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Perioperative Use of Serotonin Reuptake Inhibitors and Risks for Adverse Outcomes of Surgery

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Abstract

Background—Single site studies have described an association between selective serotoninreuptake inhibitors (SSRI) and adverse outcomes of surgery. We sought to determine whether perioperative use of SSRIs is associated with adverse outcomes of surgery in a national sample of patients.

Methods—Retrospective study of 530,416 patients 18 or older who underwent major surgery between 2006 and 2008 at 375 US Hospitals. We used multivariable hierarchical models to estimate associations between SSRI use and our outcomes. Pharmacy data were used to determine whether a patient received an SSRI in the perioperative period. Our primary outcomes included in-hospital mortality, length of stay, readmission at 30 days, bleeding events, transfusions, and incidence of ventricular arrhythmias.

Results—Patients receiving SSRI medications were more likely to have obesity, chronic pulmonary disease, or hypothyroidism ($p<0.001$ for each), and more likely to have depression (41.0% vs. 6.2%, $p<0.0001$). After adjustment, patients receiving SSRIs had higher odds for inhospital mortality (Adjusted Odds [AOR] 1.20 (1.07, 1.36), bleeding (AOR 1.09, 95% 1.04, 1.15), and readmission at 30 days (AOR 1.22, 95% CI 1.18, 1.26). Similar results were observed in propensity-matched analyses, though risk of inpatient mortality was attenuated among patients with depression. Sensitivity analyses suggest that, in order to invalidate our results, an unmeasured covariate would have to have higher prevalence and be more strongly associated with mortality than any covariate included in our models.

Conclusions—Receiving SSRIs in the perioperative period is associated with higher risk for adverse events. Determining whether patient factors or SSRIs themselves are responsible for elevated risks require prospective study.

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Introduction

Selective serotonin reuptake inhibitors (SSRI) are among the most commonly prescribed medications in the United States. In ambulatory patients, SSRI use appears to be associated with small but elevated risk for hemorrhage, particularly if co-administered with nonsteroidal antinflammatory medications or coumadin [1-3], an association thought to be due to SSRIs' serotonin-related antiplatelet effects. Ambulatory patients receiving SSRI's may also have higher risk for arrhythmias and sudden death [4,5].

In surgical patients, a small evidence base suggests SSRI use is associated with bleeding and adverse outcomes, also thought to be due to SSRIs' antiplatelet effects. In coronary bypass surgery, SSRI use has been associated with increased bleeding risk, though this risk has not been consistent across studies[6-8]. Similar findings have been seen in orthopedic surgical procedures, where higher risk for bleeding and more frequent need for transfusions has been reported [9,10].

Existing evidence has significant shortcomings due to a lack of multicenter trials or studies that included a broad range of surgical procedures or surgeons. In addition, few studies were large enough to compare rare outcomes such as bleeding or mortality. Finally, none utilized methods to account for confounding due to the indications for administration of SSRI medications.

To explore whether administration of SSRI's in surgical patients was associated with adverse outcomes, we analyzed data collected from adults undergoing major surgery in a large sample of United States hospitals. Using these data, we first examined the relationship between SSRI administration and mortality, bleeding, length of stay, readmission, and ventricular arrhythmia. To limit the potential for confounding by indication, we then examined the association between SSRI exposure and these outcomes among the subgroup of patients receiving antidepressant therapy, and according to when the SSRI medication was administered in the perioperative period.

Methods

Sites and subjects

Our data were collected on 530,416 patients cared for at 375 hospitals participating in Perspective (Premier Inc., Charlotte, North Carolina), a voluntary, fee-supported database developed for measuring quality and health care utilization, which we have used in previous research [11-14].

In addition to standard hospital discharge file data, Perspective contains a date-stamped log of all materials (e.g. serial compression devices used to prevent venous thromboembolism), and medications (e.g. beta-blockers) charged for during hospitalization. Perspective charge data are collected electronically from participating sites and audited regularly to ensure data validity. Three-quarters of hospitals that participate in Perspective report costs derived from their cost accounting systems, while others provide costs estimated from Medicare cost to charge ratios. In addition, the database contains information about hospital size, teaching status, and location. Although concentrated in Southern states, Perspective sites are generally representative of the US hospital population and perform similarly on publicly reported quality measures [15].

Patients in our analysis were admitted between 1/1/2006 and 12/31/2008, were 18 years of age or older, and underwent elective major surgery using the International Classification of

Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code specification of the Centers for Medicare & Medicaid Services Surgical Care Improvement Project [16].

Because SSRIs are administered by mouth, we were concerned about the possibility of selection bias introduced by the inability of certain patients to take oral medications during the perioperative period. To address this possibility, we restricted the analysis to patients who had received at least one orally administered medication in the two days following surgery. The UCSF institutional review board approved our study.

Data

In addition to patient age, sex, race or ethnicity, marital status, insurance information, and principal procedure, we classified comorbidities using the method of Elixhauser[17]. Data regarding length of stay and hospital costs were obtained from the Perspective discharge file. Medication administration was determined using pharmacy charge data for each day of each patient's stay.

Assessment of SSRI exposure

Exposure to SSRI medications was assessed by screening the daily pharmacy charge data files beginning at admission and ending at discharge. Target medications included: citalopram, escitalopram, fluoxetine, paroxetine, sertraline, fluvoxamine, as well as combinations containing an SSRI (e.g. Symbax, a combination of olanzapine and fluoxetine).

We defined perioperative SSRI use as any charge for one of our target medications occurring anytime during the hospitalization among patients who were taking oral medications as described. To test the notion that SSRIs administered immediately before or after surgery were more likely to represent continuation of a home medication than initiation of antidepressant therapy during a hospitalization for surgery we also created two additional SSRI variables. The first, defined as administration of SSRI medication on the day before or of surgery and afterwards, indicated likely uninterrupted use of long term SSRI, and the second, defined as administration of the SSRI beginning on the day after surgery (or later), but not before surgery, likely represented an SSRI that was temporarily held prior to surgery.

We used an identical approach to define groups who had charges for other non-SSRI antidepressants, anti-platelet agents, warfarin, heparin, and non-steroidal anti-inflammatory agents.

Definition of outcomes

Inpatient mortality was detected using discharge disposition codes. Readmission was detected by screening each site for a patient reencounter within the specified time period; readmissions to sites other than the original hospital are not available in our dataset.

We defined bleeding events using diagnosis codes thought to accurately detect major bleeding episodes in hospitalized patients [18] and which we have used in previous studies [19,20]. We further supplemented this outcome by counting the number of packed red blood cell transfusions administered during hospitalization and examining this outcome as continuous variable. Finally, we defined ventricular arrhythmias using discharge diagnosis codes for ventricular tachycardia, torsades de pointes, and ventricular fibrillation.

Analysis

We used generalized linear models to assess the independent effects of receipt of SSRIs on study outcomes, including gamma models for length of stay, negative binomial models for transfusion number, and logistic models for all dichotomous outcomes. We accounted for clustering by hospital using generalized estimating equations with exchangeable working correlation and robust standard errors. Initial analyses were unadjusted. Covariates were then selected for inclusion in adjusted models if they were associated with the outcome at $p<0.05$, if including them changed estimates for SSRI use by more than 10%, and for face validity.

We also conducted a sensitivity analysis using propensity scores to control confounding [21,22]. Specifically, we used a logistic model to estimate the probability of receiving an SSRI. Covariates with adjusted $P<0.20$ were included in this model. Calibration of the propensity score was checked using the Hosmer-Lemeshow statistic. We then used a greedy matching algorithm to identify pairs composed of one control patient without perioperative SSRI exposure and one patient who received an SSRI [23]. A total of 62892 pairs were matched, with 51218 (81%) matched within a propensity score caliper of 0 to 0.01, an additional 7206 (11.5%) within 0.01 to 0.05, and the remaining 4468 (7.1%) matched within a 0.05 to 0.1. To account for matching, we used conditional logistic models for dichotomous outcomes, and GEE negative binomial and gamma models with clustering on matched pairs for transfusion count and length of stay.

Finally, we carried out prespecified secondary and sensitivity analyses. Our secondary analyses examined SSRI effects in patients with depression, as well as in comparison with patients receiving serotonin-norepinephrine reuptake inhibitors (SNRI) medications [24]. Sensitivity analyses assessed whether our results were prone to residual confounding [25] using calculations in which we posited imbalanced unmeasured covariates of varying prognostic strength. The matched propensity score analysis was implemented using Stata Version 12 (Stata Corp, College Station, TX); all other analyses were carried out using SAS version 9.1 (SAS Institute, Inc. Cary, NC).

Results

Patient characteristics (Table 1)

530,416 patients underwent major surgery during this study; 72540 (13.7%) received an SSRI during the perioperative period. SSRI patients were more likely to be white, female, undergoing spine or knee surgery, and discharged to a skilled nursing facility (SNF). Not surprisingly, patients on SSRIs were far more likely to have depression documented in the medical record (41.0% vs. 6.2%, $p<0.001$). SSRI patients were also more likely to have obesity (17.2% vs. 14.1%, $p<0.0001$) and chronic obstructive pulmonary disease (22.9% vs. 17.0%, $p<0.001$) coded as comorbidities; due to the large sample size, we also noted small but statistically significant differences in proportions of patients having a variety of other comorbidities. Among SSRI users (*Table 2*), the most common SSRI administered was sertraline. Use of other antidepressants in addition to SSRIs was higher in the SSRI group (13.7% vs. 9.8%, $p <0.0001$).

SSRI use and association with patient outcomes (Table 3)

Patients who received SSRIs had higher inpatient mortality (adjusted odds ratio 1.26, 95% CI 1.13, 1.41, number needed to harm = 839), higher 30-day readmission (adjusted odds ratio 1.22, 95% CI 1.18, 1.26, number needed to harm = 75), and higher odds for bleeding (Adjusted odds ratio 1.09, 95% CI 1.04, 1.15, number needed to harm = 424).

Similar findings were seen when we compared SSRI-treated patients to those not on any other antidepressants, but SNRI-treated patients appeared to have similar outcomes compared to SSRI-treated patients. When the analysis was restricted to patients with a diagnosis of depression or those on antidepressant therapy, risk for mortality was attenuated but higher risk of bleeding, readmission, and higher length of stay persisted.

Adjusted outcomes based on timing of SSRI use in perioperative period (Table 4)

We then examined whether use of SSRIs throughout the surgical period was associated with different risks than if an SSRI was administered only postoperatively. Compared with patients who were not treated with an SSRI, those who received SSRIs only postoperatively continued to have higher odds for bleeding, readmission at 30 days, and more transfusions, but no difference in odds for mortality or ventricular arrhythmia. Moreover, findings from our overall analyses were essentially unchanged when we excluded patients who received their SSRI only after surgery.

Propensity-matched sample (Table 5)

In the sensitivity analysis using pair-matching on propensity scores, estimated effect sizes were essentially unchanged compared to our base analyses. SSRI exposure in the perioperative time period was associated with elevated risk for mortality and readmission, with a number needed to harm of approximately 1000.

Other sensitivity analyses

SSRI effect estimates were unaffected by additional adjustment for concomitant use of anticoagulants, thromboembolism prevention treatments, non-steroidal anti-inflammatory medications, and aspirin. We also found no evidence for modification of the SSRI effect by these co-treatments or by surgery type.

Finally, we assessed sensitivity to unmeasured confounding, first focusing on bleeding. To account for 9% increase in the adjusted odds of bleeding in the SSRI group, an unmeasured confounder that increased the odds of bleeding by 10% would need to be present in 40% (e.g. 10% vs. 50% of patients) more SSRI patients than non-SSRI patients. Conversely, if the imbalance were only 10%, the unmeasured confounder would need to increase the odds of bleeding by 40%. Even stronger or more badly imbalanced unmeasured confounders must be posited to account for the associations of SSRI use with readmission and mortality.

Discussion

In this large observational study of patients undergoing major surgery, exposure to selective serotonin reuptake inhibitors in the perioperative period was associated with higher risk for a range of adverse outcomes, particularly bleeding. Higher risk for adverse events was noted after accounting for medications that may have produced risk and regardless of whether SSRI medications were held or administered continuously throughout hospitalization. Although risk for bleeding was consistent across subgroup analyses, differences in mortality and other discrete outcomes were diminished in patients with depression. Propensity-matched results were similar, and sensitivity analyses suggested our findings are robust.

While the implications of bleeding clearly differ according to the surgical procedure, SSRI association with adverse outcomes appeared relatively consistent in a range of patient subgroups. Concern for SSRIs' potential associations with bleeding outcomes has already been incorporated into available clinical practice references, several of which suggest stopping or holding SSRIs two or more weeks prior to surgery [26-28], with particular attention to holding SSRIs in patients undergoing neurologic or orthopedic surgery. Although we

cannot directly confirm this hypothesis in our data, it seems highly likely that patients on SSRIs in our cohort had been receiving these medications prior to hospitalization. Moreover, rates of SSRI use were higher in patient groups where long-term use would appear most likely (e.g. patients with a diagnosis of depression). This limitation in our data also restricts our ability to discern an optimal management strategy, which would ideally specify the amount of time SSRIs should be held before surgery and when they should be restarted afterwards. Although we cannot discern how long SSRIs were held perioperatively, our results showed higher risk in patients receiving SSRIs after surgery only. This finding suggests that holding SSRIs for longer time periods after surgery (or potentially holding them longer preoperatively) may be worthy of investigation.

While risks for mortality were attenuated among patients who had a diagnosis of depression, and patients being treated with an antidepressant medication, patients on SSRIs appeared to have consistently higher risks for bleeding in nearly all subgroups tested, supporting the idea of a pharmacologic effect on platelet function. Rather than being a risk factor itself, use of SSRI medications in patients with depression may simply be a marker for other factors, such as more severe mood disorders, poorer functional status, neuropathy, or chronic pain, many of which are associated with higher risk for readmission or mortality. Alternatively, patients in these subgroups may represent a patient population where the need to hold SSRIs perioperatively had been recognized, thereby producing a group of patients in which those continuing on SSRIs were perceived to be at lower risk and those not on SSRIs at higher risk. While it is possible that the association between SSRIs and outcomes could have been biased towards the null in this scenario, we limited the risk of this influence by excluding patients who were not taking other oral medications and through the sensitivity analyses. Interestingly, risks for bleeding among patients on SNRIs or SSRIs alone were similar; SNRIs and SSRIs are thought to potentially have similar antiplatelet effects [24]. It is important to note that a substantial proportion of SSRI administration was among patients without depression, so while the depressed patient subgroup is important in that it helps discern the potential for confounding by indication, findings in our overall sample are more likely to represent current clinical practice.

Our study has a number of limitations. First, because we used administrative data from the inpatient stay only, and because the study was carried out prior to the onset of present-on-admission coding, we cannot easily distinguish complications from preexisting disease and may be subject to coding biases. Our medication measures were collected from electronic billing systems rather than chart abstraction and were not validated in a scientific study. However, Premier's charge and diagnosis data are regularly audited for accuracy, and estimates of medication use have been similar to those seen in studies that have relied on chart review [29]. Our cost data include those incurred during hospitalization and do not take into account costs or events occurring after hospital discharge. As an observational study, the results are subject to biases related to nonrandom assignment of patients to receive medications, as well as documentation biases described. We cannot discern how long SSRI medications may have been held prior to surgery among the group given SSRIs only postoperatively, a fact that may be partially responsible for persistent risk in these patients. In addition, it is possible that some patients we considered to not have exposure to SSRIs may have been treated up until the hospitalization and may have not had them restarted until returning to primary care; this would potentially bias our results towards the null, as mentioned. However, our results were robust even after adjusting for all available patient-level and hospital-level data associated with our measures of resource use. In addition, we were concerned about the risk of immortal time bias in our study. We addressed this potential bias by including only patients who were alive and able to take oral medications around the time of surgery, an approach that may have excluded higher risk patients in both SSRI and non-SSRI groups. Finally, some surgeries in our dataset may have been at least

partially performed by fellows or residents. To address this potential concern, we did adjust for whether the surgery was performed at a teaching hospital.

Our results suggest that SSRI medications are associated with a range of poorer outcomes following major surgery. Higher risk was seen in a range of patient groups and was not attenuated after adjusting for all available data, but may differ in subgroups that have higher prevalence of diagnosed psychiatric illness. While holding SSRI medications at the time of surgery may be an appropriately conservative approach, our data cannot frame a more tailored or nuanced strategy for managing surgical patients on SSRIs. To determine the true risks of SSRI use, and potentially outline optimal management strategies, prospective studies will need to randomly allocate patients to strategies of early discontinuation of SSRI's (e.g. weeks before surgery), holding SSRI's closer to the time of surgery, and not holding SSRI at all (e.g. usual care). Using a factorial design these studies would need to incorporate strategies whereby SSRI's are restarted postoperatively at standard time points (e.g. restart on day after surgery, or at discharge). Given the low event rates we have seen in our analyses, any trial would need to be quite large to accrue adequate patients in each subgroup to detect adverse outcomes with adequate power. Such a study would be quite costly, but given the ubiquitous nature of SSRIs in US healthcare, and the potential risks of proceeding without adequate evidence for a strategy for how to mitigate risks of perioperative SSRI use, any study costs would seem money well-spent.

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Table 1

Characteristics of patients taking and not taking SSRI medications in perioperative period (Total n = 530,416)

	No SSRI Meds N (%) N=457876 (86.3%)	Received SSRI Meds N (%) N=72540 (13.7%)	P value
Age mean (SD)	65.5 (12.8)	63.8 (12.7)	<0.0001
Male gender	203280 (44.4%)	18912 (26.1%)	<0.0001
Race/ethnicity			<0.0001
White	333290 (72.8%)	57207 (78.9%)	
Black	39583 (8.6%)	3373 (4.7%)	
Hispanic	10399 (2.3%)	1200 (1.7%)	
Other	74604 (16.3%)	10760 (14.8%)	
Type of surgery			<0.0001
Spine	54067 (11.8%)	11285 (15.6%)	
Pneumonectomy	8572 (1.9%)	1364 (1.9%)	
Cardio	71801 (15.7%)	6196 (8.5%)	
Vascular	16942 (3.7%)	2309 (3.2%)	
GI	15530 (3.4%)	2506 (3.5%)	
Nephrectomy	6718 (1.5%)	826 (1.1%)	
GYN	21009 (4.6%)	3840 (5.3%)	
Hip/femur fracture	7054 (1.5%)	1969 (2.7%)	
Arthroplasty knee	170450 (37.2%)	29012 (40.0%)	
Hip replacement	85733 (18.7%)	13233 (18.2%)	
Admit source			0.0003
Outpatient	426246 (93.1%)	67598 (93.2%)	
Transfer	25647 (5.6%)	4122 (5.7%)	
Not specified	5983 (1.3%)	820 (1.1%)	
Primary payer			<0.0001
Uninsured	5660 (1.2%)	610 (0.8%)	
Indemnity	46947 (10.3%)	7456 (10.3%)	
Managed care/capitated	4504 (1.0%)	790 (1.1%)	
Managed care/non-capitated	122268 (26.7%)	19630 (27.1%)	
Medicaid	14730 (3.2%)	3275 (4.5%)	
Medicare	259425 (56.7%)	40098 (55.3%)	
other	4342 (1.0%)	681 (0.9%)	
Disposition			<0.0001
Home	167157 (36.5%)	24361 (33.6%)	
Transfer	8498 (1.9%)	1592 (2.2%)	
SNF	90554 (19.8%)	17455 (24.1%)	
Home health care	149013 (32.5%)	21853 (30.1%)	
Died (initial hospitalization)	1937 (0.4%)	331 (0.5%)	
Rehabilitation center	40410 (8.8%)	6909 (9.5%)	
Other	307 (0.1%)	39 (0.1%)	

	No SSRI Meds N (%) N=457876 (86.3%)	Received SSRI Meds N (%) N=72540 (13.7%)	P value
Elixhauser Comorbidities			
Hypertension	299280 (65.4%)	46796 (64.5%)	<0.0001
Depression	28163 (6.2%)	29754 (41.0%)	<0.0001
Diabetes	93608 (20.4%)	15604 (21.5%)	<0.0001
Chronic pulmonary disease	77705 (17.0%)	16643 (22.9%)	<0.0001
Deficiency anemia	75127 (16.4%)	13170 (18.2%)	<0.0001
Obesity	64723 (14.1%)	12501 (17.2%)	<0.0001
Hypothyroidism	56980 (12.4%)	12574 (17.3%)	<0.0001
Fluid & electrolyte disorders	52353 (11.4%)	8965 (12.4%)	<0.0001
Peripheral vascular disease	27059 (5.9%)	3430 (4.7%)	<0.0001
CHF	19993 (4.4%)	4052 (5.6%)	<0.0001
Valve disease	21496 (4.7%)	3638 (5.0%)	0.0002
Renal failure	23515 (5.1%)	3568 (4.9%)	0.0136
Other neurological disease	15816 (3.5%)	4953 (6.8%)	<0.0001
Rheumatoid arthritis/collagen vas	14281 (3.1%)	2941 (4.1%)	<0.0001
Coagulopathy	15074 (3.3%)	1901 (2.6%)	<0.0001
Chronic blood loss anemia	11732 (2.6%)	2109 (2.9%)	<0.0001
Diabetes w/ chronic complications	11856 (2.6%)	2065 (2.9%)	<0.0001
Psychoses	6783 (1.5%)	3097 (4.3%)	<0.0001
Pulmonary circulation disease	5363 (1.2%)	950 (2.3%)	0.0014
Alcohol abuse	6030 (1.3%)	1016 (1.4%)	0.0675
Weight loss	4784 (1.0%)	913 (1.3%)	<0.0001
Metastatic cancer	5262 (1.2%)	829 (1.1%)	0.8815
Paralysis	4012 (0.9%)	960 (1.3%)	<0.0001
Liver disease	3697 (0.8%)	787 (1.1%)	<0.0001
Drug abuse	2693 (0.6%)	628 (0.9%)	<0.0001
Solid tumor w/o metastasis	3647 (0.8%)	462 (0.6%)	<0.0001
Lymphoma	1593 (0.4%)	262 (0.4%)	0.5738
Characteristics of Hospitals			
Location			<0.0001
Rural	50195 (11.0%)	8690 (12.0%)	
Urban	407681 (89.0%)	63850 (88.0%)	
Area			<0.0001
Midwest	105698 (23.1%)	16908 (23.3%)	
Northeast	67816 (14.8%)	9546 (13.2%)	
South	194412 (42.5%)	32080 (44.2%)	
West	89950 (19.7%)	14006 (19.3%)	
Number of beds			0.0003
0−99	11553 (2.5%)	1786 (2.5%)	
100−199	34937 (7.6%)	5801 (8.0%)	
200−299	65708 (14.4%)	10501 (14.5%)	

	No SSRI Meds N (%) N=457876 (86.3%)	Received SSRI Meds N (%) N=72540 (13.7%)	P value
300−399	94346 (20.6%)	14728 (20.3%)	
400−499	81890 (17.9%)	13225 (18.2%)	
≥500	169442 (37.0%)	26499 (36.5%)	
Teaching	115974 (25.3%)	17144 (23.6%)	<0.0001
Outcomes			
Mortality (initial hospitalization and readmission)	2667 (0.6%)	461 (0.6%)	0.0830
Readmission 30 days	30296 (6.6%)	5725 (7.9%)	<0.0001
Any bleeding	12193 (2.7%)	1887 (2.6%)	0.3374
LOS mean (SD)	5.3 (4.7)	5.2 (4.7)	0.0584
LOS median (IQR)	4 (3, 6)	4 (3, 5)	<0.0001
Transfusions median (IQR) (range)	0 (0, 0) (0−48)	0 (0, 0) (0−76)	<0.0001
Ventricular arrhythmia	6958 (1.5%)	709 (1.0%)	<0.0001
Transfusion count			
0	399351 (87.2%)	61787 (85.2%)	<0.0001
1	27661 (6.0%)	4950 (6.8%)	
2	23384 (5.1%)	4470 (6.2%)	
3	3765 (0.8%)	665 (0.9%)	
≥ 4	3715 (0.8%)	668 (0.9%)	

Table 2

Antidepressants administered to patients in perioperative period (Total n = 530,416)

Antidepressant	**No SSRI n=457876**	**SSRI n=72540**	**p**
	N (%)	**N (%)**	
SSRI Antidepressants	NA	72540 (13.7%)	NA
Olanzapine/fluoxetine (Symbax)	NA	18 (0.02%)	NA
Citalopram (Celexa)	NA	10334 (14.3%)	NA
Escilatopram (Lexapro)	NA	18380 (25.3%)	NA
Fluoxetine (Prozac)	NA	12885 (17.8%)	NA
Paroxetine (Paxil)	NA	11845 (16.3%)	NA
Sertraline (Zoloft)	NA	19200 (26.5%)	NA
Fluvoxamine (Luvox)	NA	193 (0.3%)	NA
Timing of SSRI	NA		NA
SSRI administered prior to surgery	NA	68095 (93.9%)	NA
SSRI administered after surgery only	NA	4445 (6.1%)	NA
Any-non SSRI Antidepressants	45004 (9.8%)	9956 (13.7%)	<0.0001
Serotonin and norepinephrine reuptake inhibitors (SNRI)	23395 (5.1%)	1315 (1.8%)	<0.0001
Tricyclic antidepressants	10737 (2.3%)	3001 (4.1%)	<0.0001
Monoamine Oxidase Inhibitors	54 (0.01%)	1 (0%)	0.0052
Other medications used in depression (e.g. trazodone)	15623 (3.3%)	6109 (8.4%)	<0.0001

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Table 3

Adjusted odds or rate ratios for outcomes for SSRI treatment in the overall sample, and in selected patient subgroups

Patient group	**Entire sample**	**Patients on SSRI or no antidepressant**	**Among patients on any antidepressants**	**Among patients on SSRI only or SNRI only**	**Among patients with depression**	**Among patients with depression**
Sample size	**n=530,416**	**n=475,456**	**n=117,544**	**n=82,134**	**n=60,777**	**N=40,213**
Overall n and % on SSRI	72,540 (13.7%)	62,584 (13.2%)	72,540 (61.7%)	62,584 (76.2%)	30,923 (50.9%)	25,824 (64.2%)
Comparison groups	SSRI vs. overall	SSRI vs. no other antidepressants	SSRI vs. other treatments	SSRI only vs. SNRI only	SSRI vs. other treatments	SSRI vs. no other antidepressants
	Adjusted OR/Rate Ratio (95% CI)	Adjusted OR/Rate Ratio (95% CI)	Adjusted OR/Rate Ratio (95% CI)	Adjusted OR/Rate Ratio (95% CI)	Adjusted OR/Rate Ratio (95% CI)	Adjusted OR/Rate Ratio (95% CI)
Mortality (Adjusted Odds, 95% CI)	1.20 (1.07, 1.36)	1.22 (1.07, 1.38)	1.04 (0.87, 1.25)	1.54 (1.18, 2.01)	0.86 (0.65, 1.13)	1.00 (0.72, 1.37)
Bleeding (Adjusted Odds, 95% CI)	1.09 (1.04, 1.15)	1.21 (1.17, 1.26)	1.00 (0.93, 1.08)	0.90 (0.85, 0.96)	1.10 (1.03, 1.18)	1.15 (1.01, 1.32)
Readmission 30 days (Adjusted Odds, 95% CI)	1.22 (1.18, 1.26)	1.08 (1.02, 1.14)	0.98 (0.94, 1.03)	1.00 (0.89, 1.12)	1.16 (1.04, 1.29)	1.08 (0.99, 1.17)
Ventricular arrhythmia (Adjusted Odds, 95% CI)	0.89 (0.83, 0.96)	0.87 (0.79, 0.96)	1.10 (0.95, 1.28)	1.05 (0.86, 1.29)	0.82 (0.68, 0.98)	0.98 (0.97, 0.99)
Transfusion count (Adjusted rate ratio, 95% CI)	1.10 (1.08, 1.13)	1.02 (1.01, 1.02)	0.98 (0.97, 0.99)	0.97 (0.96, 0.99)	0.99 (0.98, 1.00)	1.10 (1.08, 1.13)
Length of Stay (Adjusted rate ratio, 95% CI)	1.02 (1.02, 1.03)	1.10 (1.07, 1.12)	1.09 (1.06, 1.13)	1.00 (0.96, 1.03)	1.04 (1.01, 1.08)	0.98 (0.97, 0.99)

Table 4

Adjusted odds or rate ratio for outcomes for treatment with SSRI, among all patients, and excluding those treated only post-operatively

Model	All patients (n = 530416)	Excluding patients receiving SSRI after surgery only (n =525971)
Mortality (Adjusted Odds, 95% CI)		
No SSRI	Ref	Ref
SSRI administered prior to surgery*	1.25 (1.11, 1.41)	1.25 (1.11, 1.41)
SSRI administered after surgery	1.29 (0.90, 1.85)	NA
Bleeding (Adjusted Odds, 95% CI)		
No SSRI	Ref	Ref
SSRI administered prior to surgery*	1.07 (1.02, 1.13)	1.08 (1.02, 1.14)
SSRI administered after surgery	1.29 (1.12, 1.48)	NA
Readmission 30 days (Adjusted Odds, 95% CI)		
No SSRI	Ref	Ref
SSRI administered prior to surgery*	1.18 (1.14, 1.23)	1.21 (1.16, 1.25)
SSRI administered after surgery	1.66 (1.49, 1.84)	NA
Ventricular arrhythmia (Adjusted Odds, 95% CI)		
No SSRI	Ref	Ref
SSRI administered prior to surgery*	0.85 (0.78, 0.92)	0.85 (0.78, 0.93)
SSRI administered after surgery	1.31 (1.08, 1.58)	NA
Transfusion count (Adjusted rate ratio, 95% CI)		
No SSRI	Ref	Ref
SSRI administered prior to surgery*	1.14 (1.10, 1.17)	1.14 (1.10, 1.17)
SSRI administered after surgery	1.28 (1.18, 1.39)	NA
Length of Stay (Adjusted rate ratio, 95% CI)		
No SSRI	Ref	Ref
SSRI administered prior to surgery*	1.03 (1.02, 1.04)	1.03 (1.02, 1.04)
SSRI administered after surgery	1.09 (1.06, 1.12)	NA

*SSRI received before surgery and afterwards.

Table 5

Propensity-matched analysis

Outcome	No SSRI (N = 62892)	SSRI (N = 62892)	Measure of Association (95% CI)	p-value
Mortality n(%)	352 (0.56%)	419 (0.67%)	1.19 (1.03−1.37)*	0.016
Bleeding n(%)	1576 (2.51%)	1676 (2.66%)	1.07 (0.99−1.14)*	0.076
Readmission 30 days n(%)	4264 (6.78%)	4964 (7.89%)	1.18 (1.13−1.23)*	<0.001
Ventricular arrhythmia n(%)	748 (1.19%)	645 (1.03%)	0.86 (0.77−0.96)*	.005
Transfusion count n(%)				
0	54887 (87.3%)	53528 (85.1%)	1.19 (1.15−1.23)**	<0.001
1	3743 (5.95%)	4319 (6.87%)		
2	3311 (5.26%)	3870 (6.15%)		
3	474 (0.75%)	585 (0.93%)		
≧4	477 (0.76%)	590 (0.94%)		
LOS median (IQR)	4 (3, 5)	4 (3, 6)	1.01 (1.00−1.02)***	0.008

* Odds ratios using conditional logistic models

** Rate ratio estimated using GEE negative binomial model

*** Rate ratio estimated using GEE gamma model