Do Antidepressants Raise the Risk of Stroke?

Although most Americans who meet criteria for major depression do not receive treatment (1), the use of antidepressant medications has increased substantially over the past two decades. Nearly three-quarters of these prescriptions are written by general medical providers rather than psychiatrists (2). The broader use of antidepressants has been fueled in part by the availability of newer antidepressants with relatively benign side effect profiles and efficacy against disorders (depression and anxiety disorders) that are responsible for an enormous toll in suffering, disability, and economic costs. Nevertheless, with approximately one in 10 Americans receiving antidepressants, serious adverse effects, even if uncommon, may have substantial public health importance.

In this issue of the *Journal*, Wu and colleagues (3) report results of a large population-based analysis of stroke risk among antidepressant users in Taiwan. Previous studies have had conflicting results, though some have suggested a link between antidepressant use and stroke. For example, in the large Women's Health Initiative study of postmenopausal women, those receiving treatment with selective serotonin reuptake inhibitors (SSRIs) had a 45% relative increased risk of stroke compared with women not receiving antidepressant treatment (4). In addition, SSRI use was associated with a doubling of the risk of hemorrhagic and fatal stroke (4). One crucial methodologic issue facing observational studies of adverse effects in drug-exposed versus nonexposed subjects is the problem of confounding by indication. Antidepressant users likely differ from nonusers on a broad range of factors that can affect risk of cerebrovascular events, most notably the presence of depression, which itself has been implicated as a risk factor for cardio- and cerebrovascular disease. If we see an increased risk of stroke in comparing antidepressant users with nonusers, how do we know how much of the increase is attributable to the medication rather than the underlying depression, anxiety, or associated risk factors that distinguish users and nonusers? The answer is, we cannot be sure.

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Wu and colleagues attempt to address some of this ambiguity by applying a study design that uses each case as its own control. In a case-crossover study, the exposure status of a case patient during a specified period just prior to the outcome is compared with her exposure during a previous period of time. By comparing the same person at different times, the case-crossover design avoids confounding by any time-invariant characteristics that might have differed between case patients (here, antidepressant users) and comparison subjects (i.e., nonusers). The case-crossover approach is designed to address transient effects of an exposure—for example, whether it acts as an acute trigger of an outcome (5). As summarized by Maclure (6), case-control designs compare exposed and unexposed *people* to get at the question "Why me?" whereas case-crossover designs compare exposed and unexposed *periods* within cases to get at the question "Why now?"

Wu and colleagues studied 24,124 patients with incident stroke who had been prescribed antidepressants within the past year. These case patients were drawn from a

nationwide medical claims database that included 489,852 individuals who were 18 years of age or older at the time of their first hospitalization for stroke. To estimate the effect of recent antidepressant use, the authors compared the proportion of patients who had received an antidepressant prescription in the 2 weeks prior to their stroke (the case period) with those who had received a prescription in the preceding 2 weeks (the control period). Patients who received a prescription in both periods or neither period were excluded. The authors found that prescriptions during the case period were associated with an overall 48% increased risk of stroke, and results were similar when they used exposure windows of 7 or 28 days. Intriguingly, the risk was greater for antidepressants with more potent affinity for the serotonin transporter. Elevated risks were observed for both hemorrhagic and ischemic strokes, although one might expect that the antiplatelet effects of serotonin reuptake inhibition might be more relevant for hemorrhagic strokes. Also, risks were highest when the antidepressant was first started in the case period—that is, there had not been a prior antidepressant prescription in the past year. This would be consistent with the hypothesis that new antidepressant use is associated with a transient increase in stroke risk. If the results are valid, they support the worrisome conclusion that antidepressants can heighten the risk of stroke, a finding with great public health significance given the widespread use of these drugs.

However, several features of their analysis complicate the interpretability of their findings. The first issue is the selection of adjacent 2-week periods to compare exposure odds. We are not told the duration of the prescriptions given, but if patients received a 30-day supply, then many of those who received their prescription in the control period were likely exposed during both the control and case periods and should not have contributed to the analysis. In fact, a patient who filled his prescription 15 days prior to his stroke (within the control period) would have been primarily exposed during the case period. This misclassification might be more likely to bias results toward the null, suggesting that the risk of antidepressants might be greater than that found, but if the underlying exposure data are uninformative, this might also mean that an apparent effect could be spuriously inflated. The fact that the results were similar using 28-day windows mitigates this concern somewhat.

A second complexity is that the cases included a mix of new and more chronically treated patients. Approximately one-half of the sample had received three or more antidepressant prescriptions in the past year. For these patients, the prescription used to define exposure may have simply been a refill. For patients receiving standing doses of antidepressants, the "exposure" then becomes a matter of when in the month they refill their prescriptions. It is difficult to interpret this as a risk factor for stroke. In fact, for patients with six or more prescriptions in the past year, receiving an antidepressant in the case period was associated with reduced stroke risk. Of course, it may be that the antidepressant prescribed in the case period represents a resumption of interrupted treatment or a switch to a new antidepressant, but these data are not available.

Finally, while the case-crossover design may have reduced the risk of confounding by indication, it may not have completely disentangled the effects of antidepressants per se from the conditions being treated. Antidepressants are commonly used to treat depression, anxiety, and migraine, each of which has been implicated as a risk factor for stroke. If antidepressants are initiated when symptoms are at their most severe, then a new antidepressant prescription could be a proxy for untreated risk factors for stroke. The authors' observation that stroke risk was reduced with long-term antidepressant use could be consistent with this alternative explanation. In addition, the fact that stroke was associated with antidepressants with diverse pharmacodynamic actions might also mean that underlying depression was a contributor.

Overall, the study by Wu and colleagues adds to the literature on a possible link between stroke and antidepressants by suggesting that the risk may be greatest near the initiation of treatment. However, important questions remain, and the issue must be considered unresolved. Ultimately, teasing apart adverse cerebrovascular effects of an-

tidepressants from those of depression itself would likely require a large, randomized clinical trial—for example, examining cerebrovascular risks in a trial comparing antidepressant treatment to cognitive-behavioral therapy for mild-moderate depression. Given the low frequency of stroke as an outcome and the uncertainty of the time course of adverse effects, an adequately powered trial might be difficult to achieve from a feasibility standpoint. In the absence of such data, we must continue to gather and weigh evidence from well-designed observational studies but be mindful of their limitations.

References

1. Gonzalez HM, Vega WA, Williams DR, Tarraf W, West BT, Neighbors HW: Depression care in the United States: too little for too few. Arch Gen Psychiatry 2010; 67:37–46
2. Mojtabai R, Olfson M: National patterns in antidepressant treatment by psychiatrists and general medical providers: results from the National Comorbidity Survey Replication. J Clin Psychiatry 2008; 69:1064–1074
3. Wu C-S, Wang S-C, Cheng Y-C, Gau S-F: Association of cerebrovascular events with antidepressant use: a case-crossover study. Am J Psychiatry 2011; 168:511–521
4. Smoller JW, Allison M, Cochrane BB, Curb JD, Perlis RH, Robinson JG, Rosal MC, Wenger NK, Wassertheil-Smoller S: Antidepressant use and risk of incident cardiovascular morbidity and mortality among postmenopausal women in the Women's Health Initiative study. Arch Intern Med 2009; 169:2128–2139
5. Maclure M, Mittleman MA: Should we use a case-crossover design? Annu Rev Public Health 2000; 21:193–221
6. Maclure M: Why me? versus why now?: differences between operational hypotheses in case-control versus case-crossover studies. Pharmacoepidemiol Drug Saf 2007; 16:850–853

JORDAN W. SMOLLER, M.D., Sc.D.

Address correspondence and reprint requests to Dr. Smoller, Department of Psychiatry, Massachusetts General Hospital, Simches Research Building, 185 Cambridge St., Boston, MA 02114; jsmoller@hms.harvard.edu (e-mail). *Editorial accepted for publication March 2011 (doi: 10.1176/appi.ajp.2011.11020336).*

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