

Q/ Is there an increased risk of GI bleeds with SSRIs?

EVIDENCE-BASED ANSWER

A | **YES.** Selective serotonin reuptake inhibitors (SSRIs) are likely associated with a moderate increased risk of upper gastrointestinal (UGI) bleeding. Use of a non-steroidal anti-inflammatory drug (NSAID) in combination with the SSRI appears to amplify the risk (strength of recommendation [SOR]: **B**, meta-analysis of cohort and case control studies).

The increased risk from SSRIs occurs within the first 7 to 28 days after exposure (SOR: **B**, retrospective study).

SSRIs raise bleeding risk; concurrent NSAIDs raise it more

A 2014 systematic review and meta-analysis of 19 case-control and cohort studies with a total of 446,949 patients investigated the risk of UGI bleeding in patients using SSRIs and NSAIDs.¹ The studies, which included both inpatients and outpatients, were done in Europe and North America. Patients were at least 16 years old, but pooled demographics were not reported. Investigators compared SSRI use with or without concurrent NSAID use to placebo or no treatment.

SSRI use was associated with an increased risk of UGI bleeding in 15 case-control studies (393,268 patients; odds ratio [OR]=1.7; 95% confidence interval [CI], 1.4-1.9) and 4 cohort studies (53,681 patients; OR=1.7; 95% CI, 1.1-2.5). The simultaneous use of SSRIs and NSAIDs compared to non-use of both medications was associated with a larger increase in bleeding risk (10 case-control studies, 223,336 patients; OR=4.3; 95% CI, 2.8-6.4).

The meta-analysis is limited by statistically significant heterogeneity in all of the pooled results and high risk of bias in 9 of the case-control studies and all of the cohort studies. There was no evidence of publication bias, however.

Bleeding risk rises 7 to 28 days after SSRI exposure

A 2014 case-crossover study of 5377 inpatients in Taiwan with a psychiatric diagnosis evaluated the risk of UGI bleeding within the first 28 days after SSRI exposure (SSRI-mediated inhibition of platelets occurs within the first 7 to 14 days).² The average age of the patients was 58 years and 75% of the study

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TABLE

What are the odds of UGI bleeding after exposure to an SSRI?²

Window	Period of exposure to SSRIs before UGI bleed (days)		Adjusted odds ratio	95% CI
	Cases	Controls		
7-day	1-7	8-14	1.7	1.2-2.3
14-day	1-14	15-28	1.8	1.4-2.4
28-day	1-28	29-56	1.7	1.3-2

CI, confidence interval; SSRI, selective serotonin reuptake inhibitor; UGI, upper gastrointestinal.

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population was male. Each patient served as his or her own control.

ORs were calculated to compare patients who were exposed to SSRIs only during 7-, 14-, and 21-day windows immediately before a UGI bleed to controls exposed to SSRIs only during the control periods before the 7-, 14-, and 21-day windows. The ORs were adjusted through multivariate analysis to account for 7 potential confounding factors.

SSRI use was associated with an increased risk of UGI bleeding in 7-, 14-, and 21-day windows before the index event (TABLE²). An increased bleeding risk in the 14 days after SSRI initiation was observed in men (OR=2.4; 95% CI, 1.8-3.4) but not women (OR=1.0; 95% CI, 0.6-1.6). Increased bleeding risk in the 14 days after SSRI initiation was also observed in patients younger than 55 years (OR=2.1; 95% CI, 1.5-3.1), patients with a history of upper GI disease (OR=3.1; 95% CI, 1.7-6.0), and patients with no previous exposure to SSRIs (OR=2.6; 95% CI, 1.6-4.2).

This study didn't account for SSRI indication as a potential confounder, and the study's inclusion of inpatients, whose illnesses are typically more severe, may limit generalizability. **JFP**

References

1. Anglin R, Yuan Y, Moayyedi P, et al. Risk of upper gastrointestinal bleeding with selective serotonin reuptake inhibitors with or without concurrent nonsteroidal anti-inflammatory use: a systematic review and meta-analysis. *Am J Gastroenterol.* 2014;109:811-819.
2. Wang YP, Chen YT, Tsai C, et al. Short-term use of serotonin reuptake inhibitors and risk of upper gastrointestinal bleeding. *Am J Psychiatry.* 2014;171:54-61.

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