Relapse of Major Depression in Women Who Continue or Discontinue Antidepressant Medication During Pregnancy

To the Editor: We applaud Dr. Chaudron's excellent review of the treatment of depression during pregnancy (1) in the January issue. She has provided a wealth of important information that assists clinicians and their patients in making difficult decisions regarding the use of antidepressant medication during pregnancy and the risks of untreated illness. As Dr. Chaudron astutely points out, decision making can span many months preceding pregnancy and into infancy. Given the breadth and scope of issues that can arise during this time, a single review cannot address them all or provide data to guide all decisions. While the focus of the review is the treatment of depression during pregnancy, a common clinical challenge is whether to continue or discontinue antidepressant medication during pregnancy. We felt this was an important area to further elaborate on, given the prevalence of antidepressant use (2) and currently available conflicting data (3, 4).

Dr. Chaudron cites an important prospective study by Cohen et al. (3) demonstrating that women with a history of recurrent major depression who discontinued medication during pregnancy or just before conception had five times the risk of another episode of depression compared with women who continued medication during pregnancy. However, in a recent prospective study of pregnant women with a history of depression by Yonkers et al. (4), no differences were found in risk of another episode of depression among women who discontinued antidepressant treatment compared with women who did not. While methodological differences may account for these findings, the conflicting results are likely attributable to divergent populations under investigation. Individuals in the Cohen et al. study were recruited from psychiatric treatment centers and had more severe forms of depression, including early age at onset (<14 years) and comorbid psychiatric illness. Yonkers et al. recruited women from community- and hospital-based obstetric clinics. In both studies, women with at least four previous episodes of depression had a greater risk of relapse of depression during pregnancy, suggesting that those with more severe forms of the disorder are likely at greatest risk for relapse.

Both studies have great clinical importance and can assist clinicians working with women with a history of either severe or mild to moderate major depression. Women with more severe depression that includes early age at onset, psychiatric comorbidity, and at least four previous episodes of depression have a high risk of relapse during pregnancy. Great care and vigilance should be taken to monitor these patients closely, independent of a woman's decision to continue or discontinue medication. The risk of relapse in women with a less severe form of depression or with fewer previous episodes is lower than once estimated. Data from the Yonkers et al. study can provide reassurance to patients with fewer than four episodes of depression who choose to not take antidepressants during pregnancy.

Dr. Chaudron's review is a must-read for clinicians working with women with depression during pregnancy. We hope we have complemented this review by providing additional data to guide clinicians and their patients in weighing the risks and benefits of antidepressant treatment during pregnancy.

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Response to Guille and Epperson Letter

To the Editor: I want to thank Dr. Guille and Dr. Epperson for the complimentary comments and the additional important reference they provided regarding the risk for recurrence of depression during the perinatal period related to antidepressant use. As they point out, the findings by Yonkers et al. (1) highlight the complicated nature of predicting who will or will not have a recurrence of depression and who may or may not require antidepressants during the perinatal period. Drs. Guille and Epperson note that, while controlling for antidepressant use, a history of four or more depressive episodes puts women at high risk for a major depressive episode. In addition, Yonkers et al. identify other risk factors, such as having a depressive episode in the 6 months before pregnancy and being of black race or Hispanic ethnicity. These additional variables, as well as the fact that 16% of the women in the study developed major depression during pregnancy or the postpartum period, underscore the need for further research to more fully understand who is at highest risk for recurrence in the perinatal period and therefore what the risks and benefits of antidepressant treatment are for individual patients with a range of depression severity.

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In Whom Does Lithium Work?

To the Editor: In the January issue, Nierenberg et al. (1) try to answer an important question: Does lithium provide mood stabilization to a population of patients with lifetime bipolar I or II disorder who have chronic mood problems? According to the description of the sample, participants experienced an average of eight episodes per year, and although depressive episodes were fewer in number than manic or hypomanic episodes, patient scores on the Mini International Neuropsychiatric Interview at intake suggest that depression rather than mania accounted for more of their difficulties. Improvement in "mood" (it was not specified which mood) was the metric used to ascertain lithium's success.

These results were contrasted to those of Gelenberg et al. (2), whose study sample consisted of patients with bipolar I disorder who had been euthymic for 2 months before intake so that relapse into mania or depression (not just mood improvement) could be determined. Moreover, those with four or more episodes were excluded from the study. In other words, the sample assessed by Nierenberg et al. would not have been in the Gelenberg et al. study, whose participants, granted, represented only a minority of mood-disordered patients (157 of 1,200). The comparison, therefore, is between apples and oranges.

While the Nierenberg et al. study is important in addressing what may be the majority of people with a diagnosis of bipolar I or II disorder (i.e., chronically mood unstable and primarily depressed [3]), it does not provide evidence to disprove lithium's efficacy in the population for whom it was originally shown to be effective for prophylaxis and treatment: individuals with a positive family history, an interval course with a manic episode followed by a depressive episode and then a symptom-free episode, and fewer episodes (4, 5). In fact, the sample in the Nierenberg et al. study includes precisely those in whom we would not have expected a lithium response. The sample distinction is important; it is also important to remind clinicians that lithium was never touted as a panacea for general mood dysregulation.

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Response to Carlson Letter

To the Editor: We appreciate Dr. Carlson's comments on the main findings from our Lithium Moderate-Dose Use Study (LiTMUS) (1). LiTMUS included treatment-seeking patients who had at least some distress from symptoms in the context of a bipolar I or II diagnosis. Thus, in contrast to the participants included in the Gelenberg et al. study (2), this comparative effectiveness study included the types of patients who would be seen in clinical practice—and therefore the results of the study would be generalizable enough to inform clinicians. Additionally, the question addressed in LiTMUS was not whether or not lithium works, as implied by Dr. Carlson, but whether moderate doses of lithium would minimize side effects and add therapeutic benefit as a part of guideline-informed, evidence-based psychopharmacological treatment. We found that low levels of lithium did not have additive effects apart from a modest decrease in the use of second-generation antipsychotics. The study does not "disprove lithium's efficacy," but instead provides evidence that blood levels around 0.4 mEq/L may be insufficient to improve 6-month outcomes for this outpatient sample above and beyond what can be achieved with other medications. Nolen and Weisler (3) recently confirmed the lack of effectiveness for low levels of lithium for maintenance treatment.

We are applying this lesson from LiTMUS for another comparative effectiveness study funded by the Agency for Healthcare Research and Quality: the Bipolar CHOICE study (Clinical Health Outcomes Initiative in Comparative Effectiveness). Bipolar CHOICE has a similar design but will 1) use higher dosages and levels of lithium (>0.6 and <1.2 mEq/L) and 2) compare lithium with quetiapine for tolerability, safety, and effectiveness along with other treatments necessary to reach optimal outcomes.

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