

Antidepressant-associated purpura: A rare familial case presentation

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Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been a welcome addition to the armamentarium for treating depressive disorders, neuropathic pain, and anxiety disorders. Despite the more favorable side-effect profile compared with tricyclic antidepressants and monoamine oxidase inhibitors, these serotonergic agents have been associated with bleeding disorders, purpura, thrombocytopenia, and, in extreme cases, death.¹⁻⁴

We describe a case of purpura associated with different classes of antidepressants, including the non-serotonergic agent bupropion, as well as a family history of similar adverse effects to antidepressants.

CASE

Purpura resolves when drug is stopped

Ms. R, age 70, presents with major depressive disorder and fibromyalgia and is receiving duloxetine, 20 mg/d, which is gradually increased to 60 mg. She also has a history of chronic obstructive pulmonary disease (COPD), for which she is taking albuterol and a steroid inhaler. Ms. R responds well to treatment; however, she develops blue-purple purpura on her arms each measuring 1 to 2 inches. Laboratory test results including platelet count and prothrombin time/international normalized ratio are within normal ranges. Duloxetine is stopped, and purpura resolves in 1 to 2 weeks. To avoid serotonergic antidepressants, Ms. R receives bupropion XL, 150 mg; however, similar purpura develops, then resolves when the medication is discontinued. She is lost to follow

up for approximately 6 months, but returns requesting a rechallenge with duloxetine for her depression, which has worsened. Duloxetine is restarted with similar results and is then discontinued. Because she has developed neuropathy, Ms. R is started on nortriptyline, 25 mg/d, increased to 50 mg/d, but purpura develops again, which resolves when medication is discontinued. Ms. R's daughter reports she also developed a similar reaction with several antidepressants, which resolved with medication discontinuation.

Bleeding risk with antidepressants

The role of serotonin reuptake inhibitors (SRIs) in inducing bleeding has emerged as a safety concern,^{5,6} which have been documented in case reports.⁷⁻¹¹ Mechanisms of action that have been thought to affect platelet aggregation include:

- depletion of serotonin in platelets
- increase in capillary fragility
- modification of platelet plug formation
- responsiveness of peptide-induced activation of platelets through stimulation of the thrombin receptor.^{7,8,12,13}

The severity of bleeding varies with patient-related factors, such as a history of



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gastritis, peptic ulcer disease, and heavy bleeding during menses; use of gastrotoxic drugs, particularly nonsteroidal anti-inflammatory drugs (NSAIDs), also have been shown to increase this risk.^{14,15} For patients taking SRIs and gastrotoxic drugs (eg, NSAIDs), use of acid-suppressing agents have been shown to limit the risk of bleeding.¹⁶

Studies evaluating relative bleeding risks among classes of antidepressants have not shown increased risk with tricyclic antidepressants compared with SSRIs.¹⁷ Adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP) are signaling molecules in the vascular system and are important in the thromboregulatory system. Studies in rats reported significant inhibition of ATP, ADP, and AMP hydrolysis with chronic treatment with fluoxetine and nortriptyline, and suggested that both medications changed the nucleotide catabolism, which means that homeostasis of the vascular system can be altered by antidepressant treatments.¹⁸ This is one possible pathway in the role these medications play in the etiology of dysregulation of the thromboregulatory system.

We did not anticipate that our patient would develop similar purpura with bupropion because the bleeding risk associated with antidepressants has been attributed to the effect of serotonin on platelets. Studies observing the effect of SSRIs, SNRIs, and bupropion on platelets and bleeding have not shown significant risk with bupropion.¹⁹ Bleeding associated with bupropion is atypical and needs to be further studied. Although this medication is centrally selective in its action on dopamine receptors, it might have possible peripheral effect on other neurotransmitters, including serotonin.

Ms. R had no personal or family history of purpura or a bleeding disorder. Significant improvement in her physical signs after discontinuing medications and recurrence of pupura with rechallenge indi-

Drug Brand Names

Acetaminophen/ hydrocodone • Lorcet, Norco, Vicodin	Bupropion • Wellbutrin Duloxetine • Cymbalta Nortriptyline • Pamelor, Aventyl
Albuterol • Proventil	

cate that this reaction was triggered by 3 different classes of antidepressants. Family history of similar reaction further suggests a genetic predisposition to platelet dysfunction to antidepressant treatment in a select group of patients.

Limitations include the possibility of senile purpura, which cannot be ruled out despite strong indications that antidepressants were the cause. The possibility of drug interactions needs to be considered as well. Ms. R was taking albuterol and a steroid inhaler for her COPD at the time of the initial medication trials, which did not interact with duloxetine or bupropion. During the trials with duloxetine and then nortriptyline, she was taking acetaminophen/hydrocodone in addition to her inhalers, and no significant interactions with the antidepressants were identified. Interactions with unreported or over-the-counter medications or supplements are a possibility.

Before prescribing an antidepressant, we suggest taking a careful history including a family history of bleeding disorders and adverse effects of antidepressants, especially in patients who have risk factors (eg, concomitant use of gastrotoxic medications). Use of gastric acid-suppressing medications could be considered if antidepressants are used. Further investigations into the incidence, risk factors, mechanism of action, and treatment of this adverse effect are indicated.

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Clinical Point

Studies observing the effect of SSRIs, SNRIs, and bupropion on platelets and bleeding have not shown significant risk with bupropion

Clinical Point

Family history of similar reaction further suggests a genetic predisposition to platelet dysfunction with antidepressants

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