COMMENTARY

Clinical Trials in Bipolar Mania

Implications in Study Design and Drug Development

In this issue of the *Archives,* Yildiz et al[1] report a 3-week, randomized, double-blind, placebo-controlled clinical trial to determine the antimanic efficacy of the centrally active protein kinase C (PKC) inhibitor tamoxifen citrate. The study was conducted in the inpatient psychiatric unit of a university medical center in Izmir, Turkey, and included 35 patients randomly assigned to tamoxifen and 31 to placebo. Patients were aged 18 to 60 years; had a diagnosis of bipolar disorder, currently in a manic or mixed state, with or without psychotic features (based on the Structured Clinical Interview for *DSM-IV*); and had Young Mania Rating Scale (YMRS) scores of more than 20 at baseline. Use of concomitant lorazepam was allowed up to 5 mg/d throughout the 3-week study duration. The study was completed by

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83% of patients randomly assigned to tamoxifen and 68% of those who received placebo. Tamoxifen-treated patients had mean decreases of 5.84 points per week on YMRS and 0.73 point per week on the Clinical Global Impressions–Mania Scale, compared with mean increases of 1.50 points per week on YMRS and 0.10 point per week on the Clinical Global Impressions–Mania Scale among placebo-treated patients. On both scales, tamoxifen-placebo comparisons differed significantly ($P<.001$).

To my knowledge, this is the first reported randomized, double-blind, placebo-controlled trial with adequate statistical power to test the antimanic effects of tamoxifen. In addition, this is one of very few recent trials that explored the use of a selected molecular target—in this case, the PKC system—for determining novel treatments and identifying the pathophysiology of bipolar disorder. Zarate et al[2] recently reported a similar, but smaller, study with similar results. Together, these 2 studies provide important evidence of the PKC system being a possible selected target in the treatment of this devastating disorder. According to the report by Yildiz et al,[1] tamoxifen appeared to have reasonable efficacy and to be remarkably well tolerated. However, the unique circumstances under which this study was conducted make comparisons with other studies difficult. A number of issues regarding the execution and the results of this study are important to comment on.

The high retention rate may be explained by some of the unique characteristics of this single-site study. These unique characteristics included required hospitalization for all 3 weeks; having a close relative stay in the hospital with each patient throughout the trial; and, as described by Yildiz et al, the provision to patients of "individualized food preferences and enriched recreational activities."

The most surprising result, however, is the worsening of manic symptoms (measured via YMRS and the Positive and Negative Syndrome Scale) and the absence of remission in patients who received placebo, especially considering the same factors (including hospitalization) that may have contributed to the high retention rate and use of lorazepam at doses higher than in other similar studies. In most contemporary studies in acute mania,[3-5] placebo-treated patients showed improvement. However, as Yildiz et al point out, the worsening of symptoms among placebo-treated patients or low placebo response may be explained by the single-site nature of this study,[3,4] similar to the recently published study by Zarate et al.[2]

Another explanation for the worsening symptoms of placebo-treated patients may be that some of the recruited patients had not responded to previous treatments. In addition, all the ratings were conducted by the lead author who used "all the available clinical information," which is not commonly done in clinical trials. It is also possible that the high retention rate allowed the documentation of worsening in placebo-treated patients, in contrast with other studies where poor retention rates do not allow documentation of such worsening.

Although the Yildiz et al results demonstrate that the efficacy and safety of tamoxifen in acute mania may be equal to or better than the existing therapies, still 88% of all patients remained symptomatic at the end of the 3 weeks, with the mean (SD) end point YMRS score of 20.3 (11.2) among tamoxifen-treated patients (which is slightly higher than the minimum baseline score necessary for participation in this or other similar studies). The baseline YMRS score of the tamoxifen-treated patients was 38.6, which is higher than the mean baseline scores reported in similar studies.[6] This relatively modest response with tamoxifen may be due to the hard-to-treat nature of the patients' condition. Thus, the findings of this study may not be generalized to non–treatment-resistant populations. An important point raised by Yildiz et al is that symptomatic improvement is not equivalent to functional improvement, as has been previously described in the literature[6,7]; therefore, this and other similar 3-week studies may be able to detect symptom amelioration but cannot adequately address the value of new antimanic treatments in achieving functional recovery—

the outcome that really matters to patients.

The Yildiz et al study raises several issues in the design and implementation of clinical trials in bipolar disorder. Although properly designed single-site studies may be a good option for proof-of-concept studies, there are pros and cons of using a single site and a single rater vs using multiple sites and multiple raters. Having a single rater and using "all available clinical information" also carries the risk of a number of potential biases. First, a therapeutic alliance between the patient and the rater is more likely to develop, which may confound the study results. Furthermore, by using all available clinical information, there is a potential of breaking the blind, especially when adverse effects of the active treatment are noticeable and broadly known. In the case of the present study, considering the safety profile of tamoxifen, this bias is unlikely. Having the same person recruit and rate subjects of investigation carries the risk of potential inflation of baseline scores to meet the required minimum score of the severity inclusion criteria. Use of a single rater also increases the risk of expectation bias that patients' scores will improve as the trial progresses. In addition, single-rater and single-site studies certainly cannot test interrater reliability and any possible bias inherent in the single rater cannot be measured; therefore, reproducibility of the results needs to be considered before large multisite studies are initiated. Single site–single rater studies may also produce unique effect sizes; therefore, sample size estimation for larger multiple-site studies needs to proceed with caution. Finally, feasibility and time needed for completion are major limitations with single-site studies. Single-site studies, however, do have some advantages that need to be taken into consideration in the design and implementation of multiple-site studies, including limiting the heterogeneity of the study sample by the proper selection of inclusion and exclusion criteria, as well as limiting the variability of raters with the use of proper training and requiring high interrater reliability scores.

The most notable aspect of the Yildiz et al study and others that preceded it[2,8-12] is the scientific rationale that led to its development (namely, identifying molecular targets as a key to developing improved therapeutics). Findings from this study and the Zarate et al study,[2] along with their scientific rationale, support further study of agents with central anti-PKC activity. Tamoxifen was selected as an antimanic agent for these studies on the basis of data from previous preclinical (including genomic) studies and clinical trials, which explored selected molecular targets.[2,8-12] This approach undoubtedly represents a first in drug development in bipolar disorders. To date, drug development in bipolar disorders has been largely based on clinical observations of treatment response to pharmacological agents developed for other conditions. No drug has yet been developed specifically for bipolar disorder based on the understanding of its pathophysiology or the mechanism of effective treatments.

The evidence-based selection of the therapeutic targets that led to this study hopefully will lead to similar approaches by industry, government, and academia in the development of new and better treatments for bipolar disorder. Undoubtedly, this will be an important step to conquer this devastating disorder that affects millions of patients around the globe.

In conclusion, the report by Yildiz et al supports the findings of the preclinical, genetic, and clinical studies[2,8-12] that demonstrated the role of PKC in bipolar disorder. The role of tamoxifen per se in the treatment of bipolar disorder still remains to be determined, but its antiestrogen effects are likely to present a safety challenge, especially in long-term use.[2] More importantly, this study (along with all the previous genomic, preclinical, and clinical work[2,8,9]) represents an example of thoughtful drug development and improved understanding of the pathophysiology of bipolar disorder—a life-impairing medical condition of major public health concern.

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Financial Disclosure: Dr Tohen is a full-time employee and a stockholder of Eli Lilly and Company.

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1. Yildiz A, Guleryuz S, Ankerst DP, Öngür D, Renshaw PF. Protein kinase C inhibition in the treatment of mania: double-blind, placebo-controlled trial of tamoxifen. *Arch Gen Psychiatry*. 2008; 65(3):255-263.
2. Zarate CA Jr, Singh JB, Carlson PJ, Quiroz J, Jolkovsky L, Luckenbaugh DA, Manji HK. Efficacy of a protein kinase C inhibitor (tamoxifen) in the treatment of acute mania: a pilot study. *Bipolar Disord*. 2007;9(6):561-570.
3. Keck PE, Welge JA, McElroy SL, Arnold LM, Strakowski SM. Placebo effect in randomized, controlled studies of acute bipolar mania and depression. *Biol Psychiatry*. 2000;47(8):748-755.
4. Sysko R, Walsh BT. A systematic review of placebo response in studies of bipolar mania. *J Clin Psychiatry*. 2007;68(8):1213-1217.
5. Scherk H, Pajonk FG, Leucht S. Second-generation antipsychotic agents in the treatment of acute mania: systematic review and meta-analysis of randomized controlled trials. *Arch Gen Psychiatry*. 2007;64(4):442-455.
6. Tohen M, Waternaux CM, Tsuang MT. Outcome in mania: a 4-year prospective follow-up of 75 patients utilizing survival analysis. *Arch Gen Psychiatry*. 1990;47(12):1106-1111.
7. Tohen M, Zarate CA Jr, Hennen J, Khalsa HMK, Strakowski SM, Gebre-Medhin P, Salvatore P, Baldessarini RJ. The McLean-Harvard first-episode mania study: prediction of recovery and first recurrence. *Am J Psychiatry*. 2003;160(12):2099-2107.
8. Manji HK, Lenox RH. Ziskind-Somerfeld Research Award: protein kinase C signaling in the brain. Molecular transduction of mood stabilization in the treatment of manic-depressive illness. *Biol Psychiatry*. 1999;46(10):1328-1351.
9. Einat H, Yuan P, Szabo ST, Dogra S, Manji HK. Protein kinase C inhibition by tamoxifen antagonizes manic-like behavior in rats: implications for the development of novel therapeutics for bipolar disorder. *Neuropsychobiology*. 2007;55(3-4): 123-131.
10. Bebchuk JM, Arfken CL, Dolan-Manji S, Murphy J, Hasanat K, Manji HK. A preliminary investigation of a protein kinase C inhibitor in the treatment of acute mania. *Arch Gen Psychiatry*. 2000; 57(1):95-97.
11. Chen G, Manji HK, Hawver DB, Wright CB, Potter WZ. Chronic sodium valproate selectively decreases protein kinase C alpha and epsilon in vitro. *J Neurochem*. 1994;63(6):2361-2364.
12. Coyle JT, Manji HK. Getting balance: drugs for bipolar disorder share target. *Nat Med*. 2002;8 (6):557-558.