

## Drug Interactions in the Treatment of Depression in Patients With Ischemic Heart Disease

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Each month in his online column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to JCP readers in psychiatric and general medical settings.

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### Clinical Problem

Mr K is 67 years old. He has been diagnosed with major depressive disorder. He has a history of ischemic heart disease (IHD). What might be the concerns associated with treating his depression with a selective serotonin reuptake inhibitor (SSRI)?

### The Relationship Between Depression and Ischemic Heart Disease

Patients with depression are at increased risk of IHD events, and patients who have IHD are at increased risk of depression; the presence of each condition worsens the course and outcome of the other.<sup>1</sup> It is important, therefore, for depression to be identified early and treated effectively in patients with IHD.<sup>2,3</sup> Given that SSRIs are commonly used antidepressants, clinicians should be aware that SSRIs may have effects beyond antidepressant action in patients with IHD.

### Possible Benefits of SSRIs in Patients With Ischemic Heart Disease

SSRIs effectively attenuate depression, including depression that complicates the course of IHD.<sup>4</sup> SSRIs may also improve the course of IHD<sup>5–10</sup> through multiple mechanisms (Table 1)<sup>11–17</sup>—this is an important consideration, given that tricyclic antidepressants have been associated with an increased risk of IHD events.<sup>18,19</sup>

### Possible Adverse Interactions of SSRIs in Patients With Ischemic Heart Disease

Patients with IHD are usually prescribed antiplatelet treatment to reduce the risk of future ischemic events. Aspirin and clopidogrel are 2 drugs that are commonly prescribed for this purpose, separately or together. SSRIs may adversely interact with these 2 drugs, as discussed in the sections that follow. Other interactions between SSRIs and cardiovascular drugs will be examined in a future article.

**Risk of abnormal bleeding.** SSRIs increase the risk of abnormal bleeding through 2 important mechanisms: antiplatelet activity and increased gastric acidity.<sup>12</sup> The gastrointestinal (GI) tract is the most common site of SSRI-related bleeding.<sup>12</sup> A large body of literature describes an increased risk of abnormal bleeding associated with the combination of SSRIs with aspirin or clopidogrel.<sup>12</sup> A recent observational study<sup>20</sup> is briefly presented by way of example; this study was specifically conducted in IHD patients.

Labos et al<sup>20</sup> described a retrospective cohort study of 27,058 patients 50 years and older who received aspirin (n = 14,426); clopidogrel (n = 2,467); aspirin and clopidogrel (n = 9,475); aspirin and an SSRI (n = 406); aspirin, clopidogrel, and an SSRI (n = 239); or clopidogrel and an SSRI (n = 45) after an acute myocardial infarction. There were 1,070 episodes of bleeding recorded across a mean duration of follow-up of 3 years. SSRIs were associated with an increased hazard of bleeding episodes in almost all analyses (Table 2).

The absolute risk of bleeding associated with SSRI use appeared small. Relative to the use of aspirin alone, the combination of an SSRI with aspirin raised the bleeding risk by 0.5 events per 100 patient-years.

- Depression and ischemic heart disease commonly coexist, and each can worsen the course of the other.
- SSRIs (commonly used for depression) can increase the risk of bleeding events with antiplatelet therapy (commonly used for ischemic heart disease); this risk may be diminished by use of a proton pump inhibitor.
- Fluoxetine and fluvoxamine may inhibit the metabolic activation of clopidogrel and thus potentially diminish its efficacy.

**Table 1. Mechanisms Whereby SSRIs May Improve the Course of Ischemic Heart Disease**

SSRIs reduce the uptake of serotonin into platelets and thereby inhibit serotonin-mediated platelet aggregation. This could attenuate platelet-mediated hemostasis, thus protecting against intravascular thrombosis<sup>11,12</sup>

SSRIs may reduce platelet/endothelial activation over and above that associated with concomitant antiplatelet drugs<sup>13,14</sup>

SSRIs may reduce levels of vascular cell adhesion molecule-1 and intracellular adhesion molecule-1,<sup>15</sup> further reducing the risk of intravascular thrombosis

SSRIs may reduce levels of C-reactive protein and interleukin-6 and improve flow-dependent endothelium-mediated dilation (medication studied was sertraline)<sup>16</sup>

SSRIs inhibit collagen-induced platelet aggregation and activation, thereby reducing the risk of thrombosis triggered by exposure to collagen in atherosclerotic plaques or damaged blood vessel walls (medication studied was citalopram)<sup>17</sup>

Abbreviation: SSRI = selective serotonin reuptake inhibitor.

**Table 2. Hazard Ratios for Abnormal Bleeding in an Observational Study of Patients Receiving SSRIs and Antiplatelet Treatment After Myocardial Infarction<sup>a</sup>**

Relative to aspirin alone, SSRI use was associated with raised bleeding risks as follows:

SSRI + aspirin, HR = 1.42 (95% CI, 1.08–1.87)

SSRI + aspirin + clopidogrel, HR = 2.35 (95% CI, 1.61–3.42)

Relative to clopidogrel alone, SSRI use was associated with raised bleeding risk as follows:

SSRI + clopidogrel, HR = 1.54 (95% CI, 0.70–3.39)

Relative to combined use of aspirin and clopidogrel, SSRI use was associated with raised bleeding risk as follows:

SSRI + aspirin + clopidogrel, HR = 1.57 (95% CI, 1.07–2.32)

<sup>a</sup>Data from Labos et al.<sup>20</sup> With the exception of the SSRI + clopidogrel combination (the analysis of which was underpowered), all SSRI–antiplatelet treatment combinations were associated with a significant increase in the risk of abnormal bleeds.

Abbreviations: HR = hazard ratio, SSRI = selective serotonin reuptake inhibitor.

Relative to the use of aspirin combined with clopidogrel, the combination of an SSRI with aspirin and clopidogrel raised the bleeding risk by 1.5 bleeding events per 100 patient-years. These risks seem trivial at an individual level; however, they are clinically significant at the population level because they suggest that if 200 IHD patients are treated with antiplatelet and SSRI drugs for 1 year, 1 to 3 patients could experience an abnormal bleeding episode. It is also important to note that the patients in this study were followed up until admission for a bleeding episode, admission for recurrent myocardial infarction, death, or the end of the study period. Thus, given that most cases of SSRI-related bleeding occur early during treatment,<sup>12</sup> the average of 3 years of follow-up per patient would have considerably diluted the magnitude of the identified risk.

Labos et al<sup>20</sup> found that the risks were similar when the analyses were restricted to cases of GI bleeding. Finally, and especially importantly, they found that non-SSRI antidepressants were not associated with an increased risk of bleeding events.

How may this interaction be prevented? Observational studies suggest that the concurrent administration of proton pump inhibitors may decrease the risk of SSRI-related bleeds.<sup>12</sup> However, some proton pump inhibitors, such as omeprazole and esomeprazole,<sup>21–23</sup> potentially inhibit cytochrome P450 (CYP) 2C19, which can diminish the efficacy of clopidogrel if the patient happens to be receiving the drug (as discussed in the next section). In this context, lansoprazole and dexlansoprazole are less potent inhibitors of CYP2C19, and rabeprazole and pantoprazole are weak inhibitors.<sup>21–23</sup> The US Food and Drug Administration (FDA) specifically discourages the use of omeprazole in patients who are receiving clopidogrel and suggests a preference for pantoprazole.<sup>24</sup>

On a separate note, IHD is more common in elderly subjects, and the elderly may be more vulnerable to SSRI-related abnormal bleeding.<sup>12</sup>

**Risk of diminished efficacy of clopidogrel.** Clopidogrel is a prodrug that is activated by CYP2C19.<sup>25</sup> A systematic review and meta-analysis of 9 studies (pooled N = 9,685) evaluated

the influence of the *CYP2C19* genotype on outcomes in patients receiving clopidogrel; patients with reduced-function variations of one or both of the *CYP2C19* genes had significantly worse cardiovascular or cerebrovascular outcomes.<sup>25</sup> This finding suggests that, in patients who receive fluoxetine or fluvoxamine, the efficacy of clopidogrel could be similarly impaired, because both SSRIs inhibit *CYP2C19*. In November 2009, the FDA issued a warning that clopidogrel should not be combined with various *CYP2C19* inhibitors, including fluoxetine and fluvoxamine.<sup>26</sup>

## Concluding Notes: Treatment Considerations

The preceding discussion suggests the following:

1. Fluoxetine and fluvoxamine are best avoided in IHD patients who are receiving clopidogrel because both SSRIs may diminish the efficacy of clopidogrel.
2. If an SSRI is prescribed to an IHD patient who is receiving aspirin or clopidogrel, the concurrent prescription of a proton pump inhibitor that does not significantly inhibit *CYP2C19* (eg, rabeprazole, pantoprazole) could reduce the risk of GI bleeding without diminishing the efficacy of clopidogrel.

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