Neuropsychopharmacology (2004) 29, 636

www.neuropsychopharmacology.org

Letter to the Editor

Unbalanced Statistical Analysis of Combined Divalproex and Antipsychotic Therapy for Schizophrenia

Laura S Boylan*[,1] and Daniel L Labovitz[2]

[1]*Bellevue Hospital Center, New York University School of Medicine, New York, NY, USA;* [2]*St Lukes-Roosevelt Hospital Center, New York, NY, USA*

Neuropsychopharmacology (2004) **29,** 636. doi:10.1038/sj.npp.1300368

Sir

In their recent report in *Neuropsychopharmacology*, Casey *et al* (2003) conclude 'combination therapy with divalproex plus either olanzapine or risperidone improved PANSS total and positive scores compared with antipsychotic monotherapy'. Given the failure of the trial to show efficacy at the primary end point, the statement seems ill founded: apparent early gains were not sustained at 28 days. They also conclude that 'divalproex was as well tolerated as antipsychotic monotherapy', but their analysis is biased. Study groups were analyzed separately (risperidone *vs* risperidone/divalproex, olanzapine *vs* olanzapine/divalproex) or in combination (antipsychotic monotherapy *vs* antipsychotic/divalproex) in ways that enhanced the appearance of benefit and reduced evidence of risk.

The study was not designed or powered to detect equivalency between the two antipsychotics yet combined them in the efficacy analysis. The authors justify this combined analysis on the basis of a test for interaction that is underpowered to detect a meaningful difference in a study of this size. Studies directly comparing the two have indeed identified differences in efficacy (Conley and Mahmoud, 2001). As shown in Figure 1 of the paper, the analysis of uncombined data failed to demonstrate statistically significant benefit for adjunctive divalproex with either antipsychotic.

At the same time, the authors emphasize the difference between the two drugs in the safety analysis. The net result is that the safety analysis has less power than the efficacy analysis. If instead the groups are combined for the analysis of adverse events, there is significantly more somnolence among patients treated with divalproex adjunctive therapy (Mantel–Hanzel χ^2, $p = 0.0006$, data obtained from Table 3). The authors assert that there was no increased somnolence on the basis of evaluating uncombined data.

This, the largest randomized control trial to date for the use of divalproex in schizophrenia is an important study. The authors discuss several possible explanations for the failure to find benefit at 28 days, but do not entertain the possibility that it was a 'true negative' or that any initial benefit was transient or merely random. One alternative explanation suggested by the data is that accelerated improvement in symptom rating scores is achieved through nonspecific sedation. Was significant improvement found among patients without somnolence?

Regardless, the failure of the study to attain its primary end point is a major finding and should have been included in the abstract. This negative finding has important clinical implications. Added to the mixed results of smaller previous randomized trials (Dose *et al*, 1998; Hesslinger *et al*, 1999; Wassef *et al*, 2000), it further weakens support for the widespread use of divalproex for chronic schizophrenia.

*Correspondence: Dr LS Boylan, Department of Neurology, New York University School of Medicine, Bellevue Hospital Center, 462 First Avenue, New York City, NY, USA, E-mail: laura.boylan@med.nyu.edu
Received 29 May 2003; accepted 06 November 2003
Online publication: 10 November 2003 at http://www.acnp.org/citations/Npp11100303242/default.pdf

REFERENCES

Casey DE, Daniel DG, Wassef AA, Tracy KA, Wozniak P, Sommerville KW (2003). Effect of divalproex combined with olanzapine or risperidone in patients with an acute exacerbation of schizophrenia. *Neuropsychopharmacology* **28**: 182–192.

Conley RR, Mahmoud R (2001). A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. *Am J Psychiatry* **158**: 765–774.

Dose M, Hellweg R, Yassouridis A, Theison M, Emrich HM (1998). Combined treatment of schizophrenic psychoses with haloperidol and valproate. *Pharmacopsychiatry* **31**: 122–125.

Hesslinger B, Normann C, Langosch JM, Klose P, Berger M, Walden J (1999). Effects of carbamazepine and valproate on haloperidol plasma levels and on psychopathologic outcome in schizophrenic patients. *J Clin Psychopharmacol* **19**: 310–315.

Wassef AA, Dott SG, Harris A, Brown A, O'Boyle M, Meyer WJ, Rose RM (2000). Randomized placebo-controlled pilot study of divalproex sodium in the treatment of acute exacerbations of chronic schizophrenia. *J Clin Psychopharmacol* **20**: 357–361.