

## Methodologies to Avoid the Enrollment of Ineligible Patients in Clinical Trials

Mauricio Tohen, MD, DrPH, MBA

This issue of the *Journal* includes companion articles by Sachs and collaborators.<sup>1,2</sup> The first one describes a failed/negative study of adjunctive ziprasidone combined with lithium or divalproex compared to lithium or divalproex monotherapy. The second article addresses the influence of protocol-specific eligibility criteria on signal detection.

The investigators followed a similar design of a study<sup>3</sup> utilizing another atypical antipsychotic agent that was published a decade ago, which was replicated with other antipsychotic agents in subsequent years.<sup>4-6</sup> The present study, however, also utilized computer-assisted ratings. Importantly, the present and previous studies included a population that had not responded adequately to lithium or divalproex.

The study results suggest that when patients do not adequately respond to lithium or divalproex, the addition of ziprasidone does not provide additional value.<sup>1</sup> Of note, previous trials with other treatments required subjects being on a therapeutic dose of a mood stabilizer for at least 2 weeks, while the current study required only 3–7 days. A separate question not answered by this study is the difference between the monotherapy or combination treatment in de novo patients.

Why studies are positive with the other antipsychotic agents but not ziprasidone may be related to the study design or just simply lack of efficacy of ziprasidone when used in combination with mood stabilizer in patients partially nonresponsive to mood stabilizer monotherapy. Of note, a previous similar study cited by the authors<sup>7</sup> also provided negative results. However, as the authors indicate, the absence of an active control did not provide assay sensitivity, therefore not allowing clear differentiation between a failed or negative study.

We overall praise the editor, the reviewers, the authors, and the industry sponsor for publishing a negative/failed study. As we know, wide criticism has been directed at the pharmaceutical industry for not publishing negative studies or publishing them in obscure journals. In this case, neither has occurred. We also very much welcome the publication of the companion article that attempts to explain potential pitfalls with the study design, including the possible enrollment of inappropriate subjects.

As the authors point out, failed psychopharmacologic randomized controlled trials are common but poorly understood. In the companion article,<sup>2</sup> the authors describe the analyses from computer-based assessments to examine the impact of eligibility criteria in more detail. The major finding was that, on the basis of computer assessments, nearly two-thirds of randomized subjects failed to meet at least 1 protocol-specified eligibility criterion. As the authors indicate, the enrollment of ineligible subjects may contribute to the failure of acute psychopharmacologic efficacy studies.

Computer assessments may no doubt not only control rater bias but also influence the responses of subjects of investigation. As the authors recognize, the study does not measure the benefits of the site monitoring system nor does it establish that computer assessments of any of the eligibility criteria are superior to those of a well-trained site-based rater. A key message is that we need to improve the validity and reliability in the way we establish eligibility criteria and symptom severity. Possible solutions to this problem include improving the training of site raters and using central raters through videoconferencing or with the assistance of computer-generated ratings.

The authors' results provide valuable information to improve the design of clinical trials. The fact that, according to the computer assessment, close to two-thirds of patients did not meet eligibility criteria for diagnosis and symptom severity is concerning—such a large proportion of subjects in any study would lead to biased assessments. Failing to find a difference when one exists or finding spurious differences is concerning. The presented data suggest that a better signal detection will be reached when the eligibility of subjects is established with highest possible confidence, which, in this case, was achieved with the help of computer-administered assessments. Advantages of computer-administered ratings may include consistency of metrics across subjects of investigation and sites, but this system may also miss information that can be captured only by well-trained clinician raters.

To summarize, we applaud the publication of negative/failed data, but, more importantly, we value the attempt to find solutions to deal with challenges that contribute to the failure of clinical trials with psychotropic agents. By improving our clinical trial methodology, we will be able to find better and safer treatments for our patients.

**Drug names:** divalproex (Depakote and others), lithium (Lithobid and others), ziprasidone (Geodon).

**Author affiliation:** University of Texas Health Science Center, San Antonio.

**Potential conflicts of interest:** Dr Tohen is a former (1997–2008) employee of Eli Lilly; has received grant/research support from National

Submitted: August 22, 2012; accepted August 22, 2012.

Corresponding author: Mauricio Tohen, MD, DrPH, MBA, University of Texas Health Science Center, 7526 Louis Pasteur Dr, San Antonio, TX 78229 (mtohen@gmail.com).

*J Clin Psychiatry* 2012;73(11):1426–1427 (doi:10.4088/JCP.12com08119).

© Copyright 2012 Physicians Postgraduate Press, Inc.

Institute of Mental Health (NIMH), NARSAD, American Psychiatric Association, Atlas Foundation, Otsuka, and Forest; has served on speakers or advisory boards of Abbott, GlaxoSmithKline, Bristol-Myers Squibb, Eli Lilly, Wyeth, Merck, Lundbeck, Roche, Otsuka, Teva, Eli Lilly, Forest, Sepracor, Sunovion, AstraZeneca, and Mylan; and currently serves as a member of *JCP*'s Editorial Board. His spouse is an employee of Eli Lilly.

**Funding/support:** NIMH, Otsuka, Forest, American Psychiatric Association, and Atlas Foundation.

### REFERENCES

1. Sachs GS, Vanderburg DG, Karaya ON, et al. Adjunctive oral ziprasidone in patients with acute mania treated with lithium or divalproex, pt 1: results of a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2012;73(11):1412–1419.
2. Sachs GS, Vanderburg DG, Edman S, et al. Adjunctive oral ziprasidone in patients with acute mania treated with lithium or divalproex, pt 2: influence of protocol-specific eligibility criteria on signal detection. *J Clin Psychiatry*. 2012;73(11):1420–1425.
3. Tohen M, Chengappa KN, Suppes T, et al. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. *Arch Gen Psychiatry*. 2002;59(1):62–69.
4. Sachs G, Chengappa KN, Suppes T, et al. Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study. *Bipolar Disord*. 2004;6(3):213–223.
5. Sachs GS, Grossman F, Ghaemi SN, et al. Combination of mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind placebo controlled study. *Am J Psychiatry*. 2002;159(7):1146–1154.
6. Szegedi A, Calabrese J, Stel L, et al. Asenapine as adjunctive treatment for acute mania associated with bipolar disorder: results of a 12-week core study and 40-week extension. *J Clin Psychopharmacol*. 2012;(32):46–55.
7. Weisler R, Warrington L, Dunn J, et al. Adjunctive ziprasidone in bipolar mania: short- and long-term data. Poster presented at 157th Annual Meeting of the American Psychological Association; May 5, 2004; New York, NY.