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# Incident user cohort study of risk for gastrointestinal bleed and stroke in individuals with major depressive disorder treated with antidepressants

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## ABSTRACT

**Objective:** To examine the association between exposure to newer antidepressants and risk of gastrointestinal (GI) and other bleeding complications among individuals with major depressive disorder (MDD).

**Design:** This study uses an incident user cohort design to compare associations between incidence of vascular/bleeding events and the relative affinity (low, moderate or high) of the antidepressant for the serotonin transporter during an exposure risk period for each patient.

**Setting:** New England healthcare system electronic medical record database.

**Participants:** 36 389 individuals with a diagnosis of MDD and monotherapy with a selective serotonin reuptake inhibitor, serotonin–norepinephrine reuptake inhibitor or other new-generation antidepressant were identified from among 3.1 million patients in a New England healthcare system.

**Primary and secondary outcome measures:** Rates of bleeding or other vascular complications, including acute liver failure, acute renal failure, asthma, breast cancer and hip fractures.

**Results:** 601 GI bleeds were observed in the 21 462 subjects in the high-affinity group versus 333 among the 14 927 subjects in the lower affinity group (adjusted RR: 1.17, 95% CI 1.02 to 1.34). Similarly, 776 strokes were observed in the high-affinity group versus 434 in the lower affinity treatment group (adjusted RR: 1.18, 95% CI 1.06 to 1.32). No significant association with risk for a priori negative control outcomes, including acute liver failure, acute renal failure, asthma, breast cancer and hip fractures, was identified.

**Conclusions:** Use of antidepressants with high affinity for the serotonin transporter may confer modestly elevated risk for GI and other bleeding complications. While multiple methodologic limitations must be considered, these results suggest that antidepressants with lower serotonin receptor affinity may be preferred in patients at greater risk for such complications.

## ARTICLE SUMMARY

### Article focus

- Previous reports have suggested that antidepressant use may contribute to dysfunction in platelet aggregation and increased risk for bleeding outcomes.
- The authors hypothesised that antidepressants with higher affinity for the serotonin transporter would exhibit greater risk for these outcomes than those with lesser affinity.

### Key messages

- Use of antidepressants with higher affinity for the serotonin transporter was associated with modest but statistically significant increase in risk for gastrointestinal bleed and stroke.
- Electronic medical record-based pharmacovigilance systems provide an opportunity to examine treatment risk in general clinical populations, in a more systematic fashion than traditional postmarketing surveillance.

### Strengths and limitations of this study

- A strength of this report, in addition to cohort size and generalisability, is the restriction to individuals with major depressive disorder, minimising risk for confounding by indication.
- A key limitation is the absence of blood antidepressant levels or data on adherence, which might lead us to underestimate strength of effect.

## INTRODUCTION

Antidepressants are among the most widely prescribed classes of medications in all of medicine; over 255 million prescriptions for antidepressants are issued annually, and this number continues to increase.[1] Selective serotonin reuptake inhibitors (SSRIs) and other new-generation antidepressants are generally preferred over older treatments

such as tricyclic antidepressants or monoamine oxidase inhibitors on the basis of greater tolerability and safety.[2] Notwithstanding debates over the magnitude of benefit, their efficacy in the treatment of major depressive disorder has been established in numerous placebo- and active-comparator studies over the past 2 decades.[2–4]

While the precise mechanism of therapeutic action of SSRIs is not known, their common mechanism of action is inhibition of the serotonin transporter, responsible for removal of serotonin from the synapse. Apart from its central nervous system effects, serotonin is known to be a vasoactive and thrombostatic amine.[5] Since the serotonin transporter is also expressed in platelets, there has been an active debate in the literature regarding the effects of SSRIs on the vascular system. Multiple studies suggest that SSRIs are generally safe in patients with vascular disease[6] and have beneficial effects in such patients by decreasing platelet aggregation[7 8] and by vasodilation.[9 10] Other studies, however, have associated the use of SSRIs with increased incidence of vasospasm and poor clinical outcomes after subarachnoid haemorrhage[11] as well as increased mortality and poor cardiovascular outcomes after coronary artery bypass grafting.[12] Thus, while beneficial in some contexts, the peripheral effects of SSRIs and other serotonergic antidepressants might also be expected to confer increased risk for vascular or bleeding complications.

In fact, several studies provide support for an increased risk of upper GI bleeds in persons taking SSRIs.[13–16] In patients treated with non-steroidal inflammatory drugs (NSAIDs) or anticoagulants, the addition of SSRI treatment is thought to increase the risk of clinically relevant bleeds.[15 17–19] Likewise, while the absolute risks are small,[20 21] SSRI use has also been associated with an increased risk of ischaemic stroke[22–24] and haemorrhagic stroke,[20] though negative studies also exist.[25 26]

A key limitation in many of these studies is the difficulty in adequately matching antidepressant-exposed subjects with controls. This may contribute to confounding by indication: that is, the same variables (ie, depression and associated symptoms) which lead an individual to be prescribed an antidepressant may increase that individual's risk of adverse outcomes. In particular, psychological distress[27] and depression[28] have been reported to be risk factors for cardiovascular events. A recent large case-crossover study and a population-based cohort study address some of these limitations but do not fully address the substantial risk of confounding by indication.[23 24] The need for further characterisation of the relationship between SSRIs and adverse bleeding events is apparent:[29 30] beyond the need to confirm such a relationship using a methodology less subject to confounding, the magnitude and specificity of risk remains unclear.

Therefore, we adopted an alternative approach to estimate risk associated with antidepressants, contrasting those with highest affinity for the serotonin transporter with those of low or moderate affinity. Based upon the acute effects of these agents on platelet serotonin transport, we hypothesised that high-affinity agents would be associated with greater risk of bleeding or vascular events than lower affinity ones. This approach lessens risk of confounding by focusing only on depressed antidepressant-treated patients, particularly as clinicians typically do not consider affinity per se when selecting among the numerous available antidepressants. We examined data from in- and outpatient medical records for over 3 million individuals in a large New England healthcare system.

## METHODS

The Partners HealthCare electronic medical record (EMR) incorporates sociodemographic data, billing codes, laboratory results, problem lists, medications, vital signs and narrative notes from Massachusetts General Hospital and Brigham and Women's Hospital, as well as community and specialty hospitals which are part of the Partners HealthCare System in Boston (Massachusetts, USA). Altogether, these records comprise about 3.1 million unique patients.

Patients with the presence of at least one diagnosis of major depression determined by the presence of International Classification of Diseases, 9th edition codes (ICD-9 296.2×, 296.3×), in the billing data or outpatient medical record were selected from the EMR for inclusion in a data set (referred to as a data 'mart'). The data mart consists of all electronic records (psychiatric and non-psychiatric) from 127 504 patients and can be utilised with the i2b2 server software (i2b2 v1.4).[31] The present analysis included records from February 1990 to October 2009. The i2b2 system[32 33] is a scalable computational framework, deployed at over 46 major academic health centres, for managing human health data, and the i2b2 Workbench facilitates analysis and visualisation of such data. The Partners Institutional Review Board approved all aspects of this study.

Subjects were classified into groups based upon documented antidepressant treatment from three sources: (1) medications prescribed to the patient via e-prescribing in the EMR, (2) medication documented but not prescribed by the documenting clinician and (3) medication dispensed by the inpatient pharmacy. The three primary groups were labelled 'high', 'moderate' and 'low' affinity for the serotonin transporter, based upon previous work.[34] Classification of newer antidepressants, including duloxetine and escitalopram, was based upon $K_i$ (table 1) [35–37]—in the case of escitalopram, effective affinity is greater than citalopram because of the absence of the R enantiomer, which has demonstrated antagonistic effects.[38–40] As reported affinities vary across publications,[37 41–44] we prioritised comparative affinities reported by a single laboratory[42] wherever possible and categories utilised in prior studies employing similar methodology to this one.[35] Patients with multiple antidepressant prescriptions from

**Table 1** Antidepressant affinity groups by affinity for serotonin transporter*

| Affinity group | Antidepressant | Inhibition constant ($K_i$) (mean±SD) |
|---|---|---|
| High | Paroxetine | 0.065±0.006 |
| | Duloxetine | (0.07±0.01)† |
| | Sertraline | 0.29±0.01 |
| | Escitalopram | (0.79±0.13)‡ |
| | Fluoxetine | 0.9±0.06 |
| Moderate | Citalopram | 1.5±0.03 |
| | Fluvoxamine | 1.6±0.1 |
| | Venlafaxine | 7.5±0.4 |
| Low | Nefazodone | 459±28 |
| | Bupropion | § |
| | Mirtazapine | § |

*Adapted from Owens *et al*.[42]
†$K_i$ drawn from Vaishnavi *et al*[37]; relative order confirmed in Martin *et al*.[36] (*J Pharmacol Exp Ther*).
‡$K_i$ drawn from Apparsundaram *et al*[35]; relative order confirmed in Martin *et al*.[36] (*J Pharmacol Exp Ther*).
§Not reported; Tatsumi *et al*.[44] reports $K_D$=9100 for bupropion and $K_D$>10 000 for mirtazapine (vs 200 for nefazodone).

different affinity groups were excluded from the analysis, as were those receiving tricyclic antidepressants or monoamine oxidase inhibitors, out of concern that these groups would not be well matched with those receiving newer treatments and to avoid the known cardiovascular risks associated with some older agents.

For initial analysis, the 'high'-affinity group was contrasted with the other two groups to yield two similarly sized cohorts for comparison, based on investigator consensus and recognising that other groupings might be equally reasonable. A further advantage of this distinction was that it assigned duloxetine and venlafaxine to different categories based on serotonin reuptake affinity, decreasing the likelihood of confounding by non-serotonergic (ie, noradrenergic) effects. The groups were first compared in terms of sociodemographic features, including age, gender and race and antidepressant use.

As electronic medical records data are not well suited to standard survival analytic approaches, we utilised an incident user cohort design to construct an exposure risk period for each patient. This method was proposed by Schneeweiss[45] specifically for pharmacovigilance designs using electronic medical record and is conceptually related to prior approaches.[46] This approach has previously demonstrated assay sensitivity in pharmacovigilance studies using similarly structured data.[47 48] The exposure period begins on the date an antidepressant was prescribed and ends 30 days from prescription. If a second prescription is documented in the 30-day period, the period is extended another 30 days from this prescription. Patient analysis is censored as soon as their exposure risk period ends, that is, at the end of a continuous documented period of exposure. Outcomes occurring within any of the exposure periods are included in the analysis. Logistic regression was used to calculate crude RR, and RR was then adjusted for person-months of exposure and other potential confounding variables identified in the initial analysis of baseline characteristics. To examine the importance of this 30-day assumption, we also conducted a sensitivity analysis as a means of determining if the length of the exposure risk period had a meaningful impact on our analysis. We re-ran the analysis for all the outcomes with drug era windows of 60, 90 and 180 days. Adjusted RR and CIs are provided in table S3.

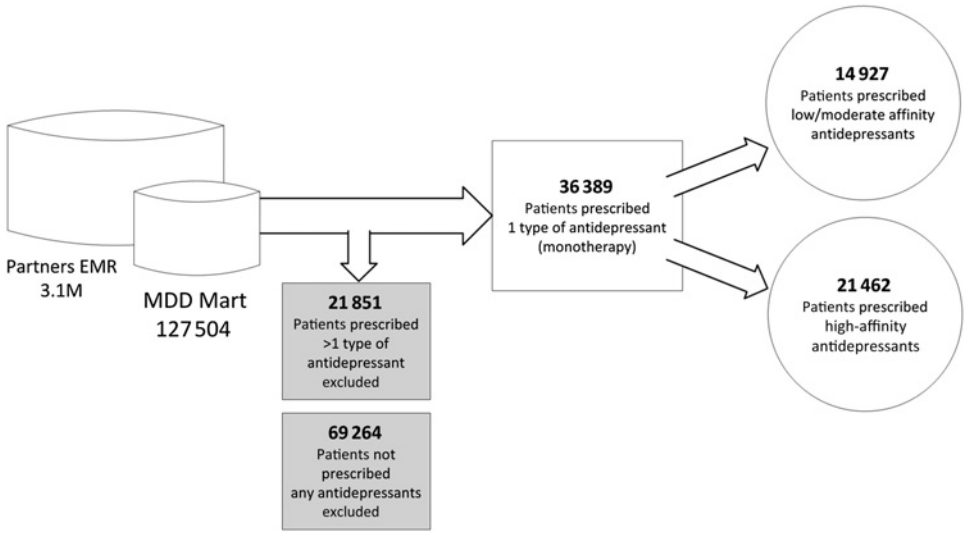
Three sets of analysis were performed. First, we examined associations between antidepressant group and vascular/bleeding events (primary outcomes) including gastrointestinal (GI) haemorrhage, myocardial infarction and stroke. Follow-up analysis examined each category of stroke (ischaemic or haemorrhagic) separately. For consistency with prior reports, we also conducted a secondary analysis on a subset of patients with more conservative criteria for selecting patients with major depressive disorder (MDD) (at lease two outpatient diagnoses or at least one inpatient diagnosis). Next, as a positive control or test for assay sensitivity, we examined association between aspirin exposure and GI bleed. Finally, as a negative control, we examined associations between antidepressant group and five outcomes selected by the clinical investigators (RHP, JWS, DVI and IK) based upon literature review as likely to be unrelated to serotonergic effects: acute liver failure, acute renal failure, asthma, breast cancer and hip fractures. Table S1 lists the ICD-9 codes used to identify these outcomes of interest.

All analyses utilised R 2.13.1 (The R Foundation for Statistical Computing).

## RESULTS

Of 127 504 individuals with MDD, 58 690 (45%) received at least one prescription for a newer antidepressant. Thirty six thousand three hundred and eighty nine of these patients were prescribed only one type of antidepressant, while 21 851 individuals were prescribed antidepressants from different affinity groups at any time during the study period and were excluded from the analysis (figure 1). Of the single group-treated patients, 14 927 were treated with low–moderate affinity and 21 462 with high affinity, representing 44 235 patient-months of treatment in the lower group and 74 706 in the higher group. Table 2 shows associations between treatment groups and baseline characteristics. Compared with low–moderate affinity treatments, patients with high-affinity treatments were more likely to be female, non-Caucasian and very slightly older (difference in mean age between groups was <1 year). They exhibited no significant differences in total number of prescription refills or overall utilisation of the healthcare system (as measured by number of 'facts' in the data mart, which include billing codes, medications, procedures or other individual data points). Our

**Figure 1** Study schematic.




adjusted models therefore included age, gender, race and aspirin use as covariates.

For a small subset of patients, depression severity (assessed using the Quick Inventory of Depressive Symptomatology-Self-Report[49]) was available in the EMR because the clinicians in some practices employ this scale routinely. To address the possibility that our results were confounded by severity, we examined depression severity by affinity group in an exploratory fashion. We did not detect a significant difference between groups as measured by mean Quick Inventory of Depressive Symptomatology-Self-Report score (L/M: 10.6±5.3, H: 10.3±5.3, p=0.728) (table 2).

Figure 2 indicates adjusted RR and 95% CIs by treatment group for outcomes of interest and negative controls. RR significantly >1 was observed in GI haemorrhage (adjusted RR: 1.17, 95% CI 1.02 to 1.34) and strokes (adjusted RR: 1.18, 95% CI 1.06 to 1.32) between the low–moderate and high-affinity groups, but not in myocardial infarctions (adjusted RR: 1.05, 95% CI 0.93 to 1.18). When stroke type (ischaemic or haemorrhagic) was examined, significant effects were observed for ischaemic strokes (adjusted RR: 1.20, 95% CI 1.06 to 1.35), but not haemorrhagic strokes (adjusted RR: 1.13, 95% CI 0.90 to 1.44). In the latter case, the point estimate of effect was similar to that for all strokes, but the smaller number of events yielded a broader CI. Outcomes of interest for each antidepressant are listed in table S2. A secondary analysis on a subset of patients with more conservative criteria for selecting patients with MDD yielded similar results (table S4).

As expected, aspirin exposure was also associated with risk for GI bleed (crude RR: 12.3995, 95% CI 2.39 to 3.12). In a fully adjusted model including age, gender, race, antidepressant treatment group, aspirin and treatment group-by-aspirin interaction, no evidence of antidepressant treatment group-by-aspirin interaction was observed (for interaction term, p=0.630) (table 3).

In our analysis of negative control conditions with no known or postulated associations to antidepressants, no significant associations with affinity group were identified (figure 2). These included both acute diagnoses (acute renal failure, acute hepatic failure, hip fracture) and chronic diagnoses (asthma, breast cancer).

In a sensitivity analysis examining the interval of risk associated with antidepressant exposure, outcomes within a 60-, 90-, or 180-day exposure window following antidepressant prescription were examined. Results were generally similar to those observed for the primary analysis (table S3), persistently indicating elevated risk for stroke and GI bleed but not for the control conditions.

## DISCUSSION

In this pharmacovigilance study using data from 127 504 individuals with MDD in a single large healthcare system, we identified a significantly elevated risk for GI haemorrhage and stroke when high-serotonin transporter affinity antidepressants were prescribed compared with low-serotonin transporter affinity antidepressants. No such effects were observed for other general medical conditions selected a priori as negative controls, suggesting that this association is less likely to represent a non-specific effect of treatment.

Our results are consistent with prior reports which detected a risk of GI bleed among SSRI-treated patients.[15 17–19 24] For example, a large Scandinavian population-based study found SSRI use to be associated with 3.6-fold greater risk of upper GI bleed, an effect potentiated by NSAID or aspirin use.[18] However, not all such studies found this risk.[50 51] While most previous studies compared antidepressant-treated patients to untreated patients, with consequent risk of confounding by indication, the present work minimises this risk by comparing antidepressant treatments based on affinity for the serotonin transporter. Thus, presence of depression alone cannot account for the observed effects.

We also detected elevated risk for stroke in high-affinity antidepressant-treated patients. A similar point estimate was identified when the analysis was limited to individuals in whom the stroke type was characterised as

**Table 2** Characteristics of patients prescribed a newer antidepressant as defined during 6 months prior to first medication use

| | Low–moderate affinity antidepressants* (n=14 927) | High-affinity antidepressants* (n=21 462) | p Value |
|---|---|---|---|
| Demographic variables | | | |
| Age (years), mean (SD) | 51.8 (16.4) | 52.6 (16.4) | <0.001 |
| Female gender | 9965 (66.8) | 15 489 (72.2) | <0.001 |
| Race/ethnicity† | | | <0.001 |
| White | 11 423 (76.5) | 16 104 (75.0) | |
| Black | 873 (5.8) | 1196 (5.6) | |
| Hispanic | 1183 (7.9) | 2058 (9.6) | |
| Asian | 202 (1.4) | 270 (1.3) | |
| Other | 1246 (8.3) | 1834 (8.5) | |
| Insurance | | | <0.001 |
| Private | 7032 (47.1) | 9779 (45.6) | |
| Public | 6082 (40.7) | 8784 (40.9) | |
| Other | 1813 (12.1) | 2899 (13.5) | |
| Health system utilisation | | | |
| Health facts per patient; median (IQR) | 224 (95–483) | 223 (91–477) | 0.152 |
| Years in health system; median (IQR) | 10 (4–15) | 10 (5–15) | |
| Use of antidepressants | | | |
| Refills per patient; median (IQR) | 2 (1–4) | 2 (1–5) | |
| High affinity | | | |
| Duloxetine | | 1421 (7.0) | |
| Escitalopram | – | 3254 (16.1) | |
| Fluoxetine | – | 10 648 (52.6) | |
| Paroxetine | – | 6107 (30.2) | |
| Sertraline | – | 10 148 (50.1) | |
| Moderate affinity | | | |
| Citalopram | 8962 (56.2) | – | |
| Fluvoxamine | 220 (1.4) | – | |
| Venlafaxine | 3869 (24.2) | – | |
| Low affinity | | | |
| Nefazodone | 473 (3.0) | – | |
| Bupropion | 5792 (36.3) | – | |
| Mirtazapine | 1621 (10.2) | – | |
| Exposure person-months | 44 235 | 74 706 | |
| Depression severity (n=136) | n=67 | n=69 | |
| QIDS-SR score; mean (SD) | 10.6 (5.3) | 10.3 (5.3) | 0.728 |
| Concomitant medications | | | |
| Aspirin | 4302 (28.8) | 6095 (28.4) | 0.721 |

*N (%), except otherwise indicated.
†Race and ethnicity are collected using a single field in the electronic medical record, so subjects who identify as Hispanic are not further characterised.
QIDS-SR, Quick Inventory of Depression Symptomatology-Self-Report.

haemorrhagic, although the 95% CI did not exclude one. In light of the smaller number of events in this analysis, as well as the potential for misclassification in diagnosis based on claims data, the difference among haemorrhagic stroke patients is perhaps not surprising. Previous studies have also suggested elevated risk of stroke with SSRI or other antidepressant treatment.[20 22 24] Data from the Women's Health Initiative found SSRI prescription to be associated with elevated stroke risk after adjustment for other cardiovascular risk factors.[20] Likewise, a large population-based cohort study of individuals age 65 or older found an association between SSRI or other (non-tricyclic) antidepressant use and stroke risk compared with untreated individuals.[24] Neither study, however, can fully exclude confounding by indication.

On the other hand, a nested case–control study reported a lack of association between SSRI use and haemorrhagic stroke,[25] and a case-crossover study likewise observed increased ischaemic but not haemorrhagic stroke risk.[23] In light of these effects, the impact of antidepressants might be better understood as dysregulation of coagulation rather than simply an increase in bleeding per se.

A notable advantage of EMR- or claims-based pharmacovigilance studies is their potential to rapidly identify risk that might otherwise go undetected in randomised controlled trials. For example, a previous study of rosiglitazone identified elevated risk of myocardial infarction, before similar data from prospective studies led the US FDA to consider withdrawing that drug from the market.[47] Confidence in our

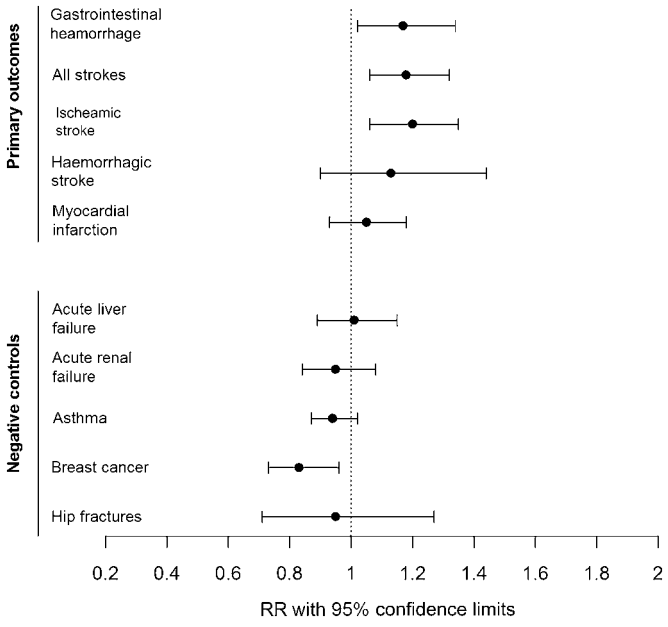



**Figure 2** Adjusted RR and 95% CIs for primary outcomes and negative controls.

ability to detect a 'true' signal using our methodology is increased by the detection of association between aspirin treatment and GI bleed, a well-known complication of aspirin treatment, as well as by the negative findings among the negative control diagnoses.

We note several limitations in considering our results. First, we cannot exclude the possibility of residual confounding arising from differences in the treatment groups in this non-randomised cohort and specifically the potential for biased assignment to one antidepressant category. In general, most clinicians are unaware of the differences in affinity between SSRIs, so this would be unlikely to influence clinical decision-making. Among the low-affinity antidepressants are primarily non-SSRIs, which may be selected based upon some clinical consideration. On the other hand, bupropion, a low-affinity antidepressant, is indicated for smoking cessation and prescribed for depressed individuals who smoke. Because smoking is a risk factor for stroke, one would expect this low-affinity antidepressant to be associated with stroke risk, which would have an effect opposing the one we observed. Similarly, non-SSRI antidepressants are often second-line treatment suggesting that individuals in the lower affinity group might be more treatment resistant and, therefore, at greater risk for vascular complications. Because we observed the opposite trend, it is unlikely that these results are confounded by greater depression severity in the high-affinity group. Further, while depression severity on a standardised scale was available only for a small subset of individuals, that measure did not support a confounding effect of severity.

Another limitation in the present analysis is the inability to reliably characterise blood levels for individual treatments, which in addition to affinity will determine extent of binding to serotonin transporter.[52] Many factors, including dose and adherence (including unfulfilled prescriptions) and individual differences in metabolism and concomitant medications will impact blood level; correlation between individual characteristics such as dosage and blood level may be modest.[53] These sources of heterogeneity should be consistent across treatment groups, however, so if anything we would anticipate them to bias our results towards an absence of association. Still, our results must be interpreted cautiously with these restrictions in mind.

**Table 3** Incidence rate and RR of bleed events and negative controls for users of low–moderate serotonin affinity antidepressants compared with users of high-serotonin affinity antidepressants

| | Low–moderate affinity antidepressant | | High-affinity antidepressant | | RR (95% CI) | |
|---|---|---|---|---|---|---|
| Outcome | No. of cases | Incidence rate (per 1000 person-months) | No. of cases | Incidence rate (per 1000 person-months) | Unadjusted | Adjusted* |
| Primary outcomes | | | | | | |
| Gastrointestinal haemorrhage | 333 | 7.5 | 601 | 8.0 | 1.16 (1.02 to 1.29) | 1.17 (1.02 to 1.34) |
| Stroke | | | | | | |
| All stroke | 434 | 9.8 | 776 | 10.4 | 1.16 (1.03 to 1.30) | 1.18 (1.06 to 1.32) |
| Ischaemic stroke | 367 | 8.3 | 672 | 9.0 | 1.17 (1.04 to 1.33) | 1.20 (1.06 to 1.35) |
| Haemorrhagic stroke | 105 | 2.4 | 176 | 2.4 | 1.10 (0.87 to 1.40) | 1.13 (0.90 to 1.44) |
| Myocardial infarction | 387 | 8.7 | 630 | 8.4 | 1.04 (0.92 to 1.18) | 1.05 (0.93 to 1.18) |
| Negative control events | | | | | | |
| Acute liver failure | 382 | 8.6 | 611 | 8.2 | 1.00 (0.88 to 1.13) | 1.01 (0.89 to 1.15) |
| Acute renal failure | 363 | 8.2 | 542 | 7.3 | 0.94 (0.82 to 1.07) | 0.95 (0.84 to 1.08) |
| Asthma | 909 | 20.5 | 1350 | 18.1 | 0.96 (0.88 to 1.04) | 0.94 (0.87 to 1.02) |
| Breast cancer | 333 | 7.5 | 469 | 6.3 | 0.90 (0.79 to 1.04) | 0.83 (0.73 to 0.96) |
| Hip fractures | 71 | 1.6 | 113 | 1.5 | 0.99 (0.74 to 1.33) | 0.95 (0.71 to 1.27) |

*Adjusted for age, sex, race, aspirin use and exposure period.

Nonetheless, our results add to a growing body of evidence that some newer antidepressants may be associated with elevated risks of GI bleeding and stroke. We emphasise that these risks must be balanced against the voluminous evidence of benefit from treatment of depression. Still, if confirmed by further investigation, it may be possible to achieve these benefits while minimising risk by selecting antidepressants with lesser affinity for the serotonin transporter. More broadly, our results further indicate the potential utility of large electronic medical record systems in understanding the clinical risks of pharmacotherapy in psychiatry.

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**Contributors** VC designed the tools for collecting data, cleaned and analysed the data and drafted and revised the manuscript. He is a guarantor. PJG contributed to interpretation of analysis and drafted and revised the manuscript. CCC contributed to preparation of the manuscript. SM designed the tools for collecting data and contributed to interpretation of analysis and preparation of manuscript. VG, MF, JW, SC, IK and DVI contributed to interpretation of analysis and preparation of manuscript. JWS designed the study and contributed to interpretation of analysis and preparation of manuscript. RP initiated the project, designed the study, monitored the analyses and drafted and revised the manuscript. He is a guarantor. All authors have approved the final version.

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**Competing interests** None.

**Patient consent** This is a retrospective health care utilization/clinical study involving potentially hundreds of thousands of patients and multiple years of data—that is, consent could not feasibly be obtained from all subjects.

**Ethics approval** Partners Institutional Review Board.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** Additional data can be found in tables S1–S4.

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