# Editorial

# Do Selective Serotonin Reuptake Inhibitor Antidepressant Drugs Promote Atherosclerosis?

Jintao Wang, Daniel T. Eitzman

Major depressive disorder is a common debilitating condition affecting ≈10% of US adults annually.[1] The lifetime prevalence of depression is ≈16% to 17%, and nearly half of depressive disorders are treated with drugs.[1,2] Depression is relevant from a cardiovascular perspective because depression is common in patients with coronary heart disease (CHD) with rates reported as high as 74% in patients with recent acute myocardial infarction,[3] 50% in patients awaiting coronary bypass surgery,[4] and 30% in outpatients with a CHD diagnosis.[5] Not only does CHD associate with depression but also depression in turn is associated with worse CHD outcomes.[6] The mechanism(s) responsible for the link between depression and CHD remain unclear but may be related to genetics,[7–9] behavioral and lifestyle factors,[10–12] autonomic nervous system dysregulation,[13,14] inflammatory/autoimmune pathways,[15] and disturbances of the hypothalamic–pituitary–adrenal axis.[15] The effect of antidepressant pharmacotherapy on cardiovascular disease outcomes is controversial with studies showing both negative and positive effects toward CHD prognosis.[16–20] Because of the association between depression and CHD, it becomes important that therapeutic strategies to improve depressive symptoms not have deleterious effects toward CHD. This can be difficult to ascertain because improvement in depressive symptoms could have beneficial effects toward CHD that could mask underlying adverse drug effects. Using therapies that positively affect both conditions should lead to the best possible outcomes.

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In this issue of *ATVB*, Rami et al[21] study the effect of a commonly used antidepressant on the progression of atherosclerosis in apolipoprotein E–deficient mice. Because depression is likely not a prominent factor in this design, the study may address the direct drug effect without confounding effects of depression. The drug studied, fluoxetine, belongs to the class of drugs known as selective serotonin reuptake inhibitors (SSRIs). Because of the salutory effects of fluoxetine on depression, the effect of this drug on vascular end points has been controversial with some studies suggesting lower cardiovascular risk[22–24] while other suggesting higher cardiovascular risk with treatment.[25,26] In the current study, mice on a Western diet were treated with fluoxetine and then analyzed for aortic root atherosclerosis. A proatherogenic effect of fluoxetine was observed as early as 2 weeks after treatment, and this effect was sustained out to 16 weeks of treatment. This proatherogenic effect was associated with enhanced myeloid CCL5 (chemokine [C-C motif] ligand 5)-induced β2 integrin–binding capacity and increased carotid arterial leukocyte–endothelial interactions. Vascular permeability was also enhanced with fluoxetine, suggesting transendothelial migration of leukocytes may be facilitated. A different SSRI, excitalopram, also increased myeloid binding to VCAM-1 (vascular cell adhesion molecule-1) in the presence of CCL5, supporting a drug class effect for this myeloid activation. No effect of fluoxetine was observed on platelet activation, platelet–leukocyte aggregates, or endothelial adhesion molecule expression. An early transient reduction of circulating leukocyte and platelet counts was observed with fluoxetine treatment that the authors speculate may be because of enhanced recruitment to the arterial wall during early lesion formation. However, this reduction in cell counts was not observed in nonatherogeneic wild-type mice, suggesting that the proatherogenic effect of fluoxetine may require a hyperlipidemic, proinflammatory background with enhanced chemokine levels. Consistent with the results reported in this study, a previous primate study demonstrated that diet-induced coronary atherosclerosis in depressed monkeys treated with the SSRI, sertraline, was 4.9× higher than that in untreated depressed monkeys and 6.5× higher than in nondepressed monkeys, suggesting both depression and SSRI treatment are proatherogenic.[27]

The current study advances our understanding of SSRIs by uncovering potential mechanisms of SSRIs toward myeloid activation. Further studies to uncover additional mechanistic details related to the effects of fluoxetine on integrin-binding activity are needed although the authors do provide evidence that the effects observed are independent of peripheral 5-HT (5-hydroxytryptamine receptor) depletion. It would also be interesting to examine this mechanism in leukocytes isolated from depressed humans pre- and post-treatment with SSRIs to determine the relevance of these findings to humans with and without hyperlipidemia. Finally, additional trials in humans treated for depression with cardiovascular end points will be useful to guide future therapeutic interventions for these common diseases.

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## Disclosures

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