A Critique of “Olanzapine Versus Divalproex in the Treatment of Acute Mania”

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“Olanzapine Versus Divalproex in the Treatment of Acute Mania” is a research article that was published in the June, 2002 issue of the American Journal of Psychiatry (Tohen et al., 2002). Both olanzapine and divalproex are medications that are commonly prescribed to treat bipolar disorder, which was formerly known as manic depression. These two drugs are relatively new; prior to their FDA approval nearly 10 years ago, the only medication that was prescribed to treat bipolar disorder was lithium (Tohen et al., 2002). The researchers point out in the article that, “The primary objective of the study…was to compare the efficacy of olanzapine versus divalproex in the treatment of mania over a 3-week period.” (Tohen et al., 2002, p. 1011).

Interestingly, although their rationale for conducting the study is made very clear, they do not openly state any hypotheses they have regarding the outcome of the study in the introduction. In the Method section, they do point out than the fact that they were attempting to assess “…the noninferiorty of olanzapine compared to divalproex…” and that they were hoping to evaluate “…whether olanzapine was no worse than divalproex in reducing manic symptoms.” (Tohen et al., 2002, p. 1012). I am suspicious though; due to the fact that many of the participants, or subjects, in the study were tested at several Lilly Research Laboratories which are affiliated with a large pharmaceutical company, Eli Lilly. I also noticed in a footnote at the end of the article before the references that Eli Lilly sponsored the research. I believe that the researchers may have been attempting to demonstrate that olanzapine is better than divalproex.

The participants in this study were number of patients between the ages of 18 and 75 who were diagnosed with bipolar I disorder. A number of these patients were removed from the study, either because they had additional diagnoses, medical illnesses, adverse reactions to the medications or other circumstances that prevented them from participating. A total of 125
participants were eventually randomly assigned to a group that received olanzapine; 126 participants were randomly assigned to a group that received divalproex (Tohen et al., 2002).

The researchers report that, “This was a 3-week, double-blind, parallel-group study with a double-blind continuation phase of 44 weeks.” (Tohen et al., 2002, p. 1012). In other words, neither the researchers, nor the participants knew who was assigned to which groups. This seems like it was a difficult task especially since the researchers needed to evaluate lab reports of the participants on a fairly regular basis. The blood work reports needed to worded in such a way as to not give the researchers any clues as to which participants were receiving olanzapine and which were receiving divalproex. The researchers looked at the lab reports in order to determine if any of the subjects might have adverse reactions to the medications (Tohen et al., 2002).

The severity of the participants’ symptoms was assessed using two tests: the Young Mania Rating Scale and the Hamilton Depression Rating Scale. These tests were administered at baseline (the start of the study) and at regular intervals during the course of the 3-week portion of the study. The safety of the medications was also assessed using a combination of information including the participants’ vitals (i.e., heart rate, blood pressure, etc.) and the participants’ responses on a few paper-and-pencil measures of adverse reactions to medications (Tohen et al., 2002).

The researchers report a lot of statistics that indicate that there were no differences between the two groups in terms of demographic features such as age, gender, race and specific symptoms of bipolar disorder that might have potentially influenced the outcome of the study (Tohen et al., 2002, p. 1013). Although the researchers were initially hoping to show no difference between the two groups in terms of reduction of manic symptoms, the olanzapine group showed an average improvement of 13.4 points on the Young Mania Rating Scale as
opposed to the average improvement of 10.4 in the divalproex group. It is pointed out that this
difference in improvement is statistically significant (Tohen et al., 2002, p. 1013). There were no
differences in improvement on the Hamilton Depression Rating Scale between the two groups
(Tohen et al., 2002, p. 1014), but this makes sense since the researchers were try to see if the
medications would affect manic symptoms, not depressive symptoms.

One intriguing table included in the article is Table 3 (Tohen et al., 2002, p. 1015). The
data presented in the table provides a comparison between the two medications in terms of the
adverse effects experienced by the participants in the study. Interestingly, although some adverse
effects were experience by members of both of the groups, there were more adverse effects
experienced by participants in the olanzapine group, such as somnolence (drowsiness), dry
mouth, increased appetite tremor and sleep disorders. This fact does not seem to be discussed
much in the text of the article. Although there was more of an improvement in manic symptoms
seen in the olanzapine group there were also more adverse reactions to the medication.

The authors of the article conclude, “Although in this trial the primary outcome favored
olanzapine, the selection of pharmacological treatment should consider both safety and efficacy
parameters as well as patient-specific considerations.” (Tohen et al., 2002, p. 1016). What is
interesting to me is the fact that these last two points made later in the article by the authors,
regarding adverse effects and patient considerations would not be immediately obvious to
someone simply reading the abstract of the article. A time-pressed psychiatrist who might only
read the abstract might conclude that olanzapine was superior to divalproex in treating mania
which may ultimately lead to him/her prescribing the drug to a patient that might potentially
experience some of the adverse reactions discussed above.
Another concern I have has to do with the fact that the article only reports the results after three weeks of treatment. Granted, a notable improvement was seen in the olanzapine group as compared to the divalproex group during that three-week period; but it is conceivable that longer-term treatment with either of these medications might prove to be worse for patients with bipolar disorder. The authors should preface the conclusions drawn in the article regarding olanzapine’s effectiveness. They should point out that long-term studies comparing the two medications have yet to be reported. Based on my reading of the article, the authors fail to do this.

Finally, a quick search of the internet confirmed my suspicions regarding the intentions of the researchers I pointed out earlier regarding their hypotheses. Olanzapine is marketed under the brand name Zyprexa by pharmaceutical company Eli Lilly (2001); divalproex, on the other hand, is marketed by Abbott Laboratories (2000) under the brand name of Depakote. Very clearly these two companies are competing for a share of the same market and so the fact that the research was sponsored by Eli Lilly and many of the tests were conducted at one of Eli Lilly’s laboratories leads me to wonder whether some potential bias existed in the way the study was conducted or the data were analyzed.

This article was fairly difficult to read, but once I got beyond the statistics and focused on the reason the research was conducted, as stated in the introduction, and the conclusions the authors drew, it was very interesting. It was also very interesting to read the fine print and speculate about the researchers’ true intentions in conducting this research.
References

