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

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Importance: Single-site studies have described an association between use of selective serotonin reuptake inhibitors (SSRIs) and adverse outcomes of surgery. Multicenter studies including a broad range of surgical procedures that explore rare outcomes, such as bleeding and mortality, and that account for indications for administration of SSRIs are needed.

Objective: To determine whether perioperative use of SSRIs is associated with adverse outcomes of surgery in a national sample of patients.

Design: Retrospective study of patients 18 years or older who underwent major surgery from January 1, 2006, through December 31, 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.

Setting: Three hundred seventy-five US hospitals.

Participants: Five hundred thirty thousand four hundred sixteen patients 18 years or older.

Exposure: Perioperative use of SSRIs.

Main Outcomes and Measures: In-hospital mortality, length of stay, readmission at 30 days, bleeding events, transfusions, and incidence of ventricular arrhythmias.

Results: Patients receiving SSRIs were more likely to have obesity, chronic pulmonary disease, or hypothyroidism ($P < .001$ for each) and more likely to have depression (41.0% vs 6.2%, $P < .001$). After adjustment, patients receiving SSRIs had higher odds of in-hospital mortality (adjusted odds ratio, 1.20 [95% CI, 1.07-1.36]), bleeding (1.09 [1.04-1.15]), and readmission at 30 days (1.22 [1.18-1.26]). Similar results were observed in propensity-matched analyses, although the risk of inpatient mortality was attenuated among patients with depression. Sensitivity analyses suggest that, 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 and Relevance: Receiving SSRIs in the perioperative period is associated with a higher risk for adverse events. Determining whether patient factors or SSRIs themselves are responsible for elevated risks requires prospective study.

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SELECTIVE SEROTONIN REUPtake inhibitors (SSRIs) are among the most commonly prescribed medications in the United States. In ambulatory patients, SSRI use appears to be associated with a small but elevated risk for hemorrhage, particularly if coadministered with nonsteroidal anti-inflammatory medications or warfarin sodium (Coumadin),[1-3] an association thought to result from the serotonin-related antiplatelet effects of SSRIs. Ambulatory patients receiving SSRIs may also have higher risk for arrhythmias and sudden death.[4,5]

In surgical patients, a small evidence base suggests that SSRI use is associated with bleeding and adverse outcomes, also thought to be due to the antiplatelet effects of SSRIs. In coronary bypass surgery, SSRI use has been associated with an increased risk of bleeding, although this risk

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has not been consistent across studies.[6-8] Similar findings have been seen in orthopedic surgical procedures, where a higher risk of bleeding and a more frequent need for transfusions have been reported.[9,10]

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Existing evidence has significant shortcomings owing 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 of the studies used methods to account for confounding due to the indications for administration of SSRIs.

To explore whether administration of SSRIs in surgical patients was associated with adverse outcomes, we analyzed data collected from adults undergoing major surgery in a large sample of US 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 among the subgroup of patients receiving antidepressants and according to when the SSRI was administered in the perioperative period.

METHODS

SITES AND SUBJECTS

Our data were collected for 530 416 patients receiving care 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 with other investigators in previous research.[11-14] In addition to standard hospital discharge file data, Perspective contains a date-stamped log of all materials (eg, serial compression devices used to prevent venous thromboembolism) and medications (eg, β-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, whereas 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 from January 1, 2006, through December 31, 2008; were 18 years or older; and underwent elective major surgery identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification* code specification of the Centers for Medicare & Medicaid Services Surgical Care Improvement Program.[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 1 orally administered medication in the 2 days after surgery. The University of California, San Francisco, 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 et al.[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 SSRIs was assessed by screening the daily pharmacy charge data files, beginning at admission and ending at discharge. Target medications included citalopram hydrobromide (Celexa), escitalopram oxalate (Lexapro), fluoxetine hydrochloride (Prozac), paroxetine hydrochloride (Paxil), sertraline hydrochloride (Zoloft), fluvoxamine maleate (Luvox), and combinations containing an SSRI (eg, a combination of olanzapine and fluoxetine [Symbyax]).

We defined perioperative SSRI use as any charge for one of our target medications during the hospitalization among patients who were taking oral medications. 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 created 2 additional SSRI variables. The first, defined as administration of the SSRI on the day before or the day of surgery and afterward, indicated likely uninterrupted long-term use of SSRIs; the second, defined as administration of the SSRI beginning on the day after surgery (or later), but not before surgery, likely represented SSRI therapy that was temporarily held before surgery. We used an identical approach to define groups who had charges for other non-SSRI antidepressants, antiplatelet agents, warfarin, heparin, and nonsteroidal 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 period; readmissions to sites other than the original hospital are not available in our data set.

We defined bleeding events using diagnosis codes thought to accurately detect major bleeding episodes in hospitalized patients[18] and that we have used in previous studies (eAppendix 1; http://www.jamainternalmed.com).[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 a 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 SSRI use 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 included in adjusted models if they were associated with the outcome at $P < .05$, if inclusion changed estimates for SSRI use by more than 10%, or for reasons of 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 $P < .20$ were included in this model. Calibration of the propensity score was checked using the Hosmer-Lemeshow goodness-of-fit statistic. We then used a greedy matching algorithm to identify pairs composed of 1 control

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Table 1. Characteristics of Patients Taking and Not Taking SSRIs in the Perioperative Period[a]

Characteristic	No SSRI (n = 457 876)	SSRI Use (n = 72 540)	*P* Value
Age, mean (SD), y	65.5 (12.8)	63.8 (12.7)	<.001
Male sex	203 280 (44.4)	18 912 (26.1)	<.001
Race/ethnicity			
White	333 290 (72.8)	57 207 (78.9)	<.001
Black	39 583 (8.6)	3373 (4.6)	
Hispanic	10 399 (2.3)	1200 (1.7)	
Other	74 604 (16.3)	10 760 (14.8)	
Type of surgery			
Spine	54 067 (11.8)	11 285 (15.6)	<.001
Pneumonectomy	8572 (1.9)	1364 (1.9)	
Cardiac	71 801 (15.7)	6196 (8.5)	
Vascular	16 942 (3.7)	2309 (3.2)	
GI tract	15 530 (3.4)	2506 (3.5)	
Nephrectomy	6718 (1.5)	826 (1.1)	
Gynecological	21 009 (4.6)	3840 (5.3)	
Hip/femur fracture	7054 (1.5)	1969 (2.7)	
Arthroplasty of the knee	170 450 (37.2)	29 012 (40.0)	
Hip replacement	85 733 (18.7)	13 233 (18.2)	
Admission source			
Outpatient	426 246 (93.1)	67 598 (93.2)	<.001
Transfer	25 647 (5.6)	4122 (5.7)	
Not specified	5983 (1.3)	820 (1.1)	
Primary payer			
Uninsured	5660 (1.2)	610 (0.8)	<.001
Indemnity	46 947 (10.3)	7456 (10.3)	
Managed care/capitated	4504 (1.0)	790 (1.1)	
Managed care/noncapitated	122 268 (26.7)	19 630 (27.1)	
Medicaid	14 730 (3.2)	3275 (4.5)	
Medicare	259 425 (56.7)	40 098 (55.3)	
Other	4342 (0.9)	681 (0.9)	
Disposition			
Home	167 157 (36.5)	24 361 (33.6)	<.001
Transfer	8498 (1.9)	1592 (2.2)	
Skilled nursing facility	90 554 (19.8)	17 455 (24.1)	
Home health care	149 013 (32.5)	21 853 (30.1)	
Died (initial hospitalization)	1937 (0.4)	331 (0.5)	
Rehabilitation center	40 410 (8.8)	6909 (9.5)	
Other	307 (0.1)	39 (0.1)	
Elixhauser comorbidities			
Hypertension	299 280 (65.4)	46 796 (64.5)	<.001
Depression	28 163 (6.2)	29 754 (41.0)	<.001
Diabetes	93 608 (20.4)	15 604 (21.5)	<.001
COPD	77 705 (17.0)	16 643 (22.9)	<.001
Deficiency anemia	75 127 (16.4)	13 170 (18.2)	<.001
Obesity	64 723 (14.1)	12 501 (17.2)	<.001
Hypothyroidism	56 980 (12.4)	12 574 (17.3)	<.001
Fluid and electrolyte disorders	52 353 (11.4)	8965 (12.4)	<.001
Peripheral vascular disease	27 059 (5.9)	3430 (4.7)	<.001
Congestive heart failure	19 993 (4.4)	4052 (5.6)	<.001
Valve disease	21 496 (4.7)	3638 (5.0)	<.001
Renal failure	23 515 (5.1)	3568 (4.9)	.01
Other neurological disease	15 816 (3.5)	4953 (6.8)	<.001
Rheumatoid arthritis/ collagen vascular disease	14 281 (3.1)	2941 (4.1)	<.001
Coagulopathy	15 074 (3.3)	1901 (2.6)	<.001
Chronic blood loss, anemia	11 732 (2.6)	2109 (2.9)	<.001
Diabetes mellitus with chronic complications	11 856 (2.6)	2065 (2.8)	<.001
Psychoses	6783 (1.5)	3097 (4.3)	<.001
Pulmonary circulation disease	5363 (1.2)	950 (1.3)	.001
Alcohol abuse	6030 (1.3)	1016 (1.4)	.07
Weight loss	4784 (1.0)	913 (1.3)	<.001
Metastatic cancer	5262 (1.1)	829 (1.1)	.88
Paralysis	4012 (0.9)	960 (1.3)	<.001
Liver disease	3697 (0.8)	787 (1.1)	<.001
Other drug abuse	2693 (0.6)	628 (0.9)	<.001
Solid tumor without metastasis	3647 (0.8)	462 (0.6)	<.001
Lymphoma	1593 (0.3)	262 (0.4)	.57

Abbreviations: COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; SSRI, selective serotonin reuptake inhibitor.
[a] Includes 530 416 patients undergoing major surgery. Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and might not total 100.

Table 2. Characteristics of Hospitals Included in the Perspective Database

Characteristic	No. (%) of Patients[a]		*P* Value
	No SSRI (n = 457 876)	SSRI Use (n = 72 540)	
Location			
Rural	50 195 (11.0)	8690 (12.0)	<.001
Urban	407 681 (89.0)	63 850 (88.0)	
Area			
Midwest	105 698 (23.1)	16 908 (23.3)	<.001
Northeast	67 816 (14.8)	9546 (13.2)	
South	194 412 (42.5)	32 080 (44.2)	
West	89 950 (19.6)	14 006 (19.3)	
No. of beds			
0-99	11 553 (2.5)	1786 (2.5)	<.001
100-199	34 937 (7.6)	5801 (8.0)	
200-299	65 708 (14.4)	10 501 (14.5)	
300-399	94 346 (20.6)	14 728 (20.3)	
400-499	81 890 (17.9)	13 225 (18.2)	
≥500	169 442 (37.0)	26 499 (36.5)	
Teaching	115 974 (25.3)	17 144 (23.6)	<.001

Abbreviation: SSRI, selective serotonin reuptake inhibitor.
[a] Includes 530 416 patients undergoing major surgery.

patient without perioperative SSRI exposure and 1 patient who received an SSRI.[23] A total of 62 892 pairs were matched, with 51 218 (81.4%) 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%), within 0.05 to 0.1. To account for matching, we used conditional logistic models for dichotomous outcomes and negative binomial and gamma models with generalized estimating equations and with clustering on matched pairs for transfusion count and length of stay.

Finally, we performed prespecified secondary and sensitivity analyses. Our secondary analyses examined SSRI effects in patients with depression and compared with patients receiving serotonin norepinephrine reuptake inhibitors (SNRIs).[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 commercially available software (STATA, version 12; StataCorp); all other analyses used a different software package (SAS, version 9.1; SAS Institute, Inc).

RESULTS

PATIENT CHARACTERISTICS

A total of 530 416 patients underwent major surgery during this study; 72 540 (13.7%) received an SSRI during the perioperative period. Patient characteristics are listed in **Table 1**; hospital characteristics, in **Table 2**; and patient outcomes, in **Table 3**. Patients who received SSRIs were more likely to be white, female, undergoing spine or knee surgery, and discharged to a skilled nursing facility. Not surprisingly, patients receiving SSRIs were far more likely to have depression documented in the medical record (41.0% vs 6.2%; $P<.001$) and more likely to have obesity (17.2% vs 14.1%; $P<.001$) and chronic obstructive pulmonary disease (22.9% vs 17.0%; $P<.001$) coded as comorbidities. Owing to the large sample size,

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Table 3. Outcomes of Patients Taking and Not Taking SSRIs in the Perioperative Period[a]

Outcome	No SSRI (n = 457 876)	SSRI Use (n = 72 540)	*P* Value
Mortality (initial hospitalization and readmission)	2667 (0.6)	461 (0.6)	.08
Readmission at 30 days	30 296 (6.6)	5725 (7.9)	<.001
Any bleeding	12 193 (2.7)	1887 (2.6)	.34
Length of stay, d			
Mean (SD)	5.3 (4.7)	5.2 (4.7)	.06
Median (IQR)	4 (3-6)	4 (3-5)	<.001
No. of transfusions			
Median (IQR)	0 (0-0)	0 (0-0)	<.001
Range	0-48	0-76	
Ventricular arrhythmia	6958 (1.5)	709 (1.0)	<.001
No. of transfusions			
0	399 351 (87.2)	61 787 (85.2)	<.001
1	27 661 (6.0)	4950 (6.8)	
2	23 384 (5.1)	4470 (6.2)	
3	3765 (0.8)	665 (0.9)	
≥4	3715 (0.8)	668 (0.9)	

Abbreviations: IQR, interquartile range; SSRI, selective serotonin reuptake inhibitor.
[a] Includes 530 416 patients undergoing major surgery. Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and might not total 100.

Table 4. Antidepressants Administered to Patients in the Perioperative Period

Antidepressant Data	No. (%) of Patients[a]		
	No SSRI (n = 457 876)	SSRI Use (n = 72 540)	*P* Value
SSRI antidepressants			
Olanzapine and fluoxetine hydrochloride (Symbyax)	NA	18 (0.02)	NA
Citalopram hydrobromide (Celexa)	NA	10 334 (14.2)	NA
Escitalopram oxalate (Lexapro)	NA	18 380 (25.3)	NA
Fluoxetine (Prozac)	NA	12 885 (17.8)	NA
Paroxetine hydrochloride (Paxil)	NA	11 845 (16.3)	NA
Sertraline hydrochloride (Zoloft)	NA	19 200 (26.5)	NA
Fluvoxamine maleate (Luvox)	NA	193 (0.3)	NA
Timing of SSRI administration			
Before surgery	NA	68 095 (93.9)	NA
After surgery only	NA	4445 (6.1)	NA
Any non-SSRI antidepressant	45 004 (9.8)	9956 (13.7)	<.001
SNRI	23 395 (5.1)	1315 (1.8)	<.001
Tricyclic antidepressants	10 737 (2.3)	3001 (4.1)	<.001
Monoamine oxidase inhibitors	54 (0.01)	1 (0.001)	.005
Other medication used in depression (eg, trazodone)	15 623 (3.4)	6109 (8.4)	<.001

Abbreviations: NA, not applicable; SRNI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitors.
[a] Includes 530 416 patients undergoing major surgery.

we also noted small but statistically significant differences in proportions of patients having a variety of other comorbidities (Table 1). Among SSRI users (**Table 4**), 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%; $P<.001$).

SSRI USE AND ASSOCIATION WITH PATIENT OUTCOMES

Compared with those who did not receive SSRIs, patients who received SSRIs had higher overall mortality (adjusted odds ratio, 1.20 [95% CI, 1.07-1.36]; number needed to harm, 839), higher 30-day readmission (1.22 [1.18-1.26]; number needed to harm, 75), and higher odds for bleeding (1.09 [1.04-1.15]; number needed to harm, 424) (**Table 5**). Similar findings were seen when we compared SSRI-treated patients with those not receiving any other antidepressants, but SNRI-treated patients appeared to have similar outcomes compared with SSRI-treated patients. When the analysis was restricted to patients with a diagnosis of depression or those receiving antidepressants, the 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

We then examined whether use of SSRIs throughout the surgical period was associated with different risks than if an SSRI was administered only postoperatively (**Table 6**). Patients who received SSRIs only postoperatively continued to have higher odds for bleeding and readmission at 30 days and more transfusions, but no difference in odds for mortality or ventricular arrhythmia, compared with those who received no SSRI. Moreover, findings from our overall analyses were essentially unchanged when we excluded patients who received their SSRI only after surgery.

PROPENSITY-MATCHED SAMPLE

In the sensitivity analysis using pair matching on propensity scores, estimated effect sizes were essentially unchanged compared with our base analyses. Exposure to SSRIs in the perioperative period was associated with elevated risk for mortality and readmission, with a number needed to harm of approximately 1000 (**Table 7**).

OTHER SENSITIVITY ANALYSES

Effect estimates for SSRIs were unaffected by additional adjustment for concomitant use of anticoagulants, thromboembolism prevention treatments, nonsteroidal anti-inflammatory medications, and aspirin. We also found no evidence for modification of the SSRI effect by these cotreatments or by surgery type (eAppendix 2 and eAppendix 3).

Finally, we assessed sensitivity to unmeasured confounding, first focusing on bleeding. To account for the 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% (eg, 10% vs 50% of patients) more SSRI-treated patients than patients receiving no SSRIs. 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.

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Table 5. Outcomes for SSRI Treatment in the Overall Sample and Selected Patient Subgroups

Outcome	Comparison Group[a]					
	Treatment Group				Depression Diagnosis	
	SSRI vs Overall (n = 530 416)	SSRI vs No Other Antidepressants (n = 475 456)	SSRI vs Other Antidepressants (n = 117 544)	SSRI Only vs SNRI Only (n = 82 134)	Depression, SSRI vs Other Treatments (n = 60 777)	No Depression, SSRI vs No Other Antidepressants (n = 40 213)
Overall SSRI use, No. (%) of patients	72 540 (13.7)	62 584 (13.2)	72 540 (61.7)	62 584 (76.2)	30 923 (50.9)	25 824 (64.2)
Mortality	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	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 at 30 d	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	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	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)

Abbreviations: SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a] Unless otherwise indicated, associations are expressed as adjusted odds ratio (95% CI).

DISCUSSION

In this large observational study of patients undergoing major surgery, exposure to SSRIs in the perioperative period was associated with a higher risk for a range of adverse outcomes, particularly bleeding. We found a higher risk for adverse events after accounting for medications that may have produced risk and regardless of whether SSRI therapy was held or administered continuously throughout hospitalization. Although the 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.

Although 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 the potential associations of SSRIs with bleeding outcomes has already been incorporated into available clinical practice references, several of which suggest stopping or holding SSRI therapy for 2 or more weeks before surgery,[26,27] with particular attention to holding SSRI therapy in patients undergoing neurological or orthopedic surgery. Although we cannot directly confirm this hypothesis in our data, patients receiving SSRIs in our cohort had likely been receiving these medications before hospitalization. Moreover, rates of SSRI use were higher in patient groups in which long-term use would appear most likely (eg, 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 afterward. Although we cannot discern how long SSRI therapy was held perioperatively, our results showed higher risk in patients receiving SSRIs after surgery only. This finding suggests that holding SSRI therapy for longer periods after surgery (or potentially holding therapy for longer preoperative periods) may be worthy of investigation.

Table 6. Outcomes for SSRI Treatment Among All Patients and Excluding Those Treated Only Postoperatively

Model, Timing of SSRI Administration	AOR (95% CI)	
	All Patients (N = 530 416)	Excluding Patients Receiving SSRI After Surgery Only (n = 525 971)
Mortality		
None	1 [Reference]	1 [Reference]
Before surgery[a]	1.25 (1.11-1.41)	1.25 (1.11-1.41)
After surgery	1.29 (0.90-1.85)	NA
Bleeding		
None	1 [Reference]	1 [Reference]
Before surgery[a]	1.07 (1.02-1.13)	1.08 (1.02-1.14)
After surgery	1.29 (1.12-1.48)	NA
Readmission at 30 d		
None	1 [Reference]	1 [Reference]
Before surgery[a]	1.18 (1.14-1.23)	1.21 (1.16-1.25)
After surgery	1.66 (1.49-1.84)	NA
Ventricular Arrhythmia		
None	1 [Reference]	1 [Reference]
Before surgery[a]	0.85 (0.78-0.92)	0.85 (0.78-0.93)
After surgery	1.31 (1.08-1.58)	NA
Transfusion Count		
None	1 [Reference]	1 [Reference]
Before surgery[a]	1.14 (1.10-1.17)	1.14 (1.10-1.17)
After surgery	1.28 (1.18-1.39)	NA
Length of Stay		
None	1 [Reference]	1 [Reference]
Before surgery[a]	1.03 (1.02-1.04)	1.03 (1.02-1.04)
After surgery	1.09 (1.06-1.12)	NA

Abbreviations: AOR, adjusted odds ratio; NA, not applicable; SSRI, selective serotonin reuptake inhibitor.
[a] Includes SSRIs received before and after surgery.

Patients receiving SSRIs appeared to have consistently higher risks for bleeding in nearly all subgroups undergoing testing, supporting the idea of a pharmacologic effect on platelet function. Risks for bleeding among patients receiving SNRIs or SSRIs alone were similar;

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Table 7. Propensity-Matched Analysis[a]

Outcome	No SSRI (n = 62 892)	SSRI Use (n = 62 892)	Measure of Association (95% CI)	*P* Value
Mortality	352 (0.6)	419 (0.7)	1.19 (1.03-1.37)[b]	.02
Bleeding	1576 (2.5)	1676 (2.7)	1.07 (0.99-1.14)[b]	.08
Readmission at 30 d	4264 (6.8)	4964 (7.9)	1.18 (1.13-1.23)[b]	<.001
Ventricular arrhythmia	748 (1.2)	645 (1.0)	0.86 (0.77-0.96)[b]	.005
No. of transfusions				
0	54 887 (87.3)	53 528 (85.1)	1.19 (1.15-1.23)[c]	<.001
1	3743 (6.0)	4319 (6.9)		
2	3311 (5.3)	3870 (6.2)		
3	474 (0.8)	585 (0.9)		
≥4	477 (0.8)	590 (0.9)		
Length of stay, median (IQR), d	4 (3-5)	4 (3-6)	1.01 (1.00-1.02)[d]	.008

Abbreviations: IQR, interquartile range; SSRI, selective serotonin reuptake inhibitor.
[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.
[b] Odds ratios using conditional logistic models.
[c] Rate ratio estimated using generalized estimating equation–negative binomial model.
[d] Rate ratio estimated using generalized estimating equation gamma model.

SNRIs and SSRIs are thought to have similar potential antiplatelet effects.[24] However, risks for mortality were attenuated in patients with a depression diagnosis and patients receiving antidepressants. Rather than being a risk factor itself, use of SSRIs 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 a higher risk for readmission or mortality. Alternatively, patients in these subgroups may represent a patient population in which the need to hold SSRI therapy perioperatively had been recognized, thereby producing a group of patients in whom those continuing to use SSRIs were perceived to be at lower risk and those not using SSRIs were perceived to be at higher risk. Although the association between SSRIs and outcomes could have been biased toward 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. A substantial proportion of SSRI administration was among patients without depression, so although the depressed patient subgroup 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, we used administrative data from the inpatient stay only. Because the study was performed before the onset of present-on-admission coding, we cannot easily distinguish complications from preexisting disease, and our analyses may be subject to coding biases. Our medication measures were collected from electronic billing systems rather than medical record abstraction and were not validated in a scientific study. However, Perspective'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 review of medical records.[28] 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 and to documentation biases described. We cannot discern how long SSRI therapy may have been held before surgery among the group given SSRIs only postoperatively, a fact that may be partially responsible for persistent risk in these patients. In addition, some patients we considered to have no exposure to SSRIs may have been treated up until the hospitalization and may not have restarted SSRI therapy until returning to primary care; this finding might bias our results toward the null, as mentioned. However, our results were robust even after adjusting for all available patient- 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 the SSRI and non-SSRI groups. Finally, some surgical procedures in our data set may have been at least partially performed by fellows or residents. To address this potential concern, we adjusted for whether the surgery was performed at a teaching hospital.

Our results suggest that SSRIs are associated with a range of poorer outcomes after 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 a higher prevalence of diagnosed psychiatric illness. Although holding SSRI therapy at the time of surgery may be an appropriately conservative approach, our data cannot frame a more tailored or nuanced strategy for management in surgical patients receiving SSRIs. To determine the true risks of SSRI use and potentially outline optimal management strategies, prospective studies will need to allocate patients randomly to strategies of early discontinuation of SSRI therapy (eg, weeks before surgery), holding SSRI therapy closer to the time of surgery, and not holding SSRI therapy at all (eg, usual care). Using a factorial design, these studies would need to incorporate strategies whereby SSRI therapy is restarted postoperatively at standard points (eg,

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the 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 health care and the potential risks of proceeding without adequate evidence for a strategy on how to mitigate risks of perioperative SSRI use, any study costs would seem money well spent.

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