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.


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), 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.

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 has not been consistent across studies. 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.

See Invited Commentary at end of article

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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.13-14 In addition to standard hospital discharge file data, Perspective contains a date-stamped log of all materials (eg, sepsis 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.33

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 (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 patients18 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...
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,
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 [95% CI, 1.07-1.36]; number needed to harm, 75), and higher odds for bleeding (1.09 [1.04-1.15]; number needed to harm, 839), higher 30-day readmission (1.22 [95% CI, 1.07-1.36]; number needed to harm, 75), and higher odds for mortality 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 antidepressants 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.
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, 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 period 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.

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; however, associations were stronger among patients receiving SNRIs or SSRIs overlapping with SNRIs (eg, patients using both types of medications for longer periods).

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SSRI vs Overall (n = 530,416)</th>
<th>SSRI vs No Other Antidepressants (n = 475,456)</th>
<th>SSRI vs SNRI Only (n = 82,134)</th>
<th>SSRI vs No Other Antidepressants (n = 82,134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall SSRI use, No. (%) of patients</td>
<td>72,540 (13.7)</td>
<td>62,584 (13.2)</td>
<td>72,540 (61.7)</td>
<td>62,584 (76.2)</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.20 (1.07-1.38)</td>
<td>1.22 (1.07-1.38)</td>
<td>1.04 (0.87-1.25)</td>
<td>1.54 (1.18-2.01)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1.09 (1.04-1.15)</td>
<td>1.21 (1.17-1.26)</td>
<td>1.00 (0.93-1.08)</td>
<td>0.90 (0.85-0.96)</td>
</tr>
<tr>
<td>Readmission at 30 d</td>
<td>1.22 (1.18-1.26)</td>
<td>1.08 (1.02-1.14)</td>
<td>0.98 (0.94-1.03)</td>
<td>1.00 (0.89-1.12)</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>0.89 (0.83-0.96)</td>
<td>0.87 (0.79-0.96)</td>
<td>1.10 (0.95-1.28)</td>
<td>1.05 (0.86-1.29)</td>
</tr>
<tr>
<td>Transfusion count</td>
<td>1.10 (1.06-1.13)</td>
<td>1.02 (1.01-1.02)</td>
<td>0.98 (0.97-0.99)</td>
<td>0.97 (0.96-0.99)</td>
</tr>
<tr>
<td>Length of stay, adjusted rate ratio (95% CI)</td>
<td>1.02 (1.02-1.03)</td>
<td>1.10 (1.07-1.12)</td>
<td>1.09 (1.06-1.13)</td>
<td>1.00 (0.96-1.03)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Model, Timing of SSRI Administration</th>
<th>All Patients (n = 530,416)</th>
<th>Excluding Patients Receiving SSRI After Surgery Only (n = 525,971)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>AOR (95% CI)</td>
<td>AOR (95% CI)</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Before surgery</td>
<td>1.25 (1.11-1.41)</td>
<td>1.25 (1.11-1.41)</td>
</tr>
<tr>
<td>After surgery</td>
<td>1.29 (0.90-1.85)</td>
<td>NA</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Before surgery</td>
<td>1.07 (1.02-1.13)</td>
<td>1.08 (1.02-1.14)</td>
</tr>
<tr>
<td>After surgery</td>
<td>1.29 (1.12-1.48)</td>
<td>NA</td>
</tr>
<tr>
<td>Readmission at 30 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Before surgery</td>
<td>1.18 (1.14-1.23)</td>
<td>1.21 (1.16-1.25)</td>
</tr>
<tr>
<td>After surgery</td>
<td>1.66 (1.49-1.84)</td>
<td>NA</td>
</tr>
<tr>
<td>Ventricular Arrhythmia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Before surgery</td>
<td>0.85 (0.78-0.92)</td>
<td>0.85 (0.78-0.93)</td>
</tr>
<tr>
<td>After surgery</td>
<td>1.31 (1.08-1.58)</td>
<td>NA</td>
</tr>
<tr>
<td>Transfusion Count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Before surgery</td>
<td>1.14 (1.01-1.17)</td>
<td>1.14 (1.10-1.17)</td>
</tr>
<tr>
<td>After surgery</td>
<td>1.28 (1.18-1.39)</td>
<td>NA</td>
</tr>
<tr>
<td>Length of Stay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Before surgery</td>
<td>1.03 (1.02-1.04)</td>
<td>1.03 (1.02-1.04)</td>
</tr>
<tr>
<td>After surgery</td>
<td>1.09 (1.06-1.12)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: AOR, adjusted odds ratio; NA, not applicable; SSRI, selective serotonin reuptake inhibitor.

4 Unless otherwise indicated, associations are expressed as adjusted odds ratio (95% CI).

Abbreviations: SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
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 coding 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 time of surgery 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,
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.

Accepted for Publication: January 21, 2013. Published Online: April 29, 2013. doi:10.1001/jamainternmed.2013.714

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Author Contributions: Dr Auerbach had full access to all the data in the study. Study concept and design: Auerbach, Young, and Lindauer. Acquisition of data: Auerbach and Maselli. Analysis and interpretation of data: Auerbach, Vittinghoff, Maselli, Pekow, and Young. Drafting of the manuscript: Auerbach and Maselli. Critical revision of the manuscript for important intellectual content: Auerbach, Vittinghoff, Pekow, Young, and Lindauer. Statistical analysis: Auerbach, Vittinghoff, Maselli, Pekow, and Young. Administrative, technical, and material support: Auerbach, Young, and Lindauer.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by grant K24 HL098372 from the National Heart, Lung, and Blood Institute (Dr Auerbach and Ms Maselli).


Additional Contributions: Kathy Belk, PhD, assembled the data set used for this analysis. Erin Hartman, MS, provided editorial review of this manuscript.

REFERENCES


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