Divalproex Sodium Treatment of Women With Borderline Personality Disorder and Bipolar II Disorder: A Double-Blind Placebo-Controlled Pilot Study

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Background: The intent of this study was to compare the efficacy and safety of divalproex sodium and placebo in the treatment of women with borderline personality disorder and comorbid bipolar II disorder.

Method: We conducted a placebo-controlled double-blind study of divalproex sodium in 30 female subjects aged 18 to 40 years who met Revised Diagnostic Interview for Borderlines and DSM-IV criteria for borderline personality disorder and DSM-IV criteria for bipolar II disorder. Subjects were randomly assigned to divalproex sodium or placebo in a 2:1 manner. Treatment duration was 6 months. Primary outcome measures were changes on the interpersonal sensitivity, anger/hostility, and depression scales of the Symptom Checklist 90 (SCL-90) as well as the total score of the modified Overt Aggression Scale (MOAS).

Results: Twenty subjects were randomly assigned to divalproex sodium; 10 subjects to placebo. Using a last-observation-carried-forward paradigm and controlling for baseline severity, divalproex sodium proved to be superior to placebo in diminishing interpersonal sensitivity and anger/hostility as measured by the SCL-90 as well as overall aggression as measured by the MOAS. Adverse effects were infrequent.

Conclusion: The results of this study suggest that divalproex sodium may be a safe and effective agent in the treatment of women with criteria-defined borderline personality disorder and comorbid bipolar II disorder, significantly decreasing their irritability and anger, the tempestuousness of their relationships, and their impulsive aggressiveness.

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Lability of mood is one of the clinical hallmarks of borderline personality disorder.[1] In terms of subsyndromal phenomenology, extreme reactivity of mood is one of the DSM-IV criteria for this disorder.[2] In addition, a substantial minority of patients with borderline personality disorder are diagnosed with comorbid bipolar II disorder.[3,4]

Because of the presence of mood lability and the comorbidity with bipolarity, mood stabilizers are often used in the psychopharmacologic treatment of borderline patients. Ten studies have examined the effectiveness of this practice: 2 studies of lithium,[5,6] 2 studies of carbamazepine,[7,8] 1 study of lamotrigine,[9] and 5 studies of divalproex sodium.[10–12,14,15]

Rifkin et al.[5] described the successful use of lithium in subjects with "emotionally unstable character disorder." This phrase was used to describe patients with poor acceptance of authority, truancy, poor work record, manipulative trends, and mood swings. Some, or most, of their subjects would have met today's criteria for borderline personality disorder. Their mood swings responded to lithium.

In a Canadian study,[6] the usefulness of lithium versus desipramine in reducing the affective symptoms in borderline personality disorder was studied. Preliminary results from this randomized, placebo-controlled trial suggested that lithium led to improvement in anger and suicidality, but not depression.

Cowdry and Gardner[7] designed a complex study in which 16 female outpatients with borderline personality disorder were treated with 4 agents in a 4-way crossover design. Subjects were treated with carbamazepine, trifluoperazine, alprazolam, and tranylcypromine. Carbamazepine led to a decrease in behavioral impulsivity and dyscontrol, although 3 patients became depressed. The raters noted a reflective delay—a phenomenon in which patients seemed to have an increased ability to reflect on their reactions before acting on them. However, in a later double-blind, parallel placebo-controlled trial of 20 borderline inpatients, De la Fuente and Lotstra[8] found no significant response to carbamazepine.

Pinto and Akiskal[9] used the new anticonvulsant agent lamotrigine in a series of 8 patients with borderline personality disorder. None of the patients had clear evidence for DSM-IV major affective disorders. All had failed previous trials of antidepressants and other mood stabilizers.

Six patients completed the trial. Three patients improved and sustained this response for more than a year. Of the 3 patients who failed lamotrigine, 1 patient responded subsequently to divalproex and 1 to lithium.

In an open-label study of low-dose divalproex sodium (125 to 750 mg/day) in outpatients with rapid cycling who met DSM-III-R criteria for cyclothymia or bipolar II disorder, 6 women with comorbid borderline personality disorder did well in terms of their cycling disorder for lengths of time ranging from 18 to 29 months.[10] Stein et al.[11] studied 11 patients who met DSM-III-R criteria for borderline personality disorder in an 8-week study of divalproex sodium. They found that medication was modestly helpful for mood and irritability. Overall improvement was noted in 50% of the patients. Wilcox[12] treated 30 inpatients with borderline personality disorder with divalproex sodium. Brief Psychiatric Rating Scale[13] scores and time in seclusion both decreased during the 6-week study. In a 10-week open-label trial of subjects who had previously failed a trial of at least 60 mg/day of fluoxetine for at least 8 weeks, Kavoussi and Coccaro[14] found that 3 of 5 subjects with borderline personality disorder and aggressiveness (but not bipolar disorder) responded with a decrease in aggression and irritability when treated with divalproex sodium. Hollander et al.[15] performed a 10-week, double-blind, placebo-controlled study of divalproex sodium in 16 outpatients with borderline personality disorder. Although there were no significant findings concerning specific symptom areas, they concluded that divalproex sodium was well tolerated and could be more effective than placebo in treating some of the core symptoms associated with borderline personality disorder.

To date, no prospective placebo-controlled double-blind studies have examined the efficacy of divalproex in subjects with borderline personality disorder and comorbid bipolar II disorder. The study described below does so.

METHOD

Advertisements were placed in newspapers in Boston, Mass., to recruit women between the ages of 18 and 40 years who were disturbed by mood changes, distrustfulness, impulsivity, and stormy relationships. Subjects who answered the advertisement were screened by telephone to assess whether they met the DSM-IV criteria for borderline personality disorder using the borderline module of the Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV).[16] A general medical and psychiatric history was also taken at the time of first telephone contact. Potential subjects were excluded if they had formerly been treated with divalproex sodium, if they were medically ill, if they had a seizure disorder, or if they were actively abusing alcohol or drugs. Due to the lability associated with pregnancy and the teratogenic effects of divalproex sodium, subjects who were pregnant, breastfeeding, planning to become pregnant, or not using reliable forms of contraception were also excluded.

Each subject who met these inclusion/exclusion criteria was then invited to participate in a face-to-face interview. After the purpose of the study was explained and possible side effects were described, written informed consent was obtained. Two semistructured diagnostic interviews were administered: (1) the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)[17] and (2) the Revised Diagnostic Interview for Borderlines (DIB-R).[18] Subjects were included if they met both DIB-R and DSM-IV criteria for borderline personality disorder and also met DSM-IV criteria for bipolar II disorder. Subjects were excluded if they met current criteria for a major depressive episode or a hypomanic episode. Subjects were also excluded if they met current or lifetime criteria for schizophrenia, schizoaffective disorder, psychotic disorder not otherwise specified, or bipolar I disorder. In addition, subjects who were acutely suicidal (i.e., had a clear-cut and pressing intent to commit suicide in the near future) were excluded. Although not an exclusion criterion for the study, continuous rapid-cycling bipolar II disorder was not found in any subject.

Subjects underwent a physical examination and laboratory analyses, including hematologic indices, serum chemistry studies, and a pregnancy screen.

We also administered 2 self-report measures: the Symptom Checklist 90 (SCL-90)[19] and the McLean version of the modified Overt Aggression Scale (MOAS) Checklist.[20] The SCL-90 is a well-established rating scale that is used widely. The MOAS was developed to monitor changes in aggressive behaviors in subjects with borderline personality disorder, and it yields a clinically meaningful total score.

Study duration was 6 months. Subjects were seen every week for the first month and then every month. The self-report scales (SCL-90 and MOAS) were readministered to each subject at subsequent visits. Subjects were also weighed and asked about side effects at every visit.

At the beginning of the study, subjects received 2 tablets per day of study medication. Each tablet contained either 250 mg of divalproex sodium or matching inert placebo. Tablets were supplied in numbered bottles containing drug or placebo as determined by a prearranged random number sequence. No other psychotropic medication was allowed during this study. Twelve-hour trough levels were done at 1 week, 1 month, and then every 2 months. One of the investigators (F.R.F.) was given either the real level or a sham level (if the subject was receiving placebo). This same investigator met with the subjects for 20- to 30-minute medication checks and adjusted the dose according to perceived response, reported or sham level, and side effects. The number of tablets was adjusted to achieve a serum divalproex level of between 50 and 100 mg/L.

Data Analysis

Data were analyzed using SPSS[21] and STATA[22] software. Between-group baseline demographic variables, clinical history variables, and baseline values for the 4 primary outcomes were analyzed using Fisher exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. Between-group percentage change from baseline to endpoint (which was determined using last observation carried forward) was analyzed using analysis of variance (ANOVA) with baseline value as a covariate.

The primary outcome measures were changes on the SCL-90 scales measuring interpersonal sensitivity, anger/hostility, and depression as well as the total score of the MOAS.

RESULTS

Thirty subjects completed all aspects of prerandomization assessment. Twenty were randomly assigned to divalproex sodium, and 10 were randomly assigned to placebo. All 30 subjects completed at least 2 postbaseline visits and were included in all subsequent analyses.

Table 1 describes the demographic characteristics and treatment histories of these 2 groups. As can be seen, no significant divalproex versus placebo differences were found. Both groups were, on average, in their mid 20s, had about 3 years of college, and came from lower middle class backgrounds as measured by the 5-point Hollingshead-Redlich scale[23] (1 = highest, 5 = lowest). In addition, both groups had a mean Global Assessment of Functioning (GAF)[24] score of about 50, indicating that they had a fair-marginal level of functioning. About one third of the subjects were nonwhite (3 were African-American, 4 were Hispanic, and 2 were biracial); about two thirds had been in psychotherapy (although none were currently in therapy or began a new therapy during the course of the study). Fewer than half had been treated with other psychotropic medications, and fewer than a quarter had ever been hospitalized for psychiatric reasons.

Attrition was quite low throughout the first 3 months of the study for both groups of subjects. More specifically, 75% of the divalproex sodium–treated subjects and 80% of the placebo-treated subjects remained in the study through week 4, while 70% in the divalproex group and 60% in the placebo group remained through week 8, and 50% in the divalproex group and 40% in the placebo group remained through week 12. A similar percentage of divalproex sodium–treated subjects and placebo-treated subjects (7 [35%] vs. 4 [40%]) remained in the study all 24 weeks.

Reasons for discontinuation in the divalproex sodium group were the following: moved out of the area (N = 1), inability to use reliable forms of contraception (N = 1), withdrawal of consent (N = 1), diarrhea and tremors (N = 1), and lost to follow-up (N = 9). Reasons for discontinuation in the placebo group were the following: development of a major depressive episode (N = 2), hair loss (N = 1), and lost to follow-up (N = 3).

Table 1. Demographic Characteristics and Treatment Histories of Divalproex Sodium and Placebo Groups[a]

Characteristic	Divalproex (N = 20) Mean	SD	Placebo (N = 10) Mean	SD	Wilcoxon Rank Sum/ Fisher Exact Tests	p Value
Age, y	27.3	7.4	26.4	7.3	0.375	NS
Education, y	15.3	1.7	15.0	2.1	0.453	NS
Socioeconomic class[b]	3.8	1.2	4.3	1.1	1.101	NS
GAF score	51.6	6.5	50.2	7.0	0.597	NS
	N	%	N	%		
White	15	75	5	50	...	NS
Individual therapy (ever)	12	60	7	70	...	NS
Taken standing medication (ever)	9	45	3	30	...	NS
Hospitalized (ever)	1	5	2	20	...	NS

[a]Abbreviations: GAF = Global Assessment of Functioning scale, NS = nonsignificant.
[b]Measured by the 5-point Hollingshead-Redlich scale[23] (1 = highest, 5 = lowest).

Table 2 shows the mean ± SD baseline and endpoint values for both groups on the primary outcome measures and the percentage change from baseline to endpoint. As can be seen, randomization was successful as the baseline values for both groups were similar (and no significant differences were found). As can also be seen, divalproex sodium was associated with a significantly greater change, even after controlling for baseline values, on SCL-90 measures of interpersonal sensitivity and anger/hostility as well as the total score of the MOAS. Although the subjects treated with divalproex became less depressed as measured by the SCL-90 measure of depression, this change was not significantly greater than that achieved by the placebo-treated subjects.

Due to the high level of attrition at 6 months, we repeated these analyses using only data collected up to week 8, which is a more typical time frame for a medication trial. At this time point, only 6 divalproex sodium–treated subjects and 4 placebo-treated subjects had discontinued their participation. We found basically the same results as we had for the 6-month time point (i.e., all outcome measures but depression showed a significant between-group difference in favor of the divalproex-treated subjects). (Data not shown but available upon request.)

Rates of adverse events and side effects were low for both groups of subjects. As noted above, 2 subjects receiving placebo developed a major depressive episode (but no subject developed a hypomanic episode). In addition, the divalproex group gained, on average, 2.6 ± 5.6 lb (range, –9 to +19 lb) and the placebo group gained 0.3 ± 4.0 lb (range, –2 to +7 lb). This difference in weight change was not significant (z = –1.565, p = .1175). We also studied the percens{age of weight change in each

Table 2. Percentage Change From Baseline to Endpoint for Divalproex Sodium and Placebo Groups[a]

Scale/Group	Baseline Value Mean	Baseline Value SD	Endpoint Value Mean	Endpoint Value SD	Change From Baseline to Endpoint[b] Change at Endpoint (%)	Treatment Status F	Treatment Status p Value
SCL-90 interpersonal sensitivity							
Divalproex	2.3	0.7	1.5	0.5	–31.7	4.62	.0408
Placebo	2.6	0.8	2.2	0.9	–14.8		
SCL-90 anger/hostility							
Divalproex	2.3	0.9	1.5	0.7	–29.6	5.27	.0117
Placebo	2.2	0.9	1.6	0.6	–11.0		
SCL-90 depression							
Divalproex	2.4	0.6	1.8	0.6	–21.3	0.08	NS
Placebo	3.0	0.9	2.2	1.1	–25.4		
MOAS total score							
Divalproex	5.6	3.8	2.6	1.9	–42.1	4.10	.0278
Placebo	5.1	3.4	3.2	2.1	–13.4		

[a]Abbreviations: MOAS = Modified Overt Aggression Scale, SCL-90 = Symptom Checklist 90.
[b]Endpoint values used in these calculations are based on last observation carried forward.

group of subjects. The divalproex group experienced a mean ± SD weight gain of 1.9% ± 3.9% (range, –4.6% to +13.8%). The placebo group experienced a mean ± SD weight gain of 0.12% ± 3.1% (range, –4.7% to +5.1%). This difference in percentage of weight change was not significant (z = –1.561, p = .1185).

The subjects were also asked about menstrual changes, given reports of polycystic ovaries and menstrual changes in epileptic women being treated with divalproex sodium.[25] A lower percentage of subjects treated with divalproex sodium reported the presence of menstrual changes than did subjects treated with placebo (5% vs. 10%; Fisher exact = 1.0). One divalproex sodium–treated subject developed tremors and diarrhea. One placebo-treated subject developed hair loss. With respect to laboratory value changes, 1 divalproex sodium–treated subject developed an asymptomatic 2-fold increase in hepatic transaminases. Divalproex sodium was continued, and her values returned to normal within 6 weeks. No subjects developed thrombocytopenia.

The average number of tablets prescribed for the divalproex group was 3.4 ± 0.9 and 2.6 ± 0.5 for the placebo group (z = –2.3, p = .0198). The average dose of divalproex sodium was 850 ± 249 mg/day.

DISCUSSION

In this long-term, double-blind, placebo-controlled study of female subjects with borderline personality disorder and comorbid bipolar II disorder, divalproex sodium was significantly more effective than placebo in reducing their irritability and anger, the tempestuousness of their relationships, and their impulsive aggressiveness. In general, symptom levels declined about 30% to 40% for those treated with divalproex sodium and about 15% for those treated with placebo.

The results of this trial concerning decreased levels of irritability and aggressiveness are consistent with the findings of earlier studies of divalproex sodium in the treatment of borderline patients.[11,12,14] However, the current study is the first to find these differences in a double-blind placebo-controlled trial. This is important because the results of open-label trials, while very important in assessing safety, are typically viewed with less confidence and more skepticism than the results of more rigorously designed trials.

Divalproex sodium was also found to be helpful in decreasing the interpersonal tempestuousness of our borderline subjects. This is an important new finding because this kind of interpersonal sensitivity or irritability may be an important barrier to the ability to use psychotherapy effectively. It may also be an important barrier to the ability to maintain satisfying relationships over time.

Divalproex sodium was not significantly more effective than placebo in leading to a decrease in depression. This is not surprising because mood stabilizers, even when effective, have not been associated with strong antidepressant effects in borderline personality disorder in earlier studies.[6,7] Also, subjects with major depression were excluded from participation in our study, making an antidepressant response more difficult to achieve.

Only the current study and that of Hollander and colleagues[15] have had a double-blind placebo-controlled design. We found divalproex sodium to be significantly more effective than placebo in a number of clinically important areas, while Hollander et al. did not. It may be that this difference is accounted for by the comorbid bipolarity of the borderline subjects in the current study. Their irritability, hostility, and aggressiveness may be more treatment responsive than the same traits or symptoms in borderline patients without a concurrent mood disorder.

Divalproex sodium was also found to be well tolerated. In general, side effects were few in number. Weight gain, the side effect of most open concern to young women, was modest in those treated with divalproex sodium and not significantly different than in those treated with placebo.

Limitations and Directions for Future Research

This study has several methodological limitations. First, the sample size was small. Second, the sample consisted only of women with borderline personality disorder. Whether these results would also apply to men meeting

criteria for borderline personality disorder is unknown. Third, the sample was comprised of moderately ill outpatients who were not suffering from a concurrent major depressive episode, abusing substances, or taking concurrent medications. It is unknown if similar results would be obtained in a more severely impaired sample of borderline patients, particularly those who are inpatients at the time that their participation in a controlled trial of divalproex sodium begins. Fourth, our retention rates throughout the first 3 months of the study were good. However, only 4 subjects in the placebo-treated group (40%) and 7 subjects in the divalproex sodium–treated group (35%) actually completed the entire 6-month trial. This result speaks to the difficulty in keeping borderline patients on medication for sustained periods of time. More frequent medication visits or concurrent psychotherapy (which none of our subjects were in) might help to ameliorate this problem. In addition, the basically equal dropout rates of the 2 study groups suggest that blindness was maintained throughout the study.

Additional research is needed to see if these results are replicated. Studies that contain male borderline patients and borderline patients with more severe morbidity are also needed. Additional research will also be helpful in sorting out the complicated question of how much of the response found in the current study was due to the presence of borderline psychopathology and how much was due to the bipolarity of these subjects. In any event, divalproex sodium seems to be a helpful agent in the not uncommon situation of a patient with both disorders.

CONCLUSION

The results of this double-blind placebo-controlled trial suggest that divalproex sodium may be a safe and effective agent for the treatment of the irritability and impulsive aggressiveness that characterize and trouble borderline patients with noticeable bipolarity. It may also be a particularly useful agent for diminishing the interpersonal sensitivity and hostility that make relationships so stormy for these patients. Sexually active women of childbearing age must use adequate contraception while taking this agent.

Drug names: alprazolam (Xanax and others), carbamazepine (Tegretol and others), desipramine (Norpramin and others), divalproex sodium (Depakote), fluoxetine (Prozac and others), lamotrigine (Lamictal), tranylcypromine (Parnate), trifluoperazine (Stelazine and others).

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