Lower Risk of First Onset of Many Cardiovascular Disorders in Antidepressant-Treated Women Veterans:

Encouraging Findings but Concerns Remain

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The reciprocal relationship between depression and cardiovascular disease (CVD) has been known for more than 2 decades; each increases the risk and worsens the course and outcome of the other.[1] In explanation, as examples, depression is associated with unhealthy patterns of eating and sleeping, inadequate exercise, and poor adherence to medical guidance, all of which can result in new-onset CVD or worsening of existing CVD. Or, CVD-associated narrowing of small arteries in the brain (and the consequences thereof) and the stressful impact of CVD events can increase the risk of depression or worsen the course and outcome of depression. Besides, as has also been known for decades, shared genetic and environmental risk factors may drive the risk of both depression and CVD.[2–6]

The multiple paths linking depression and CVD render irrelevant the determination of which came first; what is important is to recognize that the occurrence of one should alert us to the current or future risk of the other. The disorders, when identified, should be effectively treated. Depression is most commonly managed with antidepressant drugs. On the one hand, antidepressants may increase heart rate, blood pressure, body-mass index, and other risk factors for CVD. On the other hand, by effectively treating an underlying psychiatric disorder, antidepressants may attenuate risk factors for CVD that arise from the presence of that disorder.

In this context, in a study that followed 609,546 women veterans (mean age, 41 years) for a mean of 8.8 years, Sumner et al[7] found that, after adjusting for covariates and confounds (including psychiatric disorders and conventional risk factors for CVD), new prescription of antidepressant medication was associated with a lower risk of first-onset CVD at 0.5, 1, 2, 5, and 10 years follow-up. Here, the antidepressant categories studied were selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, and other antidepressants; and CVD was defined as a composite of ischemic heart disease (IHD), stroke, atrial fibrillation/flutter, heart failure/cardiomyopathy, and pulmonary hypertension.

Among the disorders comprising the composite, antidepressant prescription was clearly associated with a lower risk of only IHD and stroke. Relative risk (RR) values for IHD and stroke lay in the 0.27–0.76 range. Importantly, the benefits with antidepressants, although evident in women without psychiatric disorders, were stronger in women with psychiatric disorders; that is, major depressive disorder, posttraumatic stress disorder (PTSD), and anxiety disorders. Although statistical significances were obtained for >100 comparisons, the patterns of statistical significance were not random, as might be expected with Type 1 errors; rather, the findings were strongly consistent for antidepressant category, follow-up time point, individual CVD, and individual psychiatric diagnosis.

Whereas SSRIs were additionally associated with reduced risk of atrial fibrillation/flutter, they were also associated with an increased risk of pulmonary hypertension; and the "other antidepressants" were associated with an increased risk of heart failure/cardiomyopathy. These findings were consistent for all follow-up time points.

On the surface, these findings are unexpected. Observational studies tend to find that gestational, childhood, or adult exposure to neuropsychiatric drugs is associated with an increased risk of a wide range of adverse outcomes, including neurodevelopmental disorders, suicidal ideation and behavior, metabolic syndrome, cardiovascular events, falls, fractures, dementia, and death; in defense, at least some of the variance in these findings could be due to confounding by indication.

Evidence for the medical benefits of treating depression is however accumulating. With specific reference to CVD, an early meta-analysis of

6 randomized controlled trials (RCTs; pooled N = 2,461) in patients with coronary heart disease (CHD) and depression found that SSRIs were associated with lower risk of CHD readmission as well as a lower risk of mortality; but the findings lost statistical significance in a sensitivity analysis in which 2 trials with problematic methodology were omitted.[8] In a more recent meta-analysis of 8 RCTs (pooled N = 1,148) in patients with CHD and depression, SSRIs were associated with a lower risk of myocardial infarction but not of other CVD outcomes, nor of all-cause mortality.[9]

Thus, the findings of Sumner et al[7] add to the literature on the cardiovascular benefits of treating depression and, in fact, extend the findings in that the benefits were evident not merely with SSRIs but also with other classes of antidepressants, not merely for CHD but also for other CVDs, and not merely in women with depression but also in women with PTSD and anxiety disorders; and also in women without psychiatric diagnoses. These findings encourage the use of antidepressant medications to treat psychiatric disorders to improve not merely psychiatric but also CVD outcomes in a doubly vulnerable population: woman veterans.

As a side note related to the prescription of antidepressants to women without psychiatric diagnoses in the Sumner et al study: there are few nonpsychiatric conditions for which antidepressants may be advised. So, perhaps the women had subsyndromal psychiatric symptoms; or, for whatever reason, the diagnosis was unclear. Nevertheless, antidepressants were associated with benefits in this subgroup, though not as strongly as in the subgroup with psychiatric diagnoses.

A reality check is necessary. Strengths of the study[7] were the large sample, the long follow-up, and the use of marginal structural modeling as a statistical means of dealing with time-varying factors; this contrasts with the usual approach of defining all variables at baseline and using Cox regression in analysis. But the study[7] had its limitations. CVD was defined to include a mix of etiologically heterogenous conditions; so, if antidepressant treatment is effective for all these conditions, nonspecific explanations are necessary. The association between dose and duration of antidepressant exposure with CVD outcomes could not be examined; this limits the framing of recommendations for clinical practice. The RR values obtained in statistical models are unlikely to reflect real world risks.

The beneficial and adverse outcomes identified in this study[7] are hypothesis-generating and need further evaluation; thought must also be given to the possibility that antidepressants can differ in CVD effects even within a class. For the moment, this study provides modest support to the possibility that most antidepressants are associated with better short- and long-term outcomes for most but not all CVDs. The risk of pulmonary hypertension with SSRIs and of heart failure/cardiomyopathy with "other antidepressants" requires special study. Subgroup analyses, such as for age, sex, and ethnicity, are important in CVD studies. If CVD outcomes are pooled into a composite, pooling is best done into categories defined by disease mechanisms. Finally, in long-term studies of CVD outcomes, the study of CVD mortality and all-cause mortality is also necessary so that a more complete risk-benefit profile is obtained.

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