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LINDA H. CHAUDRON, M.D., M.S.

From the Departments of Psychiatry, Pediatrics, and Obstetrics and Gynecology, University of Rochester School of Medicine and Dentistry, Rochester, N.Y.

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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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GABRIELLE A. CARLSON, M.D.

From the Departments of Psychiatry, Pediatrics, and Child and Adolescent Psychiatry, Stony Brook University School of Medicine, Stony Brook, N.Y.

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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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