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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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Methylfolate as Adjunctive Treatment in Major Depression

To the Editor: As the principal investigator of the only previous placebo-controlled trial of methylfolate as an adjunctive treatment in major depression 22 years ago (1), I appreciated the new trial by Papakostas et al. (2) in the December 2012 issue confirming the efficacy of the vitamin in some resistant depression.

Important differences between the two trials raise interesting questions. Our study was for depressed patients with borderline or definite folate deficiency (red blood cell folate levels <200 pg/mL), but Papakostas et al. did not mention the folate status of their patients. I presume that many would not have been folate deficient. We also used 15 mg of methylfolate, but our trial was for 6 months and demonstrated increasing efficacy at 3 and 6 months in contrast to the 60-day study by Papakostas et al.

I first reported in 1967 the beneficial effect of the vitamin on mood and some aspects of cognitive and social function in an open trial of folic acid, 5 mg/day for 1 to 3 years, in folate-deficient patients with epilepsy (3). At the Medical Research Council Neuropsychiatry Research Unit, we then showed not only that folate deficiency was common in depression, as had been reported by Carney (4), but that the deficiency was associated with a poor response to antidepressant therapy (5). I subsequently collaborated with Carney and colleagues in demonstrating that depression was the most common reversible neuropsychiatric manifestation of folate-deficient megaloblastic anemia; in confirming that *S*-adenosylmethionine had antidepressant properties, thus implying that methylation is a key to understanding mood (6); and in identifying a subgroup of patients with depression, high plasma homocysteine levels, folate deficiency, and impaired neurotransmitter metabolism. This culminated in our positive trial of methylfolate, the transport form of folate into the nervous system, as adjunctive therapy in depression (1).

A crucial question for the future is to what extent the antidepressant properties of methylfolate depend on the folate status of the patient. Our own pilot observations suggest that methylfolate may have antidepressant properties as monotherapy, irrespective of folate status, but that responders show a greater rise in red cell folate levels than nonresponders (7). An important clue is the mood-elevating properties of nitrous oxide. This euphoriant effect is probably related to the instantaneous inactivation of methionine synthase, leading to an acute rise in methylfolate in the brain (7). Finally, methylation in the nervous system is a key not just to the biology of mood but to other aspects of cognitive function, including dementia. After 45 years, it is time for academic departments of psychiatry to invest more in this nonpharmaceutical approach to mental illness.

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Up-Regulation of *NOTCH4* Gene Expression in Bipolar Disorder: Future Studies

To the Editor: In the December 2012 issue, Dieset et al. (1) reported significant up-regulation of *NOTCH4* gene expression in whole blood in patients with bipolar disorder relative to healthy comparison subjects, and they identified several single-nucleotide polymorphisms (SNPs) that were significantly associated with *NOTCH4* expression. This is a nice piece of research, and their findings have encouraged future research on the molecular mechanisms of *NOTCH4* in bipolar disorder. However, several lines of their study data await further validation.

First, we are curious about whether the altered *NOTCH4* expression that was observed in patients was caused by changes in the genetic background in bipolar disorder (related to the pathogenesis of the illness) or was just an outcome of the patients' physiological conditions. This is an important issue, but was inconclusive in the article, although the authors conducted the analyses adjusting for a range of confounders. A plausible solution to this problem is the use of an intermediate group: the healthy siblings of patients. These populations shared numerous genetic risk factors with the clinical patients but did