What is the risk of gastrointestinal bleeding associated with selective serotonin reuptake inhibitors (SSRIs)?

**Background**

Various reviews and meta-analyses (1-8) have indicated that there is a link between selective serotonin reuptake inhibitor (SSRI) use and gastrointestinal (GI) bleeding, particularly upper GI bleeding (3,4,7,8). An increased risk of bleeding has been noted in elderly patients (7), and with the concomitant use of SSRIs and non-steroidal anti-inflammatory drugs (NSAIDs) (2-5,7,8).

Serotonin has an important role in the haemostatic response to injury by promoting platelet aggregation (1,9,10). SSRIs inhibit the uptake of serotonin into platelets which might lead to an increased risk of abnormal bleeding (1,9,10). The increase in gastric acid secretion caused by SSRIs could also increase the risk of ulcer development and GI bleeding (8). Due to reports of bleeding, including GI bleeding, manufacturers advise caution in patients with a history of bleeding disorders and in those taking SSRIs concomitantly with antiplatelets and other drugs that might increase the risk of bleeding (11-16).

**Answer**

To determine whether SSRIs and venlafaxine (a serotonin and noradrenaline re-uptake inhibitor [SNRI]) are associated with upper GI tract bleeding, de Abajo and colleagues (17) conducted a case-control study in which details of case and control patients were drawn from a database used by general practitioners in the UK to store clinical information about their patients. Several similar case-control studies had been conducted in the past, but this one differed in that as well as aiming to identify subgroups of patients at an increased risk of bleeds with SSRIs, it sought to determine whether acid suppressing agents were effective in minimising this risk.

Patients with upper GI tract bleeding (n=1321) who had been referred to a hospital or consultant and 10,000 control subjects were matched for age, sex and calendar year of the index date. For cases, the index date was the date of first symptoms or first diagnosis. For controls, a date within the study period was assigned randomly. Patients were defined as 'current users' if their prescribed antidepressants lasted until the index date or were discontinued within 30 days of the index date.

Before these studies, gastroprotective agents such as H2 receptor antagonists, PPIs or misoprostol had not been shown to reduce the risk of GI bleeds associated with SSRIs alone (4,6) or in combination with NSAIDs (6).

Results from cohort and case-control studies with similar objectives and comparable outcomes to those of de Abajo and colleagues (17) are shown in Table 1. The majority of these concluded that SSRIs are associated with an increased risk of GI bleeding (1,10,17-19,21), and some found this risk to be potentiated by the concomitant use of NSAIDs (1,10,17,19,20). Others found no significant association between GI bleeding and SSRI use (22,23) or no potentiation of this effect with concomitant SSRI and NSAID use (18,24).

Comparison of these results is complicated by the fact that the studies differed with regard to adjustment for confounding factors. Studies have shown that, in addition to concomitant medication, alcohol intake (25) and H pylori status (26) are important to take into account when determining the effects of SSRIs on the risk of GI bleeding.

Patient age and the degree to which different antidepressants inhibit serotonin reuptake were factors of interest in one observational study in 317,824 elderly patients who looked at upper GI bleeding rates. The antidepressants these patients were taking were split into 2 groups: those with low inhibition of serotonin reuptake (e.g. nortriptyline, doxepin, trazodone) and those with high inhibition of serotonin reuptake (e.g. paroxetine, sertraline, fluoxetine) (27). Absolute differences between these antidepressant groups were greatest (and statistically significant) for patients aged 80 and over (bleeding rates for high versus low inhibition: 14.7 per 1000 person years versus 10.6 per 1000 person years; number needed to harm [NNH] =244), and those with previous upper GI bleeding (bleeding rates for high versus low inhibition: 40.3 per 1000 person years versus 26.6 per 1000 person years; NNH =85) (27).

A recent study, in which the medical records of 36,389 patients were examined, also found the adjusted relative risk for GI bleeds to be higher in patients receiving antidepressants with a higher affinity for the serotonin transporter (relative risk for high versus low-affinity antidepressants = 1.17 (95% CI 1.02-1.34). This study was of particular interest because it was restricted to patients with major depressive disorder, thereby reducing the risk of confounding by indication. Patients in this study received monotherapy with a SSRI, serotonin-norepinephrine reuptake inhibitor or other new-generation antidepressant (28).

In a case-control study (19), the risk of upper GI bleeding was found to be greatest in patients who had recently (within the last 0-30 days) started SSRI use. This finding is supported by another study, which found that mortality was increased in the 30 days following hospital admission for peptic ulcer bleeding in patients who had started SSRIs within 60 days of admission (particularly those over 80 years). In this study, long-term exposure to SSRIs, alone or with NSAIDs did not increase 30-day mortality after peptic ulcer bleeding (29).

For a rare condition, the OR approximates the relative risk (30). Therefore, in Table 1, some results are reported as an OR and others as relative risk (both versus non-use of the specified medicines), as they appeared in the original papers.
Table 1. Studies examining the possibility of an association between SSRI use and upper GI bleeding.

<table>
<thead>
<tr>
<th>Study and type</th>
<th>Number of study participants</th>
<th>Current use</th>
<th>Risk (odds ratio [OR], relative risk [RR] or other) versus non-use</th>
<th>Conclusions</th>
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<tbody>
<tr>
<td>de Abajo FJ and Garcia-Rodriguez LA. Arch Gen Psychiat 2008;65(7):795-803 (17) <strong>Nested case-control study</strong></td>
<td>1321 patients with upper GI bleeding/ perforation referred to consultant or hospital 10,000 controls</td>
<td>SRIs (includes SSRIs and venlafaxine) only: 22 cases, 105 controls NSAID only: 173 cases, 642 controls NSAID and SRIs: 23 cases, 44 controls</td>
<td>OR, adjusted (95% CI): SRIs only: 1.8 (1.1-2.9) SRIs plus NSAIDs: 4.8 (2.8-8.3) OR (95% CI): with gastro protection: SRIs only: 1.4 (0.8-2.3) SRIs plus NSAIDs: 1.1 (0.3-3.4) With no gastro protection/remote use: SRIs only: 2.0 (1.5-2.8) SRIs plus NSAIDs: 9.1 (4.8-17.3)</td>
<td>SSRIs, and venlafaxine, increase the risk of upper GI tract bleeding. This risk was increased further by the concomitant use of NSAIDs and SRIs. Acid suppressing agents lowered the risk of upper GI tract bleeding associated with SRIs +/- NSAIDs.</td>
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<tr>
<td>Dall M et al. Clin Gastroenterol Hepatol 2009;7:1314-21(19) <strong>Case-control study</strong></td>
<td>3652 patients with serious upper GI bleeding 36,502 controls</td>
<td>SSRIs (current use): 377 cases, 1809 controls SSRI (recent use): 77 cases, 381 controls SSRI (past use): 360 cases, 2484 controls SSRI alone: 40 cases, 326 controls NSAID only: 625 cases, 2635 controls NSAID and SSRI: 99 cases, 183 controls</td>
<td>OR, adjusted (95% CI): SSRIs (current use): 1.70 (1.49-1.95) SSRIs (recent use): 1.86 (1.41-2.5) SSRIs (past use): 1.24 (1.09-1.42) SSRI only: 1.7 (1.01-2.8) NSAID only: 4.3 (3.7-5.1) NSAID plus SSRI: 8.0 (4.8-13) NSAID, OESR1 plus low-dose PPI</td>
<td>SSRI use was associated with upper GI bleeding. This risk was increased further by the concomitant use of NSAIDs and SRIs, and further still by adding in low-dose aspirin to treatment with NSAIDs and SRIs. Among users of SSRIs, the risk of upper GI bleeding was found to be highest in those who had recently started</td>
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### Table: Case-Control Studies and Population-Based Cohort Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Cases/Controls</th>
<th>SSRI and NSAID Use</th>
<th>OR, Adjusted (95% CI)</th>
<th>Conclusion</th>
</tr>
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<tr>
<td>Helin-Salmivaara A et al. Eur J Clin Pharmacol 2007;63:403-8 (21)</td>
<td>Case-control study</td>
<td>9191 cases with serious upper GI events 41,780 controls</td>
<td>SSRI only: 284 cases, 931 controls NSAID only: 1714 cases, 3089 controls NSAID and SSRI: 157 cases, 159 controls</td>
<td>OR, adjusted (95% CI): SSRIs, excluding NSAID users: 1.30 (1.13-1.50) SSRI and NSAID: 4.19 (3.30-5.31) NSAID only: 2.83 (2.65-3.03)</td>
<td>Compared with NSAID use alone, the concurrent use of SSRIs and NSAIDs is associated with a moderate excess relative risk of a serious upper GI event.</td>
</tr>
<tr>
<td>Wessinger S et al. Aliment Pharmacol Ther 2006;23:937-44 (20)</td>
<td>Case-control study</td>
<td>579 cases hospitalised with acute GI haemorrhage 1000 controls</td>
<td>SSRI (including venlafaxine): 111 cases, 136 controls NSAID: 42 cases, 38 controls</td>
<td>OR (95% CI): SSRIs (lower or upper bleeds) 1.5 (1.2-2.0) p=0.003 SSRIs (lower bleeds): 1.8 (1.2-2.8) p=0.005 SSRIs (upper bleeds): 1.3 (0.83-1.9) p=0.281</td>
<td>Patients admitted with GI haemorrhage (lower or upper) were more likely to be taking SSRIs than controls. SSRI use was statistically significantly greater among cases of lower GI bleeding, but not among those of upper GI bleeding.</td>
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<tr>
<td>Targownik LE et al. Am J Gastroenterol 2009;104:1475-1482 (18)</td>
<td>Case-control study</td>
<td>1552 patients with upper GI bleeding 68,590 controls</td>
<td>SSRI only: 62 cases, 1881 controls NSAID only: 263 cases, 5266 controls SSRI and NSAID: 23 cases, 337 controls SSRI and PPI: 6 cases, 369 controls</td>
<td>OR, adjusted (95% CI): SSRI only: 1.43 (1.09-1.89) NSAID only: 2.62 (2.26-3.03) SSRI plus NSAID: 3.17 (2.01-5.00) SSRI plus PPI: 0.56 (0.24-1.30)</td>
<td>SSRIs use was associated with a modest increase in the risk of upper GI bleeding. PPIs reduced the risk of SSRI-associated upper GI bleeding by approximately 60% (OR, 0.39; 95% CI: 0.16-0.94). The risk of developing upper GI bleeding in patients using both an SSRI and an NSAID was not increased significantly above that in patients using only an NSAID.</td>
</tr>
<tr>
<td>Dalton S et al. Arch Intern Med 2003;163:59-64 (10)</td>
<td>Population-based cohort study</td>
<td>Users of antidepressants: 26,005 Control: No antidepressants/no NSAIDs (numbers not given)</td>
<td>SSRI only: 55 cases, 17,320 persons SSRI and NSAID only: 17 cases, 4107 persons Other antidepressants only: 9 cases, 4436 persons</td>
<td>Observed/expected ratio (95% CI): SSRIs only: 3.6 (2.7-4.7) Other antidepressants only: 1.7 (0.8-3.1) SSRI and NSAID: 12.2 (7.1-19.5)</td>
<td>SSRIs, but not other antidepressants, increased the risk of upper GI bleeding, and this effect is potentiated by concurrent use of NSAIDs.</td>
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**Medicines Q&As**
<table>
<thead>
<tr>
<th>Study</th>
<th>Cases/Controls</th>
<th>RR, adjusted (95% CI):</th>
<th>Findings</th>
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<tbody>
<tr>
<td>de Abajo FJ et al.</td>
<td>1651 cases of upper GI bleeding, 248 cases of ulcer perforation, 10,000 controls</td>
<td>SSRIs only^a^: 2.6 (1.7-3.8)</td>
<td>SSRIs moderately increase the risk of upper GI bleeding. Concurrent use of NSAIDs and SSRIs greatly increases the risk of upper GI bleeding.</td>
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<tr>
<td>Dunn NR et al.</td>
<td>SSRIs: 237,609 patient months of exposure, Comparator drugs (moclobemide and salmeterol): 205,431 patient months of exposure</td>
<td>Rate ratio (95% CI) versus comparator group: 1.24 (0.91-1.70)</td>
<td>Found no evidence to suggest that SSRIs are more likely to cause GI bleeding than comparator drugs.</td>
</tr>
<tr>
<td>Vidal X et al.</td>
<td>2813 cases of upper GI bleeding, 7193 matched controls</td>
<td>OR, adjusted^a^ (95% CI): 1.24 (0.88-1.76)</td>
<td>No significant association was found between use of SRIs and risk of upper GI bleeding. The OR among concurrent users of a high-affinity SRI and an NSAID did not differ from that of users of NSAIDs alone. The risk of GI bleeding with SSRI use was slightly increased in patients aged over 70 compared to those aged under 70.</td>
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<tr>
<td>Tata LJ et al.</td>
<td>11,261 cases with upper GI bleeding, 53,156 controls</td>
<td>OR (95% CI): 2.63 (2.24-3.07)</td>
<td>The risk of GI bleeding is not substantially increased when NSAIDs and SSRIs are prescribed together when compared to alone.</td>
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</tbody>
</table>
a. No other antidepressants or NSAIDs used.
b. No antidepressants used.
c. Adjusted for smoking status, alcohol intake, antecedents of GI disorder, and concomitant use of other medications associated with upper GI tract bleeding (NSAIDs, systemic corticosteroids, warfarin, low-dose aspirin and other antiplatelet drugs).
d. Adjusted for use of aspirin and PPIs, alcohol abuse, cerebral ischemia, stroke, use of warfarin, clopidogrel, dipyridamole, and corticosteroids, prior *Helicobacter* eradication, peptic ulcer, upper GI bleed and cirrhosis.
e. No SSRIs used.
f. Adjusted for year of birth, sex, hospital catchment area, diabetes mellitus, rheumatoid arthritis, coronary artery disease, hypertension, asthma, cardiac insufficiency, use of H2 antagonist, PPI or plain misoprostol in the period extending from five years to 90 days prior to the index date (as a proxy for past GI morbidity). Also, use of H2 antagonist, plain misoprostol, PPI, warfarin, clopidogrel, oral or inhaled glucocorticoid or tramadol in the 90-day period immediately prior to the index date as well as any in-patient period lasting at least 7 days, in-patient period for an injury and a hospitalisation for hip or knee arthroplasty.
g. Adjusted for specific medical comorbidities, use of other medications believed to affect the risk of upper GI complications, and history of GI disease.
h. Adjusted for sex, age, year, antecedents of upper GI disorders, smoking status, and use of aspirin, anticoagulants, or steroids.
i. Fluvoxamine, fluoxetine, paroxetine, sertraline and included nefazodone (SNRI).
j. Included fluoxetine, paroxetine, sertraline and clomipramine, but not fluvoxamine, citalopram or venlafaxine.
k. Adjusted for history of peptic ulcer, dyspepsia, upper GI bleeding, diabetes mellitus, smoking habit, alcohol consumption and use of antacids, PPIs, sucralfate, nitrates, systemic NSAIDs, topical NSAIDs, analgesics, antiplatelet drugs, dihydropyridine calcium antagonists and HMG Co-A reductase inhibitors in the week before the GI bleeding symptoms started.
Summary

The results from most, but not all observational studies suggest that there is an association between the use of SSRIs and GI bleeds. One study indicated that patients taking SSRIs have a three-fold increased risk of developing a GI bleed compared to patients not taking SSRIs and who have no risk factors for GI bleeding. However, recent studies have found the risk to be more modest. In general, comparison of the results of studies on SSRI use and GI bleeding is complicated by the fact that the confounding factors taken into account differ in each case. Some studies have found the use of SSRIs with concomitant NSAIDs to increase the risk of GI bleed further. Being over the age of 80 or having a previous history of GI bleeding may also add to the risk of GI bleeding with SSRI use. There is some evidence that the risk of GI bleeding is higher in patients who have just started taking SSRIs. If an SSRI is required in a patient at high risk of a GI bleed then the use of a gastro-protective agent could be considered. Studies have shown the use of acid suppressing drugs, e.g. PPIs, to be protective against GI bleeds in patients receiving single-therapy SSRI or combined NSAID treatment.

Limitations

Studies that have looked at the risk of GI bleeds in SSRI users have differed with respect to outcomes and the confounding factors taken into account.
References


18. Targownik LE, Bolton JM, Metge CJ et al. Selective serotonin reuptake inhibitors are associated with a modest increase in the risk of upper gastrointestinal bleeding. Am J Gastroenterol 2009;104:1475-82.


22. Dunn NR, Pearce GL, Shakir SAW. SSRIs are no more likely than other drugs to cause gastrointestinal bleeding. Br Med J 2000;320:1405-6.


Quality Assurance

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Search strategy

- Embase (exp Serotonin Uptake Inhibitor/ae, to [Adverse Drug Reaction, Drug Toxicity] AND exp Gastrointestinal Hemorrhage/) limited to human and english language
- Medline (exp Serotonin Uptake Inhibitors/ae, to [Adverse Effects, Toxicity] AND exp Gastrointestinal Hemorrhage/) limited to human
- IDIS Drug(s): ("antidepressants-ssris 28160700" and Descriptors: "side ef digestive 78" AND All fields: “bleeding” )
- Micromedex (Searched under individual SSRI names in DrugDex and Martindale, also checked Drug Consults)
- EMC (Searched under individual SSRI names)
- In-house database/ resources (SSRI and bleed*)
- NeLM (ssri* AND bleed*; selective serotonin reuptake, ssri, gastrointestinal bleed*) (2008-12)
- Pharmline (for previous version) “serotonin reuptake inhibitors” AND “haemorrhage-gastrointestinal”
- Meyler’s Side Effects of Drugs (15th ed) selective serotonin re-uptake inhibitors
- Stockley’s (online) ssris warfarin