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# SSRI-associated risk of increased mortality and GI bleeding, when used in combination with other medications

**N Tsonev, G Valcheva, P Vasilev, I Kostov, D Notev**
Department of Gastroenterology, Clinic of Internal Medicine, Second MHAT Sofia, Bulgaria

**Abstract**
Despite the widespread use of selective serotonin reuptake inhibitors (SSRIs) in medical practice, they are associated with a number of adverse effects. severe gastrointestinal bleeding, especially if they are also taking non-steroidal anti-inflammatory drugs (NSAIDs) or certain other classes of drugs. These drugs can increase stomach acid secretion and inhibit the entry of serotonin into platelets. The report found worrisome interactions with NSAIDs such as ibuprofen and Naproxen, as well as anticoagulants - Warfarin or antiplatelet drugs - Aspirin and Clopidogrel. The real risk comes from the assumption that each of these drugs is relatively safe and benign, but they all carry a risk of bleeding, and this risk increases when these drugs are taken now. This entire article is to address bleeding often from the gastrointestinal tract associated with the concomitant use of SSRIs with anticoagulants and antiplatelets.

**Keywords:** selective serotonin reuptake inhibitor (SSRI), NSAIDs, anticoagulants, antiplatelets, GI bleeding

## Introduction

Selective serotonin reuptake inhibitors (SSRIs) belong to the group of antidepressants and are used to treat depression and anxiety disorders. They exert their effect, as the name itself indicates, by blocking the reuptake of serotonin in the synapse. Serotonin is a neurotransmitter and is believed to have a good influence on mood, emotions and sleep. The most commonly used SSRIs are: Fluoxetine (Prozac, Oxactine), Escitalopram (Lexapro), Venlafaxine (Effexor), Sertraline (Zoloft), Paroxetine (Paxil).

The frequency of use of these medications varies across countries. In 2015–2018, 13.2% of adults used antidepressants in the past 30 days (Figure 1). Use was higher among women (17.7%) than men (8.4%). The rate of antidepressant use increased with age, from 7.9% among adults aged 18-39 to 14, 4% for those aged 40-59 to 19.0% for those aged 60 and over. Similar increases in antidepressant use by age were seen in men and women. Among men, use was lowest among those aged 18-39 (5.5%) and highest among those aged 60 and over (12.8%). Among women, use increased from 10.3% among those aged 18–39 to 24.3% among those aged 60 and over. Across all age groups, antidepressant use was higher among women than men.

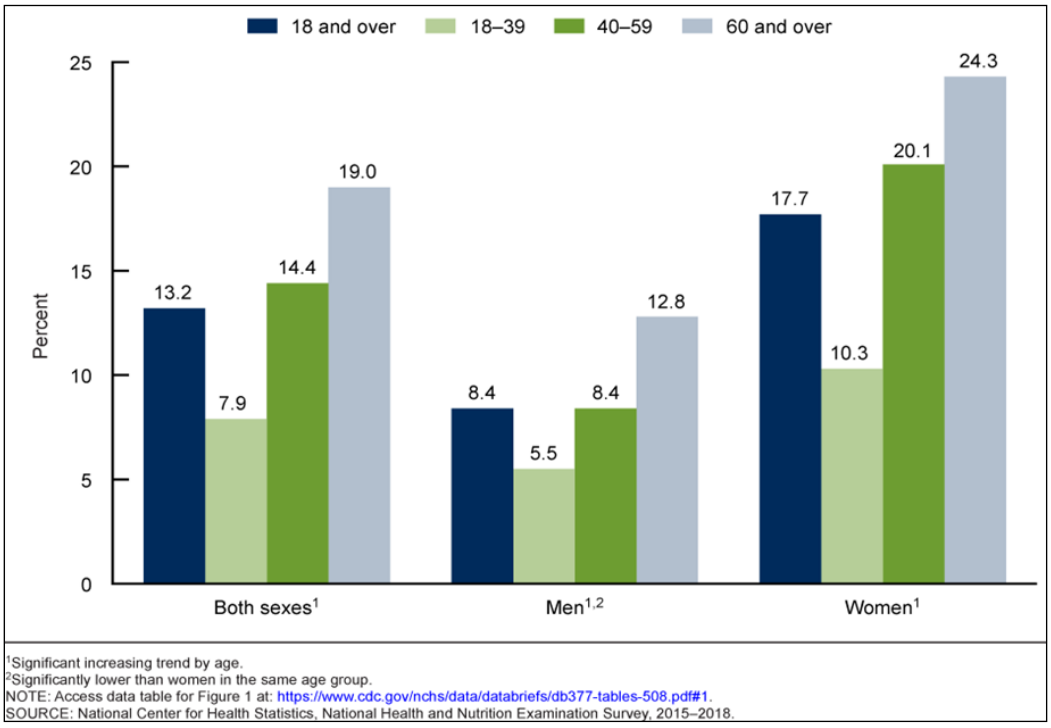


**Fig 1:** Percentage of adults aged 18 and over who used antidepressent medication over past 30 days, by age and sex. United states. 2015-2018.

**Mechanism of action**

Several pharmacological mechanisms may explain the actions of SSRIs that lead to an increased risk of bleeding. Selective serotonin reuptake inhibitors are known to downregulate serotonin (5-hydroxytryptamine [5HT]) receptors not only in the brain but also in platelets. Only neurons and platelets express 5-HT receptors in the non-activated state. The majority of 5-HT is synthesized in the gastrointestinal tract by enterochromaffin cells. It is then taken up by platelets and metabolized by the liver or pulmonary vascular endothelium. Approximately 99% of all 5-HT is stored in platelets. SSRIs interfere with the IIb/IIIa receptors further disrupting the blood clotting process. Another mechanism of action for SSRI-induced bleeding is increased gastric acidity leading to potential ulcerogenic effects. Long-term use of sertraline leads to increased expression of glycogen synthase kinase 3-b (GSK3B), which has a negative effect on platelet function. The most common sites of bleeding include upper GI tract, intracranial hemorrhage, postpartum bleeding, perioperative bleeding, bleeding associated with liver disease, rare (ecchymoses, petechiae, vaginal bleeding, epistaxis, etc.).

The association between SSRIs and increased risk of gastrointestinal bleeding is well described in the literature. A systematic review and meta-analysis by Jiang *et al* of 22 cohort and controlled studies involving more than 1 million people reported a 1.55 times higher odds of upper GI bleeding in SSRI users compared with nonusers (95 % CI, 1.35-1.78). In subgroup analyses, the risk was greatest among participants taking concomitant NSAIDs or antiplatelet drugs. The first epidemiological study to support this association was conducted in 2009 in the United Kingdom.

One of the conducted (case-control) studies of SSRI use and GI bleeding by Francisco Jospde Abajo from 1999 included 1651 cases of upper GI bleeding and 10,000 randomly selected controls. Patients with cancer, esophageal varices, Mallory-Weiss syndrome, alcoholism, chronic liver disease, and coagulopathies were excluded from the study. The author concluded that the risk of bleeding in patients using antidepressants in this group was 1 in 8000 (RR 3.0, 95% CI). It increases when used together with aspirin. Despite many studies showing a positive association between bleeding and SSRI use, one recent cohort study from 2017 showed no association between endoscopic refractory bleeding, rebleeding, or 30-day mortality in patients with ulcer disease and SSRIs (OR [95% CI] 1.03 [0.79-1.33]). A meta-analysis by La Porte *et al* 2016 of a total of 42 observational studies (37 case–controls and 11 cohorts) showed an increase in bleeding risk of at least 36% (12% to 64%) with an OR [95% CI] of 1.41 [1.25 – 1.60]. A 41% increase in risk was estimated in case-controls at OR [95% CI] 1.41 [1.25 – 1.60] and in cohorts – OR [95% CI] 1.36 [1.12 – 1.64].

Another meta-analysis of 4 controlled observational studies (1 cohort study and 3 case-control studies) including 153,000 patients that evaluated the relationship between upper GI bleeding, SSRIs and NSAIDs based on a specially designed index showed that the risk of bleeding with single use of SSRI was 2.36 (1.44-3.85), single use of NSAIDs-3.16 (2.40-4.18), combined use between the two groups of medications-6.33 (3.40-11.82)

**Table 1**

| | OR (95% CI) | P value |
|---|---|---|
| SSRIs alone | 2.36 (1.44 to 3.85) | 0.0006 |
| NSAIDs alone | 3.16 (2.40 to 4.18) | <0.00001 |
| SSRIs & NSAIDs | 6.33 (3.40 to 11.82) | <0.00001 |

**Conclusion**

In conclusion, we can say that SSRIs and NSAIDs, alone and in combination, increase the risk of upper GI bleeding and thus mortality. Older people are more likely to have co-morbidities such as osteoarthritis, which can be treated with prescription or over-the-counter NSAIDs. Patients taking NSAIDs and SSRIs together should have their treatment reviewed, especially if other risk factors for gastrointestinal bleeding are present (such as age over 65 years). Options include stopping the NSAID or switching to an alternative analgesic; using a different type of antidepressant; or co-prescribing a proton pump inhibitor.

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