Antidepressants in geriatric patients: Reduce the risk of GI bleeding

Eric C. Kutscher, PharmD, BCPP, Megan Leloux, PharmD, and Michael Lemon, PharmD

Vicki L. Ellingrod, PharmD, BCPP, FCCP
Series Editor

Mr. M, age 70, presents to the emergency department (ED) complaining of new-onset fatigue, dizziness, and black, tarry stools. He is anemic (hemoglobin 8.9 g/dL) and his stool is positive for occult blood. Mr. M denies having any symptoms until 1 week ago and reports taking his medications as prescribed. An upper endoscopy reveals a gastrointestinal (GI) bleed and his physician stops his antiplatelet medications. Mr. M's medical history includes hypertension, hyperlipidemia, and placement of a drug-eluding coronary artery stent 9 months ago. Before presenting to the ED, he had been maintained on lisinopril, 20 mg/d, simvastatin, 40 mg/d, aspirin, 325 mg/d, clopidogrel, 75 mg/d, and a daily multivitamin. Three weeks ago, Mr. M was started on citalopram, 20 mg/d, for depressed mood that he has had since his wife died a year ago.

The psychiatry service is consulted after Mr. M admits he has had thoughts of suicide and a few weeks ago was planning to take an overdose of his medications. He denies taking any extra medications and reports feeling more positive since starting citalopram. The psychiatrist discontinues citalopram, however, because of a possible drug interaction with antiplatelet medications, starts Mr. M on bupropion, 150 mg/d, and recommends he follow up with his primary care physician for management of his depressive symptoms.

Older patients frequently take multiple medications for various disease states, which increases their risk of drug-drug interactions. In addition, physiologic changes associated with aging alter how patients respond to medications. Drugs may interact pharmacokinetically and pharmacodynamically. Pharmacokinetic interactions are well understood and represent changes in absorption, distribution, metabolism, and elimination of specific medications. Pharmacodynamic drug-drug interactions, on the other hand, are less recognized and represent changes in medications' mechanism of action. A clinician who understands pharmacodynamic interactions will be able to better identify potential drug-drug interactions and could avoid adverse events.[1]

Practice Points

- **Geriatric patients who take multiple medications** for various disease states are at increased risk for drug-drug interactions.
- **Serotonergic antidepressants inhibit platelet aggregation**, which may increase a patient's risk of bleeding or bruising.
- **Closely monitor patients receiving serotonergic antidepressants** concomitantly with other medications that may increase bleeding risk.
- **Consider prophylactic acid suppressive therapy** for patients at high risk for GI bleeding who receive concomitant SSRIs.

Dr. Kutscher is Associate Professor of Pharmacy Practice, South Dakota State University College of Pharmacy, Brookings, SD, Adjunct Associate Professor of Psychiatry, Sanford School of Medicine, University of South Dakota, Director of the Psychiatry Pharmacy Practice Residency Program, and Clinical Pharmacy Specialist, Avera Behavioral Health Center, Sioux Falls, SD. Dr. Leloux is a Psychiatric Pharmacy Practice Resident, Avera Behavioral Health Center, Sioux Falls, SD. Dr. Lemon is Professor of Pharmacy Practice, South Dakota State University College of Pharmacy, Brookings, SD, and VA Black Hills Health Care System, Fort Meade, SD.

Table

Risk factors for gastrointestinal bleeding

Medications	Corticosteroids, anticoagulants (warfarin), antiplatelets (clopidogrel), NSAIDs (including aspirin), calcium channel blockers, SSRIs, SNRIs, tricyclic antidepressants
Disease state/patient factors	Age (elderly are at higher risk), history of ulcer, chronic alcohol use, peptic ulcer disease, esophageal varices, gastric or colorectal cancer, gastritis, liver disease, coagulopathy

NSAIDs: nonsteroidal anti-inflammatory drugs; SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors

Source: References 2-5

Antidepressants and bleeding

In Mr. M's case, a pharmacodynamic drug-drug interaction among citalopram, aspirin, and clopidogrel caused a GI bleed. This type of interaction may be overlooked because of the relatively safe drug-drug interaction profile of selective serotonin reuptake inhibitors (SSRIs). However, any antidepressant that increases serotonin concentration, including serotonin-norepinephrine reuptake inhibitors, may cause this pharmacodynamic interaction.[1]

Platelets release serotonin to promote aggregation, but do not produce it themselves and are dependent on the serotonin transporter system (reuptake pump) to acquire serotonin. Because SSRIs act on serotonin transporters found on platelet cell membranes, these drugs deplete platelets' supply of serotonin, leading to diminished platelet aggregation. This effect may propagate the action of other medications that inhibit platelet aggregation, which may increase a patient's risk of bruising and/or bleeding. This increased risk of bleeding is not associated with non-serotonergic antidepressants such as bupropion, and seems to decrease when SSRIs are discontinued.[2]

A modest increase in bleeding risk with SSRIs when used alone and with other platelet-inhibiting therapies has been described in case reports, case controlled studies, and chart reviews.[2-4] The agents studied include aspirin and clopidogrel, which Mr. M was receiving, but also other, often-overlooked medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors, calcium channel blockers, and systemic corticosteroids. Patient factors and diseases—including a history of peptic ulcer disease, previous bleeding, heavy alcohol use, and older age—also may increase bleeding risk ***(Table)***.[2-5]

Serotonin reuptake inhibitor medications have been associated with various bleeding events.[5] Most case-control and cohort analyses have examined the risk of GI bleeding with SSRIs; however, serotonergic antidepressants also have been associated with an increased risk of uterine bleeding and perioperative blood loss and transfusions in various surgical procedures.[6] Some reports have suggested that there may be a small increase in the incidence of hemorrhagic and fatal stroke with SSRI use[5,7]; however, many studies have not found an association between SSRI use and increased risk of intracranial hemorrhage stroke.[8] The Women's Health Initiative Study, which reviewed cardiovascular morbidity and mortality data, showed that antidepressant use in postmenopausal women was associated with an increased risk of all-cause mortality, but not coronary heart disease.[7] SSRI use was associated with an increased risk of stroke, specifically hemorrhagic stroke, although the absolute event risks were low and cannot be used to predict risk.

Reducing bleeding risk

In a case-control study, de Abajo et al[4] found that patients taking acid-suppressing drugs—proton pump inhibitors and histamine H2 receptor antagonists—had a lower risk of upper GI tract bleeding associated with serotonergic antidepressants compared with those not taking acid-suppressing medications. These drugs further reduced the risk of bleeding in patients taking NSAIDs or antiplatelet medications con-

Clinical Point

Any antidepressant that increases serotonin may cause a pharmacodynamic interaction leading to a GI bleed

comitantly with SSRIs. We suggest initiating prophylactic acid suppression therapy for any patient who is considered at high risk for a GI bleed and is taking an SSRI with or without other medications that inhibit platelet aggregation. Specifically, start with an H2 antagonist because of these medications' faster onset of action and lower cost vs proton pump inhibitors.

Although the association between SSRIs and bleeding have been described in observational studies, it is impossible to rule out alternate causes and potential confounders that may have contributed to these events. Due diligence and therapeutic drug monitoring of all known and predicted drug-drug interactions is warranted for all patients taking serotonergic antidepressants in combination with medications known to increase bleeding risk.

Clinical Point

Acid-suppressing drugs reduced the risk of bleeding in patients taking SSRIs and NSAIDs or antiplatelet medications

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Related Resources

- Indiana University School of Medicine. P450 drug interaction table. http://medicine.iupui.edu/clinpharm/ddis/table.asp.
- Hansten PD, Horn JR. The top 100 drug interactions: a guide to patient management. Edmonds, WA: H&H Publications; 2010.

Drug Brand Names

Bupropion • Wellbutrin
Citalopram • Celexa
Clopidogrel • Plavix
Lisinopril • Zestril, Prinivil
Simvastatin • Zocor
Warfarin • Coumadin

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.