

Supplementary Online Content

Renoux C, Vahey S, Dell'Aniello S, Boivin J-F. Association of selective serotonin reuptake inhibitors with the risk for spontaneous intracranial hemorrhage. *JAMA Neurol*. Published online December 5, 2016. doi:10.1001/jamaneurol.2016.4529

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. List of Antidepressants for Cohort Entry

SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.

TCAs: amitriptyline, amoxapine, clomipramine, desipramine, dosulepin, doxepin, imipramine, iprindole, lofepramine, nortriptyline, trimipramine, maprotiline, mianserin, protriptyline.

Others (third generation antidepressants): agomelatine, bupropion, duloxetine, mirtazapine, reboxetine, venlafaxine, nefazodone.

eMethods 2. List of Antidepressants According to the Degree of Serotonin Reuptake Inhibition

Strong: clomipramine, duloxetine, fluoxetine, paroxetine, sertraline.

Intermediate: amitriptyline, citalopram, escitalopram, fluvoxamine, imipramine, venlafaxine.

Weak: agomelatine, amoxapine, desipramine, dosulepin, doxepin, isocarboxazide, iprindole, lofepramine, maprotiline, mianserin, mirtazapine, moclobemide, nefazodone, nortriptyline, reboxetine, phenelzine, protriptyline, tranylcypromine, trimipramine, viloxazine.

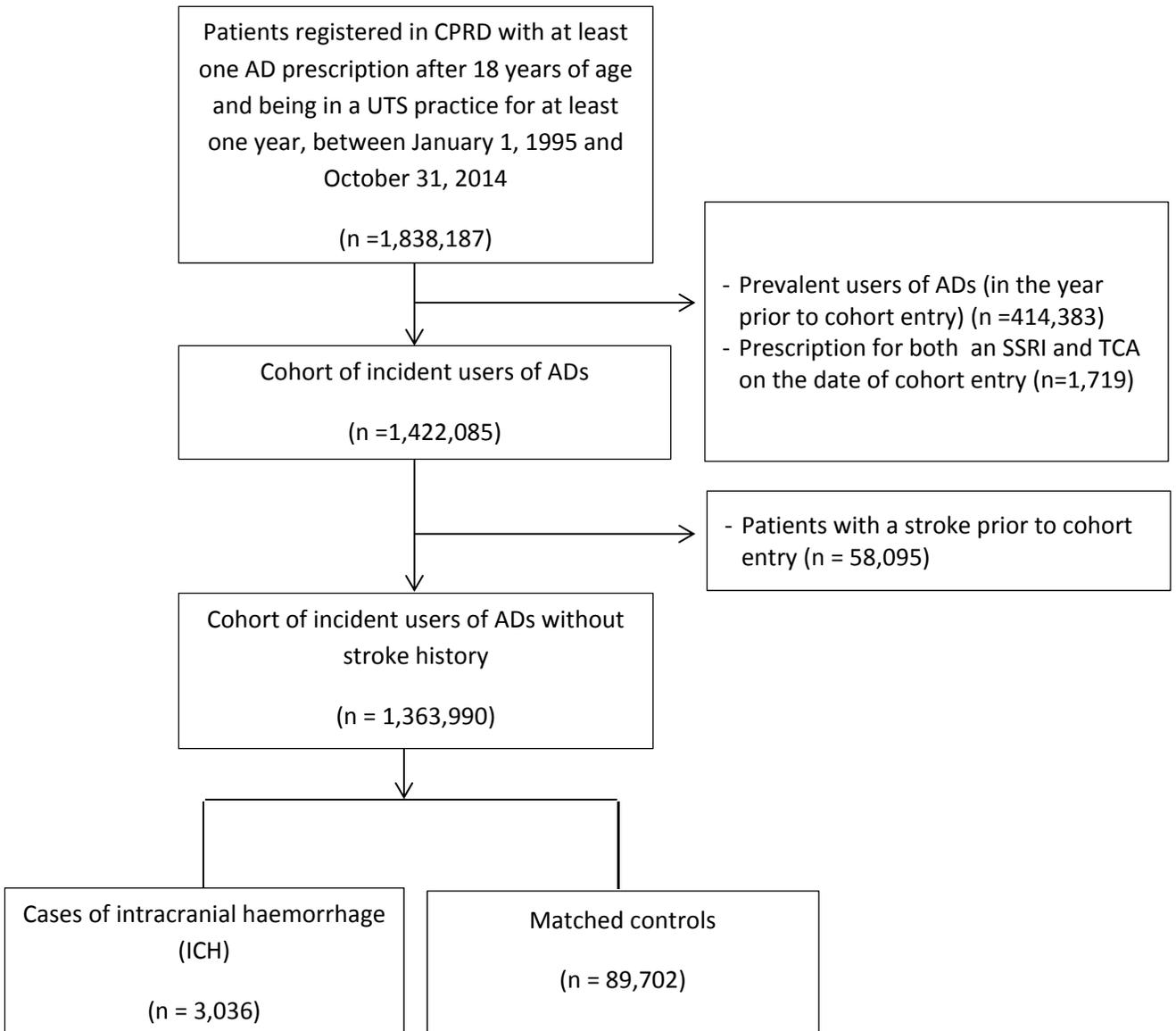
eMethods 3. Potential Confounding Variables Included in Multivariate Models

Potential confounding variables included vascular risk factors and comorbidities such as obesity (body mass index ≥ 30), smoking status, alcohol abuse, hyperlipidemia, hypertension, diabetes, transient ischemic attack, atrial fibrillation, coronary artery disease, congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, renal failure, depression, neuropathic pain, cancer, liver disease, disorders of hemostasis, cerebral vascular malformation, history of bleeding, and one measure of health utilisation (number of physician visits). Missing data were expected for body mass index and smoking so that a separate category was created to classify this missing information. All comorbidities were measured in the year before index date and identified using all relevant Read codes except diabetes, hyperlipidemia, and hypertension that were identified with diagnostic codes or use of antidiabetics, statins, and antihypertensive medications (beta-blockers, thiazide diuretics, calcium-channel blockers, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors), respectively. We also measured use of the following drugs in the year before index date: anticoagulants, antiplatelets, non-steroidal anti-inflammatory drugs (NSAIDs), and antipsychotics.

eMethods 4. Sensitivity Analyses

We performed several sensitivity analyses to assess the robustness of our results. To explore the effect of potential misclassification of current exposure on the estimated RRs, the definition of current use was changed to 15 days and 60 days prior to the index date. To assess the potential for residual confounding, we repeated the primary analyses (SSRIs vs TCAs and then strong inhibitors vs weak) while including high dimensional propensity scores (hdPS) deciles in the models along with all other covariables. Briefly, the hdPS were estimated for incident users of SSRIs and TCAs (or strong and weak inhibitors) using information up to and including the 365 days before cohort entry. The cohorts were trimmed by excluding 5% of patients (or more if needed) at either end of the distribution of the hdPS to ensure an overlap in the distribution of covariates for SSRIs and TCAs users (or strong and weak inhibitors). Finally, to assess the potential adjustment for covariates in the causal pathway, we repeated the primary analysis while adjusting for covariates measured 6 months to 18 months before the index date.

eFigure. Flowchart of Incident Antidepressant (AD) Cohort Definition and Case-Control Selection



eTable 1. Crude and Adjusted Rate Ratios of Intracerebral Hemorrhage Associated With Current Use of SSRIs Relative to TCAs				
Variable	Cases n (%)	Controls* n (%)	Crude RR	Adjusted RR† (95% CI)
Current use				
SSRIs	238 (17.2)	6310 (15.5)	1.12	1.07 (0.87-1.32)
TCAs	166 (12.0)	4951 (12.2)	1.00	1.00 (Reference)
Duration of use (until index)				
≤ 30 days				
SSRIs	36 (2.6)	839 (2.1)	1.39	1.34 (0.80 – 2.25)
TCAs	28 (2.0)	923 (2.3)	1.00	1.00 (Reference)
31-90 days				
SSRIs	42 (3.0)	1191 (2.9)	1.45	1.42 (0.88 – 2.29)
TCAs	32 (2.3)	1304 (3.2)	1.00	1.00 (Reference)
> 90 days				
SSRIs	70 (5.1)	2315 (5.7)	0.90	0.89 (0.62 – 1.29)
TCAs	56 (4.1)	1674 (4.1)	1.00	1.00 (Reference)
RR, rate ratio; CI, confidence interval.				
Current users of other antidepressants in the year prior to index date, multiple users, non users, and past users were also included in the model for proper estimation of treatment effect.				
*Cases and controls were matched on age, sex, calendar time, and duration of follow-up.				
†Adjusted for variables listed in table 1.				

eTable 2. Crude and Adjusted Rate Ratios of Subarachnoid Hemorrhage Associated With Current Use of SSRIs Relative to TCAs				
Variable	Cases n (%)	Controls* n (%)	Crude RR	Adjusted RR† (95% CI)
Current use				
SSRIs	198 (19.0)	5145 (16.5)	1.04	1.10 (0.85-1.42)
TCAs	109 (10.5)	2957 (9.5)	1.00	1.00 (Reference)
Duration of use (until index)				
≤ 30 days				
SSRIs	33 (3.2)	721 (2.3)	1.59	2.14 (1.13 – 4.06)
TCAs	16 (1.5)	548 (1.8)	1.00	1.00 (Reference)
31-90 days				
SSRIs	36 (3.4)	1147 (3.7)	0.94	0.97 (0.56 – 1.68)
TCAs	24 (2.3)	725 (2.3)	1.00	1.00 (Reference)
> 90 days				
SSRIs	67 (6.4)	1727 (5.6)	1.28	1.38 (0.87 – 2.18)
TCAs	28 (2.7)	921 (3.0)	1.00	1.00 (Reference)
RR, rate ratio; CI, confidence interval.				
Current users of other antidepressants in the year prior to index date, multiple users, non users, and past users were also included in the model for proper estimation of treatment effect.				
*Cases and controls were matched on age, sex, calendar time, and duration of follow-up.				
†Adjusted for variables listed in table 1.				

eTable 3. Crude and Adjusted Rate Ratios of Intracranial Extracerebral Hemorrhage Associated With Current Use of SSRIs Relative to TCAs				
Variable	Cases n (%)	Controls* n (%)	Crude RR	Adjusted RR† (95% CI)
Current use				
SSRIs	152 (24.8)	2886 (16.1)	1.43	1.38 (1.03-1.83)
TCAs	89 (14.5)	2473 (13.8)	1.00	1.00 (Reference)
Duration of use (until index)				
≤ 30 days				
SSRIs	29 (4.7)	552 (3.1)	1.30	1.25 (0.71 – 2.20)
TCAs	27 (4.4)	685 (3.8)	1.00	1.00 (Reference)
31-90 days				
SSRIs	29 (4.7)	564 (3.2)	1.52	1.43 (0.80 – 2.55)
TCAs	24 (3.9)	691 (3.9)	1.00	1.00 (Reference)
> 90 days				
SSRIs	49 (8.0)	1039 (5.8)	1.82	1.89 (1.09 – 3.29)
TCAs	19 (3.1)	715 (4.0)	1.00	1.00 (Reference)
RR, rate ratio; CI, confidence interval.				
Current users of other antidepressants in the year prior to index date, multiple users, non users, and past users were also included in the model for proper estimation of treatment effect.				
*Cases and controls were matched on age, sex, calendar time, and duration of follow-up.				
†Adjusted for variables listed in table 1.				

eTable 4. Crude and Adjusted Rate Ratios of Intracerebral Hemorrhage Associated With Current Use of Antidepressants With Strong Degree of Inhibition of Serotonin Reuptake Relative to Weak				
Variable	Cases n (%)	Controls* n (%)	Crude RR	Adjusted RR† (95% CI)
Current use				
Strong	125 (9.1)	3073 (7.6)	1.13	1.13 (0.83 – 1.54)
Intermediate	267 (19.4)	7624 (18.7)	0.99	1.00 (0.75 – 1.31)
Weak	68 (4.9)	1896 (4.7)	1.00	1.00 (Reference)
Duration of use (until index)				
≤ 30 days				
Strong	14 (1.0)	406 (1.0)	1.38	1.26 (0.46 – 3.40)
Weak	6 (0.4)	249 (0.6)	1.00	1.00 (Reference)
31-90 days				
Strong	22 (1.6)	520 (1.3)	1.12	1.14 (0.55 – 2.39)
Weak	12 (0.9)	303 (0.7)	1.00	1.00 (Reference)
> 90 days				
Strong	28 (2.0)	934 (2.3)	1.15	1.09 (0.56 – 2.14)
Weak	13 (0.9)	502 (1.2)	1.00	1.00 (Reference)
RR, rate ratio; CI, confidence interval.				
Current multiple users, non users, and past users in the year prior to index date were also included in the model for proper estimation of treatment effect.				
*Cases and controls were matched on age, sex, calendar time, and duration of follow-up.				
†Adjusted for variables listed in table 1.				

eTable 5. Crude and Adjusted Rate Ratios of Subarachnoid Hemorrhage Associated With Current Use of Antidepressants With Strong Degree of Inhibition of Serotonin Reuptake Relative to Weak				
Variable	Cases n (%)	Controls* n (%)	Crude RR	Adjusted RR† (95% CI)
Current use				
Strong	118 (11.3)	2838 (9.1)	1.29	1.31 (0.90 – 1.91)
Intermediate	189 (18.1)	5027 (16.2)	1.16	1.14 (0.80 – 1.64)
Weak	38 (3.7)	1176 (3.8)	1.00	1.00 (Reference)
Duration of use (until index)				
≤ 30 days				
Strong	17 (1.6)	377 (1.2)	3.26	3.65 (0.82 – 16.14)
Weak	S‡	145 (0.5)	1.00	1.00 (Reference)
31-90 days				
Strong	15 (1.4)	580 (1.9)	1.07	1.01 (0.35 – 2.89)
Weak	S‡	206 (0.7)	1.00	1.00 (Reference)
> 90 days				
Strong	32 (3.1)	783 (2.5)	1.05	1.02 (0.48 – 2.18)
Weak	9 (0.9)	231 (0.7)	1.00	1.00 (Reference)
RR, rate ratio; CI, confidence interval.				
Current multiple users, non users, and past users in the year prior to index date were also included in the model for proper estimation of treatment effect.				
*Cases and controls were matched on age, sex, calendar time, and duration of follow-up.				
†Adjusted for variables listed in table 1.				
‡ Small cells (counts <=5) were suppressed due to privacy restrictions according to CPRD policy				

eTable 6. Crude and Adjusted Rate Ratios of Intracranial Extracerebral Hemorrhage Associated With Current Use of Antidepressants With Strong Degree of Inhibition of Serotonin Reuptake Relative to Weak				
Variable	Cases n (%)	Controls* n (%)	Crude RR	Adjusted RR† (95% CI)
Current use				
Strong	59 (9.6)	1246 (7.0)	1.36	1.33 (0.84 – 2.11)
Intermediate	181 (29.5)	3936 (22.0)	1.36	1.36 (0.90 – 2.05)
Weak	29 (4.7)	840 (4.7)	1.00	1.00 (Reference)
Duration of use (until index)				
≤ 30 days				
Strong	14 (2.3)	200 (1.1)	1.62	1.51 (0.55 – 4.13)
Weak	6 (1.0)	138 (0.8)	1.00	1.00 (Reference)
31-90 days				
Strong	8 (1.3)	228 (1.3)	1.89	1.65 (0.42 – 6.47)
Weak	S‡	161 (0.9)	1.00	1.00 (Reference)
> 90 days				
Strong	16 (2.6)	353 (2.0)	1.14	1.04 (0.42 – 2.59)
Weak	7 (1.1)	184 (1.0)	1.00	1.00 (Reference)
RR, rate ratio; CI, confidence interval.				
Current multiple users, non users, and past users in the year prior to index date were also included in the model for proper estimation of treatment effect.				
*Cases and controls were matched on age, sex, calendar time, and duration of follow-up.				
†Adjusted for variables listed in table 1.				
‡ Small cells (counts ≤5) were suppressed due to privacy restrictions according to CPRD policy by CPRD				