Key Words: divalproex, valproic acid, valproate, bipolar disorder, mania

Divalproex in the Treatment of Bipolar Disorder

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ABSTRACT ~ *Valproate is commonly used as a first-line agent for the treatment of acute bipolar I mania. Its efficacy in the treatment of acute mania has been established in randomized, controlled trials versus placebo, lithium, haloperidol, and olanzapine. Only preliminary data regarding the efficacy of valproate in acute bipolar depression are currently available. The efficacy of valproate in the maintenance treatment of bipolar disorder has not been definitively established but most evidence from randomized, controlled trials suggests that it may have comparable efficacy to lithium and olanzapine. The results of randomized, controlled trials of valproate in the treatment of bipolar disorder are reviewed along with their implications for clinical practice.* Psychopharmacology Bulletin. *2003;37(Suppl 2): 67-73*

INTRODUCTION

In 1966, shortly after its introduction as an antiepileptic agent, Lambert et al reported beneficial effects of valpromide, a prodrug converted to valproic acid, in the treatment of bipolar disorder.[1] Although a number of subsequent open trials continued to find evidence of mood-stabilizing properties associated with valproate treatment,[2-7] the first randomized, controlled trials of valproate did not appear until the early 1980s.[8,9] Subsequent large, randomized, placebo-controlled trials in acute bipolar mania[10,11] led to the approval by the US Food and Drug Administration of the divalproex formulation of valproate for the treatment of acute bipolar mania. Divalproex and other valproate formulations are now internationally recognized in treatment guidelines as among the first- line treatments for acute bipolar mania.[12-14] We review below the randomized, controlled trials of valproate in the bipolar mania, depression, and as maintenance treatment and their implications for clinical practice.

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ACUTE BIPOLAR MANIA

Randomized, controlled trials of valproate in acute bipolar mania are summarized in the Table.[8-22] In these trials, valproate was superior to placebo as monotherapy[8,9,10,11] or as adjunctive therapy to typical antipsychotics,[22] and comparable in efficacy to lithium,[11,16,18] haloperidol,[17] and olanzapine.[19] However, in a second comparison trial with olanzapine, olanzapine-treated patients displayed significantly greater mean reductions in Young Mania Rating Scale (YMRS) total scores and response rates compared with patients receiving divalproex.[20]

Several additional clinically relevant findings emerged from these studies. First, pooled response rates revealed that approximately 50% of patients who received valproate displayed a moderate to marked reduction in manic symptoms.[23] Second, post hoc analyses from the largest parallel-group, placebo-controlled trial[11] suggested that patients with depressive symptoms during mania (including patients with subthreshold symptoms to meet criteria for a mixed episode)[24] and with multiple prior (ie, >10) mood episodes[25] were more likely to respond to acute treatment with

TABLE

RANDOMIZED, CONTROLLED STUDIES OF DIVALPROEX IN THE TREATMENT OF ACUTE MANIA

STUDY	N	DESIGN	DURATION (DAYS)	OUTCOME
Emrich et al.[8]	5	A-B-A	Variable	4/5 marked response; 1/5 no response
Brennan et al.[9]	8	A-B-A	14	6/8 marked response; 2/8 no response
Post et al.[15]	1	Crossover	Variable	No response to VPA
Pope et al.[10]	36	VPA vs. P	21	VPA > P
Bowden et al.[11]	179	VPA vs. L vs. P	21	VPA = L > P
Freeman et al.[16]	27	VPA vs. L	21	VPA = L
McElroy et al.[17]	36	VPA vs. HAL	6	VPA = HAL
Hirshfeld et al.[18]	59	VPA loading, Titration, vs. L	10	VPA = L
Zajecka et al.[19]	120	VPA vs. OLZ	21	VPA = OLZ
Tohen et al.[20]	248	VPA vs. OLZ	21	VPA < OLZ
Muller-Oerlinghausen et al.[21]	136	VPA vs. P + antipsychotics	21	VPA > P
Oluboka et al.[22]	11	VPA loading vs. titration	7	VPA loading = titration

VPA=valproate; P=placebo; L=lithium; OLZ=olanzapine[2]

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valproate than with lithium. Freeman et al16 also found valproate to be more efficacious than lithium in patients with mixed episodes. Third, the onset of antimanic response usually occurred within several days to 2 weeks after achieving a serum valproic acid concentration of ≥ 50 μg/mL.

Seven studies have examined the safety and tolerability of divalproex rapid oral loading in acute mania, a strategy designed to achieve therapeutic serum concentrations within a day of treatment initiation and thereby hasten response.[17-19,22,26-28] In studies that compared divalproex rapid loading with gradual titration,[18,22] there were no significant differences in adverse events or overall tolerability between the two approaches. Unfortunately, none of the studies of divalproex rapid loading conducted to date included sufficient sample sizes to establish whether this strategy provides for more rapid onset of therapeutic response than gradual titration.

One preliminary open-label study found that hypomanic episodes in patients with cyclothymia responded to lower valproate doses (eg, 125-500 mg/d) and serum concentrations (eg, 20-45 μg/mL) than required for the treatment of acute bipolar I manic and mixed episodes.[29] These observations require confirmation in controlled studies. Case reports, case series, and the results of four randomized, controlled trials indicate that the antimanic effects of valproate can be augmented by lithium, carbamazepine, typical antipsychotics, clozapine, risperidone, olanzapine, and quetiapine.[21,30-37]

ACUTE BIPOLAR DEPRESSION

In contrast to the considerable number of studies of valproate in the treatment of acute mania, there are few studies of the efficacy of valproate in the treatment of acute bipolar depression. Data from open-label trials suggested that valproate was less effective in treating acute depressive episodes compared with its efficacy in treating manic and mixed episodes.[23] Sachs et al recently reported the results of the first placebo-controlled, randomized trial of divalproex in patients (N=45) with acute bipolar I or II depression.[38] There was no significant difference in the proportion of patients meeting recovery criteria receiving divalproex (43%) compared with placebo (27%) at the end of the 8-week trial. Similarly, there was no significant difference between treatment groups in mean change in Hamilton Depression Rating Scale (HDRS) total scores from baseline to endpoint. However, the divalproex group had significant improvement in HDRS total scores compared with the placebo group at weeks 2, 4, and 5 of the 8 week trial. The results of this trial are limited by the small sample size and it is possible that more consistent drug-placebo differences may have been evident with a larger study.

MAINTENANCE TREATMENT OF BIPOLAR DISORDER

The efficacy of valproate in the maintenance treatment of bipolar disorder has been assessed in five randomized, controlled trials.[39-43] In the only placebo-controlled trial, there was no significant difference in the time to development of any mood episode among patients receiving divalproex, lithium, or placebo.[39] However, there were a number of unanticipated methodological problems that limit the interpretation of these negative findings.[44] In a post hoc analysis, patients who received divalproex for treatment of the index manic episode in the open-label treatment period prior to randomization, divalproex was superior to placebo in early termination due to any mood episode (29% versus 50%) during the subsequent treatment year. This is a clinically relevant finding, because it reflects the common practice of maintaining an agent effective in acute manic episodes into long-term treatment. An earlier open randomized trial found slightly greater efficacy for the valpromide formulation in the mean reduction of overall affective episodes in an 18- month study compared with lithium.[40]

Tohen et al[41] compared divalproex with olanzapine in a 47-week maintenance trial of patients who responded initially to monotherapy with each agent in an acute treatment 3-week trial.[20] Patients receiving olanzapine had significantly greater improvement in mean YMRS total scores compared with patients receiving divalproex until 15 weeks of treatment. However, there were no significant differences in manic or depressive symptom improvement between the two treatment groups for the remainder of the trial. In addition, there were no significant differences in relapse rates between the olanzapine (45%) and divalproex (52%) groups. Patients receiving olanzapine displayed significantly greater mean weight gain (3.4 kg) compared with patients treated with divalproex (1.7 kg). Notably, by the end of the 47-week maintenance period, only 15% of patients remained in each treatment group, underscoring the difficulty of managing bipolar I disorder with a single agent.

The only two randomized, controlled trials of combination compared with monotherapy maintenance treatment of bipolar disorder involved divalproex.[42, 43] In a pilot trial, Solomon et al compared the efficacy of lithium and placebo with the combination of lithium and divalproex in relapse prevention in 12 patients with bipolar I disorder.[42] The lithium/divalproex group (n=5) had no relapses during the 1-year follow-up compared with a 71% relapse rate in the lithium/placebo group (n=7). Side effects were twice as common in the lithium/divalproex group. In the second study, Tohen et al.43 found the combinations of olanzapine/divalproex or olanzapine/lithium to be superior to placebo/divalproex or placebo/lithium in relapse prevention over 18 months in patients who had initially responded to the olanzapine/mood stabilizer combinations

acutely36 and then were rerandomized. These findings suggest that patients who respond acutely to combinations of olanzapine and divalproex or olanzapine and lithium may have a lower risk of mood episode relapse by staying on these combinations. Patients in the mood-stabilizer combination group experienced twice the weight gain as patients in the monotherapy (plus placebo) group, however.

SERUM CONCENTRATIONS

Bowden et al found evidence for a serum valproic acid therapeutic range of 45-125 μg/mL in acute mania.[45] Within this range, there was also evidence of greater efficacy at higher rather than lower serum concentrations. Dose-related side effects (eg, gastrointestinal, tremor, sedation) became more common at serum concentrations of > 100 μg/mL.

For maintenance therapy, serum concentrations ranging from 75-100 mcg/mL were optimal in preventing relapse into mania or depression and were most tolerable as defined by discontinuation for any reason from the placebo-controlled maintenance study.[39,46]

CONCLUSION

Valproate and its formulations (valproic acid, sodium valproate, and divalproex sodium) are among the most rigorously studied agents in the treatment of acute bipolar mania, with substantial evidence of efficacy in a number of randomized, controlled trials. It has not been well studied in the treatment of acute bipolar depression, to date. Data from maintenance studies suggest that it also has efficacy in the prevention of recurrent mood episodes in the long-term management of patients with bipolar I disorder. ⌘

DISCLOSURE

Dr. Keck is a consultant to, or member of the scientific advisory boards of: Abbott Laboratories, AstraZeneca Pharmaceuticals, Bristol-Meyers Squibb, Corcept, GlaxoSmithKline, Janssen Pharmaceutica, Eli Lilly and Company, Novartis, Ortho-McNeil, Pharmacia, Pfizer, UCB Pharma, Shire, Solvay, and Wyeth. In addition, Dr. Keck is a principal or coinvestigator on research studies sponsored by: Abbott Laboratories, AstraZeneca Pharmaceuticals, Bristol-Meyers Squibb, GlaxoSmithKline, Elan, Eli Lilly, Merck, National Institute of Mental Health (NIMH), National Institute of Drug Abuse (NIDA), Organon, Pfizer, the Stanley Medical Research Institute (SMRI), and UCB Pharma.

DISCLOSURE OF UNLABELED OR UNAPPROVED USES OF DRUGS

Please note that this review article contains discussions of unlabeled uses of FDA-approved pharmaceutical products. Please refer to the official prescribing information for approved indications, contraindications, and warnings.

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