

## SSRIs and Upper Gastrointestinal Bleeding

### **Background**

Gastrointestinal (GI) hemorrhage is a well-recognized potential adverse effect associated with the use of several classes of medications, including non-steroidal anti-inflammatory drugs (NSAIDs), oral glucocorticoids, and anticoagulants. Much less appreciated, however, is the GI risk imparted by serotonergic antidepressants, especially the selective serotonin reuptake inhibitors (SSRIs), with some studies showing that this class may increase the risk of gastric or duodenal hemorrhage to a similar degree as the NSAIDs.<sup>1</sup> Although established sources of drug information (package inserts, Micromedex, Facts and Comparisons) describe these risks, many prescribers frequently remain unaware of the link between SSRIs and upper GI bleeding, as well as the potential magnitude of this adverse effect.<sup>2</sup>

Although well-known as an important neurotransmitter in the central nervous system, serotonin also has several peripheral actions. A proposed mechanism by which serotonergic antidepressants increase upper GI bleeding risk involves the role serotonin plays in platelet aggregation and vasoconstriction. Peripheral serotonin is synthesized mainly in enterochromaffin cells in the GI tract, where it functions in the regulation of gut motility. Following synthesis, some serotonin is taken up and stored in platelets. Triggers for thrombosis, including thrombin and collagen, cause platelets to release stored serotonin, which then acts to stimulate platelet aggregation and increases vasoconstriction of vessels with damaged endothelium. Serotonergic antidepressants decrease the uptake of serotonin into platelets, thereby decreasing serotonin stores, diminishing serotonin's function in hemostasis, and increasing bleeding time.<sup>3,4</sup>

### **Literature Review**

Evidence of upper GI bleeding involving antidepressants comes from retrospective cohort studies, case-control studies, and case reports. No randomized clinical trials have been published on this subject. Table I below summarizes data from retrospective studies of upper GI bleeding that required hospitalization. The annual incidence of GI bleed in the general adult population is estimated at about 1 case per 1,000.<sup>5</sup> With SSRI use alone, the adjusted relative risk (RR) of upper GI hemorrhage increases nearly three-fold (RR=2.6; 95% CI 1.7 to 3.8) and with NSAID use alone, the adjusted relative risk of upper GI hemorrhage was slightly higher at 3.7 (95% CI 3.2 to 4.4).<sup>1</sup> When concurrent use of aspirin with an SSRI was considered, the adjusted relative risk was reported at 7.2 (95% CI 3.1 to 17.1).<sup>1</sup> Most importantly, when concurrent use of an NSAID and an SSRI was considered, the adjusted relative risk increased nearly sixteen-fold; reported as 15.6 (95% CI 6.6 to 36.6).<sup>1</sup>

### **Risk Factors**

Generally accepted risk factors for upper GI hemorrhage include a history of prior hemorrhage (relative risk 5.0; 95% CI 4.1-6.1), age greater than 80 years (relative risk 3.0; 95% CI 2.6-3.6), smoking, alcohol consumption, and the use of certain classes of medications, especially NSAIDs, glucocorticoids, and anticoagulants.<sup>6</sup> Among the NSAIDs, piroxicam (Feldene<sup>®</sup>), ketoprofen (Oruvail<sup>®</sup>), and ketorolac tromethamine (Toradol<sup>®</sup>) appear to be the most damaging.<sup>8</sup> In addition, the risk of NSAID-induced GI bleed is likely dose and duration dependent. Some clinicians employ gastroprotectant agents in at-risk patients including proton-pump inhibitors (PPIs), misoprostol, histamine-2 receptor blockers, and bismuth compounds, but the full magnitude of such protection has yet to be fully elucidated.

**Table I: Comparison of SSRI- and NSAID-induced GI Bleeding**

Study	Type	Place	Pts (n)	Pt age (yrs)	RR NSAID (95% CI)	RR SSRI (95% CI)	RR SSRI + NSAID (95% CI)
de Abajo 1999 <sup>1</sup>	case control	UK	69,593	40- 79	3.7 (3.2-4.4)	2.6 (1.7-3.8)	15.6 (6.6-36.6)
van Walraven 2001 <sup>6</sup>	cohort	CN	317,824	65+	2.8 (2.4-3.3)	3.1 (not avail)	6.2 (not avail)
Dalton 2003 <sup>7</sup>	cohort	DN	26,005	16- 105	4.5 (3.9-5.2)	3.6 (2.7-4.7)	12.2 (7.1-19.5)

Pts=patients using any antidepressant; RR=relative risk; UK=United Kingdom; CN=Canada; DN=Denmark

### ***Serotonergic Antidepressants***

Although the role of serotonin in platelet aggregation is becoming better understood, clinically significant differences among SSRIs in the periphery have not been clearly established. In an analogous fashion to the NSAIDs, it has been theorized that different SSRIs may be associated with different levels of GI bleeding risk. The potential for disparity among serotonin-affecting antidepressants (within the SSRI class itself, as well as between SSRIs and non-SSRIs such as trazodone, bupropion, and mirtazapine) is being explored. While published studies have attempted to identify such differences, results have been largely inconclusive.<sup>1,6,7</sup>

### ***Recommendations***

Given the available information, it is recommended that before initiating treatment with a serotonergic antidepressant, any history of prior upper GI hemorrhage should be reviewed, as well as documentation of known or suspected GI risk factors including age, smoking status, alcohol consumption, and use of other medications that may potentiate GI risk. Concurrent use of an SSRI and an NSAID is best avoided when possible. For patients who must take serotonergic antidepressants chronically, alone or in combination with NSAIDs, increased monitoring for signs of upper GI hemorrhage is recommended, with serious consideration given to concurrent use of a PPI or other gastroprotective agent.

### ***References***

1. de Abajo FJ, Rodriguez LA, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *BMJ*. 1999 Oct 23;319(7217):1106-1109.
2. Scott GN. Selective serotonin reuptake inhibitors (SSRIs) and antiplatelet activity. *Pharmacist's Letter/Prescriber's Letter* 2005 Jul;21(7):210715.
3. Berk M, Jacobson BF. Selective serotonin reuptake inhibitor-induced disturbances of haemostasis. *CNS Drugs*. 1998 Dec;10(6):441-446.
4. Sanders-Bush E, Mayer SE. 5-Hydroxytryptamine (serotonin): receptor agonists and antagonists. *In Goodman & Gilman's the Pharmacological Basis of Therapeutics*, 10<sup>th</sup> ed. Hardman JG, Limbird LE editors. McGraw-Hill:New York. 2001:274-275.
5. Longstreth GF. Epidemiology of hospitalization for acute upper gastrointestinal hemorrhage: a population-based study. *Am J Gastroenterol*. 1995 Feb;90(2):206-210.
6. van Walraven D, Mamdani MM, Wells PS, Williams JI. Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. *BMJ*. 2001 Sep 22;323(7314):655-658.
7. Dalton SO, Johansen C, Mellekjaer L, Norgard B, Sorensen HT, Olsen JH. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. *Arch Intern Med*. 2003 Jan 13;163(1):59-64.
8. Lanas A. Gastrointestinal injury from NSAID therapy. How to reduce the risk of complications. *Postgrad Med*. 2005 Jun;117(6):23-28, 31.