The Diagnostic and Pharmacological Variances of Bipolar Disorder Versus Attention-Deficit/Hyperactivity Disorder

TO THE EDITOR: The hypotheses by Dr. Wagner et al. regarding the ineffectiveness of oxcarbazepine in the article "A Double-Blind, Randomized, Placebo-Controlled Trial of Oxcarbazepine in the Treatment of Bipolar Disorder in Children and Adolescents" may need to be modified over time because of the nearly 50% of bipolar disorder I subjects comorbid for ADHD that continued taking stimulants during the study. This stimulant subgroup introduces an ambiguous diagnostic heterogeneity into the study that will hopefully be sorted out over time as ADHD symptoms become better realized as a persistently distinct disorder or as an unfolding aspect of a disorder that is inherently bipolar. The use of stimulants in this subgroup may ultimately be at pharmacological odds with the overall goal of mood stability in bipolar mania (such as the use of nortriptyline in bipolar depression). Even though a data analysis was done to adjust for diagnostic variance due to ADHD in the comparison of scores on the Young Mania Rating Scale-50% response rate (because nearly one-half of the 70+% ADHD subjects remained on stimulants), the potential for pharmacological variance exists. We are reminded of Dr. DelBello's work associating stimulant treatment with a younger age of bipolar onset, indicating there is at least some link between stimulant use and bipolarity (1).

Reference

1. DelBello M, Soutollo C, Hendricks W, Niemeier R, McElroy S, Strakowski S: Prior stimulant treatment in adolescents with bipolar disorder: association with age at onset. Bipolar Disord 2001; 3:53–57

D. HOWARD LYSNE, M.D., M.DIV.
THOMAS PETERSON, M.D.
KEITH ERICKSON, M.D.
MICHAEL URIELL
Grand Forks, N.D.

Dr. Wagner and Colleagues Reply

TO THE EDITOR: We appreciate the comments of Dr. Waslick on our study. First, with regard to study subjects, DSM-IV criteria for bipolar I disorder, manic or mixed were required for both our study and the study conducted by Geller et al. However, Geller et al. also required subjects to have at least one cardinal symptom of elation and/or grandiosity. Also, Geller et al. redefined manic/hypomanic episodes in their study as the entire length of illness, whereas we used DSM-IV definitions for manic episodes. This may account for some differences between the two study groups. Second, in response to Dr. Waslick and Dr. Lysne et al., the investigators in the study had the option of discontinuing stimulants prior to randomization in this study if they thought that stimulants were exacerbating the subject's mania. The presence of concurrent ADHD and stimulant treatment did not affect baseline ratings of psychopathology or treatment response.

KAREN DINEEN WAGNER M.D., PH.D.
Galveston, Tex.
ROBERT A. KOWATCH, M.D.
Cincinnati, Ohio
GRAHAM J. EMSLIE, M.D.
Dallas, Tex.
ROBERT L. FINDLING, M.D.
Cleveland, Ohio
TIMOTHY E. WILENS, M.D.
Boston, Mass.
KEVIN MCCAGUE
JOSEPH D'SOUZA, PH.D.
East Hanover, N.J.
ARTUR WAMIL, M.D., PH.D.
Malvern, Pa.
ROBERT B. LEHMAN, M.D.
Baltimore, Md.
DOUGLAS BERV, M.D.
New Haven, Conn.
DAVID LINDEN, M.D.
Oklahoma City, Okla.

Comment on "What Happened to Lithium?: Antidepressant Augmentation in Clinical Settings"

TO THE EDITOR: I am very surprised at the article by Marcia Valenstein, M.D., M.S., et al. (1) showing that only 1,106 (0.5%) of 244,855 patients with depression received lithium augmentation. On the other hand, the most popular augmenting drugs were a second antidepressant and a second-generation antipsychotic, received by 26,739 (11%) and 17,797 (7%) patients, respectively. Moreover, 9,053 (4%) patients received augmentation with anticonvulsants, while 11,054 (5%) received other augmenting drugs, such as thyroid hormone, stimulants, and buspirone.

Taking strong evidence for lithium as an augmenting drug of refractory depression (2) into consideration, I cannot accept the findings by Dr. Valenstein et al. (1) as they are. At least two possibilities are yet to be investigated. The first possibility is that most patients receiving lithium had been apparently and/or automatically diagnosed as suffering from bipolar disorder, which was excluded from their subjects. Because, according to Food and Drug Administration, lithium is indicated in the treatment of manic episodes of manic-depressive illness (i.e., bipolar disorder) and in maintenance therapy of bipolar disorder, but not in augmentation therapy for depression. Therefore, many patients actually receiving lithium augmentation for refractory depression might have been excluded from their analysis. The second possibility is that a significant proportion of patients had discontinued lithium augmentation within 60 days because lithium augmentation can bring about rapid responses in some patients (3). They also might have been excluded from the subjects.

References

1. Valenstein M, McCarthy JF, Austin KL, Greden JF, Young EA, Blow FC: What happened to lithium?: antidepressant augmentation in clinical settings. Am J Psychiatry 2006; 163: 1219–1225
2. Bauer M, Dopfmer S: Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. J Clin Psychopharmacol 1999; 19: 427–434
3. de Montigny C, Cournoyer G, Morissette R, Langois R, Caille G: Lithium carbonate addition in tricyclic antidepressant-resistant unipolar depression: correlations with the neurobiologic ac-