3.2. Risk of ischemic stroke associated with antidepressant drug use in elderly persons

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Gianluca Trifirò[1,2,3], MD, MSc, Jeanne Dieleman, PhD[1], Elif F. Sen[1], MSc, Giovanni Gambassi[4], professor, Miriam C.J.M. Sturkenboom[1], professor

1. Pharmacoepidemiology unit, Departments of Medical Informatics and Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands;
2. Department of Clinical and Experimental Medicine and Pharmacology – University of Messina, Messina – Italy;
3. IRCCS Centro Neurolesi 'Bonino-Pulejo', Messina, Italy
4. Centro Medicina Invecchiamento - Universita' Cattolica Sacro Cuore, Rome - Italy.

ABSTRACT

Background: Competing hypotheses have been formulated about a possible association between selective serotonin reuptake inhibitors (SSRIs) and ischemic stroke. However, the relationship between antidepressant drug use and ischemic stroke is still unclear. Aim of the study was to assess the association between use of different types of antidepressants and the risk of ischemic stroke in elderly outpatients.

Methods: A population-based, nested, case-control study was conducted in persons 65 years and older in the Integrated Primary Care Information (IPCI) database (1996-2005). Cases were all patients with a validated first ischemic stroke. Controls were matched on year of birth, sex and index date. Exposure to antidepressants was divided in current, past and non-use and further categorized by type (SSRI, tricyclic [TCA], other antidepressants), dose and duration. Conditional logistic regression was used to compare the risk of ischemic stroke between users of antidepressants and non-users.

Results: Overall, 996 incident ischemic strokes were identified. Current use of SSRIs was associated with a significantly increased risk as compared to non-use (OR: 1.55; 95% CI: 1.07-2.25) in elderly, particularly when used longer than 4 months. No associations were observed for current use of TCAs and other AD.

Conclusion: Compared to non use, only SSRI use appears to be associated with an increased risk of ischemic stroke in elderly patients, particularly as short term effect.

BACKGROUND

Antidepressant drugs (ADs) are widely used in elderly people for indications such as depressive symptoms, anxiety disorders and neuropathic pain [**1-2**].

The selective serotonin reuptake inhibitors (SSRIs) are considered the first-choice for the elderly with depressive symptoms, as these drugs are supposed to have similar efficacy to other antidepressants but better tolerability [**3**]. Recently, the effects of SSRIs on cerebral circulation have garnered attention after preliminary reports suggested an association between SSRI exposure and risk of abnormal bleeding, including hemorrhagic stroke [**4-6**]. SSRIs decrease the intracellular contents of serotonin in platelets by blocking serotonin transporter 5-HTT, thus inhibiting platelet function. This anti-platelet effect of SSRIs may ultimately increase the risk of hemorrhage, such as intracranial bleeding [**7**]. The same mechanism might theoretically protect against arterial thrombotic events, including ischemic stroke [**7**]. Previous investigations documented a significant reduction in the risk of myocardial infarction associated with SSRI use [**8-9**]. On the other hand, SSRIs may cause vasoconstriction in cerebral arteries as a result of serotoninergic activation which may lead to ischemic stroke [**10-11**]. To date the net effect of SSRIs on the risk of ischemic and hemorrhagic stroke remains unclear.

Several studies explored the association between hemorrhagic stroke and SSRI and other antidepressant drug use but failed to show any significant associations [**12-14**]. Little is known about the risk of ischemic stroke in elderly persons using antidepressants, although approximately 80% of total strokes are ischemic ones in these patients [**15**].An Italian study did not find an increased risk of cerebrovascular adverse effects in elderly patients who were treated with antidepressants, but did not differentiate between ischemic and hemorrhagic stroke [**16**]. Two studies did demonstrate an increased risk of ischemic stroke for SSRIs but did not consider the elderly specifically [**17**] or were limited to hospitalized stroke only and not considering other antidepressants and indication of use [**18**]. Altogether, the epidemiologic evidence about antidepressant use and risk of ischemic stroke is inconclusive.

Thus, the aim of this study was to assess the association between the use of various antidepressant drug types and the risk of a first-ever ischemic stroke in community-dwelling elderly persons.

METHODS

Setting

We employed a population-based, nested, case-control study. Data for this study were retrieved from the Integrated Primary Care Information (IPCI) database. The IPCI database is a longitudinal general practice research database set up in 1992 and containing data from electronic medical records from a group of 150 Dutch general practitioners' (GPs) practices. In the Netherlands, all persons have their own GP who serves as the gatekeeper to medical care and files all relevant medical details on their patients from primary care visits, hospital admissions and visits to outpatient clinics. A detailed description of the database has been previously reported **[19]**. Briefly, IPCI contains the medical records of approximately 800,000 patients with an age and gender distribution representative of the Netherlands. The electronic records contain coded and anonymous data on patient demographics, reasons for visits, signs, symptoms and medical diagnoses (using the International Classification for Primary Care **[20]**) from GPs and specialists, hospitalizations, as well as drug prescriptions. Drug prescriptions include product name, anatomical therapeutic chemical (ATC) classification, dispensed quantity, dosage regimen and coded indication. To maximize completeness of the data, GPs participating in the IPCI project are not allowed to maintain a system of paper-based records, aside from the electronic medical records. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research **[21]**. The Scientific and Ethical Advisory Board of the IPCI project approved the study.

Study population

The study started on January 1, 1996, and ended on December 31, 2005. The source population comprised all individuals 65 years and older with at least 1 year of data registered in the database. All individuals were followed from the study entry date until one of the following events, whichever came first: transient ischemic attack (TIA), stroke, death, moving out of the practice area, or end of the study period. Patients who had a recorded diagnosis of TIA or stroke in the medical history prior to the study entry were excluded. Patients with a diagnosis of cerebral tumor, either before or during the study period, were also excluded.

Case Identification and Ascertainment

Cases were all patients with a first-ever ischemic stroke that occurred during the study period. The case identification and ascertainment included two phases. First, we applied a broad search on patient clinical diary and summaries of specialist

letters, using coded diagnoses and key words for free text. Second, the electronic medical records of all potential cases of cerebrovascular accidents were manually reviewed by two medically trained researchers (G.T. and E.F.S), who were blinded to the exposure. Patients were classified as having a TIA, a hemorrhagic stroke, an undefined stroke, or an ischemic stroke. Ischemic stroke was considered if the diagnosis was confirmed by a CT-scan or explicitly mentioned by a consulting specialist or listed among discharge diagnoses. The date of initial symptoms (e.g. dizziness, unexplained falling, and headache) was considered as the index date. Only if a stroke was preceded by a TIA occurring less than one month before, TIA was taken as the index date. Otherwise, a TIA was not considered in order to avoid case misclassification. TIA, however, was used as a censoring point to avoid protopathic bias since some patients with TIA may receive treatment with antidepressants subsequently **[22]**. In case of disagreement between the two assessors in classifying the cases and identifying the index date, a consensus was found via discussion. For each case, all persons in follow-up at the time of the index date and of the same age and sex as the case served as a control in the statistical analyses.

Exposure definition

Information on antidepressant drug use was obtained from the prescription files. We created antidepressant exposure categories based on drug type, and recency, dose and duration of use. The legend duration was calculated as the total number of units per prescription divided by the prescribed daily number of these units. Antidepressant drugs were grouped according to the mechanism of action into: 1) Selective serotonin reuptake inhibitors (SSRIs): paroxetine, fluoxetine, citalopram, fluvoxamine and sertraline; 2) Tricyclic antidepressants (TCAs): clomipramine, amitriptyline, dothiepin, imipramine, trimipramine, lofepramine, maprotiline, doxepin, nortriptyline, desipramine, bupropion, moclobemide, opipramol, dosulepin and reboxetine; 3) Other antidepressants: venlafaxine, mirtazapine, mianserine, nefazodone and trazodone. A combination category was considered for concomitant use of more antidepressants belonging to different classes. We performed a secondary analysis in which we grouped antidepressant drugs based on the affinity to the serotonin transporter **[14]**: 1) high affinity (paroxetine, fluoxetine, sertraline, and clomipramine); 2) intermediate affinity (citalopram, fluvoxamine, amitriptyline, dothiepin, imipramine, and venlafaxine); 3) low affinity (trimipramine, lofepramine, maprotiline, doxepin, nortriptyline, desipramine, bupropion, moclobemide, opipramol, dosulepin, reboxetine, mirtazapine, mianserine, nefazodone and trazodone). Exposure to different types of antidepressants was further divided into current, past and never use. Drug use was defined as current if the prescription length covered the index date or ended less than 30 days

(carry-over effect) prior. Past use meant that the last prescription ended more than 30 days prior to the index date. Patients were defined as non users if antidepressant prescriptions were never recorded prior to the index date. To be able to study the dose-effect, we expressed daily dosing regimens as the prescribed number of defined daily dosages (DDD), as defined by the World Health Organization (see website: http://www.whocc.no/atcddd/indexdatabase/). Duration of antidepressant use was calculated as the cumulative number of prescription days during the follow-up period. The duration was divided into short term use if ≤180 days and long term use if >180 days, as the median duration of any antidepressant use was 180 days.

Covariates

As potential confounders, we considered age, sex, and calendar time (matching factors), smoking cigarettes, presence of cardiovascular disease (heart failure, hypertension, angina, history of myocardial infarction, peripheral arterial disease, atrial fibrillation, phlebitis/thrombophlebitis), neuropsychiatric diseases (Parkinson's disease, dementia, and migraine), chronic obstructive pulmonary disease (COPD), diabetes mellitus, lipid metabolism disorders, coagulation/platelet abnormalities, malignant tumors, pneumonia (within 3 months prior to the index date). We also considered chronic use of diuretics, digoxin, ACE-inhibitors, angiotensin receptor blockers, calcium-channel blockers, beta-blockers, lipid-lowering drugs, vasodilators and concomitant use (within 3 months prior to index date) of low dose aspirin, anticoagulants, antibiotics, systemic corticosteroids, NSAIDs, benzodiazepines, antipsychotic drugs, and opioids. Depression itself may be a risk factor for stroke and therefore confounding by indication cannot be easily ruled out **[23]**. To address this issue, two medically trained researchers (G.T. and E.F.S.) manually assessed the indication of use of antidepressant drugs from the free text of the medical records. Reasons for use were classified as depression, anxiety, headache, neuropathic pain, and other/unspecified disorders. This approach was taken for all exposed cases and for a randomly selected sample of the exposed controls (N=425).

Data Analysis

Relative risks of ischemic stroke plus 95% confidence intervals [CIs] were estimated by calculating odds ratios by using conditional logistic regression analysis. We performed adjustment for all covariates that were associated with ischemic stroke at the univariate analyses. In these analyses current and past use of different types of antidepressants (SSRI, TCA and other antidepressants) were compared to non-use. To compare directly the risk for ischemic stroke among

different antidepressant types, we performed an additional analysis with current use of TCA as comparator. A secondary analysis was carried out considering as exposure categories antidepressants with high, intermediate and low affinity to the serotonin transporter. A linear trend across strata of increasing affinity to the serotonin transporter was tested by including affinity as an ordinal variable in the logistic regression model. A sensitivity analysis was conducted in which we removed the carry over effect of 30 days. Among current users of antidepressants, we further calculated odds ratios for the risk of ischemic stroke with individual medications, daily dosage (≤ 0.5 and > 0.5 DDD), and cumulative duration of use (≤ 180 days and >180 days). Stratified analyses were conducted to study age and history of ischemic vascular disease as effect modifiers. To evaluate the presence of confounding by indication we also performed an analysis according to the type of antidepressant and the indication of use.

Antidepressant drugs may be prescribed to treat symptoms of cerebral ischemic disorders occurring shortly before stroke, thus some cases of ischemic stroke could be mistakenly attributed to antidepressant exposure (i.e. protopathic bias). To further assess the possible effect of protopathic bias on the association between antidepressants and ischemic stroke, we performed sensitivity analyses in which all patients, who started antidepressant treatment within 30, 60 and 90 days before the index date, were excluded. All analyses were conducted in SPSS/PC, version 13 (SPSS Inc, Chicago, Ill). The level of significance for all statistical tests was 2-sided $P < 0.05$.

RESULTS

The source population for this study comprised 70,392 individuals of 65 years and older. Of them, 1,176 (1.7%) were excluded because of cerebral tumors (n= 138) or history of cerebrovascular event (n=1,038) prior to the study entry. The final study population comprised 69,216 elderly persons (43% males, average age: 72.7±7.6 years). Within this population, 1,354 (2.0%) persons experienced a first-ever stroke (ischemic, hemorrhagic and undefined subtypes) during the study period, of which 996 (74%) were classified as incident ischemic stroke. Per case there were on average 493 age and sex matched controls available as a comparator. Demographic and clinical characteristics of cases and controls are reported in **Table 1**. Co-morbidities like hypertension, coronary heart diseases, atrial fibrillation, coagulation abnormalities, diabetes mellitus, COPD, and dementia, and concomitant use of corticosteroids, anticoagulants and opioids were associated with ischemic stroke. Among cases, 151 (15.2%) received at least one antidepressant drug at any time

Table 1. Demographic and clinical characteristics of cases compared to age and sex matched non-cases.

Current Use	Cases N=996 (%)	Controls (%)	Crude OR* (95% CI)
Age groups (years)			**Matching factor**
65-74	321 (32.2)	233,006 (47.4)	
75-84	447 (44.9)	220,358 (44.9)	
≥ 85	228 (22.9)	37,912 (7.7)	
Gender			**Matching factor**
Males	416 (41.8)	187,250 (38.1)	
Females	580 (58.2)	304,026 (61.8)	
Smoking cigarettes	55 (5.5)	27,274 (5.6)	1.19 (0.90-1.58)
Cardiovascular diseases			
Hypertension	386 (38.8)	143,231 (29.1)	*1.56 (1.37-1.77)*
Angina	141 (14.2)	51,312 (10.4)	*1.30 (1.08-1.55)*
History of myocardial infarction	57 (5.7)	17,059 (3.5)	*1.62 (1.24-2.12)*
Peripheral arterial disease	27 (2.7)	10,616 (2.2)	1.20 (0.82-1.77)
Atrial fibrillation	59 (5.9)	16,314 (3.3)	*1.65 (1.27-2.15)*
Heart failure	135 (13.6)	30,468 (6.2)	*1.87 (1.55-2.25)*
Phlebitis/thrombophlebitis	34 (3.4)	13,642 (2.8)	1.21 (0.86-1.71)
Other diseases potentially related to stroke			
Lipid metabolism disorders	53 (5.3)	38,440 (7.8)	0.79 (0.59-1.04)
Coagulation/platelet abnormalities	10 (1.0)	1,937 (0.4)	*2.47 (1.32-4.61)*
Obesity	9 (0.9)	5,920 (1.2)	0.87 (0.45-1.69)
Chronic obstructive pulmonary disease (COPD)	145 (14.6)	53,773 (10.9)	*1.34 (1.12-1.60)*
Diabetes mellitus	163 (16.4)	49,321 (10.0)	*1.76 (1.49-2.08)*
Tumours (except for cerebral ones)	107 (10.7)	48,122 (9.8)	1.06 (0.87-1.30)
Pneumonia (within 3 months prior to ID)	3 (0.3)	1,311 (0.3)	0.96 (0.31-2.99)
Neuropsychiatry diseases			
Parkinson's diseases	7 (0.7)	3,651 (0.7)	0.81 (0.30-1.71)
Dementia	45 (4.5)	12,451 (2.5)	*1.44 (1.06-1.95)*
Migraine	11 (1.1)	5,632 (1.1)	1.16 (0.64-2.10)
Prior use of cardiovascular medications			
Diuretics	7 (0.7)	1,948 (0.4)	1.56 (0.74-3.29)
Digoxin	1 (0.1)	395 (0.1)	NA
ACE-inhibitors	2 (0.2)	1,509 (0.3)	NA
Sartanes	1 (0.1)	651 (0.1)	NA
Calcium-channel blockers	3 (0.3)	1,106 (0.2)	1.26 (0.41-3.93)
Beta-blockers	9 (0.9)	2,483 (0.5)	1.84 (0.95-3.57)
Lipid-lowering drugs	1 (0.1)	1,056 (0.2)	NA
Vasodilators	2 (0.2)	612 (0.1)	NA
Aspirin	4 (0.4)	1,687 (0.3)	1.15 (0.43-3.07)
Anticoagulants	15 (1.5)	1,585 (0.3)	*4.29 (2.56-7.18)*
Concomitant use of psychotropic drugs			
Benzodiazepines	4 (0.4)	1,462 (0.3)	1.20 (0.45-3.21)
Antipsychotic drugs	1 (0.1)	140 (0.1)	NA
Opioids	3 (0.3)	154 (0.1)	*9.09 (2.87-28.4)*
Concomitant use of other drugs			
Systemic corticosteroids	3 (0.3)	285 (0.1)	*4.74 (1.51-14.83)*
Antibiotics	3 (0.3)	711 (0.1)	2.10 (0.68-6.55)
NSAIDS	3 (0.3)	1,122 (0.2)	1.22 (0.39-3.81)

* Conditional logistic regression analysis;

NA= not applicable as too few cases

prior to the first ischemic stroke: 29 (2.9%) were current users of SSRI, 17 (1.7%) of TCA and 6 (0.6%) of other antidepressants. Compared to non-use, current use of SSRIs was associated with an increased risk of ischemic stroke (OR: 1.55; 95% CI: 1.07-2.25), while no significant associations were found for current use of TCA (OR: 1.18; 95% CI: 0.73-1.91) or other antidepressants (OR: 1.01; 95%CI: 0.45-2.25) **(Table 2)**. Past use of either SSRI or TCA showed an increase in the risk of ischemic stroke as well. Compared to current use of TCA the risk of ischemic stroke with current use of SSRIs (OR: 1.32; 95%CI: 0.72-2.40) or other Ads (OR: 0.86; 95%CI: 0.34-2.18) was not statistically significant different. Among current users, SSRIs were used at a higher dosage (on average, 1±0.05 DDD per day) and for longer periods (on average 270 days) than TCAs (on average 0.5±0.1 DDD and 158 days) and other antidepressants (on average 0.8±0.1 DDD and 245 days). These differences in mean dosage and duration of use across antidepressant types lowered if considering depressed patients only (SSRI: 1±0.05 DDD, 259 days; TCA: 0.8±0.1 DDD, 211 days; and other antidepressant: 0.8±0.1 DDD, 248 days).

Table 2. Risk of ischemic stroke with use of different antidepressant groups, stratified by dosage** and duration** of use

Exposure category	Cases N=996 (%)	Controls N=491,276 (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
Non Use	844 (84.7)	437,718 (89.1)	1.00	1.00
Current Use				
SSRI	29 (2.9)	9,410 (1.9)	1.67 (1.15-2.42)	1.55 (1.07-2.25)
≤1 DDD	26	8,508	1.65 (1.03-2.44)	1.52 (0.98-2.26)
>1 DDD	3	902	1.92 (0.62-5.99)	1.78 (0.57-5.54)
≤ 180 days	16	3,468	2.26 (1.36-3.78)	2.07 (1.24-3.46)
> 180 days	13	5,942	1.22 (0.70-2.11)	1.14 (0.65-1.97)
TCA	17 (1.7)	7,155 (1.5)	1.24 (0.77-2.01)	1.18 (0.73-1.91)
≤1 DDD	16	6,658	1.25 (0.76-2.06)	1.18 (0.72-1.93)
>1 DDD	1	477	1.22 (0.17-8.67)	1.19 (0.17-8.46)
≤ 180 days	13	4,938	1.37 (0.79-2.37)	1.27 (0.73-2.20)
> 180 days	4	2,217	0.98 (0.37-2.61)	0.96 (0.0.36-2.56)
Other ADs	6 (0.6)	2,995 (0.6)	1.06 (0.48-2.38)	1.01 (0.45-2.25)
≤1 DDD	6	2,595	1.21 (0.54-2.71)	1.15 (0.51-2.56)
>1 DDD	-	400	NA	NA
≤ 180 days	2	1,397	0.75 (0.19-3.00)	0.71 (0.18-2.83)
> 180 days	4	1,598	1.35 (0.51-3.62)	1.28 (0.48-3.44)
Combination	-	284 (0.01)	NA	NA
Recent/Past use				
SSRI	49 (4.9)	17,219 (3.5)	1.49 (1.11-2.00)	1.39 (1.03-1.86)
TCA	43 (4.3)	13,729 (2.8)	1.64 (1.21-2.24)	1.53 (1.12-2.08)
Others	8 (0.8)	2,766 (0.6)	1.46 (0.73-2.94)	1.35 (0.67-2.72)
Combination	-	-	NA	NA

*Analysis was adjusted for hypertension, angina, history of myocardial infarction, atrial fibrillation, heart failure, coagulation/platelet abnormalities, COPD, diabetes mellitus, dementia, concomitant use of anticoagulants, systemic corticosteroids and opioids.

** As cut off point for dosage and duration categories, the median values for all current users of antidepressant were considered.

There was no dose effect on the risk of ischemic stroke for current users of any antidepressant type. However, we did observe a duration effect, where shorter use (i.e. ≤180 days) of SSRIs was associated with a larger risk increase (OR: 2.07; 95% CI: 1.24-3.46) than longer use (i.e. >180 days, OR: 1.14; 95%CI: 0.65-1.97). Considering the affinity to the serotonin transporter, a significant increase in the risk of ischemic stroke was observed only for the current users of antidepressants with high affinity to the serotonin receptor (OR: 1.43; 95% CI: 1.00-2.15), compared to non users. The linear trend test of increasing affinity and the risk of ischemic stroke was statistically significant ($p < 0.05$) **(Table 3)**. The indication of use was validated and assessed in all the cases (N=152) and in a sample of controls (N=425), who were currently or formerly exposed to an antidepressant drug. Among the 52 cases, 36 (69%) were currently treated with antidepressants because of depressive symptoms, and two thirds of these subjects received SSRIs **(Table 4)**. For patients with depression as an indication for treatment, the risk of ischemic stroke with SSRIs use (OR: 1.99; 95% CI: 1.20-3.30) was higher than that with TCAs (OR: 1.07; 95% CI: 0.43-2.65), although the difference was not statistically significant. We still observed a risk increase with current use of SSRIs if the indication was not depression, but the OR was lower and not statistically significant (OR: 1.50; 95% CI: 0.54-4.19). We performed a stratified analysis on presence of ischemic cardiovascular disease and on age, which showed that these factors did not modify

Table 3. Risk of ischemic stroke associated to different antidepressant groups (classified according to affinity for serotonin reuptake receptor), compared to non-use

AD exposure based on serotonin transporter affinity	Cases N=996 (%)	Controls N=491,276 (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
Non-Use	844 (84.7)	437,718 (89.1)	1.00	1.00
Current Use				
High affinity [1]	24 (2.4)	8,752 (1.8)	1.55 (1.05-2.27)	1.43 (1.00-2.15)
Intermediate affinity [2]	21 (2.1)	7,863 (1.6)	1.40 (0.91-2.16)	1.30 (0.84-2.00)
Low affinity [3]	6 (0.6)	2,926 (0.6)	1.05 (0.47-2.34)	0.98 (0.44-2.19)
Combination	1 (0.1)	303 (0.1)	NA	NA
Recent/Past Use				
High affinity [1]	43 (4.3)	15,978 (3.3)	1.44 (1.05-1.96)	1.34 (0.98-1.83)
Intermediate affinity [2]	49 (4.9)	14,873 (3.0)	1.70 (1.27-2.27)	1.57 (1.18-2.10)
Low affinity [3]	8 (0.8)	2,863 (0.6)	1.38 (0.68-2.77)	1.29 (0.64-2.59)
Combination	-	-	NA	NA

* Analysis was adjusted for hypertension, angina, history of myocardial infarction, atrial fibrillation, heart failure, coagulation/platelet abnormalities, COPD, diabetes mellitus, dementia, concomitant use of anticoagulants, systemic corticosteroids and opioids.

Legend:

1. Paroxetine, fluoxetine, sertraline, clomipramine;
2. Citalopram, fluvoxamine, amitriptyline, dothiepin, imipramine, venlafaxine;
3. Trimipramine, lofepramine, maprotiline, doxepin, nortriptyline, desipramine, bupropion, moclobemide, opipramol, dosulepin and reboxetine, mirtazapine, mianserine, nefazodone and trazodone.

the effect of the association between antidepressant and ischemic stroke (data not shown). To test for protopathic bias, we excluded patients who received the first prescription of antidepressant within 30, 60 and 90 days prior to the index date. Compared to non-use, the risk in current users was only somewhat diluted (from 1.55 to 1.42 for SSRI; from 1.18 to 1.01 for TCA; from 1.01 to 1.07 for other antidepressants). Although our analysis was underpowered to assess the risk of each individual drug, sertraline (4 exposed cases, OR: 2.03; 95% CI: 0.76-5.44) and paroxetine (18 exposed cases, OR: 1.59; 95% CI: 1.00-2.55) were associate with the greatest risks of ischemic stroke.

DISCUSSION

To our knowledge, this is the first observational study that explored specifically the association between antidepressant drug use and the risk of ischemic stroke in a cohort of elderly patients. The results show that in comparison to non use, current use of SSRIs confers a significantly increased risk of ischemic stroke (adj. OR: 1.55; 95% CI: 1.07-2.25), especially during the first 6 months of treatment.

Table 4. Risk of ischemic stroke associated with current use of different antidepressant types and different indications of use, with non use as reference (OR=1.00)

Antidepressant exposure by indication of use	Cases N=152 (%)	Control N=425 (%)	Adjusted* OR (95% CI)
Current use of SSRI			
Depression	24 (15.8)	43 (10.1)	1.99 (1.20-3.30)
Others	5 (3.3)	13 (3.1)	1.50 (0.54-4.19)
Current use of TCA			
Depression	7 (4.6)	23 (5.4)	1.07 (0.43-2.65)
Others	10 (6.6)	29 (6.8)	1.38 (0.68-2.81)
Current use of Other AD			
Depression	5 (3.3)	16 (3.8)	0.67 (0.23-1.96)
Others	1 (0.1)	5 (1.2)	1.00 (0.13-8.05)
Recent/Past use of SSRI			
Depression	32 (21.1)	97 (22.8)	1.30 (0.86-1.96)
Others	17 (11.2)	31 (7.3)	1.73 (0.94-3.19)
Recent/Past use of TCA			
Depression	13 (8.6)	31 (7.3)	1.58 (0.86-2.88)
Others	30 (19.7)	124 (29.2)	1.09 (0.72-1.65)
Recent/Past use of Other AD			
Depression	5 (3.3)	18 (4.2)	0.93 (0.34-2.53)
Others	3 (2.0)	4 (0.9)	2.32 (0.52-10.36)

* Analysis was adjusted for hypertension, angina, history of myocardial infarction, atrial fibrillation, heart failure, coagulation/platelet abnormalities, COPD, diabetes mellitus, dementia, concomitant use of anticoagulants, systemic corticosteroids and opioids

Legend: Others= neuropathic pain, headache, anxiety disorders, other or unspecified psychiatric disorders.

This increased risk instead does not appear to be dose-dependent. We did find a linear risk increase with increasing affinity to the serotonin transporter. Past use of both SSRIs and TCAs was associated with ischemic stroke as well.

The results of our study are mostly in line with the very few reports that have previously explored aspects of the association between SSRI use and stroke **[16-18]**. Barbui et al found no difference in the risk of cerebrovascular accidents between SSRI and TCA use (adj. OR: 1.31; 95% CI: 0.87-1.97) but could not differentiate between ischemic and hemorrhagic stroke **[16]**. A Danish study, which analyzed hemorrhagic and ischemic stroke separately, but considered only events leading to hospital admission, found that past use but not current use of SSRIs was associated with an increased risk of ischemic stroke (adj. OR: 1.3; 95% CI: 1.0-1.5 vs. non-use) **[18]**. In this study the analytic strategy could have resulted in a misclassification of the index date and, as a result, a misclassification of the exposure. We did found an association between past use of both SSRIs and TCAs and the risk of ischemic stroke. This finding could point at a potential effect of confounding by indication on our results. Depression itself is a known risk factor of cerebrovascular disorders in young patients **[23-24]**, while the role of depression as predictor of stroke in elderly patients remains very controversial **[24]**. To deal with confounding by indication, Chen et al recently conducted a nested case-control study among patients with depression in a large population-based, U.S. medical claims database **[17]**. In line with our study, the risk of ischemic stroke for current users of SSRIs was significantly higher as compared to non-use (adj. OR: 1.55; 95% CI: 1.00-2.39), while the increase in the risk in current users of TCAs (OR: 1.59; 95%CI: 0.89-2.83) or other antidepressants (OR: 1.33; 95%CI: 0.81-2.17) was not statistically significant. Also, in our study, when we selected exclusively depressed elderly (depression as the indication for treatment), only SSRI use was associated with an increased risk of stroke. TCA or other antidepressants show no association whatsoever. This finding argues against the influence of confounding by indication. Possible mechanisms supporting a potential causal association between exposure to SSRIs and ischemic stroke have been previously hypothesized. Serotoninergic activation secondary to SSRI use can induce a vasoconstrictive effect that is mediated by the 5-hydroxytryptamine-2 (5HT-2) receptor on smooth muscle cells **[25-26]**. A recent review about the cerebrovascular effects of SSRIs pointed out that use of these medications may increase the risk of ischemic stroke by triggering thromboembolism through its vasoconstrictive effect in patients with large cerebral arteries atherosclerosis **[7]**. A significant linear trend between the risk of ischemic stroke and the affinity to the serotonin transporter was evident in our study. Also, paroxetine and sertraline, antidepressants showing the highest affinity to the serotonin transporter **[27]**, seemed to confer a greater risk of ischemic

stroke. These findings support the hypothesis that a serotoninergic activation may play a role in the association between ischemic stroke and SSRI use. The effect of SSRIs was predominantly observed within the first six months of therapy, which could point at an immediate effect of SSRIs and depletion of susceptibles during continued use.

Strength and limitations

The strength of this study is the availability of information on many confounders and details on antidepressant use. Moreover, we were able to review the medical records of all potential cases to identify the real incident, first-ever ischemic strokes. However, several limitations warrant caution. As in any observational study, selection bias, information bias and residual confounding should be considered as alternative explanations for the study finding. Selection bias was minimal as all data were obtained from prospectively collected medical records that are maintained for patient care purposes. To minimize the potential effect of information bias by misclassification of the outcome a two-step case validation was undertaken and, for the same purpose, TIA itself was not considered as a study endpoint, due to high probability of misclassification for this event. However, if a stroke was preceded by a TIA occurring less than one month before, the case was retained and the onset of TIA was taken as the index date.

To exclude all patients with history of cerebrovascular events at the study entry, we required at least one year of data registered in the database as inclusion criteria. Nevertheless, we could have missed information on prior cerebrovascular events without sequelae occurring long time before the study entry. Misclassification of exposure cannot be excluded since we used outpatient prescription data and had no information about whether the drug prescriptions were actually filled and taken. Non-adherence to antidepressant medication may be a relevant issue particularly in older patients, although a U.K. study reported that the level of adherence did not differ across various antidepressant types in community dwelling elderly **[28]**. Not filling of prescriptions or non-adherence most likely results in non-differential misclassification of the exposure, in which case our study underestimates the actual risk. Moreover, we may have missed specialist prescriptions of antidepressants. Many risk factors for ischemic stroke were considered in our study. Despite this, residual confounding due to unmeasured confounders or severity of (underlying) disease cannot be excluded. It is however unlikely that highly prevalent and strong risk factors were missed in our study. Finally, since the study considered only community dwelling elderly, the findings may not be generalized to elderly inpatients or those living in nursing homes. Likewise, exclusion of patients with prior TIA

or stroke prevents the generalizability of the results to elderly patients with a prior history of cerebrovascular events.

In summary, our study shows that among elderly people living in the community current use of SSRI may increase the risk of ischemic stroke, especially within the first 6 months of treatment. Further studies employing larger samples are needed to confirm these results and to conclusively establish the effect of the affinity to the serotonin transporter. Meanwhile, it seems advisable that SSRI treatment is carefully tailored and that a close monitoring is established in the first few weeks of treatment.

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