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ORIGINAL ARTICLE

Antidepressant drug use and subdural hematoma risk

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Abstract

Background: Selective serotonin reuptake inhibitors (SSRIs) use may be associated with development of subdural hematoma (SDH).

Objectives: To estimate SDH risk associated with antidepressant use, including when combined with antithrombotics, or nonsteroidal anti-inflammatory drugs (NSAIDs).

Patients/Methods: We performed this case-control study based on Danish registries. We included 10 885 incident cases of SDH and 435 379 matched general population controls. We calculated odds ratios (95% confidence interval) adjusted for comorbidity, co-medication, education level, and income (aOR).

Results: We found that current use of SSRIs (aOR1.32 [1.25-1.38]) and non-SSRIs (aOR 1.19 [1.13-1.26]) was associated with a higher SDH risk, compared with non-use of antidepressants. Risks were higher with short duration of current use (eg, <1 month of current use: aOR 2.55 [2.07-3.15] for SSRI, 1.88 [1.46-2.41] for non-SSRIs; >3 years of current use: 1.04 [0.93-1.17] for SSRI and 1.12 [0.98-1.28] for non-SSRIs). Combined use of antidepressants with either antithrombotics or NSAIDs yielded similar ORs to those observed for single use of antithrombotics or NSAIDs. Stronger associations were observed for antidepressants combined with both vitamin K antagonists (VKAs) and NSAIDs (SSRI, VKA, & NSAID: aOR 5.51 [2.70-11-22]; non-SSRI, VKA, & NSAID: 6.81 [2.37-19-60]).

Conclusions: Antidepressant use was associated with higher risk of SDH that seemed largely restricted to first year of treatment. In absolute terms this risk is judged to be small, given the low SDH incidence rate. With one possible exception (triple use of antidepressants, NSAIDs, and VKAs), risk estimates of SDH for combined regimens of antidepressants with antithrombotics or NSAIDs provided little evidence of interactions.

KEYWORDS

anticoagulants, antidepressants, antithrombotics, selective serotonin reuptake inhibitor, subdural hematoma

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1 | INTRODUCTION

The incidence of subdural hematoma (SDH) has been increasing since the 1980s.[1-3] In Denmark, a recently observed marked increase in SDH incidence can be partially explained by increased use of antithrombotic drugs, especially warfarin use among older patients.[3] Whether other commonly used drugs with effects on hemostasis increase the risk of SDH is less clear. Selective serotonin reuptake inhibitors (SSRIs) are frequently used to treat depression and other psychiatric disorders[4,5] and have been suspected of increasing the risk of bleeds through mechanisms affecting platelet function.[6,7] Several studies of SSRI use as a risk factor for severe bleeds have been published,[8] including studies of intracranial hemorrhage.[9-13] However, in most studies, different intracranial bleed events have been pooled, a practice criticized by some, as it may conceal effects particular to one type of bleed.[14] Current knowledge regarding the specific risk of SDH in association with antidepressant use is limited.[13,15] Importantly, the risk factor profile of SDH differs from other intracranial bleeds, as it is more frequently associated with trauma.[16,17] As some antidepressants increase the risk of falls,[18] and thereby trauma risk, it is conceivable that use of SSRIs increases SDH risk to levels not explained by their antiplatelet effect alone. Previous research supports that pharmacodynamic drug-drug interactions are of importance in the context of upper gastrointestinal bleeds,[19] but the literature specifically addressing the risk of intracranial hemorrhage in patients receiving such concomitant treatments is scant.[13,20-23] The purpose of this study was to provide estimates of the risk of SDH associated with SSRI use and to explore potential interactions due to concomitant use of this class of drugs, antithrombotic drugs, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Essentials

- Selective serotonin reuptake inhibitors may be linked to subdural hematoma risk.
- SDH risk in users of antidepressants was studied in a nationwide case-control study.
- Higher SDH risk was restricted to first year of SSRIs and non-SSRI antidepressant treatment.
- There was little evidence of interaction for combined use of SSRIs with antithrombotics or NSAIDs.

2 | MATERIALS AND METHODS

This study was designed as a nationwide case-control study based on information from population-based Danish registries. Cases were persons with incident SDH and controls were selected randomly from the Danish source population, as described previously.[3] Subjects' exposure to drugs was assessed through prescription data.

2.1 | Setting and data sources

In Denmark (population 5.7 million) health care is tax funded and free of charge and expenses toward the vast majority of medications (including all antidepressants) are wholly or partially subsidized. For this study data were obtained from the following nationwide registries: Danish National Patient Register (Patient Registry),[24] the Danish National Prescription Registry (Prescription Registry),[25] registries on education and income available at Statistics Denmark,[26,27] and the Danish Civil Registration System.[28] The Patient Registry holds information on all hospital contacts in Denmark (inpatient data since 1977, outpatient data since 1995) including discharge diagnoses coded according to the International Classification of Diseases (ICD) (version 8 1977-1994, version 10 since 1994). The Prescription Registry (operational since 1995) records data on prescriptions presented at community pharmacies anywhere in the country. Information recorded includes the date each prescription was filled and a full description of the dispensed product. The indication for use and the dose prescribed by the physician are, however, not recorded. The Danish Civil Registration System holds information on the migration and vital status of all Danish residents and is continuously updated. Data sources were linked using the unique and permanent civil registration number assigned to all residents of Denmark.

2.2 | Cases

Cases were patients aged 20-89 years with a first-ever primary diagnosis code of SDH in the period 2000-2016 according to Patient Registry data (discharge, outpatient, procedure, and medication codes appear in Tables S1 and S2 in supporting information).[24] The diagnosis code used in this study (S065 according to ICD version 10), in spite of being labelled "traumatic SDH" has been shown to capture both traumatic and non-traumatic cases of SDH in Denmark with a positive predictive value (PPV) of 96%.[29] A corresponding ICD-10 code for non-traumatic SDH (I620) was not used in this study due to its low validity (PPV of 62%) and relatively uncommon use (6% of cases with a discharge diagnosis of SDH) in a Danish setting.[29] For each case, the date of the first hospital contact under a primary diagnosis of SDH was identified (index date). Cases with SDH diagnoses recorded before 2000 and individuals with residency in Denmark for less than 10 consecutive years before the index date were excluded.

2.3 | Controls

Using risk set sampling[30] and applying the same eligibility and exclusion criteria as for cases, 40 birth year- and sex-matched controls were sampled from the Danish population for each case via the Danish Civil Registration System.[28] Controls were assigned an index date identical to their corresponding case. Cases could be selected as controls prior to their index date. By this design, the generated

odds ratios (ORs) are unbiased estimates of the incidence rate ratio that would have emerged from a cohort study based on the same source population.[30]

2.4 | Assessment of antidepressant drug exposure and potential confounders

Data on filled prescriptions were extracted from the Prescription Registry.[25] Based on prescriptions dispensed during the period from 1995 up to 1 day prior to the index date, study subjects were classified with regard to use of SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram) or non-SSRIs (tricyclic antidepressants [TCA; imipramine, clomipramine, amitriptyline, nortriptyline, maprotiline, trimipramine, lofepramine, doxepin, dosulepine, desipramine, amoxapine], serotonin and noradrenalin reuptake inhibitors [SNRI, e.g., venlafaxine, duloxetine], and other antidepressants [moclobemide, mianserin, nefazodone, mirtazapine, bupropion, reboxetine, agomelatine, vortioxetine]), based on the drug's inhibitory action on the serotonin reuptake mechanism. Non-use of antidepressants was used as reference group (except when comparing treatments combined with antithrombotics or NSAIDs; see below). To calculate length of supply, each prescription was set to last the number of days that corresponded to the number of pills dispensed divided by two for amitriptyline, imipramine, moclobemide, doxepin, maprotiline, reboxetine; divided by three for clomipramine; and by one for all other antidepressants, according to prevailing patterns of use of these drugs in Denmark[31] (see Table S2 for tablet strengths of antidepressants). To this we added a grace period of 60 days (to allow some degree of noncompliance or irregular dispensing) to all prescriptions prior to index date. A treatment episode lasted for as long as consecutive prescriptions were presented with no gap, ie, overlapped within the time window defined by the length of supply of the preceding prescription including the grace period. Based on the most recent treatment episode prior to the index date, we divided exposure into current use (supply with grace period extended up to cover index date), recent use (supply with grace period ended 1-90 days before index date), past use (supply with grace period ended 91-365 days), and distant use (supply with grace period ended >365 days before index date). Current use was further subdivided by the duration of the current treatment episode: <1 month, ≥1 to <3 months, ≥3 to <12 months, ≥1 to <3 years, ≥3 years. The assessment of drug exposure is further detailed in the Data S1 in supporting information.

As recently reported, antithrombotic drugs, particularly vitamin K antagonists (VKAs), are associated with a higher risk of SDH, compared with non-users of these drugs.[3] According to previous studies, the risk of intracranial bleeds in users of SSRIs may be increased further if these drugs are combined with antithrombotic drugs,[13] and for gastrointestinal bleeds, if combined with NSAIDs.[19] Therefore, within each group of antidepressants (ie, SSRI versus non-SSRI), we explored the risk of SDH associated with current use of antidepressants alone, concurrent use of antidepressants and antithrombotic drugs (classified into low-dose aspirin, clopidogrel, VKA, and direct oral anticoagulants [DOAC]), and concurrent use of antidepressants and NSAIDs, see Data S1. Non-use of any of the three drug groups in the year prior was used as reference group in this analysis.

Register data from the continuously updated Danish Civil Registration System[28] were used to ascertain 30-day fatality rates for cases.

2.5 | Regional data

The Patient Registry does not routinely collect data to permit classification of SDH into acute versus subacute or chronic. Acute SDH is more frequently the result of severe trauma and is clinically apparent within 72 hours. Chronic SDH, on the other hand, is mainly associated with modest trauma, exemplified by falls among elderly patients, and may take weeks to months to manifest clinically.[16] As outlined previously,[3] this information was available to us in a subsample (Data S1).

2.6 | Statistical analyses

Conditional logistic regression was used to compute adjusted ORs and 95% confidence intervals (CIs) for SDH associated with use of antidepressants. National register data recorded up to 1 day before the index date were used to classify individuals with regard to a number of disorders and use of drugs that were potential confounders (also see Table S1). Based on this information, the analyses were adjusted for (a) chronic obstructive pulmonary disease (COPD, as a marker of smoking), disorders or drug use indicative of high alcohol consumption, hypertension, chronic hepatic diseases, chronic renal failure, diabetes, atrial fibrillation, myocardial infarction (MI), angina, unstable angina, peripheral artery disease, coagulopathy, epilepsy, dementia, stroke; (b) use of NSAIDs, low-dose aspirin, clopidogrel, "other" adenosine diphosphate (ADP) receptor antagonists (ticagrelor, prasugrel), DOAC, VKA, statins, hypnotics and sedatives (including benzodiazepines), postmenopausal hormone replacement therapy (HRT), or oral corticosteroid drugs; and (c) highest education level attained and income level as proxies for socioeconomic status. Regarding additional adjustments specific to analyses pertaining to regiments involving use of antithrombotics, see Data S1.

Differences in strength of association between subgroups or exposures were evaluated using the 2-sample Wald test.

A number of secondary analyses and sensitivity analyses were performed. These are described in the Data S1.

Probability results of 2-tailed tests less than .05 were considered statistically significant. All analyses were performed using Stata SE 15 (StataCorp). The study was approved by the Danish Data Protection Agency and the Danish Health Data Board. According to Danish law, approval from an ethics board is not required for register studies.[27]

3 | RESULTS

A total of 10 885 incident cases of SDH (7080 men [65%]) were identified in Denmark during the 17-year study period with a mean age of

69.5 years (median 72 years [interquartile range (IQR), 61-81 years) and 22.2% were current users of antidepressants (15.7% on SSRIs and 9.2% on non-SSRIs). The 30-day mortality of patients with SDH was 15.9%.

Compared with 435 379 matched controls from the general population, cases had higher levels of comorbidity for all disorders included in the present analyses, which was particularly marked for diagnoses indicative of high alcohol consumption (18.2% versus 4.7%), stroke (17.5 versus 7.1), atrial fibrillation (17.9 versus 8.5), epilepsy (6.9 versus 1.8), dementia (6.1 versus 2.8), chronic renal failure (3.1 versus 1.6), chronic hepatic failure (2.7 versus 1.0), and coagulopathy (0.6 versus 0.2) (Table 1).

Drug use was more prevalent among cases compared with controls for the drugs included in the analyses (Table 1). A higher risk of SDH was associated with current use of SSRI (OR 1.60, CI: 1.50-1.71) and current use of non-SSRIs (OR 1.35, CI: 1.25-1.47), compared with non-use of any antidepressant (Table 2). For both groups of antidepressants, risk of SDH was inversely related to duration of current use. For less than 1 month of current use of antidepressants, OR for SDH risk was 2.55 (CI: 2.07-3.15) for SSRI and 1.88 (CI: 1.46-2.41) for non-SSRIs; the corresponding risks for >3 years of current use of antidepressants were 1.04 (CI: 0.93-1.17) and 1.12 (CI: 0.98-1.28), respectively. Analyses of dose of antidepressants returned similar results for high versus low-medium dose of SSRI (OR 1.37, CI: 1.24-1.51 versus OR 1.67, CI: 1.55-1.81), and non-SSRIs (OR 1.38, CI: 1.20-1.58 versus OR 1.33, CI: 1.21-1.45) (Table 3). Limiting analyses to patients that had only used antidepressants from a single group (ie, exclusively SSRI or exclusively non-SSRI) had little impact on the results (Table 4). Likewise, analyses of first-time use of SSRI or non-SSRI returned results similar to the main analyses (Table S3 in supporting information).

In analyses of the risk of SDH associated with single or combined use of antidepressants, antithrombotics, or NSAIDs, we used as reference non-use of any of the three drug groups in the year prior (as opposed to a reference group of non-use of antidepressants only in the main analyses). In these analyses single use of SSRI or non-SSRI was associated with a risk of SDH of 1.68 (CI: 1.50-1.87) and 1.26 (CI: 1.09-1.45), respectively. Risk estimates of SDH varied across regimens (Figure 1, Table S4 in supporting information). Combined use with either antithrombotics or NSAIDs yielded similar ORs to those of the single drug regimen associated with the highest risk. For instance, SSRI combined with DOAC returned a risk of SDH of OR 0.84, CI: 0.42-1.68, compared with SSRI combined with VKA (OR 2.91, CI: 2.15-3.94), results that were similar to single use of DOAC (OR 1.20, CI: 0.87-1.65), or single use of VKA (OR 3.01, CI: 2.62-3.46). A similar pattern was observed for non-SSRIs (combined with DOAC: 0.56, CI: 0.21-1.48; combined with VKA: 3.79, CI: 2.66-5.42). The highest risk of SDH was observed in patients receiving combined therapy of antidepressants with VKA and NSAIDs (combined with SSRI: OR 5.51, CI: 2.70-11.22; combined with non-SSRI: OR 6.81, CI: 2.37-19.60). Of note, dual treatment with VKA and NSAIDs was associated with risk of SDH (OR 3.04, CI: 2.17-4.28) that did not materially differ from the risk associated with single use of VKA (OR 3.01, CI: 2.62-3.46). Limited data did not permit analyses of regimens of combined DOAC, NSAID, and antidepressant treatment or of dual treatment of DOAC combined with NSAIDs.

3.1 | Secondary and sensitivity analyses

We performed a number of additional analyses that are outlined in Tables S5-S15 in supporting information and commented on in the Data S1. Of note, secondary analyses of the risk of SDH for specific antidepressant drugs varied from OR of 1.04 (CI: 0.84-1.29) for mianzerine to OR 1.95 (CI 1.52-2.50) for fluoxetine (Table S5).

3.2 | Regional data

In analyses of regional data limited to cases in which the diagnosis and type of SDH had been verified as part of a validation study,[29] risks of SDH by recency and duration of SSRI and non-SSRI use provided results similar to the main analyses, albeit with slightly higher estimates (eg, current use of SSRI: OR 2.04, CI 1.65-2.54; current use of non-SSRIs: OR 1.67, CI: 1.26-2.21) (Table S14). Analyses by type of SDH revealed higher ORs for subacute/chronic SDH compared with acute SDH (eg, for SSRI, OR 2.3, CI: 1.7-3.0 versus OR 1.7, CI: 1.2-2.4) (Table S15).

4 | DISCUSSION

In this nationwide case-control study including 10 885 patients with SDH, use of antidepressants was associated with a small to moderate risk of SDH that was slightly higher for SSRI than non-SSRI treatment. Several additional points are worth emphasizing. First, the highest period of excess risk of SDH was during the first year of antidepressant treatment (short term), decreasing thereafter and close to null after 3 years of treatment (long term). In a clinical scenario, this means that SDH is unlikely to be related to antidepressant use in a patient on long-term treatment. Second, as SDH is rare (19 per 100 000 person-years in Denmark in 2015),[3] the observed excess risk associated with short-term antidepressant treatment is in absolute terms small. Third, no dose-response relationship was found with SSRI or non-SSRIs. Fourth, this study provides clinically reassuring information for use of antidepressants combined with either antithrombotic drugs or NSAIDs, a type of therapeutic regimen that is relatively common among older individuals, particularly among vulnerable patients, eg, stroke survivors. A possible exception, which should be interpreted with caution due to sample size limitations, was the finding of increased risk of SDH in those taking a triple medication regimen comprising antidepressants, VKAs, and NSAIDs.

Intracranial hemorrhage is a complex entity, as it comprises several types of bleeds (mainly SDH, intracerebral hemorrhage [ICH], or subarachnoid hemorrhage [SAH]) that differ to varying degrees with regard to etiology and prognosis. For instance, most cases of SDH are considered related to often relatively mild trauma.[16,17,29] Previous studies on risks associated with antidepressant use have focused on ICH, or outcomes pooled as intracranial hemorrhage, or hemorrhagic

TABLE 1 Characteristics of cases with incident subdural hematoma and their general population controls, Denmark 2000-2016

	Cases (n = 10 885)	Controls (n = 435 379)
Sex		
Men	7080 (65.0)	283 200 (65.0)
Women	3805 (35.0)	152 179 (35.0)
Age, median (IQR), years	72 (61 - 81)	72 (61 - 81)
Age, categories, years		
20-64	3357 (30.8)	134 259 (30.8)
65-74	2653 (24.4)	106 120 (24.4)
75-89	4875 (44.8)	195 000 (44.8)
30-day case fatality rate	1729 (15.9)	NA
Admitted to neurosurgery department	7911 (72.7)	NA
Surgical procedure performed		
Burr hole	4217 (38.7)	NA
Craniotomy	1589 (14.6)	NA
None	5079 (46.7)	NA
Index year		
2000-2006	4156 (38.2)	166 228 (38.2)
2007-2016	6729 (61.8)	269 151 (61.8)
Medications		
Antidepressants, current use		
Selective serotonin reuptake inhibitors (SSRIs)	1704 (15.7)	29 287 (6.7)
Fluoxetine	77 (0.7)	1200 (0.3)
Citalopram	1095 (10.1)	18 779 (4.3)
Paroxetine	98 (0.9)	1458 (0.3)
Sertraline	215 (2.0)	4355 (1.0)
Fluvoxamine	(n < 5)	50 (0.0)
Escitalopram	253 (2.3)	3793 (0.9)
Non-SSRIs	1006 (9.2)	20 123 (4.6)
Tricyclic antidepressants	349 (3.2)	6585 (1.5)
Various antidepressants	711 (6.5)	14 210 (3.3)
Antithrombotic drugs, current use		
Low-dose aspirin	2859 (26.3)	96 273 (22.1)
Clopidogrel	621 (5.7)	10 943 (2.5)
Other ADP-receptor blockers	32 (0.3)	535 (0.1)
Vitamin K-antagonists	1580 (14.5)	21 988 (5.1)
Direct oral anticoagulants	169 (1.6)	3963 (0.9)
Non-aspirin NSAIDs, current use		
Any NSAID	1332 (12.2)	37 105 (8.5)
Any of four NSAIDs listed below	1153 (10.6)	31 702 (7.3)
Diclofenac	214 (2.0)	6287 (1.4)
Etodolac	76 (0.7)	2818 (0.6)
Ibuprofen	836 (7.7)	21 619 (5.0)
Naproxen	54 (0.5)	1625 (0.4)
Hypnotics and sedatives[a]	3014 (27.7)	70 831 (16.3)
Antipsychotic drugs[a]	796 (7.3)	13 724 (3.2)
Statins[a]	2886 (26.5)	98 710 (22.7)
Oral steroids[a]	731 (6.7)	27 725 (6.4)
Hormone replacement therapy[a]	654 (17.2)	24 480 (16.1)
Comorbidity		
Hypertension	6073 (55.8)	207 028 (47.6)
Stroke	1902 (17.5)	30 942 (7.1)
Atrial fibrillation	1947 (17.9)	36 923 (8.5)
Epilepsy	752 (6.9)	8031 (1.8)
Dementia	664 (6.1)	12 190 (2.8)
COPD	863 (7.9)	27 720 (6.4)
Diabetes	1442 (13.2)	41 879 (9.6)
Chronic renal insufficiency	339 (3.1)	7030 (1.6)
Chronic hepatic disease	297 (2.7)	4505 (1.0)
Coagulopathy	69 (0.6)	940 (0.2)
High alcohol intake[b]	1980 (18.2)	20 577 (4.7)
Myocardial infarct	964 (8.9)	30 616 (7.0)
Unstable angina	388 (3.6)	11 017 (2.5)
Other angina	1465 (13.5)	46 398 (10.7)
Peripheral artery disease	294 (2.7)	9354 (2.1)
Schooling, years		
7-10	4424 (40.6)	167 168 (38.4)
11-12	3857 (35.4)	158 678 (36.4)
13+	1793 (16.5)	78 655 (18.1)
Missing values	811 (7.5)	30 878 (7.1)
Income, tertiles		
Low	5334 (49.0)	145 124 (33.3)
Middle	3103 (28.5)	145 129 (33.3)
High	2448 (22.5)	145 126 (33.3)

Note: Numbers (%) unless otherwise specified.
[a]Use of drug between 1 year and 1 day before index date.
[b]Disorders indicative of high alcohol use or use of medication for alcohol dependence syndrome.

stroke (ICH and SAH).[9,32] An analysis focused exclusively on the risk of SDH associated with antidepressant use has not previously been published. Other factors further complicate comparisons with previous results, as emphasized in a recent systematic review of 12 studies,[12,13,15,33-41] which reported substantial heterogeneity with regard to design.[32] However, two previous studies[13,39] were noted for their large size and lack of major methodological limitations.[32] One study employed non-use of antidepressants as the reference group and reported higher risks of intracranial hemorrhage associated with current

TABLE 2 Use of antidepressants and risk of subdural hematoma in Denmark, 2000-2016

	Cases (n = 10 885)	Controls (n = 435 379)	Crude OR[a] (95% CI)	Adj. OR[b] (95% CI)
Never use of any antidepressant	6873 (63.1)	336 579 (77.3)	1.00 (ref.)	1.00 (ref.)
SSRI				
Recency of use				
Current use	1704 (15.7)	29 287 (6.7)	2.93 (2.77-3.10)	1.60 (1.50-1.71)
Recent use	128 (1.2)	2236 (0.5)	2.85 (2.37-3.42)	1.65 (1.36-2.01)
Past use	188 (1.7)	4623 (1.1)	2.00 (1.73-2.33)	1.17 (1.00-1.37)
Distant use	1246 (11.4)	37 447 (8.6)	1.67 (1.57-1.78)	1.05 (0.98-1.12)
Duration of current use				
≤1 month	115 (1.1)	1274 (0.3)	4.45 (3.65-5.43)	2.55 (2.07-3.15)
>1 month, ≤3 months	191 (1.8)	2614 (0.6)	3.57 (3.07-4.16)	1.95 (1.66-2.29)
>3 months, ≤12 months	576 (5.3)	7242 (1.7)	3.90 (3.56-4.27)	2.11 (1.91-2.33)
>12 months, ≤3 years	427 (3.9)	8673 (2.0)	2.41 (2.17-2.67)	1.28 (1.15-1.43)
>3 years	395 (3.6)	9484 (2.2)	2.08 (1.87-2.32)	1.04 (0.93-1.17)
Non-SSRI				
Recency of use				
Current use	1006 (9.2)	20 123 (4.6)	2.48 (2.32-2.66)	1.35 (1.25-1.47)
Recent use	104 (1.0)	1933 (0.4)	2.67 (2.18-3.26)	1.58 (1.27-1.95)
Past use	166 (1.5)	4061 (0.9)	2.03 (1.73-2.38)	1.25 (1.06-1.47)
Distant use	1025 (9.4)	31 566 (7.3)	1.62 (1.52-1.74)	1.05 (0.98-1.13)
Duration of current use				
≤1 month	77 (0.7)	1124 (0.3)	3.19 (2.51-4.04)	1.88 (1.46-2.41)
>1 months, ≤3 months	123 (1.1)	1994 (0.5)	2.95 (2.45-3.56)	1.76 (1.44-2.14)
>3 months, ≤12 months	277 (2.5)	4797 (1.1)	2.83 (2.50-3.21)	1.49 (1.30-1.71)
>12 months, ≤3 years	235 (2.2)	5166 (1.2)	2.20 (1.92-2.52)	1.20 (1.03-1.38)
>3 years	294 (2.7)	7042 (1.6)	2.10 (1.86-2.37)	1.12 (0.98-1.28)

Abbreviations: CI, confidence interval; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor.
[a]Adjusted for age, sex, and calendar period (year) by design.
[b]Adjusted for age, sex, and calendar period (by design) and the following based on register data: hypertension, stroke, epilepsy, dementia, chronic obstructive pulmonary disease, high alcohol consumption, chronic hepatic disease, chronic renal insufficiency, diabetes, myocardial infarct, angina, unstable angina, peripheral artery disease, use of low-dose aspirin, clopidogrel, direct oral anticoagulant, vitamin K antagonist, nonsteroidal anti-inflammatory drugs, hormone replacement therapy, or oral corticosteroid drugs, and socioeconomic status (education level and income).

use of antidepressants (any antidepressant: OR 1.41 [CI 1.21-1.64]; SSRIs: OR 1.39 [CI: 1.13-1.70]).[39] The other study employed an active comparator design (current use of TCA) and reported risk estimates for intracranial hemorrhage of OR 1.17 (CI 1.02-1.35) with slightly higher estimates (OR of 1.38 [CI: 1.03-1.83]) in a subanalysis restricted to cases with extracerebral hemorrhage (defined as spontaneous subdural and extradural hemorrhage).[13] In subanalyses with antidepressants classified by their affinity for serotonin receptors, Renoux et al found evidence of higher risks of intracranial hemorrhage for antidepressants with higher affinity for serotonin reuptake transporter,[13] while Verdel et al reported null associations.[39] With the above-mentioned caveats in mind, it is noted that the results of the present study are in line with the two cited studies regarding antidepressant risk estimates. Analyses by serotonin affinity were not conducted in the present study, but supplementary analyses with classification of non-SSRI drugs in subgroups according to mechanisms of action[42] had little impact on results.

The choice of "never use" of antidepressants as reference group may have resulted in some residual confounding due to this group of individuals potentially having a different background profile than ever users of antidepressants. We note that such residual confounding, to the extent it is present, should not affect comparisons of SSRI use with non-SSRI use, as the same reference group was used in all analyses (apart from estimates of antidepressants in combination with NSAIDs and antithrombotics, see Data S1). It has furthermore been suggested,[32] that the higher risk of intracranial hemorrhage observed with both SSRIs and non-SSRIs, rather than expressing a true drug side effect, is due to confounding by indication, ie, that depression per se is a risk factor for bleeding.[43] Another possibility is that the antidepressants have a common underlying indirect mechanism that results in higher risk of SDH, eg, through an increased risk of falls.[18] Provided SDH is a result of such a side effect, the findings of this study regarding duration of current use could be explained by depletion of

TABLE 3 Dose of antidepressant drug and risk of subdural hematoma in Denmark, 2000-2016

	Cases (n = 10 885)	Controls (n = 435 379)	Crude OR[a] (95% CI)	Adj. OR[b] (95% CI)
Never use of any antidepressant	6873 (63.1)	336 579 (77.3)	1.00 (ref.)	1.00 (ref.)
Current antidepressant use[c]				
SSRI – high dose[d]	656 (6.0)	11 469 (2.6)	2.85 (2.62-3.10)	1.37 (1.24-1.51)
≤3 months	28 (0.3)	323 (0.1)	4.36 (2.93-6.48)	2.08 (1.37-3.16)
>3 months, ≤12 months	193 (1.8)	1860 (0.4)	4.98 (4.27-5.81)	2.44 (2.06-2.88)
>12 months, ≤3 years	200 (1.8)	3661 (0.8)	2.69 (2.32-3.12)	1.27 (1.08-1.49)
>3 years	235 (2.2)	5625 (1.3)	2.08 (1.82-2.38)	0.93 (0.80-1.08)
SSRI–low and medium[d]	1048 (9.6)	17 818 (4.1)	2.92 (2.72-3.12)	1.67 (1.55-1.81)
≤3 months	278 (2.6)	3565 (0.8)	3.83 (3.38-4.36)	2.18 (1.90-2.49)
>3 months, ≤12 months	383 (3.5)	5382 (1.2)	3.49 (3.13-3.89)	1.92 (1.71-2.16)
>12 months, ≤3 years	227 (2.1)	5012 (1.2)	2.18 (1.90-2.50)	1.26 (1.09-1.46)
>3 years	160 (1.5)	3859 (0.9)	2.06 (1.75-2.42)	1.18 (1.00-1.40)
Non-SSRI – high dose[d]	290 (2.7)	4916 (1.1)	2.94 (2.60-3.33)	1.38 (1.20-1.58)
≤3 months	5 (0.0)	56 (0.0)	4.99 (1.94-12.84)	1.85 (0.66-5.20)
>3 months, ≤12 months	44 (0.4)	578 (0.1)	3.71 (2.71-5.09)	1.43 (1.02-2.00)
>12 months, ≤3 years	90 (0.8)	1391 (0.3)	3.14 (2.52-3.91)	1.58 (1.25-1.99)
>3 years	151 (1.4)	2891 (0.7)	2.64 (2.23-3.13)	1.25 (1.04-1.50)
Non-SSRI – low and medium[d]	716 (6.6)	15 207 (3.5)	2.32 (2.14-2.51)	1.33 (1.21-1.45)
≤3 months	195 (1.8)	3062 (0.7)	3.00 (2.59-3.49)	1.79 (1.53-2.10)
>3 months, ≤12 months	233 (2.1)	4219 (1.0)	2.70 (2.36-3.10)	1.50 (1.29-1.73)
>12 months, ≤3 years	145 (1.3)	3775 (0.9)	1.85 (1.56-2.19)	1.04 (0.87-1.24)
>3 years	143 (1.3)	4151 (1.0)	1.72 (1.45-2.04)	1.00 (0.84-1.20)

Note: In this table strata corresponding to exposure to antidepressants of ≤1 month and 1-3 months were collapsed into a single stratum (≤3 months) owing to sparse data.

Abbreviations: CI, confidence interval; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor.

[a]Adjusted for age, sex, and calendar period (year) by design.

[b]Adjusted for age, sex, and calendar period (by design) and the following based on register data: hypertension, stroke, epilepsy, dementia, chronic obstructive pulmonary disease, high alcohol consumption, chronic hepatic disease, chronic renal insufficiency, diabetes, myocardial infarct, angina, unstable angina, peripheral artery disease, use of low-dose aspirin, clopidogrel, direct oral anticoagulant, vitamin K antagonist, nonsteroidal anti-inflammatory drugs, hormone replacement therapy, or oral corticosteroid drugs, and socioeconomic status (education level and income).

[c]Defined as treatment extending to at least 1 day prior to index date.

[d]High dose was defined as average daily treatment in latest treatment episode prior to index date exceeding one defined daily dose (DDD) daily, and non-high dose was defined less than or equal to 1 DDD daily.

susceptibles, ie, the phenomenon that the number of patients likely to experience a side effect drops over time as patients that experience the untoward effect stop taking the drug.[44] The slightly higher ORs observed with current use of SSRIs compared with non-SSRIs could be due to additional antiplatelet effects of the former class of drugs.[45]

Data on risk of intracranial events associated with combined use of antidepressants with antithrombotics or NSAIDs are sparse with equivocal results. No previous studies specifically addressed the risk of SDH in this context. Of note, findings by Renoux et al suggested increased risk of intracranial hemorrhage in patients concomitantly exposed to SSRIs and anticoagulants, but not antiplatelets.[13] Conversely, a study of hemorrhagic stroke in the United States reported no potentiation of risk by warfarin or antiplatelets.[34] A study from the Netherlands nested within a cohort of VKA users reported no significantly increased risk of intracranial hemorrhage in users of SSRIs or NSAIDs, but was underpowered for these subanalyses.[20] Finally, a study from Korea investigated risk of intracranial hemorrhage within 30 days of initiation of NSAIDs and reported increased risk of intracranial hemorrhage;[22] however, this study was criticized methodologically, eg, for lacking an adequate comparator group.[46] Given the above equivocal findings, the present study offers reassuring results concerning the risk of SDH in patients taking antidepressants combined with either antithrombotics or NSAIDs. However, even in this study of more than 10 000 patients with SDH we were not able to address issues of triple co-medication (antidepressants, anticoagulants, and NSAIDs) with sufficient precision.

The present study has a number of strengths. It was conducted in Denmark, where health-care services are free of charge to all residents of the country. This setting also provided access to population-based continuously updated registries with prospectively collected data, use of which eliminated recall bias and minimized selection bias. The code

TABLE 4 Single group antidepressant use and risk of subdural hematoma in Denmark, 2000-2016

	Cases (n = 10 885)	Controls (n = 435 379)	Crude OR[a] (95% CI)	Adj. OR[b] (95% CI)
Never use of any antidepressant	6873 (66.1)	336 579 (78.7)	1.00 (ref.)	1.00 (ref.)
Current use of SSRI only[c], duration	1316 (12.7)	23 043 (5.4)	2.84 (2.66-3.02)	1.59 (1.49-1.71)
≤1 month	94 (0.9)	1025 (0.2)	4.54 (3.65-5.65)	2.72 (2.16-3.43)
>1 month, ≤3 months	150 (1.4)	2035 (0.5)	3.57 (3.00-4.23)	2.01 (1.68-2.41)
>3 months, ≤12 months	425 (4.1)	5599 (1.3)	3.70 (3.33-4.10)	2.08 (1.86-2.33)
>12 months, ≤3 years	333 (3.2)	6877 (1.6)	2.34 (2.09-2.63)	1.27 (1.12-1.44)
>3 years	314 (3.0)	7507 (1.8)	2.08 (1.85-2.34)	1.06 (0.94-1.21)
Current use of non-SSRI only[c], duration	609 (5.9)	13 794 (3.2)	2.17 (1.99-2.37)	1.28 (1.17-1.41)
≤1 month	40 (0.4)	711 (0.2)	2.60 (1.88-3.60)	1.64 (1.17-2.30)
>1 month, ≤3 months	69 (0.7)	1296 (0.3)	2.53 (1.97-3.23)	1.67 (1.29-2.16)
>3 months, ≤12 months	139 (1.3)	2902 (0.7)	2.32 (1.94-2.76)	1.30 (1.08-1.56)
>12 months, ≤3 years	148 (1.4)	3452 (0.8)	2.08 (1.75-2.46)	1.22 (1.02-1.46)
>3 years	213 (2.0)	5433 (1.3)	1.98 (1.71-2.28)	1.14 (0.98-1.33)

Abbreviations: CI, confidence interval; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor.
[a]Adjusted for age, sex, and calendar period (year) by design.
[b]Adjusted for age, sex, and calendar period (by design) and the following based on register data: hypertension, stroke, epilepsy, dementia, chronic obstructive pulmonary disease, high alcohol consumption, chronic hepatic disease, chronic renal insufficiency, diabetes, myocardial infarct, angina, unstable angina, peripheral artery disease, use of antiplatelet drugs, anticoagulants, nonsteroidal anti-inflammatory drugs, hormone replacement therapy, or oral corticosteroid drugs, and socioeconomic status (education level and income).
[c]Single group antidepressant use: Only used antidepressants within one group (ie, SSRIs only, or "other" antidepressants only; referred to as "single group antidepressant use") within 12 months of the index date (ie, subjects switching antidepressant group in the last 12 months were excluded).

used to identify patients with SDH in this study has been reported to be highly valid with a positive predictive value of 96%.[29]

This study also has limitations. The data are observational and as such potentially subject to bias or residual confounding. Adjustment for smoking and alcohol use, for example, was incomplete owing to the use of proxy variables. Also, misclassification of date of the intracranial hemorrhage onset,[47] or reverse causation (ie, that the earliest symptom of yet undiagnosed SDH is misconstrued as depression and treated accordingly),[48] could explain part of the higher risk observed with short-term current

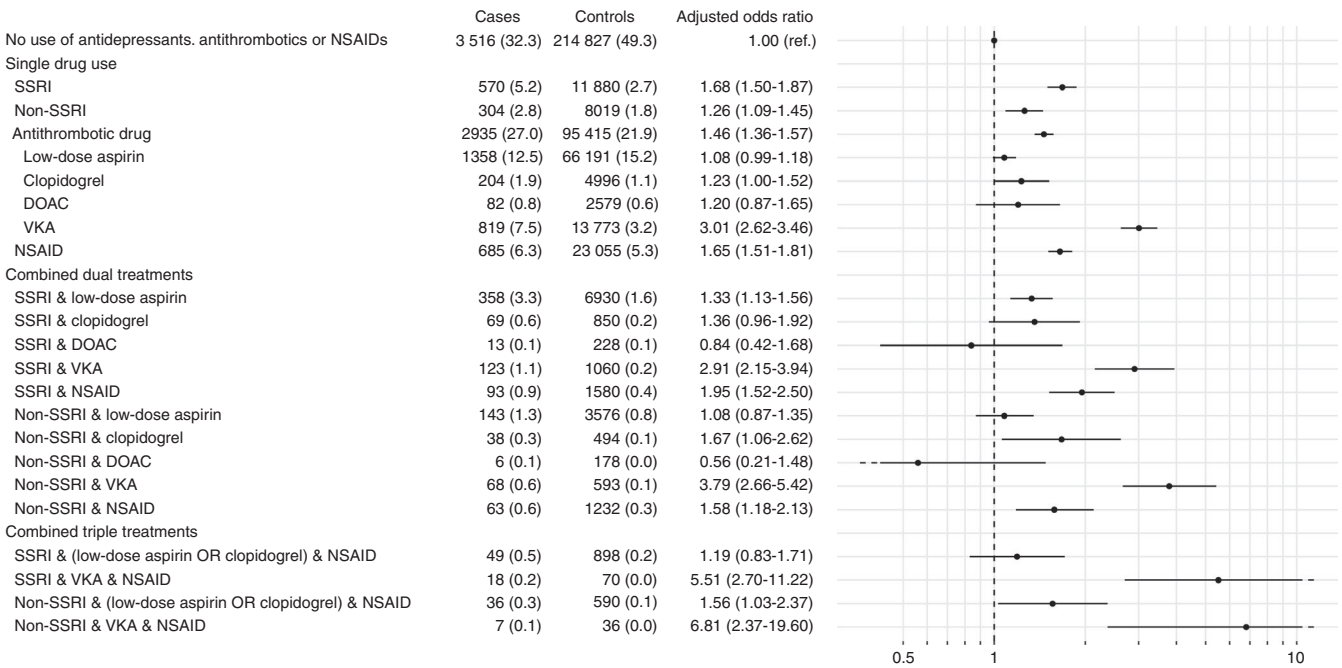

FIGURE 1 Risk of subdural hematoma (bars indicate 95% confidence intervals) associated with current use of antidepressant drugs alone, or in combination with antithrombotics, or nonsteroidal anti-inflammatory drugs (NSAIDs), or both antithrombotics and NSAIDs

use of antidepressants. Although the regional analyses that were based on more granular data provided reassuring results, this possibility needs to be considered, particularly as a similar pattern of high ORs restricted to short-term current use (≤3 months) was also observed for NSAIDs, a class of drugs quite distinct from antidepressants both in terms of effects and side effects. Over-the-counter (OTC) use of certain drugs needs to be considered. The Prescription Register offers 100% coverage of the majority of prescribed drugs.[25] Low-dose aspirin, ibuprofen (200 mg tablets only), and diclofenac (from 16 July to 14 December 2008) are also available OTC in Denmark.[49] However, as costs toward low-dose aspirin and NSAIDs are reimbursed if the drug is prescribed, the percentage of drug use recorded in the Prescription Registry is high, eg, in 2012 the fraction of all sales in Denmark recorded in the Prescription Registry was 92% for low-dose aspirin, 66% for ibuprofen, and 100% for all other NSAIDs.[49]

5 | CONCLUSION

In Denmark, use of SSRI and non-SSRI antidepressants was associated with a higher risk of SDH, compared to no antidepressant use. In absolute terms, the risk was small and it appeared to be mainly restricted to the first year of treatment. Dual treatment of antidepressants and co-medication purported to increase bleeding risk (ie, NSAIDs, or antithrombotics) was not associated with higher risks than expected from the co-medication in question. Whether these reassuring findings extend to treatment of antidepressants with both an NSAID and an anticoagulant, in particular VKA, warrants further study.

ADDENDUM

D. Gaist conceived the study. D. Gaist and A. Pottegård generated and analyzed the data. B. Halle and F. R. Poulsen evaluated clinical material in the regional substudy. All authors contributed to the design and interpreted the study and wrote the paper. All authors reviewed and edited the final manuscript.

CONFLICT OF INTERESTS

Dr Gaist reported receiving honoraria from Astra Zeneca (Sweden) for participation as a coinvestigator on a research project. Dr García Rodríguez reported receiving institutional research grants from Bayer Pharma AG (Germany) and Astra Zeneca (Sweden); and serving on an advisory board for Bayer Pharma AG. Dr Hellfritzsch reported receiving a travel grant from LEO Pharma and speaker honorarium from Bristol-Myers Squibb and Pfizer outside the submitted work. Dr Hallas reported participation in research projects funded by Servier with funds paid to the institution where he is employed. Dr Pottegård reported participation in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Novo Nordisk, Servier, and LEO Pharma, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this paper. Drs Stine Munk Hald, Frantz Rom Poulsen, and Bo Halle disclosed no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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