

# International Mental Health Conference Report

► Last Week's Highlights Reported from Philadelphia, PA, USA

May 28, 2002 • Volume 1, Issue 5

## Summary of the Highlights from the APA 2002 Annual Meeting: Divalproex as a Treatment for a Variety of Psychiatric Conditions

During certified programs held in conjunction with the American Psychiatric Association (APA) annual meeting this week in Philadelphia, PA, several researchers presented study results showing that divalproex is effective in treating a wide range of psychiatric conditions, including bipolar disorder in children and adults, schizophrenia, and cluster B personality disorders. Highlights from their presentations and related presentations follow.

### Childhood/Adolescent Bipolar Disorder

The association of bipolar disorder in children and adolescents with significant morbidity and mortality (eg, suicide) makes it a key target for treatment, concluded Karen Dineen Wagner, MD, PhD, Department of Psychiatry and Behavioral Sciences and Division of Child and Adolescent Psychiatry, University of Texas Medical Branch, Galveston. Although placebo-controlled trials are lacking, promising results in the treatment of pediatric bipolar disorder have been reported by Dr Wagner and her colleagues.[1] In their study of 40 children (ages 7 to 17 years) with bipolar disorder who were treated for 2 to 8 weeks with divalproex, 22 responded with a  $\geq 50\%$  reduction in Young Mania Rating Scale score. However, 23 (58%) of the patients discontinued—an outcome that may be improved through use of an extended-release formulation of divalproex (see below).

### Adult Bipolar Disorder

In what he described as “the only controlled study of maintenance therapy for bipolar disorder conducted in the last 25 years,” Charles L. Bowden, MD, Department of Psychiatry at the University of Texas Health Science Center at San Antonio, presented data from a 1-year, randomized, double-blind, placebo-controlled trial of maintenance divalproex vs lithium for treatment of bipolar I disorder. Those patients who were administered divalproex (n=187) had better outcomes on several secondary outcome measures than those administered lithium (n=91) or placebo (n=94). Specifically, the study found that discontinuation rates due to either a recurrent mood episode or a depressive episode were significantly lower in those taking divalproex compared with placebo.[2]

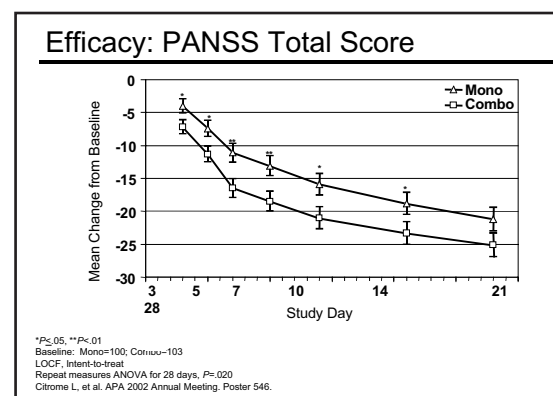
In addition, the time to 50% relapse to any episode was 275 days for divalproex vs 189 days and 173 days for lithium and placebo, respectively. These results provide further evidence that divalproex is an effective treatment for bipolar disorder in adults.

### Schizophrenia

Daniel Casey, MD, VA Medical Center and Department of Psychiatry, Oregon Health & Science University, Portland, OR, concluded that anticonvulsants have a growing role in treating psychosis, specifically as adjunct treatments for schizophrenia and schizoaffective disorder. He presented results of a large (N=249), 28-day, double-blind, multicenter study comparing the efficacy and safety of atypical antipsychotic monotherapy vs combination treatment with divalproex.[3] Patients were randomized to either olanzapine plus placebo or divalproex, or to risperidone plus placebo or divalproex. The primary efficacy measure was Positive and Negative Symptom Scale (PANSS) scores.

The combination-therapy group exhibited statistically significantly better PANSS total scores than the monotherapy (placebo) group at days 3, 5, 7, 10, 14 and 21 (Figure 1). Dr Casey indicated that the addition of divalproex also resulted in an accelerated response. The percentage of patients experiencing a  $>20\%$  improvement in the PANSS total score was not only significantly greater in the combination-therapy group, but there was also a “shift to the left” of approximately 1 week in the time required for at least 50% of the group to reach the  $>20\%$  improvement in PANSS total score. Thus, divalproex can accelerate response by approximately 7 days.

Figure 1



Most adverse events (AEs) were mild or moderate, and they were similar between the two treatment groups. In fact, discontinuation rates were lower in the combination-therapy

group (28%) than in the monotherapy group (38%), thus showing that divalproex combination therapy appears to be as well tolerated overall as antipsychotic monotherapy. Overall, Dr Casey concluded, “divalproex offers a new treatment option for psychosis with schizophrenia.”

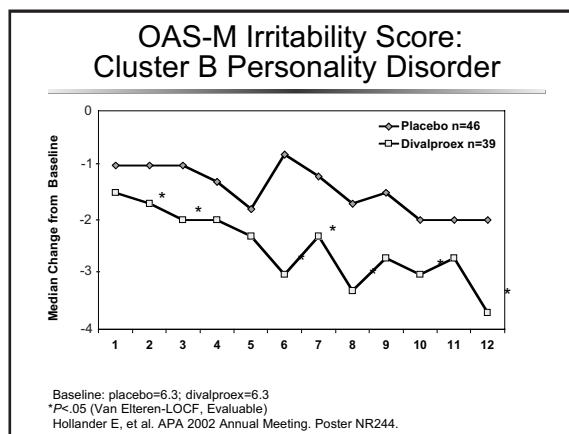
### Cluster B Personality Disorders

Cluster B personality disorders, which include borderline, narcissistic, antisocial, histrionic and not otherwise specified personality disorders, are common and highly disabling, reported Eric Hollander, MD, Mt Sinai School of Medicine, New York, NY. Dr Hollander and colleagues presented a poster at the APA study session that demonstrated the superiority of divalproex in treating impulsive aggression in cluster B personality disorders.[4]

In this double-blind, placebo-controlled, multicenter study, 96 patients were randomized after a 2-week washout baseline period to either divalproex or placebo for a 12-week treatment period followed by a 1-week taper. The recommended target divalproex serum level was 80 to 120 µg/mL by week 3. It should be noted that 15% and 5% of the placebo and divalproex groups, respectively, were on concomitant antidepressants, and 4% and 9% were on concomitant zolpidem tartrate. The primary endpoints of the study were Overt Aggression Scale (OAS-M) aggression and irritability scores.

Patients treated with divalproex in the study scored significantly lower on OAS-M total aggression scores during the last 4 weeks of treatment compared with those treated with placebo, and there was a significant treatment effect from baseline to the end of the study for divalproex, Dr Hollander reported. Additionally, greater decreases from baseline in OAS-M irritability score were observed for divalproex (vs placebo) at weeks 2, 3, 6, 7, 8, 10 and 12 (Figure 2) and improvements were reported in patients’ subscores pertaining to verbal assault, assault against objects and assault against others. Significant improvement in Clinical Global Impressions (CGI) and irritability scores was noted throughout the study period and as early as weeks 1 and 2, respectively. In terms of safety, Dr Hollander indicated that there was a relatively high rate of discontinuation in the study overall; 46% dropped out (45% placebo, 47% divalproex), although most of the AEs observed were mild to moderate and no new safety concerns were noted. Dr Hollander and his colleagues concluded that “divalproex is an effective pharmacologic agent in the treatment of impulsive aggression and irritability in patients with cluster B personality disorders.”

Figure 2



### Divalproex Extended-Release

In his talk, Dr Bowden noted that effective drug treatment requires good patient compliance. One strategy to enhance compliance, he noted, is the use of extended-release products, with studies demonstrating that patient compliance decreases as the number of daily doses increases.[5] Therefore, extended-release divalproex, which is dosed once daily, should theoretically improve patient compliance and thus increase effective treatment.

Dr Bowden presented data derived from various studies comparing mean plasma valproate concentration after administration of 500-mg doses of various forms of the drug. The data showed that divalproex extended-release tablets resulted in smoother peak plasma concentrations than divalproex enteric-coated tablets, valproic acid and divalproex sprinkle.

Data consistent with its slower release were presented by Trisha Suppes, MD, PhD, University of Texas Southwestern Medical Center in Dallas. In her discussion of the literature regarding extended-release divalproex, she indicated that it “is better tolerated. . . with studies showing less appetite increase and lower alopecia” than the original formulation.

### References

1. Wagner KD, et al. *J Am Acad Child Adolesc Psychiatry*. In press.
2. Bowden CL, et al. *Arch Gen Psychiatry*. 2000;57:481-489
3. Citrome L, et al. American Psychiatric Association 2002 Annual Meeting. Poster 546
4. Hollander E, et al. American Psychiatric Association 2002 Annual Meeting. Poster NR244.
5. Iskedjian M, et al. *Clin Ther*. 2002;24:302-316.