A Simple Question Answered: Adding Moderate-Dosage Lithium Does Not Help Patients With Bipolar Disorder

Bipolar disorder is conventionally defined by the presence of discrete episodes of mania (or hypomania in the case of bipolar II disorder) and depression, but this definition does not fully encompass the true character and course of the syndrome. The majority of patients with bipolar disorder experience persistent interepisode mood symptoms and an intrinsic vulnerability to affective lability (1, 2). Thus, the lives of many patients with bipolar disorder (as well as those who love them) are complicated—and to a certain extent limited—by this persistent mood burden. It leads to markedly diminished quality of life, functioning, and productivity both for the patients (3, 4) and for their family and friends (5).

Effective pharmacotherapy for patients with bipolar disorder began in 1949 with Cade's original article (6) describing the salutary effects of lithium carbonate for the treatment of patients with acute mania. This report led to double-blind active comparator studies that confirmed lithium's efficacy as an acute antimanic agent (7). We now have a variety of pharmacological agents for treating acute mania, ranging from lithium to anticonvulsants to atypical antipsychotics. Effective pharmacotherapies and psychotherapies are also available for the acute treatment of bipolar depression, and many agents are effective against the recurrence of full mood episodes. However, we do not have evidence-based treatment strategies for eliminating persistent mood symptoms in bipolar patients or successful pharmacological strategies that decrease their vulnerability to mood lability. Currently, the majority of patients with bipolar disorder take multiple mood-stabilizing medications (8). Polypharmacy is costly, increases the side effect burden, increases the risk of untoward medication interactions, and greatly complicates the lives of our patients.

Low-dosage lithium augmentation should drop toward the bottom of any list of medication options for enhancing mood stabilization in outpatients with bipolar disorder.

In this issue, Nierenberg et al. (9) report the primary results of the Lithium Treatment Moderate-Dose Use Study for bipolar disorder (LiTMUS), an effectiveness trial designed to determine if low-dosage lithium added to an optimized personalized treatment (OPT) regimen improves clinical outcome for bipolar I and bipolar II patients. There is some level of uncertainty about the minimum effective lithium level required for the treatment and prophylaxis of mood episodes in bipolar disorder, with several trials indicating that serum concentrations ≥0.8 mEq/L are associated with improved outcomes (10–12). However, clinicians frequently use low-to-moderate dosages of lithium in addition to other medications as a strategy to maximize mood stability and reduce suicidality (13). Before LiTMUS, the question of whether this common clinical strategy offers meaningful therapeutic benefit had not been carefully addressed.

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To be eligible for LiTMUS, patients had to have clinically significant symptoms that warranted a change in treatment, for which the treating physician believed lithium was a reasonable therapeutic option. Medications selected by the physician were guided by the Texas Implementation of Medication Algorithm for bipolar I disorder (14), with oversight by a study-independent bipolar disorder expert to ensure adherence to the guidelines. Patients were randomly assigned to receive either OPT (requiring treatment with at least one mood stabilizer, exclusive of lithium) or OPT plus a dosage of lithium fixed at 600 mg/day for the first 2 months, with subsequent dosage adjustments as clinically indicated. Two primary outcome measures were evaluated: the Clinical Global Impression Scale for Bipolar Disorder–Severity and "necessary clinical adjustments," which consisted of any medication adjustments required to respond to a clinical need.

The primary conclusion of the trial was that low-dosage lithium did not provide any additional benefit beyond guideline-driven care. Only one-quarter of the patients in either group achieved sustained remission. The two groups of participants had similar scores on secondary outcome measures of mood symptoms, functioning, and suicidal ideation. Twenty-one percent of the lithium-plus-OPT patients discontinued lithium, compared with only 2% of the OPT patients who elected to discontinue their mood stabilizers. Thus, even with low to moderate dosages of lithium, problems with adherence remained. In both groups, patients had an average of 2.6 prescriptions in addition to the lithium for the lithium-plus-OPT group. The one intriguing difference between the treatment groups was that the lithium-treated patients were less likely to receive an atypical antipsychotic. Given that the lithium-plus-OPT group reported significantly more manic or hypomanic episodes in the year before the randomized study than the OPT group (5.2 and 3.2, respectively), this finding may merit follow-up investigation.

The failure to detect a difference between the OPT-only and lithium-plus-OPT groups may stem in part from the design of the study. Patients who reported a treatment failure with lithium therapy in a previous episode were allowed to participate in the study. Thus, the authors may have inadvertently biased the sample against lithium augmentation. A second factor that may have affected the outcome of the study was that over half of the lithium-treated patients had blood levels <0.4 mEq/L; this concentration may have been too low for lithium augmentation to have a true pharmacological effect. Another study design feature that "raised the bar" was the use of the Texas Implementation of Medication Algorithm by expert psychopharmacologists. With treatment optimized in this fashion, lithium augmentation would have to demonstrate a rather profound additional clinical benefit to differentiate itself from OPT.

A number of important lessons can be learned from the LiTMUS trial. First, one sees the power of employing a well-organized network of investigators to perform a clinical trial. The authors completed a 6-month randomized trial with 283 patients within a 2-year period. This is a remarkably rapid recruitment and completion time for any type of clinical study. Second, this trial pioneered the use of a new ecologically important approach to assessing outcome—the number of necessary clinical adjustments. This is a clinically relevant method of capturing the impact of a treatment intervention for patients suffering from a chronic syndrome that has a fluctuating course. The study also highlights the importance and value of investing in large trials that are designed to answer common clinical treatment questions. The results of this trial suggest that the addition of moderate dosages of lithium to optimized guideline-driven therapy does not confer any advantage in terms of symptom relief, functioning, or quality of life.

The authors anticipate future analyses to identify predictors or subgroups of patients for whom lithium plus OPT is effective. Individual-level predictors of response to specific treatments are an important research priority. They offer the promise of a more effective and satisfying experience for patients with psychiatric syndromes. Predictors of lithium response identified from this study may complement the Pharmacogenomics of Bipolar Disorder research collaboration that is exploring the predictive value of genetic markers of lithium response (15). However, until the promise of individual predictors of response is realized, patients will be best served by treatment based on large-scale, pragmatic studies such as LiTMUS.

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