The Role of Divalproex in the Treatment of Bipolar Disorder

Charles L. Bowden, MD; Diane M. Lawson, PharmBS; Muriel Cunningham, MEd; James Randall Owen, MD; and Katherine A. Tracy, MD, PhD

Bipolar disorder is a chronic, cyclic illness. The hallmark feature of bipolar I is a history of mania, characterized by an elevated, expansive, or irritable mood in association with affective, behavioral, and psychotic symptoms. Depression is common and may occur concurrently with mania resulting in a condition known as a mixed state. Psychosis may be associated with either mania or depression and, if present, represents a severe form of bipolar disorder. Behavioral disturbances such as disinhibition and impulsivity are associated with faulty insight and judgment.

Divalproex sodium (Depakote, Abbott Laboratories) has become an established treatment for the many manifestations of bipolar disorder. Divalproex sodium is available as enteric-coated delayed-release tablets and in a once-daily extended-release formulation (Depakote ER). Depakote is indicated for the treatment of acute mania associated with bipolar disorder, complex partial seizures, and migraine headache prophylaxis, while Depakote ER is currently approved for the prophylaxis of migraine headache. This review examines the recent literature on the expanding knowledge regarding the efficacy and safety of divalproex in bipolar disorder, and further uses in psychiatry.

MANIA

The efficacy of divalproex in the treatment of acute mania associated with bipolar disorder was established in two pivotal trials1,2 that led to its approval by the Food and Drug Administration in 1995. Bowden et al. demonstrated the superiority of divalproex compared to placebo on the Mania Rating Scale (MRS); divalproex efficacy was comparable to lithium.2 Marked improvement was reported in 48% of divalproex-treated patients versus 25% of the placebo-treated patients. Divalproex-treated patients had greater improvement (over placebo and lithium) on the MRS score as early as day 10 of treatment. This hallmark study utilized a gradual dosing strategy that is in contrast to alternative loading strategies (see Dosing).

Valproate was compared with carbamazepine in a randomized, double-blind, 3-week study of hospitalized manic patients.3 Patients treated with valproate had earlier improvement, greater over-
all improvement (73% versus 53%), required less rescue medication, and reported fewer adverse events than patients receiving carbamazepine.

Two randomized, double-blind clinical trials examined divalproex versus olanzapine in the treatment of acute mania in patients with bipolar I disorder.\textsuperscript{4,5} Zajecka et al. found that the two drugs demonstrated similar efficacy in the acute (3 weeks) treatment of mania.\textsuperscript{4} A significant difference favoring olanzapine was observed by Tohen et al.\textsuperscript{5} The difference was in part a function of the sedative effects of olanzapine, as indicated by a significant treatment difference in motor activity, sleep, and thought-disorder. Additionally, Tohen et al. initiated divalproex at a daily dose of 750 mg rather than a loading dose of 20 mg/kg, and the final mean modal dose was approximately 1400 mg/d.\textsuperscript{5} This dose is below that observed in other acute mania trials with divalproex.\textsuperscript{2,4} Of interest, divalproex and olanzapine had similar improvement in manic patients with psychotic features.\textsuperscript{5}

Adverse events were more frequent among olanzapine-treated patients in both studies. In Zajecka et al. olanzapine-treated patients had significantly more weight gain, somnolence, slurred speech, rhinitis, and edema.\textsuperscript{4} The olanzapine-treated patients had significant elevations in the change from baseline to final evaluation on total cholesterol and low-density lipoprotein cholesterol compared to the divalproex-treated patients. The average weight gain with olanzapine treatment was greater than with divalproex treatment during the initial 3-week treatment period in both trials, and at 12 weeks was found to be 8.8 lbs and 5.5 lbs in the olanzapine-treated and divalproex-treated groups, respectively. In addition, outpatient costs over the 12-week study were significantly lower for the divalproex-treated group compared to the olanzapine-treated group.\textsuperscript{6}

Valproate has also demonstrated efficacy in alleviating manic symptoms when combined with other medications used in bipolar disorder treatment in both open and randomized, blinded studies.\textsuperscript{7,8} Valproate added to haloperidol provided greater improvement in hospitalized manic patients than did haloperidol plus placebo in a randomized, blinded study.\textsuperscript{8} Furthermore, lower dosage of haloperidol occurred among patients who concurrently received valproate than among patients who received haloperidol alone. In a recent study by Sachs et al., bipolar patients (n = 156) were randomized to placebo, risperidone, or haloperidol in addition to divalproex or lithium.\textsuperscript{9} Mean modal doses were 3.8 mg/d for risperidone and 6.2 mg/d for haloperidol. Significantly greater reductions in Young Mania Rating Scale (YMRS) scores were seen at endpoint in the risperidone and haloperidol groups, compared to placebo. Young Mania Rating Scale total scores improved with risperidone and with haloperidol, both in patients with or without psychotic features at baseline. The advantage of the antipsychotic plus mood stabilizer was limited to patients who had breakthrough mania while taking valproate or lithium. Rate of improvement did not differ among patients started on either valproate or lithium concurrently with start of risperidone or haloperidol.

**MAINTENANCE TREATMENT**

Divalproex has been shown to be safe and effective in the long-term management of patients with bipolar disorder.\textsuperscript{10} Patients treated with divalproex had lower rates of discontinuation for either a recurrent mood episode or depressive episode compared to placebo-treated patients. Compared to lithium, divalproex treatment resulted in a longer overall retention in the study, less average depressive symptomatology, and improvement in Global Assessment Scale scores. However, the treatments did not differ significantly in time to recurrence on any mood episode during maintenance therapy.

**RAPID CYCLING BIPOLAR DISORDER**

Rapid cycling in bipolar disorder affects 15% to 20% of bipolar patients and of these, 72% to 82% do not respond well to lithium therapy.\textsuperscript{11,12} Calabrese et al. examined the efficacy of divalproex in an open study of divalproex, both as monotherapy and in conjunction with other medications, in 78 patients with rapid cycling. A marked response in 54% of patients with mania and 87% of those with mixed states was observed.\textsuperscript{13} The researchers also reported a markedly prophylactic response in 72% of manic patients and 94% of mixed state patients.
DEPRESSION

Several lines of evidence suggest that divalproex has potential efficacy in the treatment of depressive symptoms. Divalproex was demonstrated to be more effective than lithium in the treatment of acute mania in patients who exhibit prominent comorbid depressive symptoms. In another study, depressed bipolar II patients who were either medication naive (no exposure to psychotropics) or mood stabilizer naive, were treated with open-label divalproex. Sixty-three percent of all patients responded (greater than 50% decrease in Hamilton Depression Rating Scale score). Interestingly, the medication naive patients showed greater improvement than the mood-stabilizer naive patients.

Small, largely open studies suggest that divalproex may be effective for treating major depressive episodes both in patients with unipolar depression or bipolar disorder. In an 8-week open trial of divalproex for major depressive disorder, 15 of 28 patients (54%) who completed the study had demonstrated a significant clinical response (defined as a score reduction of 50% or more or a total score of 9 or lower on the Hamilton Depression Rating Scale) by the fourth week.

In the 12-month, placebo-controlled maintenance trial study of divalproex compared to placebo or lithium in outpatients with bipolar I disorder, divalproex was superior to placebo or lithium on several measures related to depressive efficacy. Patients treated with divalproex who had been previously hospitalized, or who received divalproex during the open phase to bring a manic episode under control, remained free of depression longer than did patients treated with lithium. Divalproex-treated patients had less worsening of depressive symptoms than did patients who received placebo. Divalproex coupled with use of a selective serotonin reuptake inhibitor for breakthrough depression was significantly more effective than was a selective serotonin reuptake inhibitor plus placebo.

PSYCHOSIS

There is evidence that divalproex is beneficial among patients with psychotic mania. McElroy et al. compared the efficacy of divalproex oral loading to haloperidol in the initial treatment of patients hospitalized with acute psychotic mania. Subjects were randomly assigned to receive either 20 mg/kg/d of divalproex (n = 21) or 0.2 mg/kg/d of haloperidol (n = 15) in divided doses for 6 days. Divalproex and haloperidol appeared to be equally effective in reducing manic and psychotic symptoms, as measured by total YMRS scores and the Scale for Assessment of Positive Symptoms. The greatest rate of improvement occurred during the first 3 days of treatment. Adverse events were reported as infrequent and mild for both treatment groups; however eight (53%) patients in the haloperidol group reported extrapyramidal side effects versus none in the divalproex-treated group.

Divalproex has demonstrated benefit in the treatment of psychotic symptoms associated with other psychiatric disorders. Augmentation of haloperidol with divalproex in the treatment of an acute exacerbation of schizophrenia provided substantially better therapeutic outcomes, including decreased costs due to fewer hospitalization days for patients who were adjunctively treated with divalproex. In addition, Casey et al. assessed the safety and efficacy of divalproex used in combination with either risperidone or olanzapine, versus risperidone or olanzapine in combination with placebo for the treatment of psychosis associated with schizophrenia. When added to olanzapine or risperidone, divalproex significantly improved acute psychosis compared to atypical antipsychotic monotherapy with improvement seen as early as day three.

EFFECTIVENESS IN SPECIAL POPULATIONS

In addition to treating adults for mania associated with bipolar disorder, divalproex has demonstrated effectiveness in children and adolescents. In this age group, mania often manifests as impulsivity, aggression, and behavioral dyscontrol. Wagner et al. reported on the safety and effectiveness of open-label divalproex in bipolar pediatric patients (n = 40; ages 7 to 19) with a manic, hypomanic, or mixed episode. Sixty-one percent of patients showed greater than or equal to 50% improvement in MRS scores. Mean scores of all efficacy measures showed significant improvements from baseline. Compared
with baseline, mean MRS, Manic Syndrome Scale, and Behavior and Ideation Scale scores were significantly reduced at final evaluation. Mania Rating Scale scores declined with the first week of the study and continued to decline throughout the open-label period. Adverse events were mild or moderate in severity. The findings of this study are consistent with those of Kowatch et al.23 and provide preliminary support for the safety and effectiveness of divalproex treatment for bipolar disorder in this age group.

Divalproex may also be effective in treating either pediatric or adult patients with symptoms of aggression, symptoms that may be observed in bipolar disorder.24,25 Donovan et al. conducted a double-blind, crossover outpatient study in children and adolescents (n = 20; ages 10 to 18) with a disruptive behavior disorder who met the criteria for explosive temper and mood lability.24 Divalproex-treated patients had a superior anti-aggression response compared to placebo-treated patients. In a multicenter, randomized, double-blind, placebo-controlled study in patients with Cluster B personality disorder (n = 96), divalproex improved symptoms of aggression as measured by the Overt Aggression Scale-modified.25 In addition, symptoms of irritability and the Clinical Global Impression Severity improved compared to placebo-treated patients.

Divalproex has been widely used in the treatment of behavioral disturbances in geriatric patients.26,27 Tariot et al. explored divalproex use with elderly patients with dementia who exhibited symptoms of mania.27 Divalproex treatment was initiated at 250 mg/d divided twice daily, followed by a daily titration of 125 mg/d to a target dose of 20 mg/kg/d. Although the study did not demonstrate a statistically significant treatment difference for symptoms of mania, both the total agitation score and verbal agitation subscale of the Cohen-Mansfield Agitation Inventory decreased significantly from baseline in the divalproex-treated group compared to the placebo-treated group. Increased side effects (primarily somnolence) were associated with early withdrawal from the study. Somnolence typically occurred at or above daily dosages of approximately 15 mg/kg; lower doses were well tolerated. The results of this study suggested that additional studies investigating the use of divalproex for agitation, at lower doses and slower titration, are needed to define optimal therapy in the population of elderly patients with behavioral disturbances.

Several reports suggest that divalproex therapy, especially in patients refractory to conventional treatment, may have a beneficial effect for the treatment of schizoaffective disorder,28 for the treatment of patients with borderline personality disorder and bipolar II disorder,29 to reduce aggression and anxiety in borderline personality disorder patients,30 and to reduce symptoms associated with alcohol31 or benzodiazepine withdrawal.

**DOsing CONsiderations**

Divalproex sodium dissociates to the valproate ion in the gastrointestinal tract prior to systemic absorption.33 Depakote delayed-release tablets release divalproex sodium in the small intestine. Administration with food increases the time to peak plasma concentration (Tmax) of valproate from 4 to 8 hours.

In contrast, Depakote extended-release formulation (Depakote ER) begins to release divalproex in the stomach, followed by the small intestine and large intestine over an 18- to 24-hour period.34 Maximum valproate plasma concentrations (Cmax) are achieved, on average, 7 to 14 hours after Depakote ER administration. Depakote ER is currently approved for the prophylaxis of migraine headache.

When given in equal doses, Depakote ER is not bioequivalent to Depakote but instead attains an average bioavailability that is 8% to 20% lower than that of Depakote tablets.35 To attain equivalent levels of drug exposure, patients may need to receive an increase in the Depakote ER dose. Peak plasma levels of Depakote ER are lower than and trough plasma levels are higher than the corresponding Depakote plasma levels. Consequently, valproate concentrations of Depakote ER exhibit less fluctuation throughout the day, compared to those of regular Depakote (administered multiple times daily). Bowden et al. reported that manic patients who have serum trough valproate concentrations of 45 to 125 μg/mL had an improved response rate, and therapy was better tolerated than those who had serum valproate concentra-
tions lower or higher than this range.36

In certain situations, administering rapid oral loading doses may enhance patient response to divalproex therapy, and several studies have explored this methodology.37–39 Keck et al. administered divalproex (20 mg/kg/d in divided doses for 5 days) to patients with acute mania.37 Responders showed a greater than 50% reduction in the YMRS scores from baseline, with the greatest improvement during the first 3 days. Adverse events were infrequent and minor, suggesting that rapid loading can achieve symptomatic control quickly and safely. Higher loading doses have also been examined. Hirschfeld et al.38 loaded patients with 30 mg/kg/d of divalproex on days 1 and 2, followed by 20 mg/kg/d on days 3 to 10. Sixteen of 19 (84%) patients in the divalproex-loading group (compared to 6 of 20 [30%] in the divalproex nonloading group) achieved valproate levels above 50 μg/mL by day 3. No statistically significant differences in the number and type of adverse events were found among treatment groups, indicating oral loading of divalproex was as well tolerated as conventional divalproex and lithium dosing.

SAFETY

Medication Side Effects

Since the first report of valproate use for the treatment of epilepsy in 1964,40 the drug and its derivatives have been subject to extensive safety evaluation. The most common adverse events associated with divalproex are nausea, gastrointestinal upset, somnolence, and weight gain.33 Clinicians should also be aware of other less common adverse events that may occur in patients taking divalproex.

Hair breakage, thinning, and hair loss are most commonly seen in the first 6 months of therapy.41 These adverse events may be minimized by the prophylactic treatment of zinc and selenium-containing multivitamins.42

Thrombocytopenia may occasionally occur, especially when total valproate concentrations are greater than 135 μg/mL in males and greater than 110 μg/mL in females.43 Thrombocytopenia may not be clinically significant, unless it results in prolongation of bleeding time.44 Bleeding is usually not common44–46 until platelets fall below 50,000 mm³.

Transient, dose-related, reversible, asymptomatic elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels have been reported with the use of divalproex. Serum levels of these liver enzymes generally return to normal following a reduction in dosage.46 A more rare divalproex-associated hepatotoxicity is irreversible hepatic failure. Onset, often idiosyncratic and not dose-related, usually occurs within the first 6 months of therapy, although cases occurring following more than one year of therapy have been reported.47 Clinical symptoms include nausea, vomiting, headache, lethargy, edema, or jaundice. Children younger than age 2 are at an increased risk (1 in 500) of developing fatal hepatotoxicity,48 especially when administered multiple anticonvulsants.49 Other risk factors include a medical history of congenital metabolic disorders, severe seizure disorder accompanied by mental retardation, and organic brain disease. The incidence of this event decreases considerably with age. The suspected incidence of hepatic fatality is in patients on valproate monotherapy for the years 1987 to 1993 was 1 in 101,602.

Pancreatitis coincident with valproate use appears to be an idiosyncratic reaction unrelated to serum concentration or total daily dose and the exact mechanism remains unknown.40 Most cases of pancreatitis appear to develop during the first year (especially during the first 3 months of valproate therapy), in the first 2 decades of life, and in patients taking antiepileptic drugs.40 In a review of 3007 valproate-treated patients in 34 clinical trials, two pancreatitis cases were judged by investigators as probably related to valproate; the outcome in both cases was favorable.51 Nevertheless, since prompt detection and withdrawal of valproate may improve outcomes, clinicians must be aware of the possibility of pancreatitis. Data suggest that serum amylase elevation alone is not sufficient for a diagnosis, and that elevated serum amylase combined with severe abdominal pain are more valuable diagnostic indicators.51

Divalproex should not be used in patients with known urea cycle disorders, which involve rare genetic defects or deficiencies in the enzymes of the urea cycle. Divalproex use in patients with
this rare disorder may result in hyperammonemic encephalopathy, which is sometimes fatal.\textsuperscript{52,53} Symptomatic hyperammonemia associated with divalproex use may include changes in mental status, gastrointestinal disturbances, drowsiness, lethargy, cognitive slowing, and confusion.\textsuperscript{54,55} Signs and symptoms, including elevated blood ammonia levels, have been reported to resolve within days to weeks following either a reduction in dose or discontinuation of divalproex.\textsuperscript{55}

Endocrine abnormalities, menstrual irregularities, or polycystic ovaries have been reported in women with epilepsy or bipolar disorder (especially if overweight), regardless of whether or not they are undergoing treatment with divalproex.\textsuperscript{56} Rasgon et al. studied 22 female outpatients (n = 22; ages 18 to 45) with a DSM-IV diagnosis of bipolar disorder who were taking lithium and/or divalproex.\textsuperscript{57} The daily dose of divalproex ranged from 750 to 1500 mg/d (mean = 1112.5 mg), and the mean length of exposure was 34.1 ± 30.4 (7 to 108 months). No significant hormonal or radiologic evidence of polycystic ovary-like changes in women receiving divalproex (or lithium) was detected. Consider following menstrual history and a weight management program in the treatment of women with bipolar disorder.

Divalproex is rated as Pregnancy Category D. Accordingly, the use of divalproex in women of childbearing potential requires that the benefits of its use be weighed against the risk of injury to the fetus. The Centers for Disease Control and Prevention\textsuperscript{58,59} estimated that the overall risk of divalproex-coincident neural tube defect is 1% to 2%, compared to 0.1% to 0.2% incidence\textsuperscript{60,61} in the general population. Current clinical practice is to recommend prophylactic supplementation of 4 to 5 mg folic acid daily for all women using divalproex and planning a pregnancy.\textsuperscript{62} Further assessment of fetal risk from antiepileptic drug therapy in women who become pregnant is being studied by means of a pregnancy registry run by Massachusetts General Hospital in association with Harvard Medical School (1-888-233-2334).

\textbf{ Drug Interactions }

Several commonly prescribed medications may influence the pharmacokinetics of divalproex. Drugs that affect the level of expression of hepatocellular enzymes, particularly those that elevate levels of glucuronosyltransferases, may increase the clearance of divalproex.\textsuperscript{53} For example, phenytoin, carbamazepine, phenobarbital, and primidone can double the clearance of divalproex.

Aspirin, however, may inhibit the metabolism of divalproex. One study demonstrated that higher doses of aspirin (11 to 16 mg/kg) combined with divalproex resulted in a decrease in protein binding, an inhibition of metabolism of valproate, and a 4-fold increase in the free fraction of serum valproate.\textsuperscript{64} Caution should be observed if divalproex and aspirin are to be coadministered.

Divalproex has been shown to have effects on other drugs when both are administered simultaneously. For example, amitriptyline administered to patients taking divalproex resulted in a 21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline.\textsuperscript{65} Divalproex can also increase the unbound fraction of warfarin so coagulation should be monitored if divalproex therapy is instituted in patients taking anticoagulants.\textsuperscript{66}

Effects of divalproex on total carbamazepine plasma concentrations may be unpredictable. These effects include altering carbamazepine metabolism, displacing carbamazepine from plasma protein-binding sites, and increasing the level of the epoxide. On co-administration of divalproex and carbamazepine to epileptic patients, serum levels of carbamazepine decreased 17% while that of carbamazepine-10,11-epoxide (an active metabolite of carbamazepine) increased by 45%.\textsuperscript{53} This is complicated further by the fact that the epoxide metabolite of carbamazepine is not detected by routine assays. Therefore, serum level of carbamazepine may be much higher in patients than that noted by lab values. The unpredictable effects of valproate on total carbamazepine plasma concentration and a lack of conclusive evidence on the displacement of carbamazepine by valproate makes interpretation of carbamazepine plasma concentration difficult.

Divalproex has also been demonstrated to inhibit lamotrigine metabolism, resulting in increased serum concentrations.\textsuperscript{67} Patients on lamotrigine combination therapy with divalproex had a significantly higher risk of cutaneous rash.
when compared to patients on lamotrigine monotherapy. Addition of lamotrigine to existing divalproex therapy must be done gradually and conservatively at low doses.

Unlike other anticonvulsant agents, divalproex does not reduce the efficacy of oral contraceptives. Administration of a single-dose of ethinylestradiol/levonorgestrel to women on divalproex therapy for 2 months did not reveal any pharmacokinetic interaction. This study has shown that divalproex produces no clinically significant changes in the pharmacokinetics in the ethinylestradiol/levonorgestrel oral contraceptive steroids.

CONCLUSION

Divalproex has established efficacy in bipolar disease, and additional evidence supporting its use in other conditions continues to grow. Future research will continue in several promising areas of psychiatry, as well as in neuroprotection and cancer therapy. Divalproex has been used widely for many years and has a well-known safety profile, but in determining the optimal use of divalproex alone or in combination with other agents, one must consider the complexity of the clinical situation.

REFERENCES


60. Centers for Disease Control and Prevention. Periconceptional use of multivitamins and the occurrence of anencephaly and spina bifida. MMWR Morb Mortal


