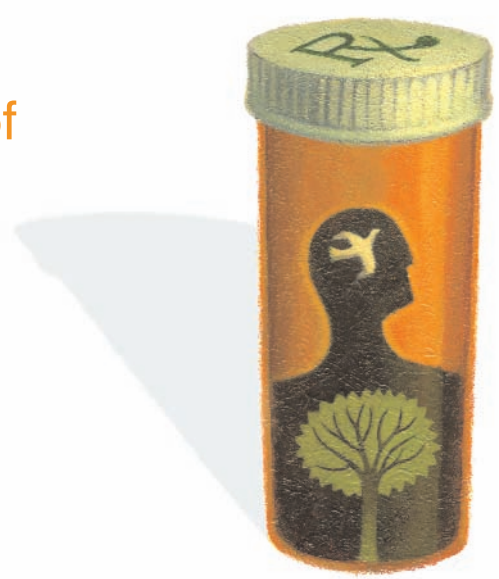
Commentary on N. Ghaemi's "Hippocratic Psychopharmacology of Bipolar Disorder"



Maintenance Treatment in Bipolar Disorder

by Mauricio Tohen, MD, DrPH; and Daniel Lin, PhD

ABSTRACT: Bipolar disorder is a chronic recurring condition that is associated with high mortality and severe functional and psychosocial impairments. Treatment strategies that prolong recovery from a mood episode and delay relapse into a new mood episode are essential for long-term improvements in outcomes. Maintenance treatments for bipolar disorder should be evaluated on the strength of the empirical evidence and with the recognition that some treatments may be more effective in preventing relapse into manic, depressive, or mixed episodes.

Key Words: bipolar disorder, relapse, maintenance, psychopharmacology

The opinion piece, "Hippocratic Psychopharmacology for Bipolar Disorder," by Dr. Ghaemi provides the reader with interesting insights into psychopharmacology in general and on research design of maintenance studies in bipolar disorder in particular.

Dr. Ghaemi contends that reviews of the literature can be presented and interpreted selectively to favor a particular point of view, and we concur. However, it should be noted that systematic reviews of data (e.g., meta-analyses) are similarly susceptible to biases held by the reviewers. Dr. Ghaemi's statement that most clinicians and researchers base their decisions on underlying beliefs about psychopharmacology rather than available data may also be true.

We agree that lithium, more than any other available treatment, has had a major impact on the lives of those who suffer from bipolar disorder; however, Dr. Ghaemi's contention that lithium is the closest thing to a "cure" in psychiatry is a stretch that cannot be substantiated by the existing empirical evidence.

The concept of Hippocratic psychopharmacology is creative, but may give the impression that the best pharmacology is the absence of pharmacology. A fundamental difficulty in applying Dr. Ghaemi's suggested Hipprocratic approach to psychopharmacology with respect to bipolar disorder lies in the incomplete understanding of the etiology and underlying biological bases for the disorder. We very much agree with Holmes's approach that proof of efficacy is a *sine qua non* before prescription of any treatment.

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We agree with the assertion that maintenance treatments for bipolar disorder should focus on reducing recurrence and that mood stabilizers should be able to treat the illness as a whole. Dr. Ghaemi points out that the term *mood stabilizer* has been abused—we agree that the term has been used very broadly, and establishing consensus on a valid definition would be useful to the field. We would emphasize that in order for a treatment to be considered a mood stabilizer, it should be able to prevent both manic and depressive episodes; however, there may be mood stabilizers that are more effective in preventing relapse into one pole over the other. Furthermore, we feel that the prevention of mixed episodes has been understudied and that "true mood stabilizers" should also be able to prevent mixed episodes.

The discussion of prophylaxis in bipolar disorder is stimulating, and Dr. Ghaemi offers an interesting proposal—maintenance should be considered at least 6 months, considering an estimated 3- to 6-month range for untreated bipolar depression and 2 to 4 months for mania. If we follow this proposal, then the type of index episode becomes quite relevant, as has been proposed by Calabrese and others.[1] In other words, if the index episode is mania then maintenance treatment would consist of at least 4 months after the onset of the episode. The question of defining maintenance for mixed index episodes remains unanswered, especially in the absence of empirical data.

The proposal of new terminology such as *relapse prevention* versus *prophylaxis* is conceptually useful but perhaps will lead to confusion among practicing clinicians. An alternative term to relapse prevention is *enriched design*. From a clinical perspective, the relapse prevention design is valuable, since it likely reflects common clinical practices. For the prophylaxis design, the drawbacks of treatment discontinuation and initiation of a new treatment are challenges.

The description of the lamotrigine studies is not entirely consistent with the study procedures described in the original publications.[2,3] During the 8- to 16-week open-label phase of these studies, patients were permitted to receive adjunctive therapy, and concomitant treatments were discontinued a minimum of 1 week (2 weeks for some agents) before entry into the double-blind maintenance phase. We do, however, agree that since the design was *enriched* for lamotrigine and not for lithium, comparisons between lithium and lamotrigine may be biased to include patients that are likely to respond to and have better tolerance to lamotrigine.

In the review of the olanzapine data, a noticeable absence is the 2005 publication of Tohen et al.,[4] which compared olanzapine with lithium. Only a vague reference is made to an abstract of that study. The study had an enriched design for both lithium and olanzapine. The main finding of the study by Tohen, et al., was the superiority of olanzapine over lithium in the prophylaxis of manic episodes. In the placebo-controlled study,[5] Dr. Ghaemi indicates that the longer time to relapse to a mood episode observed in olanzapine relative to placebo-treated patients likely represents a withdrawal syndrome. However, he fails to mention that findings from additional analyses reported in the manuscript addressed this concern. These analyses demonstrated significant differences between olanzapine and placebo that were still observed for patients who remained in remission for 2 or 8 weeks. The interpretation of the the Kaplan-Meier curve is also inaccurate as the relapse rate was 72.5 percent. More importantly following Dr. Ghaemi's proposal, maintenance should be determined 2 to 4 months after onset of the index manic episode. In this population, the median length of the index episode was 28 days, plus an additional 6 to 12 weeks during the open-label stabilization period. Furthermore, if we only include patients who had been in remission for 8 weeks after randomization, then in the first 2 months 86 percent of olanzapine-treated and 72 percent of placebo-treated patients remained free of relapse; moreover, time to relapse was significantly different between treatment groups (χ^2= 8.97, *df*=1,

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p=0.003).

Findings from a 26-week trial of aripiprazole in recently manic patients were published recently.[6] According to Dr. Ghaemi's conceptual framework, this study would not be considered an adequate test of efficacy for maintenance, even though it involved a 6-month follow-up phase, and especially considering that before randomization patients remained in the acute treatment open-label phase from 6 to 18 weeks. In a sense, the imposition of arbitrary constraints based on the personal opinion of Dr. Ghaemi, rather than empirical evidence with respect to study duration, unnecessarily dismisses the value of information that might be useful for guiding decisions in clinical practice to the detriment of patients.

To summarize, we agree with Dr. Ghaemi that reviews involve selective presentation and interpretation of the data, and as stated by Dr. Ghaemi, "The problem with that approach, as is well known, is that any data can be selectively presented and interpreted to make any point."

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