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

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## Background

An association between selective serotonin reuptake inhibitor (SSRI) use and upper gastrointestinal (GI) bleeding was reported in 1999 following analysis of data from a UK general practice research database (1). Since then, further evidence supporting this association has emerged (2-6). In several studies in which an increased risk has been noted with SSRIs alone, the risk has been found to be elevated further by the concomitant use of SSRIs and non-steroidal anti-inflammatory drugs (NSAIDs) (5,6).

Two main mechanisms have been proposed for SSRI-associated upper GI bleeding. Firstly, serotonin plays an important role in the haemostatic response to injury by promoting platelet aggregation (1,7, 8). Serotonin is not synthesised in platelets but is taken up into platelets from the bloodstream. At therapeutic doses SSRIs block this reuptake of serotonin leading to a depletion of serotonin and, ultimately, an increased risk of bleeding. Secondly, SSRIs have been shown to directly increase gastric acidity which could increase the risk of ulcer development, and therefore, bleeding (4). Due to reports of bleeding, including GI bleeding, manufacturers of SSRIs and serotonin and noradenaline re-uptake inhibitors (SNRIs) advise caution in patients with a history of bleeding disorders/those predisposed to bleeding and in those taking SSRIs or SNRIs concomitantly with antiplatelets and other drugs that might increase the risk of bleeding (9-18).

## Answer

**SSRIs alone and in combination with NSAIDs**

In a systematic review and meta-analysis designed to estimate the risk of upper GI bleeding with SSRIs, with or without concomitant NSAID use (5)**,** results were analysed from 15 case-control studies (393,268 participants) and four cohort studies. An increased risk of upper GI bleeding with SSRIs (no concomitant NSAID use) was found in both analyses (case-control studies: odds ratio [OR] 1.66; 95% confidence interval [CI]:1.44-1.92; cohort studies: OR 1.68; 95% CI: 1.13-2.50). Using data from 10 case-control studies (223,336 participants), the risk was found to be increased further in patients taking both SSRIs and NSAIDs (OR 4.25; 95% CI: 2.82-6.42) (5).

The effects of acid suppressing agents in patients receiving SSRIs were investigated in a different meta-analysis of 16 case-control studies and six cohort studies, conducted by Jiang et al (2015) and involving 1,073,000 patients (6). This meta-analysis showed the incidence of upper GI bleeding to be 55% higher in patients taking SSRIs compared with non-users of SSRIs (OR 1.55; 95% CI: 1.35-1.78, p<0.001).The risk of upper GI bleeding was higher still in patients receiving both SSRIs and NSAIDs (OR 3.72; 95% CI: 3.01-4.67) or SSRIs and antiplatelet drugs (OR 2.48 (1.70-3.61). Using the odds ratios from the meta-analysis, and assuming a baseline incidence of upper GI bleeding in the general population of 23 per 10000 patients, the authors estimated a number needed to harm (NNH, the number of patients who would have to receive therapy to induce one episode of upper GI bleeding) of 791 per year with SSRIs. This changed to 160 per year with concomitant SSRI and NSAID use and 294 with concomitant SSRI and antiplatelet use (6).

In patients receiving acid suppressing drugs in addition to SSRIs, the risk of upper GI bleeding remained low (OR 0.81;95% CI: 0.43-1.53), as it did in patients receiving acid suppressing drugs, SSRIs and NSAIDs (OR 0.98;95% CI: 0.51-1.88) (6).

Abajo et al (2008) (19) (study included in the meta-analysis by Jiang et al (2015) (6), found that, without GI protection, an upper GI bleed would be experienced by one in every 2000 patients receiving an SRI (serotonin reuptake inhibitor; includes SSRIs and venlafaxine, an SNRI) only, or one in every 250 patients receiving an SRI with an NSAID, With GI protection, 5000 or more patients would need to be treated with an SRI or SRI plus NSAID for one case to be attributed to these drugs (19).

**Concomitant clopidogrel, low-dose aspirin or warfarin**

An increased risk of GI bleeding with combined SSRI and clopidogrel/low-dose aspirin use has also been shown in studies, but conflicting evidence exists (20). In one retrospective study, when compared to aspirin alone, SSRIs increased the risk of GI bleeding in post-acute myocardial infarction patients who were receiving prophylactic treatment with aspirin (Hazard ratio (HR) =1.50; 95% CI=1.05 to 2.15), and the risk of bleeding was higher still when both clopidogrel and an SSRI were added to the aspirin (HR 3.11, 95% CI 2.00 to 4.85) (21).

Masclee et al (2014) (22) analysed data on 114,835 patients with upper GI bleeding from seven population-based healthcare databases, with each patient acting as their own control. The relative risk of diagnosed upper GI bleeding with SSRI monotherapy was 2.06 (95% CI: 1.94-2.18), but rose to 4.60 (95% CI: 4.09-5.17) when SSRIs were combined with low-dose aspirin, and to 6.95 (95% CI: 5.97-8.08) when SSRIs were combined with NSAIDs (22).

There is an established pharmacokinetic interaction between fluvoxamine and warfarin, resulting in increased anticoagulant effects but no known similar interaction for other SSRIs (23). One case-controlled study found patients receiving warfarin to have an increased odds ratio of gastrointestinal bleeding on starting citalopram (OR = 1.73 [95% CI, 1.25–2.38]), fluoxetine (OR = 1.63 [95% CI, 1.11–2.38]), paroxetine (OR = 1.64 [95% CI, 1.27–2.12]), amitriptyline (OR = 1.47 [95% CI, 1.02–2.11]), and mirtazapine (OR = 1.75 [95% CI, 1.30–2.35]) (24).

**Duration of exposure to SSRIs**

It has been suggested that recent initiation of SSRIs increases the risk of upper GI bleeding. In a case-control study (25), the highest adjusted OR for serious upper GI bleeding was in patients who had started using SSRIs within the last 0-30 days. Another study reported 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 in those over 80 years. In this study, long-term exposure to SSRIs (i.e. current use of SSRIs with first prescription prior to 60 days before admission with GI bleeding), either alone, or with NSAIDs did not increase 30-day mortality after peptic ulcer bleeding (26).

In the meta-analysis by Jiang et al (2015) (6), upper GI bleeding risk was increased significantly when the duration of exposure was less than 30 days (OR 2.35; 95% CI: 1.24-4.46) or more than 90 days (OR 1.71; 95% CI: 1.07-2.76). For cases in which patients were exposed to SSRIs for 30-90 days, there was a non-statistically significant trend towards an increased risk of upper GI bleeding (OR 2.23; 95% CI: 0.97-5.90) (6). An editorial by Targownik et al in 2015 (27) concluded that there was no clear evidence from studies of a durational effect. Another review suggested that the risk of abnormal bleeding is elevated throughout SSRI treatment, and that patients who bleed shortly after treatment initiation are likely to have already been at risk when the SSRIs were initiated (28).

**Affinity for serotonin transporter and other risk factors**.

There is limited evidence that the risk of gastrointestinal bleeds with individual SSRIs is related to their affinity for the serotonin transporter. Studies have reported a statistically significantly increased risk of gastrointestinal bleeding with high and intermediate-affinity SSRIs such as fluoxetine, paroxetine, sertraline and (es)citalopram (29,30). In the meta-analysis by Jiang et al (2015) (6) a significant and similar increase in risk of upper GI bleeding was reported for paroxetine (OR 1.68 ;95% CI: 1.08-2.26), sertraline (OR 1.67; 95% CI: 1.37-2.04) and fluoxetine (OR 1.77 ; 95% CI: 1.32-2.38) compared with no treatment. The risk was even higher for citalopram (OR 2.07; 95% CI: 1.47-2.92) and escitalopram (OR 2.45; 95% CI: 1.35-4.42). However, a non-significant increase in upper GI bleeding risk was reported for fluvoxamine (OR 1.74; 95% CI: 0.37-8.29) and venlafaxine (OR 1.39;95% CI: 0.96-2.01) (6), both of which have an intermediate affinity for the serotonin transporter (29,30). Evidence that the risk of GI bleeds is low for antidepressants with a low affinity for the serotonin transporter is lacking. One meta-analysis (31) found the pooled OR for GI bleeding with mirtazapine to be similar to those reported for SSRIs in other meta-analyses (5,6) (mirtazapine pooled OR for GI bleeding compared to non-antidepressant use:1.17, 95% CI=1.01-1.37) (31).

Patient age and history of GI bleeding were risk factors considered in an observational study in 317,824 elderly patients that looked at upper GI bleeding rates. The antidepressants these patients were taking were split into 3 groups, low (e.g. nortriptyline, doxepin, trazodone), intermediate (e.g. imipramine, amitriptyline, fluvoxamine, venlafaxine) and high (paroxetine, sertraline, fluoxetine, clomipramine) inhibition of serotonin reuptake (7). 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; NNH =244), and those with previous upper GI bleeding (bleeding rates for high versus low inhibition: 40.3 per 1000 person years versus 28.6 per 1000 person years; NNH=85) (7).

**SNRIs**

The effects of both serotonin-noradrenaline reuptake inhibitors (SNRIs) and SSRIs on gastrointestinal bleeding were investigated by Cheng et al (2015) (32), who examined records from the National Health Insurance Research Database of Taiwan. Incidences of upper and lower GI bleeding in patients taking SSRIs (n=8809) or SNRIs (n=944) were compared with those of 39,012 age, sex and enrolment time-matched controls for a 10-year time period (2000-2010). After adjustment for known risk factors, SSRI use was found to be an independent risk factor for both upper GI bleeding (hazard ratio (HR): 1.97, 95% CI:1.67-2.31; p<0.001) and lower GI bleeding (HR: 2.96, 95% CI: 2.46-3.57; p<0.001). Neither the risk of upper nor lower GI bleeding was increased by SNRI use (for upper GI bleeding: HR: 1.09, 95% CI: 0.58-2.04; p=0.786) and for lower GI bleeding: HR: 0.84, 95% CI: 0.32-2.27; p=0.737) (25), perhaps surprising given the proposed mechanism of bleeding with SSRIs. In contrast, de Abajo et al (2008) (19) found current use of SNRIs (venlafaxine) to significantly increase the risk of upper GI bleeding (OR: 2.9, 95% CI: 1.5-5.7) compared with no use of an antidepressant.

Current NICE guidance on depression states that SSRIs are associated with an increased risk of bleeding, especially in older people or in people taking other drugs that have the potential to damage the gastrointestinal mucosa or interfere with clotting. NICE recommends considering prescribing a gastroprotective drug in older people who are taking NSAIDs or aspirin (33). For patients who are taking multiple drugs that could cause bleeding, seeking informed medical advice before starting regular use of non-prescription drugs, such as ibuprofen is recommended. Paracetamol should be considered as an alternative to an NSAID in patients who are taking SSRIs (23).

## Summary

* Observational study results have indicated that there is an association between the use of SSRIs and upper GI bleeds, with a number needed to harm (NNH, the number of patients who would have to receive therapy to induce one episode of upper GI bleeding) of 791.
* The use of SSRIs with concomitant NSAIDs has been found to increase the risk of upper GI bleeding further (NNH=160)
* An increased risk of gastrointestinal bleeding with combined SSRI and clopidogrel/low-dose aspirin use has also been shown in studies, but conflicting evidence exists (NNH=294 for combined SSRI and antiplatelet use in one meta-analysis).
* Being over the age of 80 or having a previous history of GI bleeding adds to the risk of upper GI bleeding with SSRIs. The risk may also be higher in patients who have just started taking SSRIs, and in those taking SSRIs with a high/intermediate affinity for the serotonin receptor.
* If an SSRI is required in a patient at high risk of an upper GI bleed, consider the use of a gastro-protective agent. Studies have shown that acid suppressing drugs, e.g. PPIs, protect against upper GI bleeds in patients receiving single-therapy SSRI or combined NSAID and SSRI treatment. Current NICE guidance on depression recommends considering a gastroprotective drug in older people on SSRIs who are also taking NSAIDs or aspirin.
* People taking multiple drugs that could cause bleeding should seek informed medical advice before starting regular use of non-prescription drugs such as ibuprofen.
* Consider paracetamol as an alternative pain-killer to an NSAID in people who are taking SSRIs.

LimitationsStudies that have looked at the risk of GI bleeds in SSRI users have differed widely with respect to the confounding factors taken into account. Many are retrospective studies (selection bias not always accounted for) with heterogeneous populations.

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## Quality Assurance

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### Search strategy

1. Embase (exp Serotonin Uptake Inhibitor/ae, to [Adverse Drug Reaction, Drug Toxicity] AND exp Gastrointestinal Hemorrhage/) limited to human and english language
2. Medline (exp Serotonin Uptake Inhibitors/ae, to [Adverse Effects, Toxicity] AND exp Gastrointestinal Hemorrhage/) limited to human
3. Micromedex (Searched under individual SSRI names in DrugDex and Martindale, also checked Drug Consults)
4. EMC (Searched under individual SSRI names)
5. In-house database/ resources (SSRI and bleed\*)
6. Stockley’s (online) ssris nsaids, ssris warfarin
7. NeLM (for previous version)/NHS Evidence (ssri\* AND bleed)
8. Pharmline (for previous version) “serotonin reuptake inhibitors” AND “haemorrhage-gastrointestinal”
9. Meyler’s Side Effects of Drugs (16th ed) selective serotonin re-uptake inhibitors