A Preliminary Double-Blind, Placebo-Controlled Trial of Divalproex Sodium in Borderline Personality Disorder

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Background: Borderline personality disorder is characterized by affective instability, impulsivity, and aggression and is associated with considerable morbidity and mortality. Since anticonvulsant agents may be helpful in such symptomatology, we compared divalproex sodium with placebo in patients with borderline personality disorder.

Method: A 10-week, parallel, double-blind design was conducted. Sixteen outpatients meeting Structured Clinical Interview for DSM-IV Axis II Personality Disorders criteria for borderline personality disorder were randomly assigned to receive placebo (N = 4) or divalproex sodium (N = 12). Change was assessed in global symptom severity (Clinical Global Impressions-Improvement Scale [CGI-I]) and functioning (Global Assessment Scale [GAS]) as well as in specific core symptoms (depression, aggression, irritability, and suicidality).

Results: There was significant improvement from baseline in both global measures (CGI-I and GAS) following divalproex sodium treatment. A high dropout rate precluded finding significant differences between the treatment groups in the intent-to-treat analyses, although all results were in the predicted direction.

Conclusion: Treatment with divalproex sodium may be more effective than placebo for global symptomatology, level of functioning, aggression, and depression. Controlled trials with larger sample sizes are warranted to confirm these preliminary results.

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Borderline personality disorder (BPD) is characterized in DSM-IV by instability in interpersonal relationships, self-image, and affect; feelings of emptiness; dissociative experiences; and marked impulsivity, including impulsive risk-taking behavior, inappropriate/intense anger, self-injurious behavior, and suicide attempts. BPD is a common disorder, occurring in 1% to 2% of the U.S. population,[1] 10% of psychiatric outpatients, and 20% of psychiatric inpatients.[2] Up to 10% of BPD patients commit suicide,[3] and few patient groups require more mental health resources than do BPD patients. Several psychotherapies have been developed for the treatment of BPD,[4] but patients may remain refractory to such treatments, and a combination of pharmacotherapy and psychotherapy is generally utilized.

Three symptom clusters in BPD can be targeted with pharmacotherapy: impulsivity and aggression, mood instability, and psychotic-like symptoms. No single medication may be effective for all symptom clusters, and antidepressants, neuroleptics, benzodiazepines, and mood stabilizers have been studied in BPD.

Tricyclic antidepressants may be helpful in reducing some depressive symptoms in BPD patients, but increase

irritability, anger, and suicidal symptoms; are lethal in overdose; and have side effects such as weight gain.[5] Monoamine oxidase inhibitors may be helpful for affective instability, but are associated with sleep disturbance and the risk of hypertensive crisis.[6] Selective serotonin reuptake inhibitors (SSRIs) have demonstrated some efficacy in decreasing anger, irritability, and aggression in BPD. A number of early open-label trials are varied in outcome. Although some trials show improvement, others show minimal and sometimes transient decreases in symptoms.[7–10] In the only published double-blind, placebo-controlled study of SSRIs specifically in BPD, Salzman et al.[11] treated 22 patients, 9 of whom received placebo during a 12-week trial of fluoxetine. Decreases in anger and depression were reported; however, results may not generalize because the study patients were unrepresentative of BPD (they did not meet full DSM-IV criteria, had never been hospitalized, and had mild symptomatology, no history of self-mutilation, and no suicidality). Although SSRIs may hold promise for the treatment of BPD, to date there are no well-controlled studies with an adequate sample size involving patients representative of BPD. In addition, SSRIs are not without side effects, including iatrogenic mania,[12] and many patients are not able to tolerate them.

Most studies of neuroleptics in BPD have included a more psychotic/schizotypal population than current DSM-IV criteria for BPD allow. Double-blind, placebo-controlled studies in BPD patients with at least one psychotic symptom treated with thiothixene[13] found improvement in a wide range of symptomatology, but primarily in measures of psychosis/paranoia. However, given the minimal efficacy, risks of tardive dyskinesia, and high incidence of side effects, only patients with marked psychotic symptomatology should be considered for treatment with thiothixene.[13] Soloff et al.[5,14] also investigated the efficacy and tolerability of haloperidol in their 5-week, double-blind, placebo-controlled study of acutely decompensated inpatients with BPD. Although haloperidol produced modest symptom improvement and its superiority to placebo was statistically significant, it was poorly tolerated secondary to side effects. Cowdry and Gardner[6] included the neuroleptic trifluoperazine in their placebo-controlled, double-blind, crossover-design multidrug study and concluded that it was ineffective. A recent open-label study[15] of olanzapine in BPD suggests that it may be effective and well tolerated. In summary, no double-blind study has demonstrated neuroleptics to be both effective and well tolerated in the treatment of individuals with BPD.

The use of benzodiazepines in BPD is not supported in the literature. In fact, benzodiazepines have been shown to result in increased episodes of serious behavioral dyscontrol and suicidality.[6]

Mood stabilizers may have promise in BPD treatment, although evidence to date is mixed and, as with the medications discussed above, adverse effects can occur. On the basis of open-label studies, lithium was one of the first medications reported to be effective in decreasing mood instability in a diagnostic precursor of BPD, namely "unstable character disorder."[16] Lithium may reduce impulsive aggression in BPD. A trend of decreased anger and suicidal symptoms was reported in a placebo-controlled trial of lithium in a small number of patients with BPD, but depressive symptomatology did not improve.[17] Lithium has been reported to reduce impulsive aggression in prison inmates in a double-blind, placebo-controlled trial[18]; however, it may exacerbate aggression in persons with seizure-associated (ictal and interictal) behavioral dyscontrol.[19] In addition, it requires plasma level monitoring, causes frequent side effects of tremor and weight gain, and is lethal in overdose. The anticonvulsant carbamazepine has demonstrated efficacy in reducing impulsive aggression and mood instability in BPD in a controlled trial.[6] In their review of preliminary research available on divalproex sodium and carbamazepine in treating several psychiatric disorders, Keck et al.[20] reported that available data support the potential value of these anticonvulsants for decreasing temper outbursts and aggression, symptoms frequently prominent in BPD. Improvement has been observed in open case studies of bipolar-spectrum temperamental disorders.[21] Small, short-term open-label trials with divalproex sodium have also demonstrated clinical improvement in BPD patients.[22,23]

The current study is the first double-blind trial of divalproex sodium in BPD. We hypothesized that, compared with the placebo group, patients receiving divalproex sodium (1) would improve on global measures of illness severity and functioning and (2) would show a greater decrease in the severity of specific core symptoms (depression, aggression, irritability, and suicidality).

METHOD

The 21 outpatients who were entered into this study met criteria for BPD on the Structured Clinical Interview for DSM-IV Axis II Personality Disorders.[24] This initial sample consisted of 10 men and 11 women, of which 14 were white, 3 black, and 4 Hispanic; 15 were single, 5 married, and 1 divorced. Their mean ± SD age was 38.6 ± 10.37 years (range, 18–62). Patients were obtained by referral from private psychiatrists and mental health professionals in the community, self-help groups, outpatient clinics at Mount Sinai Medical Center and the Bronx Veterans Affairs Medical Center (New York, N.Y.), advertisements, and the media. Patients had no medical or neurologic illness, psychotic disorders, current substance abuse, bipolar disorder type I or II, current major depression, or current suicidal ideation and were not pregnant. After a complete description of the study including an explanation of possible side effects was given to the patients, written informed consent was obtained.

Patients were randomly assigned to 10 weeks of double-blind treatment with either divalproex sodium or placebo at an approximate ratio of 2:1 (divalproex sodium:placebo). Patient visits occurred at baseline, weekly for the next 4 weeks, and every 2 weeks thereafter. Dosage was started at 250 mg at bedtime and increased gradually to a dose sufficient to maintain a blood valproate level at 80 μg/mL or the highest tolerated dose. The treating psychiatrist was kept blind to patient medication; blood valproate levels were read and dose adjustments to both divalproex sodium and placebo were determined by a psychiatrist not seeing patients for this study.

Two global clinician-rated outcome measures were used, each based on the average of the ratings of the treating psychiatrist and independent evaluator (a psychologist blind to side effects as well as to medication group): (1) the Clinical Global Impressions-Improvement scale (CGI-I),[25] which characterizes responders by a rating of 1 to 7 (with 1 = very much improved and 2 = much improved to 7 = very much worse), and (2) the Global Assessment Scale (GAS),[26] which assesses overall level of functioning during the preceding week, with a lower score denoting worse functioning. The Beck Depression Inventory (BDI)[27] and the Aggression Questionnaire (AQ)[28] are self-report scales; the AQ comprises 4 factors (physical aggression, verbal aggression, anger, and hostility). The Overt Aggression Scale-Modified (OAS-M),[29] which measures aggressive and irritable behaviors and suicidal ideation and behavior, was assessed by the independent evaluator only.

Both completer and intent-to-treat (ITT) analyses were planned for the 2 global measures (CGI-I and GAS). Because all patients in the placebo-control group dropped out of the study, the completer analysis was based on divalproex sodium patients only. For the GAS, a paired-sample t test was computed comparing pretreatment and posttreatment scores. For the CGI-I, a 1-sample t test was used to compare posttreatment scores with "no change" (a score of 4). Patients were categorized as responders if they received a score of 2 or 1 on the CGI-I. In addition, the Pearson chi-square was used to compare the divalproex sodium and placebo groups on dropout rate and rate of response to treatment.

The ITT analyses included all patients who were randomly assigned to treatment, with no minimum number of weeks required, and used the last observation carried forward. For each measure (CGI-I, GAS, BDI, AQ, and OAS-M aggression, irritability, and suicidality), an analysis of covariance was used to compare the posttreatment (week 10) scores of the 2 treatment groups, covaried by the corresponding baseline scores.

RESULTS

Twenty-one patients provided signed consent to participate in the study; 16 of these were randomly assigned to a treatment group, evaluated at week 0, and provided with medication. Six of the randomly assigned patients completed the study, and 10 dropped out. Of the 10 who dropped out after random assignment, 9 dropped out during the first 3 weeks: 2 patients (both taking placebo) completed 1 week or less, 6 completed 2 weeks (1 placebo, 5 divalproex sodium), 1 patient taking placebo completed 3 weeks. One patient, who was in the divalproex sodium group, dropped out after 7 weeks. Therefore, proportionally fewer patients dropped out from the divalproex sodium group than from the placebo group ($\chi^2 = 3.20$, df = 1, p = .074). Patients taking divalproex sodium had a 50% dropout rate (6 completers, 6 dropouts) versus 100% dropout in the placebo group (0 completers, 4 dropouts). No patients dropped out owing to side effects; all dropped out owing to either lack of efficacy or impulsive decisions. Blood draws every 2 weeks determined that no patients had elevated liver function enzymes, and mean ± SD endpoint blood valproate level was 64.57 ± 15.21 μg/mL (range, 47–85 μg/mL).

Table 1. Global Responses to Divalproex Sodium and Placebo

	Placebo		Divalproex Sodium	
Group	N	%	N	%
Completers				
Responders[a]	...	...	5	83
Nonresponders	...	...	1	17
Intent-to-treat population[b]				
Responders[a]	0	0	5	42
Nonresponders	4	100	7	58

[a]Defined as Clinical Global Impressions-Improvement score ≤ 2.
[b]$\chi^2 = 2.42$, df = 1, p = .119.

All completers (6/6) were in the divalproex sodium group, and 83% (5/6) of these were considered responders, defined as a CGI-I score of 1 or 2 (Table 1). There were no placebo completers or responders. Those who completed treatment with divalproex sodium improved on both of the global measures (GAS and CGI-I). On the GAS, the mean score of patients taking divalproex sodium significantly improved from 52.17 ± 8.50 to 66.67 ± 4.08 (t = –5.51, df = 5, p = .003) (higher score corresponds to better functioning); on the basis of this finding, the effect size is 0.75, which is slightly below the standard criteria for a large effect size (0.80). On the CGI-I, the mean score of patients taking divalproex sodium was much improved, from 4.00 ± 0.98 to 2.17 ± 0.98 (t = –4.57, df = 5, p = .006); for this analysis, the effect size is 1.0.

Of the ITT group, 42% (5/12) of the patients taking divalproex sodium were responders versus 0% taking placebo ($\chi^2 = 2.42$, df = 1, p = .119) (see Table 1). None of the ITT analyses reached statistical significance. In the divalproex sodium group, the GAS score improved from serious symptomatology or impairment in functioning to moderate symptomatology or impairment in functioning;

in the placebo group, the GAS scores stayed in the moderate range. The endpoint CGI-I scores did not differ significantly for divalproex sodium versus placebo. (Table 2; see ITT last-observation-carried-forward data.)

Continuing to look at the ITT data, the 2 measures of aggression showed different results, although none reached statistical significance. On the AQ, which includes aggressive feelings and actions, patients taking divalproex sodium decreased slightly in aggression (80.7 ± 15.7 at baseline and 76.1 ± 17.2 at endpoint), while the placebo group increased (79.8 ± 15.1 at baseline and 85.3 ± 12.0 at endpoint) (Figure 1). However, on the OAS-M, the divalproex sodium and placebo groups did not differ in aggression, irritability, or suicidality; this may be attributable to these scores being very low at baseline, thus reflecting a "floor effect." There were substantial decreases in depression among the divalproex sodium patients; their BDI scores decreased from 18.1 ± 12.2 at baseline to 8.2 ± 9.1 at endpoint. In contrast, placebo patients' depression remained essentially unchanged as measured by the BDI (19.7 ± 8.5 at baseline and 18.0 ± 7.0 at endpoint) (Figure 2). The apparent difference between the divalproex sodium and placebo groups reached only marginal significance owing to the small sample size ($F = 2.69$, $df = 1,12$; $p = .135$).

Thus, results from this preliminary study suggest that divalproex sodium may be effective in the treatment of global severity and some core symptoms of borderline personality disorder; however, the results were limited by small sample size and high dropout rate.

Table 2. Measures of Aggression and Depression With Divalproex Sodium and Placebo: Intent-to-Treat Analyses[a]

	Placebo				Divalproex Sodium				
	Baseline		End		Baseline		End		Significance
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Level (p)
Aggression									
AQ	79.8	15.1	85.3	12.0	80.7	15.7	76.1	17.2	.22
OAS-M									
Aggression	6.0	4.4	6.0	4.4	2.4	2.6	1.8	2.9	.68
Irritability	5.7	0.6	5.7	0.6	2.4	2.2	2.4	1.9	.53
Suicidality	0.3	0.6	0.3	0.6	0.6	1.2	0.9	1.2	.38
Depression									
BDI	19.7	8.5	18.0	7.0	18.1	12.2	8.2	9.1	.14

[a]Abbreviations: AQ = Aggression Questionnaire, BDI = Beck Depression Inventory, OAS-M = Overt Aggression Scale-Modified.

Figure 1. Mean Aggression Questionnaire Scores Across Time for Intent-to-Treat Sample: Last Observation Carried Forward

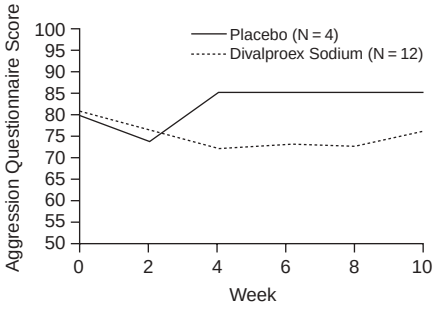
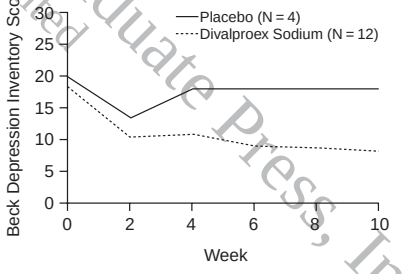


Figure 2. Mean Beck Depression Inventory Scores Across Time for Intent-to-Treat Sample: Last Observation Carried Forward



DISCUSSION

Few, if any, patient groups require more mental health resources than do BPD patients, and research on pharmacologic interventions for BPD to date has shown mixed results, with the best outcomes pairing modest efficacy with poor tolerability. This study provides preliminary data suggesting that divalproex sodium is well tolerated and may be more effective than placebo in the treatment of global severity and some core symptoms of BPD. However, the study is limited by the small sample size and high dropout rate. Our findings for global improvement are similar to or more robust than those found in prior studies of anticonvulsants in BPD.[6,22,23] Although we did not find an improvement in aggression, unlike other studies, we did not specifically select patients with high levels of this symptom.

All findings are in the hypothesized direction, but the small sample size, high variability of the measures, imbalance in the number of patients in the 2 conditions, and high dropout rate contributed to the limited significant findings. Although the planned patient assignment ratio was 2:1 (divalproex sodium:placebo), the ratio was actually 3:1. This highlights the risk inherent in departing from a 1:1 ratio in the assignment of patients to treatment groups, particularly in the absence of blocking. Studies of BPD are especially difficult, given the inherent impulsivity and instability of the patient group, and often have a high dropout rate. It is difficult to compare the dropout rate across studies, owing to variability in such factors as severity of symptoms and concomitant treatments allowed. Lower

dropout rates are sometimes, but not always, found in studies that are conducted among inpatients,[5,14,16,30,31] require or allow ongoing psychotherapy,[6,7,22] or include patients with primarily mild-to-moderate borderline symptomatology.[11,13] In this study, the dropout rate was particularly high during the first few weeks, especially in the placebo group; this underscores the importance of taking steps in the early weeks of medication trials in BPD to minimize the problem of dropouts. A power analysis utilizing the BDI results suggests that a sample of 14 patients per group would be needed to achieve 80% power at the .05 level; 28 patients per group would be needed for the AQ, and 37 for the GAS.

These preliminary findings should be viewed with caution, given the small sample size and high dropout rate. Nevertheless, the findings appear promising. The medication was well tolerated in this common and disabling disorder, and larger, well-controlled trials with divalproex sodium appear warranted.

Drug names: carbamazepine (Tegretol and others), divalproex sodium (Depakote), fluoxetine (Prozac), haloperidol (Haldol and others), olanzapine (Zyprexa), thiothixene (Navane), trifluoperazine (Stelazine and others).

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