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Gastrointestinal bleeding

Depression and anxiety disorders CHAPTER 3 Caution should be exercised when prescribing serotonergic antidepressants for people with medical conditions such as gout, asthma, COPD, lupus, psoriasis, interferon- induced depression in patients with hepatitis C10 and arthritis, when patients might also be taking corticosteroids, aspirin or NSAIDS. Gastrointestinal bleeding The use of serotonergic antidepressants is an independent risk factor for all bleeding events. SSRIs increase the rate of upper GI bleeding (UGIB), with hazard ratio (HR) of 1.97, and lower GI bleeding (LGIB; HR 2.96) after adjusting for all relevant risk factors.11 In absolute terms, it is likely that SSRIs are responsible for an additional 3 episodes of bleeding in every 1,000 patient years of treatment,7,12,13 but this figure masks large variations in risk. For example, 1 in 85 patients with a history of GI bleeding will have a further bleed attributable to treatment with a SSRI.14 Gastroprotective drugs (proton-pump inhibitors, PPIs) decrease the risk of GI bleeds associated with SSRIs (either alone or in combination with NSAIDs), although not quite to control levels.15 A 2020 study found that SSRIs increased the risk of GI bleeding in people taking direct-acting anticoagulants for atrial fibrillation and that this risk was increased further in those not prescribed PPIs.16 Another found no increased risk of bleeding for SSRIs prescribed alongside any anticoagulants.17 People who take SSRIs are at significantly increased risk of being admitted to hospital with a UGIB compared with age- and sex-matched controls.7,15,18,19 This association holds when age, gender and the effects of other drugs such as aspirin and NSAIDs are controlled for.2 In addition to this, a meta-analysis of 22 studies concluded that current users of SSRIs are 55% more at risk of UGIB compared with those who do not take SSRIs. This risk was significantly and further increased by concurrent use of antiplatelet drugs or NSAIDs.5 Co-prescription of low--dose aspirin may double the risk of GI bleeding associated with SSRIs alone,20 as does co--prescription of NSAIDs.21 Combined use of SSRIs and NSAIDs greatly increases the use of anti-acid drugs.22 The elderly and those with a history of GI bleeding are at greatest risk of GI bleeds.14,15,19 Early studies found that in patients who take warfarin, SSRIs increase the risk of a non-GI bleed two- to three-fold (similar to the effect size of NSAIDs) but did not seem to increase the risk of a GI bleed.23,24 A later study11 showed an increased risk of UGIB and LGIB in concomitant users of warfarin and serotonergic antidepressant (Table 3.20). This effect does not seem to be associated with any change in INR, making it difficult to identify those at highest risk.24 In keeping with these findings, SSRI use in patients taking anticoagulants being treated for acute coronary syndromes may decrease the risk of minor cardiac events at the expense of an increased

risk of a bleed.25 SSRIs may decrease mortality overall in this group.26 Thus, the increased risk of UGIBs associated with SSRIs may be balanced by a decreased risk of embolic events. One database study failed to find a reduction in the risk of a first MI in patients treated with SSRIs,27 while another28 found a reduction in the risk of being admitted to hospital with a first MI in smokers on SSRIs. The effect size in the second study was large: approximately 1 in 10 hospitalisations were avoided in patients treated with SSRIs.28 This is similar to the effect size of other antiplatelet therapies such as aspirin.29 A 2021 meta-analysis suggested that SSRIs halved the risk of MI in people with coronary artery disease.26

434 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 3 Many studies do not state changes in absolute risk of intestinal bleeding and some of those that do fail to provide denominator details (i.e. duration of treatment). Ideally, risk should be defined as the number of additional cases per 1,000 patient years. Table 3.20 shows approximate absolute risks (without a denominator) derived from a single study11 and a personal communication.31 Risk decreases to the same level as controls in past users of SSRIs, indicating that bleeding is likely to be associated with treatment itself rather than some inherent characteristic of the patients being treated.7 It also means that the effect of SSRIs disappears after their withdrawal. The excess risk of bleeding is not confined to UGIBs (Table 3.20). The risk of LGIBs may also be increased32 and an increased risk of uterine bleeding (see later) has also been reported.12 Intracranial/intracerebral haemorrhage There is a clear association between the use of SSRIs and intracranial/intracerebral haemorrhage (ICH) and risk is further increased by concomitant use of NSAIDs and anticoagulants. Elevated risk of ICH has been observed across all classes of antidepressants with serotonergic activity. In a cohort study of 1,363,990 users of antidepressants,6 the overall rate of ICH was 3.8 per 10,000 patient years. Current use of SSRI increased the risk of ICH (relative risk 1.17) compared with TCA with an absolute adjusted rate difference of 6.7 per 100,000 persons per year. Among the SSRI group, the risk of ICH was 25% greater in those who used strong inhibitors of serotonin reuptake system in comparison with users of weak inhibitors (Table 3.20). This correlates to an absolute adjusted rate difference of 9.5 events per 100,000 persons per year. Overall risk was highest during the first 30 days of use. A 2018 meta-analysis of 12 studies confirmed an increased risk of ICH for SSRIs (OR 0.8–2.42), with an indication that stronger reuptake inhibitors had a greater effect.33 Since then, one study reported no increased risk of ICH with SSRIs, either alone or alongside anticoagulants,34 whereas another35 found that SSRIs increased risk of recurrence of ICH by 31%. A 2022 meta- analysis including nearly 2 million patients found an increased risk of ICH only when SSRIs were prescribed with anticoagulants.36 Table 3.20 Approximate absolute risk of GI bleeding with concomitant use of SSRIs. Drug Absolute risk of UGIB (%)* Absolute risk of LGIB (%)* Aspirin + SSRI 3 Warfarin + SSRI 3 NSAID + SSRI* 1 SSRI alone 1 LGIB, lower gastrointestinal bleeding; UGIB, upper gastrointestinal bleeding. * Percentage figures rounded to nearest integer. ** A 2023 meta-analysis suggested that the risk of a GI bleed was over 40% for people on SSRI + NSAIDs.30 This seems to be the result of erroneous interpretation of case–control study data.

Revision #1
Created 2026-01-04 20:15:00 UTC by Omar Ayman
Updated 2026-01-04 20:15:00 UTC by Omar Ayman