Selective serotonin reuptake inhibitors (SSRIs) have been noted in several case reports to be associated with bleeding episodes, including ecchymoses, purpura, epistaxis, gastrointestinal (GI) bleeding, and intracranial bleeding. SSRIs are effective antidepressants in part because they block proteins responsible for the transport of serotonin back into the presynaptic neuron. Platelets also utilize stored cellular serotonin to assist in the aggregation response triggered by collagen, thrombin, and adenosine diphosphate. During the chronic administration of SSRIs, platelet reuptake of serotonin is reduced, and the platelets become serotonin deficient. This deficiency of platelet serotonin is thought to inhibit the platelets’ normal hemostatic function.

The first report of a potential drug interaction between SSRIs and non-steroidal anti-inflammatory agents (NSAIDs) was a case-controlled study. This study compared the use of SSRIs and NSAIDs in patients with nonesophageal upper GI bleeding (UGB) and in control patients without UGB. Antidepressants were divided into 3 subgroups: drugs with only SSRI activity, drugs with mixed SSRI and norepinephrine reuptake activity, and antidepressants without an effect on serotonin. Compared with nonusers of NSAIDs, patients taking NSAIDs had a relative risk of UGB of 3.7. The relative risk associated with NSAIDs and non-SSRIs was 4.6. The relative risk of UGB in patients taking SSRIs was 2.6. Patients taking both NSAIDs and SSRIs had a relative risk of 15.6, compared with patients taking neither group of drugs. The authors estimated that the rate of UGB in SSRI users was 1/1300 patients, or 1/8000 prescriptions. The data indicate a large increase in the rate of UGB during the coadministration of SSRIs and NSAIDs. A UGB would still be a fairly uncommon event, however.

A second study compared the prescribing of antiulcer drugs to patients who were new users of antidepressants. Compared with tricyclic antidepressants, the relative incidence of treated GI events associated with SSRIs was 1.2, while the combination of SSRIs and NSAIDs raised the relative incidence to 12.4. The authors calculated that the risk of a GI side effect was increased from 0.06 to 0.63 events per patient year of exposure to the combination.

Another large epidemiologic study found that the relative risk to require hospitalization for a UGB was 3.6 times greater in users of SSRIs and 12.2 times greater in patients taking both SSRIs
The coadministration of SSRIs and aspirin also increased the risk of UGB—5.2 times and 11.6 times with low- and high-dose aspirin, respectively. The use of non-SSRI antidepressants did not significantly change the risk of developing a UGB. These studies all demonstrate a small but consistent increased risk of UGB associated with SSRI use. When combined with NSAIDs, the risk is increased about 10-fold. The mechanism of this interaction is likely due to the additive inhibition of platelet aggregation via SSRI-induced serotonin depletion, the NSAID inhibition of thromboxane-mediated platelet aggregation, and the gastric irritation produced by the NSAID. Whereas the absolute risk of a UGB is thought to be small, however, some patients may be at an increased risk of bleeding. For example, elderly patients, patients with a history of GI bleeding or gastric or peptic ulcers, patients taking other drugs that affect platelet activity (eg, ticlopidine, clopidogrel, abciximab), or concurrently using agents that predispose to gastric irritation may be more likely to develop an adverse outcome from the combination of an SSRI and an NSAID.

For these higher-risk patients, alternative therapies should be considered that could avoid the combined administration of an SSRI and NSAID. Several approaches could be weighed, including substituting acetaminophen or salicylic acid for the NSAID. If an NSAID is required, the cyclooxygenase-2 selective NSAIDs do not affect platelet function and reduce the risk of stomach irritation. Antidepressants that do not alter serotonin reuptake (eg, tricyclics [except clomipramine] or mianserin) could be substituted for the SSRI. For patients in whom alternative therapies are not possible, the addition of a histamine2-receptor antagonist, a proton pump inhibitor, or misoprostil would likely offer some protection from GI irritation caused by the NSAID.

The patient should be instructed to report any evidence of bleeding immediately to the physician or pharmacist and to report the use of combination therapy prior to invasive procedures or surgery where altered hemostasis could present a risk. By taking these simple steps, it should be possible to mitigate the potential increased risk of UGB resulting from the concurrent administration of SSRIs and NSAIDs.