Double-Blind, Placebo-Controlled Trial of Divalproex Monotherapy in the Treatment of Symptomatic Youth at High Risk for Developing Bipolar Disorder

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Objective: To determine if divalproex sodium was superior to placebo in the treatment of symptomatic youths who suffer from a bipolar spectrum disorder and who also have a parent with a diagnosis of a bipolar illness.

Method: Youths, ages 5 to 17 years, meeting DSM-IV criteria for bipolar disorder not otherwise specified (NOS) or cyclothymia who also had at least 1 biological parent with bipolar illness were randomly assigned in a double-blind fashion to receive treatment with either divalproex sodium or placebo for up to 5 years. Study participation ended if the subject required additional clinical intervention, if the patient developed treatment-related adverse events, or if the participant was not adherent with study procedures. The primary outcome measure was time to study discontinuation for any reason. The study was conducted from August 1997 to April 2003.

Results: Fifty-six youths with a mean (SD) age of 10.7 (3.1) years were randomly assigned and received either divalproex sodium (N = 29) or placebo (N = 27). In spite of statistical power of 80% to detect hazard ratios of 2.2 or larger, the treatment groups did not significantly differ in survival time for discontinuation for any reason ($p = .93$) or discontinuation due to a mood event ($p = .55$). Changes in mood symptom ratings and psychosocial functioning from baseline to study discontinuation did not differ between groups (most significant $p > .14$). However, both groups did show improvements in mood symptoms and psychosocial functioning over time (all p values $< .002$). One patient, from the placebo group, ended study participation due to an adverse event.

Conclusion: These results suggest that, although well tolerated, divalproex sodium does not produce clinically meaningful improvements in the treatment of symptomatic youths suffering from either bipolar NOS or cyclothymia who are at genetic risk for developing bipolar disorder.

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In adult patients meeting diagnostic symptom criteria for bipolar disorder (bipolar I or II), it is generally appreciated that less severe expressions of bipolarity (cyclothymia (CYC) and bipolar disorder not otherwise specified [NOS]) may antecede the more pronounced expressions of this illness.[1–3] Substantial proportions of adults with bipolar disorder have reported experiencing their first symptoms during childhood or adolescence.[4] Consistent with these findings, longitudinal research has indicated that youths with bipolar symptoms show frequent mood fluctuations ranging from subsyndromal to fully syndromal symptom presentations.[5] More specifically, it has been reported that youths suffering from bipolar NOS may subsequently develop either bipolar I or bipolar II. For example, Birmaher et al.[5] reported that over a mean observation period of approximately 2 years, 25% of youths with bipolar NOS developed either bipolar I or bipolar II. These findings suggest that many youths with bipolar symptoms will eventually develop bipolar disorder. Heredity is an important risk factor in the development of bipolar disorder.[6,7] Research has confirmed a link between early onset of bipolar symptoms and greater

familial loading of bipolar disorder.[8,9] Substantial rates of social, academic, and family impairment, increased rates of attempted suicide, and poorer parent and peer relationships are also often observed in youth with symptoms of bipolarity.[10–12] Analogous to the construct of schizotaxia being a potential prodrome to schizophrenia,[13] it has been proposed that genetically at-risk youths with bipolar symptoms suffer from "cyclotaxia," a putative prodrome to more malignant expressions of bipolar disorder.[14] These patients with cyclotaxia are at genetic high risk for developing bipolar disorder and suffer from substantial mood symptomatology resulting in psychosocial dysfunction. For this reason, it has been recommended that treatment studies be performed in youths with cyclotaxia.[14]

Despite the need for intervention in genetically at-risk youths suffering from bipolar spectrum illnesses, there are limited research data about the treatment of this patient population. In one study, Chang and colleagues[15] reported that open-label treatment with divalproex sodium was an effective intervention. Approximately 78% of patients were considered good responders to divalproex sodium based on a priori criteria. However, the authors are unaware of any previous double-blind, placebo-controlled studies that have directly examined the safety and efficacy of pharmacotherapy in the treatment of bipolar symptoms in genetically at-risk youths.

The objectives of the present study were to determine the efficacy and safety of divalproex sodium in the treatment of offspring of parents with bipolar disorder who also met diagnostic symptom criteria for a bipolar illness. It was hypothesized that divalproex sodium would be relatively well tolerated and more efficacious than placebo in the treatment of these youth.

METHOD

The University Hospitals of Cleveland Institutional Review Board for Human Investigation approved the procedures of this outpatient protocol. The parents/guardians of all study subjects provided written informed consent, and all youths provided written assent before participation. The study was conducted from August 1997 to April 2003.

Study Design

This was a single site, double-blind, placebo-controlled, outpatient, randomized clinical trial. Patients were followed for up to 5 years. At the baseline visit, patients were randomly assigned to receive either divalproex sodium or placebo. Patients were seen at baseline, weeks 1, 2, 3, 4, 6, and 8, and monthly thereafter.

Subjects

Families were recruited from an outpatient child and adult psychiatric research center and an adult mood disorders program at a Midwestern academic medical center. A major focus of the child/adolescent research performed at this center is treatment studies for children and adolescents with bipolar disorders. Participants included guardians and youths who initially inquired about possible participation in one of the treatment studies being performed at this center.

Study participants were youths aged 5 to 17 years, diagnosed with either cyclothymia or bipolar NOS, with at least 1 biological parent diagnosed with a bipolar disorder. Unmodified *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) criteria were used to assign diagnoses. It should be noted that only children and adolescents who experienced spontaneous, dysfunctional mood episodes that did not meet full criteria for any other mood disorder were to be given the diagnosis of bipolar NOS. In addition, in order for youths to be eligible for entry into this trial, (1) they also had to have experienced a distinct period of unusually elated mood unrelated to an environmental event or to a psychoactive substance and lasting at least 4 hours within the past 2 months and (2) the period of elated mood would have resulted in a score ≥ 13 on the Young Mania Rating Scale.

Exclusion criteria included (1) clinical evidence of mental retardation; (2) significant past or current medical/neurologic disorders; (3) meeting diagnostic symptom criteria for bipolar disorder type I or type II; (4) meeting diagnostic symptom criteria for a major depressive episode of 1 month's length, with a Children's Depression Rating Scale-Revised score ≥ 40, and without any period of unusually elated mood for the past 4 weeks; (5) past or current episodes of psychosis; (6) history of a suicide attempt requiring medical/psychiatric care within the past year; (7) positive diagnosis on DSM-IV criteria for drug/alcohol abuse or dependence within the past 6 months; (8) significant suicidal/homicidal ideation that could jeopardize the subject or others; (9) allergy or hypersensitivity to divalproex sodium; (10) treatment with a psychotropic medication within the past 2 weeks; (11) females currently pregnant or lactating; (12) sexually active females who in the investigators' opinion are not using an adequate form of birth control; and (13) inability to swallow tablets/capsules.

Subject Diagnosis and Assessment

All eligible children were assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version (K-SADS-E)[16] or the -Present and Lifetime Version (K-SADS-PL).[17] The change in procedure of using K-SADS-PL instead of using the K-SADS-E occurred early in the study, once the K-SADS-PL became available, in order to decrease subject burden. Both the K-SADS-E and the K-SADS-PL assess for the presence or absence of previous or current psychiatric symptomatology based upon information pro-

vided by both the youth and the youth's guardian. In addition, patients who appeared to be eligible for study enrollment after the K-SADS assessment were then given a separate clinical assessment by a child and adolescent psychiatrist, generally lasting 90 minutes, in order to ensure subject eligibility.

Physicians or interviewers at the master's or bachelor's level administered the K-SADS interviews. Interrater reliability on the K-SADS was assessed with the κ statistic. Before leading a K-SADS interview, all research assistant raters needed to demonstrate adequate interrater reliability ($\kappa > 0.85$) based on the results of 5 K-SADS interviews. Subsequently, interrater reliability was maintained ($\kappa > 0.85$) by having joint assessments at every tenth interview.

Patient eligibility for the study was also contingent upon a parent diagnosis directly obtained using the Schedule for Affective Disorders and Schizophrenia (SADS)[18] or by clinical diagnostic evaluation at the Mood Disorders Program at University Hospitals of Cleveland, Cleveland, Ohio. At least 1 parent had to receive a diagnosis of bipolar disorder in order for a patient to be eligible for the study. The Family History-Research Diagnostic Criteria[19] method was only used to determine the other parent's diagnosis if they were not available to complete the SADS interview and were not evaluated in the Mood Disorders Program. In addition, parents were queried as to whether there were other biological family members with emotional or behavioral problems. Familial loading for psychiatric illness was quantified as the total number of relatives reported as having emotional or behavioral difficulties divided by the total number of relatives identified during the assessment interview.

Medication Treatment Procedures

Subjects were randomly assigned to receive either active divalproex sodium or matching placebo. The study medication was administered twice daily or 3 times daily based upon the judgment of the treating physician. The study medication and placebo capsules were initiated at a starting dose of approximately 10 mg/kg/day (maximum daily dose = 750 mg/day) and titrated to 15 mg/kg/day (maximum daily dose = 1250 mg/day) by the end of week 1. The treating physician could then request that doses be decreased, increased, or maintained based on clinical response. The unblinded medical monitor accepted or rejected requests for study medication dosing based on reported adverse events and blood levels.

All subjects had blood obtained for the determination of serum divalproex sodium concentrations obtained after 2 weeks, 4 weeks, and 3 months of treatment and then every 3 months thereafter and as clinically indicated. Serum divalproex sodium blood concentrations were monitored by an unblinded study physician. The nonblinded medical monitor adjusted doses to ensure that divalproex sodium serum concentrations were maintained between a predetermined target range of 50 and 100 μg/mL.

At week 4, if subjects were experiencing symptoms associated with a comorbid diagnosis of attention-deficit/hyperactivity disorder (ADHD), psychostimulant treatment was permitted at the U.S. Food and Drug Administration (FDA)-labeled doses. In addition, if necessary, patients could receive concomitant treatment with clonidine at doses up to 6 μg/kg per day for residual ADHD symptoms not adequately responsive to psychostimulant medication.

Safety Assessments

Subjects underwent a complete physical examination during the screening period, at the end of the study participation, and anytime deemed appropriate by the patient's physician. Blood pressure, pulse, and body weight were recorded at each study visit. Height was assessed every 3 months and at the end of the study.

Prior to receiving study medication, a complete blood count, a prothrombin time, an activated partial thromboplastin time, a comprehensive metabolic profile, a thyrotropin level, a urinalysis, and a urine toxicology screen were obtained. In addition, a urine qualitative pregnancy test was obtained in peripubertal and postpubertal females. With the exception of a thyrotropin level, these laboratory tests were also repeated at the end of study participation. Additionally, every 3 months during the course of the study, a complete blood count and a comprehensive metabolic profile were obtained. All laboratory results were reviewed by a study physician. Subjects treated with clonidine also received an electrocardiogram prior to treatment.

Side effects were evaluated at each treatment visit by direct query of the guardian and patient. If a patient experienced an abnormal laboratory value(s) or a clinical side effect(s) deemed significant by the child's physician, the patient was able to be withdrawn from the study.

Outcome Measures

The primary outcome measure to assess the efficacy of divalproex sodium was time to discontinuation for any reason. Time to discontinuation due to a mood-related event and change in psychometric measures were secondary outcomes. Patients who developed either a major depressive episode or a manic episode during study participation were to be removed from this study. However, youths who had, in the treating physician's opinion, a clinically significant worsening of clinical status (regardless of whether or not the subject was suffering from a major depressive or manic episode) were also to have had their study participation ended.

The Young Mania Rating Scale (YMRS),[20] the Children's Depression Rating Scale-Revised (CDRS-R),[21] and the Children's Global Assessment Scale

(CGAS)[22] were additional secondary outcome measures. The YMRS is an 11-item, clinician-rated scale, with total scores ranging from 0 (no manic symptoms) to 60 (severely manic). The CDRS-R is a 17-item, clinician-administered scale that assesses the presence and severity of depression symptoms in children and adolescents. Scores range from 17 to 113, with higher scores reflecting greater degrees of depressive symptoms. The CGAS was used to assess child and adolescent overall functioning. This clinician-rated instrument has scores ranging from 0 to 100, with 100 being superior functioning at home, school, and with peers. These measures were completed at baseline and during subsequent follow-up visits.

Analyses

Preliminary analyses examined the comparability of treatment groups on demographic, diagnostic, and symptom variables. To examine treatment efficacy, separate Kaplan-Meier survival analyses were computed to determine differences in time in study before discontinuation for any reason and discontinuation as a result of development of a mood episode. Based upon N = 29 in the divalproex arm and N = 27 in the placebo arm, statistical power was 79% to detect hazard ratios of 2.2 or larger, equivalent to the participants remaining in the placebo arm for a median of 3.2 months versus 6.9 months in the divalproex arm.[23]

Cox regression analyses were also computed, using discontinuation for any reason as the endpoint, to examine the effects of possible covariates including age, gender, presence of comorbid ADHD, concomitant treatment with stimulant medication, family loading of psychiatric illness, and the interaction between treatment and family loading of psychiatric illness.

To further compare the efficacy of divalproex sodium and placebo, separate repeated measures analyses of variance were computed using baseline and last-observation-carried-forward (LOCF) data with each of the 3 symptom rating measures (YMRS, CDRS-R, and CGAS) as dependent variables. The independent variables in these analyses were time (baseline and last follow-up observation) and treatment (divalproex sodium vs. placebo).

To examine safety and tolerability of study medication, an independent samples t test was computed with treatment arm as the independent variable and the total number of adverse events reported for each patient as the dependent variable. A χ^2 analysis was computed to examine whether the number of individuals reporting any adverse events differed across treatment arms. Separate χ^2 analyses or Fisher exact test, as appropriate, were conducted for each adverse event to determine whether the number of individuals reporting specific events differed across treatment arms.

The comparability of treatment groups on weight gain was examined using a repeated measures analysis of variance, with treatment as the between-subjects variable and time (baseline and end of study) as the within-subjects variable.

A significance level (α) of .05, 2-tailed, was used for all analyses.

Table 1. Baseline Demographic Information, Diagnostic Status, and Symptom Measures for the Overall Sample and Separately by Treatment Group

Characteristic	Divalproex Sodium (N = 29)	Placebo (N = 27)	Overall (N = 56)
Age, mean (SD), y	11.1 (3.4)	10.2 (2.7)	10.7 (3.1)
Males, N (%)	19 (65.5)	17 (63.0)	36 (64.3)
Diagnosis, N (%)			
Bipolar NOS	20 (69.0)	15 (55.6)	35 (62.5)
Cyclothymia	9 (31.0)	12 (44.4)	21 (37.5)
Comorbid ADHD, N (%)	13 (44.8)	12 (44.4)	25 (44.6)
Comorbid ODD, N (%)	5 (17.2)	7 (25.9)	12 (21.4)
Baseline YMRS score, mean (SD)	10.3 (4.3)	10.8 (4.6)	10.6 (4.4)
Baseline CDRS-R score, mean (SD)	25.5 (7.0)	26.7 (6.9)	26.5 (7.4)
Baseline CGAS score, mean (SD)	56.0 (8.8)	54.3 (8.0)	55.9 (9.3)

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CDRS-R = Children's Depression Rating Scale-Revised, CGAS = Children's Global Assessment Scale, NOS = not otherwise specified, ODD = oppositional defiant disorder, YMRS = Young Mania Rating Scale.

RESULTS

Subject Demographics

Table 1 presents baseline demographic information, diagnostic status, and symptom ratings for all subjects and separately by treatment group. No significant differences were observed between treatment groups at baseline evaluation for any demographic, diagnostic, or symptom rating variables (all p values > .05). Twelve patients (41.4%) in the divalproex sodium group and 10 patients (37.0%) in the placebo group were treated with stimulant medication. One individual in the placebo group received clonidine.

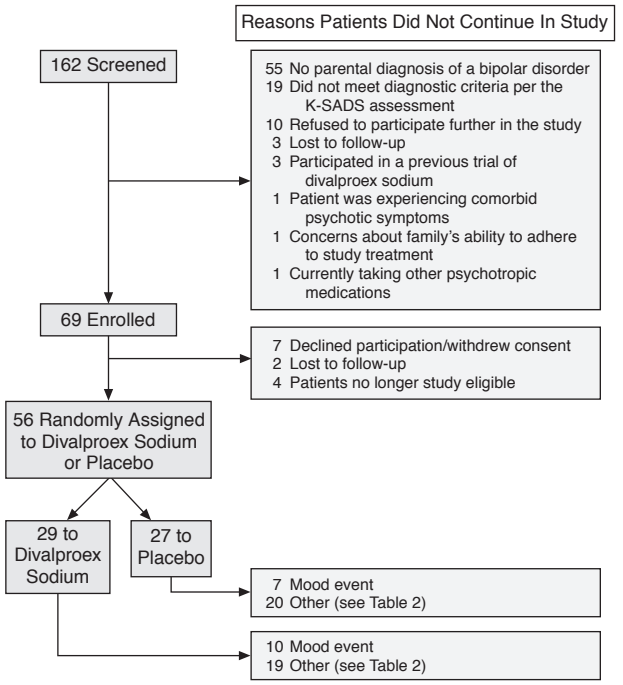
As expected, there were high rates of bipolar disorder in these subjects' parents. Of the subjects' mothers, 31 had bipolar I, 12 had bipolar II, and 2 had bipolar NOS. As far as the fathers were concerned, 11 had bipolar I, 3 had bipolar II, and 1 had cyclothymia. Of note, 4 subjects had both parents suffering from bipolar I.

Figure 1 summarizes the study design and subject accountability. Table 2 summarizes reasons for study discontinuation separately for each treatment arm. As can be seen from Figure 1 and Table 2, the most common reason for study discontinuation was not due to a mood-related event.

Divalproex Sodium Serum Concentrations

Mean serum concentrations at end of weeks 4 and 12 for the actively treated group were 87.2 μg/mL (SD = 29.2 μg/mL) and 88.6 μg/mL (SD = 24.7 μg/mL), respectively.

Figure 1. Study Design and Subject Accountability



Abbreviation: K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children.

At the end of study participation, the mean total daily dose of divalproex sodium was 1056.0 mg (SD = 532.0 mg), with a mean weight-adjusted dose of 22.8 mg/kg (SD = 7.2 mg/kg). In addition, the mean divalproex sodium serum concentration was 78.8 μg/mL (SD = 28.5 μg/mL) at study's end for youth receiving divalproex sodium.

Efficacy

Figures 2 and 3 present Kaplan-Meier curves indicating time in study prior to discontinuation for any reason and discontinuation as a result of a mood event, respectively. Patients randomly assigned to placebo (mean = 186.5 days, SE = ± 45.8 days; median = 83.0 days, SE = ± 57.1 days) and divalproex sodium (mean = 164.4 days, SE = ± 39.3 days; median = 78.0 days, SE = ± 16.1 days) did not significantly differ in the time enrolled until discontinuation for any reason; log-rank $\chi^2 = 0.01$, df = 1, p = .927). Furthermore, time until discontinuation for any mood event did not differ between placebo (mean = 571.8 days, SE = ± 87.1 days) and divalproex sodium (mean = 532.9 days, SE = ± 93.0 days); log-rank $\chi^2 = 0.37$, df = 1, p = .546.

Cox regression analyses using discontinuation for any reason as the dependent variable indicated that covariates yielded a significant overall prediction of time until discontinuation, $\chi^2 = 25.21$, df = 7, p = .001. Youths with greater family loading of psychiatric illness discontinued more quickly (Wald $\chi^2 = 4.79$, df = 1, p = .029). Individuals taking stimulant medications continued in the study longer (Wald $\chi^2 = 13.13$, df = 1, p < .001). Treatment, gender, age, comorbid ADHD, and the interaction of treatment and family history were not significantly associated with time until study discontinuation (largest Wald $\chi^2 = 2.55$, df = 1, p = .110 for gender). Cox regressions using any mood event as the dependent variable indicated no significant overall prediction of time until discontinuation (mood event, $\chi^2 = 8.20$, df = 7, p = .315), and none of the covariates were significant (largest Wald $\chi^2 = 2.95$, df = 1, p = .086 for stimulant medication).

Symptom Ratings

Figure 4 presents mean YMRS, CDRS-R, and CGAS scores at baseline, end of study weeks 1, 2, 3, 4, 6, and 8, and LOCF. At end of study, the mean outcome measure scores for all study subjects were a YMRS score of 6.8 (SD = 7.0), a CDRS-R score of 19.8 (SD = 4.3), and a CGAS score of 66.3 (SD = 12.6). For all measures, significant decreases in depression and mania symptoms and increases in functioning were observed (smallest F = 13.34, df = 1,54; p = .001). However, all main effects and interactions involving treatment were nonsignificant (largest F = 2.22, df = 1,54; p = .142), indicating no significant between-group treatment effects on symptom ratings.

Safety

No suicides or deaths occurred during the conduct of this study. One subject who was randomly assigned to receive placebo discontinued from study due to adverse events (heartburn, nausea, vomiting, and headaches). However, no patients who were randomly assigned to receive divalproex sodium discontinued due to adverse events.

Table 3 presents adverse events that were reported in greater than 5% of study participants by treatment group. Using χ^2 analysis, there were no significant differences between treatment arms in the overall number of adverse events, the number of individuals reporting any adverse events, or the number of patients experiencing any single adverse event (all p values > .05).

There was no significant difference between patients who received divalproex sodium versus placebo in terms of changes in weight from baseline to the end of the study (p > .05).

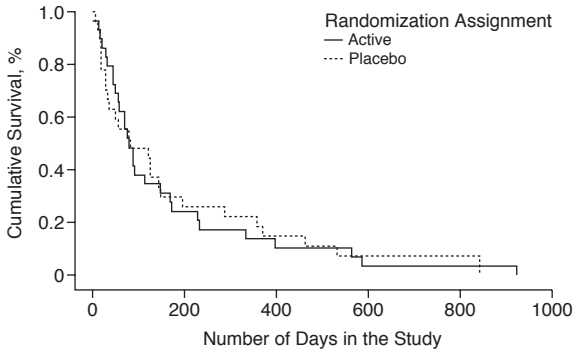
COMMENT

The present study was undertaken to examine the efficacy of divalproex sodium in the treatment of an impaired and recently symptomatic group of youths with cyclotaxia. Our findings indicate that, overall, divalproex sodium and placebo did not differ in time to study discon-

Table 2. Study Exit Reasons for Youths Treated With Divalproex Sodium or Placebo

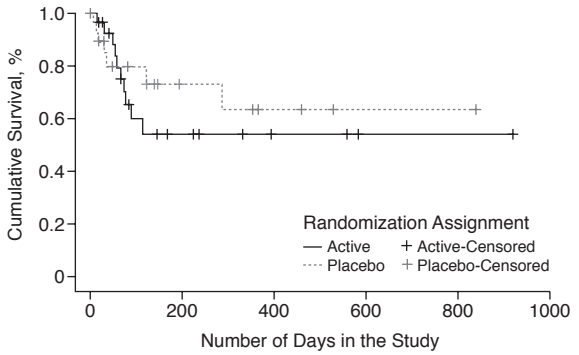
Exit Reason	Randomization Assignment: Divalproex Sodium (N = 29), N (%)	Placebo (N = 27), N (%)	Overall (N = 56), N (%)
Mood related	10 (34.5)	7 (25.9)	17 (30.4)
Lack of efficacy-hypomania/mania/mixed states	10 (100.0)	6 (85.7)	16 (94.1)
Lack of efficacy-depression	0 (0.0)	1 (14.3)	1 (5.9)
Other reasons	19 (65.5)	20 (74.1)	39 (69.6)
Lack of efficacy for comorbid diagnosis	1 (5.3)	0 (0.0)	1 (2.6)
Adverse events	0 (0.0)	1 (5.0)	1 (2.6)
Hospitalization	1 (5.3)	0 (0.0)	1 (2.6)
Withdrew consent	10 (52.6)	5 (25.0)	15 (38.5)
Refused to participate further in the study	7 (70.0)	4 (80.0)	11 (73.3)
Difficulty traveling to the clinic	1 (10.0)	1 (20.0)	2 (13.3)
Family discord	1 (10.0)	0 (0.0)	1 (6.7)
Family wanted open-label treatment	1 (10.0)	0 (0.0)	1 (6.7)
Lost to follow-up	2 (10.5)	8 (40.0)	10 (25.6)
Visit noncompliance	2 (10.5)	1 (5.0)	3 (7.7)
Medication noncompliance	1 (5.3)	3 (15.0)	4 (10.3)
Administrative reason	2 (10.5)	2 (10.0)	4 (10.3)

Figure 2. Kaplan-Meier Curve Indicating Overall Time in Study Prior to Discontinuation for Any Reason for 56 Youths Treated With Either Divalproex Sodium or Placebo[a]



[a]Log-rank $\chi^2 = 0.01$, df = 1, p = .927.

Figure 3. Kaplan-Meier Curve Indicating Overall Time in Study Prior to Discontinuation for a Mood Event for 56 Youths Treated With Either Divalproex Sodium or Placebo[a]



[a]Log-rank $\chi^2 = 0.37$, df = 1, p = .546.

tinuation for any reason. Although divalproex sodium was less efficacious when compared to placebo than expected, it was well tolerated. There were also no significant differences observed in the pattern of symptom ratings between treatment groups. However, both treatment groups exhibited significant decreases in symptoms and improvements in psychosocial functioning. The response to divalproex sodium observed in this trial is consistent with the high response rate to open-label divalproex sodium treatment described in the study of Chang and colleagues.[15] However, the present results suggest the previously observed high response rate may not have been due to divalproex sodium treatment per se.

The lack of differences in outcome measures between divalproex sodium and placebo were not due to inadequate power to detect a between-group treatment effect. Based on the median survival times of 2.60 months in the divalproex sodium group versus 2.77 months in the placebo group (with a hazard ratio of approximately –1.08), more than 3000 participants would have to be enrolled in each arm to achieve 80% power for detecting a significant effect.

Youths with the highest family loading of psychiatric illness discontinued more quickly than youth with lower loadings. These youths, with the highest family loading of psychiatric illness, appear to be in greatest need of intervention to reduce symptoms and improve psychosocial functioning.

Concomitant use of stimulant medication to treat residual ADHD symptoms resulted in increased length in study participation. These results may be consistent with the nonspecific effect of additional intervention. Alternatively, the effectiveness of stimulant medication in the treatment of individuals with bipolar disorder and ADHD symptoms is consistent with previous studies showing both the short- and long-term efficacy and safety

Figure 4. Mean Young Mania Rating Scale (YMRS), Children's Depression Rating Scale-Revised (CDRS-R), and Children's Global Assessment Scale (CGAS) Scores at Baseline, End of Weeks 1, 2, 3, 4, 6, and 8, and Last Observation Carried Forward (LOCF) in 56 Youths Randomly Assigned to Divalproex Sodium or Placebo for up to 8 Weeks

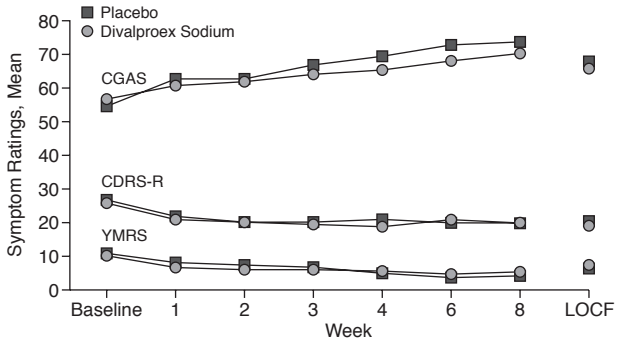


Table 3. Adverse Events Reported in Greater Than 5% of Youths Treated With Divalproex Sodium or Placebo[a]

Side Effect	Divalproex Sodium (N = 29), N (%)	Placebo (N = 27), N (%)
Nausea/vomiting	14 (48.3)	8 (29.6)
Sedation/fatigue	10 (34.5)	4 (14.8)
Headache	8 (27.6)	8 (29.6)
Stomach pain	6 (20.7)	6 (22.2)
Diarrhea	6 (20.7)	3 (11.1)
Increased appetite	6 (20.7)	1 (3.7)
Coughing	3 (10.3)	2 (7.4)
Tremor	3 (10.3)	1 (3.7)
Decreased appetite	3 (10.3)	1 (3.7)
Dizziness	3 (10.3)	0 (0.0)
Insomnia	3 (10.3)	0 (0.0)
Enuresis/encopresis	2 (6.9)	2 (7.4)
Constipation	2 (6.9)	1 (3.7)
Body pain	1 (3.4)	3 (11.1)
Epistaxis	0 (0.0)	3 (11.1)

[a]Significance levels were > .05 for all between-group comparisons based on χ^2 analysis or Fisher exact test, as appropriate.

of stimulant medications in improving ADHD symptoms after mood stabilization has been achieved.[24,25]

Limitations

The largest decrement in symptoms occurred shortly after baseline, consistent with a possible placebo effect. This initial decrement may have hindered detection of between-group treatment effects due to a "floor effect." Additionally, introducing open-label stimulant intervention appears to have modified the risk of study discontinuation substantially for both treatment groups, thereby capturing substantial amounts of variance that could no longer be attributed to other predictors, including the primary intervention.

Future Directions

The manifest effectiveness of placebo seen in this trial suggests it may be useful to eventually explore the value of psychosocial interventions in this patient population.[26–28] Analogous literature examining treatment responses of individuals at risk of psychosis has suggested that nonpharmacologic interventions may be helpful. For example, Morrison and colleagues[29] have found that cognitive therapy significantly reduced the likelihood of progression to psychosis in patients at high risk for developing psychosis.

Because youths with cyclotaxia suffer from significant mood symptomatology and psychosocial impairment,[14] they require safe and effective treatments. Based on the results of this clinical trial, future pharmacologic and nonpharmacologic studies may wish to focus on youth with cyclotaxia who are at greater genetic risk for developing bipolar illness.

CONCLUSION

In a study that required only one parent to suffer from bipolar illness, divalproex sodium was not superior to placebo in the treatment of recently symptomatic youth with cyclotaxia.

Drug names: clonidine (Catapres and others), divalproex sodium (Depakote).

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