
Respiratory medications	27.2	18.2

Abbreviations: SD: standard deviation; ADs: antidepressants; COPD: chronic obstructive pulmonary disease; NSAIDs: non-steroidal anti-inflammatory drugs; BMI: Body Mass Index

*Data are presented as % (denominator at the top of column for cases and controls), unless otherwise indicated.

Table 2 Crude and adjusted rate ratios of chronic atrial fibrillation associated with the use of antidepressant, classified according to recency of use and chemical class*

	Cases N=1271	**Controls N=12 271**	**Crude RR**	**Adjusted RR****	**95% CI**
*Recency of use****					
Past use	665 (52.3)	6894 (54.4)	1.00	Reference	Reference
Current use	429 (38.7)	4740 (37.3)	1.08	0.98	0.86-1.12
Recent use	114 (9.0)	1076 (8.5)	1.13	1.02	0.86-1.30
Chemical class					
TCA	151 (11.9)	1554 (12.0)	1.04	0.93	0.76-1.13
SSRIs	254 (20.0)	2310 (18.2)	1.15	1.06	0.89-1.24
Others	50 (3.9)	617 (4.9)	0.85	0.80	0.59-1.10
Combinations	37 (2.9)	289 (2.3)	1.34	1.07	0.73-1.59
Potency in reducing serotonin reuptake					
LPISR	98 (7.7)	1088 (8.6)	0.94	0.90	0.71-1.14
IPISR	217 (17.1)	2044 (16.1)	1.11	0.98	0.82-1.16
HPISR	140 (11.0)	1320 (10.4)	1.11	1.02	0.83-1.25
Combinations	37 (2.9)	288 (2.3)	1.34	1.10	0.75-1.61

Abbreviations: TCA=tricyclic antidepressant; SSRIs=selective serotonin reuptake inhibitors; LPISR=low potency inhibitors of serotonin reuptake; IPISR: intermediate potency inhibitors of serotonin reuptake; HPISR: high potency inhibitors of serotonin reuptake.

*Data are presented as n (%; denominator at the top of column for cases and controls) and RR (Rate Ratio) with 95% Confidence Intervals (CI).

**Adjusted for covariates listed in Table 1.

***Current use: within 6 months before the index date; recent use: from 6 to 12 months before the Index date; past use: more than 12 months before the index date.

Table 3 Crude and adjusted rate ratios of chronic atrial fibrillation associated with 'current' users of high-potency antidepressants according to cumulative use, degree of adherence, and individual molecules*

	Cases N=1271	**Controls N=12 271**	**Crude RR**	**Adjusted RR****	**95 % CI**
Past use	665 (52.3)	6894 (54.4)	1.00	Reference	Reference
HPISR					
Cumulative use					
<12 months	41 (3.2)	337 (2.7)	1.34	1.26	0.86-1.83
12-24 months	29 (2.3)	253 (2.0)	1.21	1.22	0.80-1.86
>24 months	70 (5.5)	730 (5.7)	0.99	0.88	0.67-1.15
*Adherence****					
<80%	97 (7.6)	992 (6.2)	1.28	1.23	0.97-1.57
≥80%	43 (3.4)	528 (4.2)	0.85	0.73	0.52-1.02
Individual molecule					
Clomipramine	4 (0.3)	47 (0.4)	0.89	0.82	0.29-1.36
Duloxetine	2 (0.2)	14 (0.1)	1.48	1.29	0.26-6.40
Fluoxetine	48 (3.8)	521 (4.1)	0.96	0.87	0.63-1.20
Paroxetine	51 (4.0)	470 (3.7)	1.13	1.10	0.80-1.51
Sertraline	35 (2.8)	268 (2.1)	1.37	1.22	0.83-1.81
Combinations	37 (2.9)	288 (2.3)	1.34	1.10	0.75-1.61

Abbreviations: HPISR=high potency inhibitors of serotonin reuptake

*Data are presented as n (%; denominator at the top of column for cases and controls) and RR (Rate Ratio) with 95% Confidence Intervals (CI); current use: within 6 months before the index date; recent use: from 6 to 12 months before the index date; past use: more than 12 months before the index date.

**Adjusted for covariates reported in Table 1.

***Proportion of Days Covered (PDC) during follow-up.

Supplemental Table S1 Crude and adjusted rate ratios of chronic atrial fibrillation according to the recency of use of antidepressants, their chemical class and degree of potency in reducing serotonin reuptake (current time-window: 3 months)*

	Cases N=1271	Controls N=12 271	Crude RR	Adjusted RR**	95 % CI
Recency of use					
Past use	779 (61.3)	7970 (54.2)	1.00	Reference	Reference
Current Use	426 (33.5)	4148 (32.6)	1.05	0.97	0.84-1.10
Recent use	66 (5.2)	592 (4.7)	1.15	1.07	0.80-1.42
Chemical class					
TCA	127 (10.0)	1281 (10.1)	1.02	0.92	0.75-1.14
SSRIs	220 (17.3)	2027 (16.0)	1.11	1.03	0.87-1.21
Others	43 (3.4)	571 (4.5)	0.77	0.76	0.54-1.06
Combinations	36 (2.8)	269 (2.1)	1.38	1.13	0.77-1.65
Potency in reducing serotonin reuptake					
LPISR	84 (6.6)	965 (7.6)	0.89	0.87	0.68-1.11
IPISR	191 (15.0)	1768 (13.9)	1.11	0.99	0.83-1.18
HPISR	115 (9.1)	1146 (9.0)	1.03	0.96	0.77-1.19
Combinations	36 (2.8)	269 (2.1)	1.38	1.16	0.79-1.70

Abbreviations: ADs=AntiDepressants; TCA=TriCyclic Antidepressant; SSRIs=Selective Serotonin Reuptake Inhibitors; LPISR=Low Potency Inhibitors of Serotonin Reuptake; IPISR: Intermediate Potency Inhibitors of Serotonin Reuptake; HPISR: High Potency Inhibitors of Serotonin Reuptake.

*Data are presented as n (%;denominator at the top of column for cases and controls) and RR (Rate Ratio) with 95% Confidence Intervals (CI).

**Adjusted for covariates listed in Table 1.

Supplemental Table S2 Crude and adjusted rate ratios of chronic atrial fibrillation according to the recency of use of antidepressants, their chemical class and degree of potency in reducing serotonin reuptake (current time-window: 2 months)*

	Cases N=1271	Controls N=12 271	Crude RR	Adjusted RR**	95 % CI
Recency of use					
Past use	826 (65.0)	8330 (65.5)	1.00	Reference	Reference
Current Use	392 (30.8)	3766 (29.6)	1.05	0.97	0.85-1.11
Recent use	53 (4.2)	614 (4.8)	0.87	0.85	0.63-1.15
Chemical class					
TCA	115 (9.1)	1141 (9.0)	1.02	0.93	0.75-1.16
SSRIs	201 (15.8)	1843 (14.5)	1.10	1.02	0.86-1.21
Others	42 (3.3)	531 (4.2)	0.80	0.79	0.56-1.11
Combinations	34 (2.7)	251 (2.0)	1.37	1.18	0.80-1.74
Potency in reducing serotonin reuptake					
LPISR	79 (6.2)	881 (6.9)	0.90	0.90	0.70-1.16
IPISR	170 (13.4)	1610 (12.7)	1.07	0.95	0.79-1.15
HPISR	108 (8.5)	1026 (8.1)	1.06	0.99	0.79-1.15
Combinations	35 (2.8)	249 (2.0)	1.42	1.25	0.85-1.85

Abbreviations: ADs=AntiDepressants; TCA=TriCyclic Antidepressant; SSRIs=Selective Serotonin Reuptake Inhibitors; LPISR=Low Potency Inhibitors of Serotonin Reuptake; IPISR: Intermediate Potency Inhibitors of Serotonin Reuptake; HPISR: High Potency Inhibitors of Serotonin Reuptake.

*Data are presented as n (%; denominator at the top of column for cases and controls) and RR (Rate Ratio) with 95% Confidence Intervals (CI).

**Adjusted for covariates listed in Table 1.

Supplemental Table S3 Crude and adjusted rate ratios of chronic atrial fibrillation according to the recency of use of antidepressants, their chemical class and degree of potency in reducing serotonin reuptake (cases of chronic atrial fibrillation requiring procedure/intervention or pharmacological therapy)[*]

	Cases N=821	Controls N=8210	Crude RR	Adjusted[**] RR	95 % CI
Recency of use					
Past use	447 (54.5)	4560 (55.5)	1.00	Reference	Reference
Current Use	306 (37.3)	2992 (36.4)	1.05	0.94	0.80-1.12
Recent use	68 (8.3)	658 (8.0)	1.07	0.98	0.71-1.35
Chemical class					
TCA	93 (11.3)	941 (11.5)	1.01	0.88	0.68-1.13
SSRIs	166 (20.2)	1470 (17.9)	1.16	1.07	0.87-1.32
Others	28 (3.4)	385 (4.7)	0.75	0.73	0.48-1.11
Combinations	19 (2.3)	196 (2.4)	0.99	0.76	0.45-1.28
Potency in reducing serotonin reuptake					
LPISR	54 (6.6)	653 (8.0)	0.84	0.83	0.60-1.14
IPISR	150 (18.3)	1342 (16.4)	1.15	1.01	0.81-1.25
HPISR	83 (10.1)	805 (9.8)	1.05	0.97	0.74-1.27
Combinations	19 (2.3)	192 (2.3)	1.01	0.75	0.44-1.28

Abbreviations: ADs=AntiDepressants; TCA=TriCyclic Antidepressant; SSRIs=Selective Serotonin Reuptake Inhibitors; LPISR=Low Potency Inhibitors of Serotonin Reuptake; IPISR: Intermediate Potency Inhibitors of Serotonin Reuptake; HPISR: High Potency Inhibitors of Serotonin Reuptake.

[*]Data are presented as n (%; denominator at the top of column for cases and controls) and RR (Rate Ratio) with 95% Confidence Intervals (CI).

**Adjusted for covariates reported in Table 1.