

Do Antidepressants Increase Warfarin Bleeding Risk?

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Evidence from case reports and epidemiologic studies suggests that selective serotonin reuptake inhibitors (SSRIs) alone may increase bleeding risk in susceptible patients. There is also evidence of an additive increase in bleeding risk when SSRIs are used concurrently with other drugs that can cause bleeding.

For example, it is now generally accepted that the combined use of SSRIs and nonsteroidal anti-inflammatory drugs (NSAIDs) can increase the risk of serious bleeding, especially in the gastrointestinal tract.^{1,2} The absolute increase in risk is relatively small, but the bleeding can be life threatening.

Given these data, one would expect that SSRIs could increase the bleeding risk in patients receiving warfarin or other anticoagulants, and there is new evidence that adds to our understanding of this interaction. An initial study did not find an increase in bleeding risk,³ but 3 subsequent studies did.⁴⁻⁶ Now 2 recent reports agree with the positive studies, suggesting that SSRIs, and perhaps some other antidepressants, do in fact increase the incidence of serious bleeding in patients taking warfarin.^{7,8}

NEW EVIDENCE

A case-control outpatient study of the incidence of bleeding in patients receiving warfarin found an increased risk of hospitalizations for gastrointestinal bleeding when warfarin was used concomitantly with citalopram, fluoxetine, paroxetine, amitriptyline, or mirtazapine.⁷ There was a trend of increased bleeding for some other antidepressants including venlafaxine and nortriptyline.

Another recent study was smaller, but involved a detailed review of medical records for minor or major bleeding, and they also controlled for concomitant medications, diet, and use of alcohol and other substances.⁸ They found that SSRIs were associated with an increased risk of bleeding, but the effect was most

marked for major bleeding. When all antidepressants were combined (SSRIs, tricyclic antidepressants, mirtazapine, bupropion, trazodone) there was no increase in bleeding risk, but the number of patients taking some of these drugs was small.

CLINICAL SIGNIFICANCE

Taken together, the bulk of the current evidence suggests that SSRIs are associated with an increased risk of bleeding in patients taking warfarin. Of course, retrospective epidemiological studies by themselves rarely establish the existence of drug interactions, and we must continue to look for other factors that might confound the results.

For example, could patients who are started on antidepressants improve their adherence to their warfarin dosing, thereby increasing the risk of bleeding? Or is there something about the depressive state itself that predisposes to bleeding? Nonetheless, for now we should assume that SSRIs do increase the risk of bleeding in individuals taking warfarin, and make clinical decisions accordingly.

WHAT IS THE MECHANISM?

Although the mechanism has not been established, it has been proposed that the ability of SSRIs to inhibit the uptake of serotonin into platelets inhibits the ability of platelets to aggregate. This is a plausible explanation and may be the cause of the interaction, but not all of the data are consistent, so more study is needed.

WHAT ABOUT OTHER ANTIDEPRESSANTS?

Given the proposed mechanism, one would expect all SSRIs to interact similarly with warfarin. Other antide-

pressants that inhibit serotonin uptake would also be expected to interact, such as serotonin-norepinephrine reuptake inhibitors and certain tricyclic antidepressants (eg, clomipramine, imipramine). The antidepressant mirtazapine is not considered an inhibitor of serotonin uptake (although it may cause release of serotonin), but in 1 study mirtazapine was associated with an increased risk of bleeding in patients taking warfarin. More study is needed to assess whether or not mirtazapine increases bleeding risk when combined with warfarin.

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increased risk of bleeding in patients taking warfarin.

WHAT ABOUT OTHER ANTICOAGULANTS?

Theoretically, SSRIs and other drugs that inhibit serotonin uptake would increase the risk of bleeding when combined with other anticoagulants, but little information is available.

MANAGEMENT

It does not appear necessary to avoid using SSRIs or other antidepressants in people taking warfarin, but the possibility of increased bleeding risk should be considered when selecting treatment for depression. If an antidepressant is added to warfarin therapy, monitor closely for evidence of bleeding, especially during the first 2 or 3 months of antidepressant therapy. Note that antidepressants are not likely to affect the international normalized ratio in patients on warfarin. **PT**

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