
Selective serotonin reuptake inhibitors: depressing perioperative outcomes?

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In recent years, prescriptions for antidepressant agents have increased substantially. Selective serotonin reuptake inhibitors (SSRIs) have gradually superevolved tricyclic agents as drugs of choice because of their lower toxicity and generally better tolerability. They cause less sedation with fewer anticholinergic effects and are now widely used for the treatment of many conditions including depression and obsessive-compulsive disorder. Recent evidence suggests that they are amongst the most commonly prescribed medications in the United States.

Why should SSRIs depress perioperative outcomes?

Beyond effects upon the QT interval, drugs with serotonergic activity have been previously associated with an increase in bleeding risk particularly when administered in combination with warfarin. Serotonin promotes platelet activation; it is released from platelets in response to vascular injury, promoting both vasoconstriction and a conformational change in shape that enhances aggregation through secondary mediators. Platelets lack the ability to synthesize further serotonin, therefore inhibition of the reuptake transport by SSRIs can thus deplete intracellular concentrations with the development of impaired haemostasis. The relative frequency of bleeding complications appears proportionate to the degree of serotonin reuptake inhibition. An association between the risk of bleeding and increasing affinity for the serotonin transporter has been noted by a number of authors. Drugs such as clomipramine, fluoxetine, sertraline, and paroxetine produce more potent blockade of the serotonin transporter and further increase bleeding potential.

Clinical evidence for the effects on haemostasis

Observational studies have demonstrated an increased risk of bleeding complications in various settings. SSRIs have been independently associated with gastrointestinal blood loss. Estimates of risk are variable but significant; a retrospective analysis of database studies demonstrated an odds ratio in SSRI-treated patients of increased bleeding from 1.38 to 3.6 although the confidence intervals in this setting remained wide. This association holds true after adjustment for age, gender, and the effects of other drugs such as aspirin and non-steroidal anti-inflammatories (NSAIDS) suggesting an additional if not synergistic effect. This risk decreases to pre-existing levels upon cessation. Similar large case series have demonstrated an increase risk of bleeding in patients undergoing hip fracture surgery, although without effect upon postoperative morbidity or mortality.

Both selective and non-selective serotonin antagonists have been implicated in the development of postpartum haemorrhage. A large cohort study of women from the United States demonstrated 12% of women were exposed to SSRIs at the time of delivery: the risk of postpartum haemorrhage was 2.8% among women with mood disorders without exposure to antidepressants and 4.0% in current users of SSRIs. This study was conducted among women enrolled in the US Medicaid program who were more likely to be younger, low income and non-Caucasian compared with national figures for pregnant women that may have resulted in significant confounding. This finding has not been borne out in other cohorts, although increase in bleeding during early pregnancy was seen in some groups albeit without effects upon outcome. A slight increase in intracerebral haemorrhage and bleeding after ischaemic stroke have also been reported, although given the rarity of these events absolute risk remains small. Case reports have also implicated SSRIs in spontaneous epidural haematoma, airway bleeding and retrobulbar haemorrhage.

The perioperative period

Recent data suggests associations of SSRIs and an increased risk of perioperative bleeding and other adverse outcomes however it is important to note patients receiving SSRIs are also more likely to have conditions such as obesity and cardiovascular disease which also impact upon surgical risk. However, an increased requirement for red-cell transfusion has been demonstrated in patients taking SSRIs who undergo coronary artery bypass and

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orthopaedic procedures\textsuperscript{20} (see the Supplementary Table 1 of further details of the analysis). Perhaps of most impact, a recent retrospective analysis of more than 500 000 non-cardiac surgical patients found patients receiving SSRIs (and serotonin norepinephrine reuptake inhibitors) had higher odds of in-hospital mortality, bleeding and readmission at 30 days.\textsuperscript{21} Patients receiving SSRIs were more likely to be depressed, obese, suffer from chronic pulmonary disease and hypothyroidism.\textsuperscript{22} Nonetheless, these results were similar in propensity-matched analyses, although an increased risk of inpatient mortality did not occur in patients with depression.\textsuperscript{21} Continuing SSRIs in the perioperative period was associated with increased risk of bleeding, transfusions and readmission within 30 days. Of course, interpretation of this retrospective, observational study that remains vulnerable to confounding, must be cautious. However the large sample size and biological rationale must trigger further enquiry into the safety of these drugs. The risk appears most significant for those with an elevated perioperative risk; patients predicted to have higher rates of complications incur a greater chance of bleeding with concomitant SSRI use than those of lower predicted risk.\textsuperscript{21}

Other perioperative concerns require consideration. Regional blockade is a commonly performed and effective method of administering anaesthesia and analgesia yet it is relatively contraindicated in disturbed coagulation.\textsuperscript{23} SSRIs are not included in current recommendations regarding the safety of anti-platelet agents in regional blockade and formal assessment of platelet function is rarely performed before administration of these modalities.\textsuperscript{23} Fluroxetine has been implicated in the development of haematoma after an epidural technique.\textsuperscript{24} Current evidence would suggest that NSAIDs are safe in this arena\textsuperscript{25} \textsuperscript{26} but it is unclear that about the effects of NSAIDS and SSRIs in combination.\textsuperscript{27} Dual administration of these medications appears to increase the rates of gastrointestinal bleeding although this may strongly represent local effects of NSAIDS upon gastrointestinal mucosa.\textsuperscript{28} In the large recent study, Auerbach and colleagues\textsuperscript{21} did not identify important interactions of SSRIs with NSAIDs or other anticoagulants. The exact effects within those surgical fields where bleeding may be particularly catastrophic such as neurosurgery require further investigation. Further data are required on the safety of SSRIs on their own and in combination with other drugs on perioperative outcomes.

**Caveats**

Despite these concerns, SSRIs offer a number of significant potential benefits in the preoperative field. They may be effective treatments for depression which may be a contributing factor to recovery from surgery.\textsuperscript{29} Cessation may worsen emotional state and increase confusion perioperatively.\textsuperscript{30} There may also be a role for these drugs in the treatment of delirium, itself a significant contributor to postoperative morbidity although as yet the evidence is scanty.\textsuperscript{51} The standard indications for these medications are relatively robust, hence a ‘one-size-fits-all’ approach is unhelpful.

**Conclusions**

Accumulating clinical evidence, supported by biological rationale, supports a statistically significant impact of SSRIs on the risk of bleeding. However the current data do not unequivocally support this to be of clinically importance in the preoperative period. The first step is to confirm these early reports with further observational data; however, this alone will not necessarily inform us how to manage SSRIs at this time. To understand this a large randomised controlled trial of the discontinuation vs continuation of therapy is required.\textsuperscript{30} Clinicians should be aware that SSRI’s may contribute to perioperative bleeding and mortality and in individual patients at high risk of this complication may choose to actively discontinue the SSRI. Any future research should carefully examine this perioperative bleeding risk alongside overall outcome.\textsuperscript{12}

Many commonly administered medications which have benefits more strongly geared towards secondary prevention and improving quality of life have inconsistent benefits in the operative arena, yet many patients present for anaesthesia and surgery on a combination of aspirin, beta blockers, statins, angiotensin converting enzyme inhibitors and antidepressants. More recent evidence has questioned the perceived benefit of some of these drugs.\textsuperscript{22} Further observational data are required on the effects of these drugs, singularly and in combination.

**Supplementary material**

Supplementary material is available at British Journal of Anaesthesia online.

**Declaration of interest**

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**References**

From educational theory to clinical practice: self-regulated learning

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Workplace-based assessments are designed to formatively assess components of daily clinical practice.1 With concerns regarding training of medical postgraduates, changes in working legislation and the knowledge of the educational impact of

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