# Divalproex Monotherapy in the Treatment of Bipolar Offspring With Mood and Behavioral Disorders and at Least Mild Affective Symptoms

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***Background:*** Offspring of parents with bipolar disorder, by virtue of their high-risk status for developing bipolar disorder, merit an investigation of the efficacy of treatment with mood stabilizers. Behavioral and mood difficulties in this population may represent prodromal forms of bipolar disorder. We studied the efficacy of divalproex in treating child and adolescent bipolar offspring with mood or behavioral disorders who did not yet meet criteria for bipolar I or II disorder.

***Method:*** We studied 24 children aged 6–18 years (mean = 11.3 years; 17 boys/7 girls) with at least 1 biological parent with bipolar disorder. Participants were diagnosed by the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia with at least 1 of the following DSM-IV disorders: major depressive disorder, dysthymic disorder, cyclothymic disorder, or attention-deficit/hyperactivity disorder. Subjects all had at least moderate affective symptoms (28-item Hamilton Rating Scale for Depression or Young Mania Rating Scale score > 12). After a 2-week washout period, subjects were treated with divalproex for 12 weeks, titrated to achieve serum levels of 50–120 μg/mL (mean final dose = 821 mg/day; mean final serum level = 79.0 μg/mL).

***Results:*** One subject discontinued after 2 weeks due to continuation of symptoms. Of the remaining 23 subjects, 18 (78%) were considered responders by primary outcome criteria ("very much improved" or "much improved" on the Clinical Global Impressions-Improvement scale). Divalproex was well tolerated with no discontinuations due to adverse effects.

***Conclusion:*** Bipolar offspring with mood or behavioral disorders and at least mild affective symptoms may respond to divalproex treatment. Our study was limited by the open treatment, lack of a placebo group, and the heterogeneous nature of the sample. Controlled studies are warranted in the use of divalproex in symptomatic bipolar offspring.

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Children of parents with bipolar disorder have been shown to be at high risk for development of psychopathology. A meta-analysis of 16 studies of bipolar offspring, between 1983 and 1996, found bipolar offspring to have 4.0 times the risk of developing a mood disorder than children of healthy controls.[1] More recent studies have indicated high rates of depression, attention-deficit/hyperactivity disorder (ADHD), and bipolar spectrum disorders in bipolar offspring.[2,3] Although the precise incidence of bipolar disorder in bipolar offspring is not clear, cross-sectional studies have reported estimates as high as 24%.[2,4] Longitudinal assessment of bipolar offspring may yield even higher rates of bipolar disorder, as the majority of offspring in these studies were under 18 years at time of assessment, and 20% to 30% of depressed children in general may eventually develop bipolar disorder.[5]

Furthermore, a positive family history of bipolar disorder has been identified as a risk factor for progression from depression to bipolar disorder in children.[5,6] Similarly, presence of ADHD may be an early sign of bipolar disorder in some children.[7] Studies have suggested that adults with bipolar disorder who had childhood ADHD had an earlier onset of bipolar disorder than those without ADHD.[2,8]

**Table 1. Characteristics of 24 Child and Adolescent Offspring of Parents With Bipolar Disorder**

| Subject | Age (y) | Gender[a] | Race[b] | Diagnosis[c] | Past Medication Exposure[d] | Responder Status (CGI-I)[e] | Bipolar Parent |
|---|---|---|---|---|---|---|---|
| 1 | 8 | M | W | ADHD | ST | * | Mother |
| 2 | 16 | F | W | CYC | 0 | Yes | Mother |
| 3 | 17 | F | H | CYC | 0 | Yes | Mother |
| 4 | 6 | M | W | ADHD | ST | Yes | Mother |
| 5 | 18 | M | A | CYC | AD | Yes | Father |
| 6 | 6 | M | H | ADHD | 0 | No | Father |
| 7 | 11 | M | W | ADHD, ODD | AD | Yes | Father |
| 8 | 9 | M | A | ADHD | 0 | No | Mother |
| 9 | 7 | M | W | ADHD, ODD, CYC | ST, SRI | Yes | Mother |
| 10 | 17 | F | W | MDD, GAD | 0 | Yes | Father |
| 11 | 9 | M | W | ADHD | ST | No | Mother |
| 12 | 12 | M | W | ADHD | ST, TCA, AD | No | Father |
| 13 | 8 | M | H | DYS | AD | Yes | Mother |
| 14 | 10 | M | W | CYC, ADHD | 0 | Yes | Mother |
| 15 | 7 | F | W | MDD | SRI | Yes | Mother |
| 16 | 10 | M | W | ADHD | ST, AD | Yes | Father |
| 17 | 16 | M | W | MDD | AD | No | Mother |
| 18 | 16 | M | W | CYC | 0 | Yes | Father |
| 19 | 10 | M | W | ADHD | 0 | Yes | Mother |
| 20 | 9 | M | B | ADHD | ST, SRI, AD | Yes | Mother |
| 21 | 7 | F | W | DYS | 0 | Yes | Both |
| 22 | 16 | M | W | MDD, ADHD | 0 | Yes | Father |
| 23 | 12 | F | W | CYC, ADHD | SRI, AP | Yes | Mother |
| 24 | 8 | F | A | MDD | SRI, AD | Yes | Mother |

[a]M = male, F = female.
[b]A = Asian, B = black, H = Hispanic, W = white.
[c]ADHD = attention-deficit/hyperactivity disorder, CYC = cyclothymia, DYS = dysthymia, GAD = generalized anxiety disorder, MDD = major depressive disorder, ODD = oppositional defiant disorder.
[d]AD = atypical antidepressant, AP = antipsychotic, SRI = serotonin reuptake inhibitor, ST = stimulants, TCA = tricyclic antidepressant, 0 = none.
[e]CGI-I = Clinical Global Impressions-Improvement.
Symbol: * = dropped out.

Children with depression or ADHD may be at further risk for development of bipolar disorder due to exposure to stimulants[9,10] and antidepressants,[11–16] which have been reported to cause or exacerbate mania in children and adolescents. Thus, in accordance with the kindling theory of affective disorders proposed by Post,[17] these medications may be provocative agents in bipolar offspring, who are already predisposed to development of bipolar disorder. In one cohort of adolescents with bipolar disorder, those with prior exposure to stimulants were reported to have an earlier age at onset of bipolar disorder than those not exposed, regardless of presence of ADHD.[18] Furthermore, in mood stabilizer–naive adults with bipolar II depression, those with prior stimulant or antidepressant exposure tended to have a lower response rate to divalproex than those who were medication-naive.[19]

In light of the putative susceptibility of bipolar offspring to this kindling phenomenon, mood stabilizers may prove to be safer and more effective for bipolar offspring. However, Geller and colleagues[20] found lithium no more effective than placebo in treating 30 prepubertal children with depression, all with family histories of mood disorder and 40% with a parent with bipolar disorder. In contrast to lithium, divalproex has been proposed as an antikindling agent,[21,22] as it has prevented the onset of spontaneous seizures in laboratory animals given a series of electrical charges designed to kindle a seizure disorder. In controlled studies, divalproex has already demonstrated efficacy in the treatment of mania in adults[23] and has been suggested to be effective in children and adolescents with bipolar disorder in open studies.[24,25] Because of its putative antikindling properties and efficacy in treatment of mania, we studied the efficacy of open divalproex in bipolar offspring with mood or behavioral disorders (but not yet with fully developed bipolar disorder) and at least mild affective symptoms. We hypothesized that divalproex would yield overall clinical improvement.

## METHOD

The sample of bipolar offspring included 17 males and 7 females. Subjects ranged in age from 6 to 18 years (mean ± SD age = 11.3 ± 3.9 years). Socioeconomic status derived from the Hollingshead scale indicated a modal socioeconomic status (SES) level of III. Seventy-one percent were white, 13% Hispanic, 13% Asian, and 4% black (Table 1).

The sample was drawn from an ongoing phenomenology study of bipolar offspring. Families were recruited from the Stanford Bipolar Disorders Clinic (for adults),

the Stanford Pediatric Mood Disorders Clinic, and from the surrounding community within Stanford, Calif. Oral and written informed consent was obtained from at least 1 parent, and oral and written assent was obtained from subjects after an explanation of possible adverse effects and alternatives to study participation. The study was approved by the Stanford University Administrative Panel on Human Subjects.

Inclusion criteria required a diagnosis of at least 1 of the following: major depressive disorder, ADHD, dysthymic disorder, or cyclothymic disorder, either past or current. Subjects also had to have at least mild affective symptoms, as determined by a score of at least 12 on the Young Mania Rating Scale (YMRS)[26] or 12 on the 28-item Hamilton Rating Scale for Depression (HAM-D).[27] Exclusion criteria were a current or past history of substance abuse, comorbid neurologic disease such as a seizure disorder, or mental retardation.

For each subject, at least 1 parent had bipolar I or II disorder by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID).[28] Family history was obtained using the Family History-Research Diagnostic Criteria (FH-RDC).[29] Children were assessed by the affective module of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS)[30,31] and the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime (K-SADS-PL).[32] Diagnoses were made according to DSM-IV criteria. The WASH-U-KSADS is a semistructured diagnostic interview based on the KSADS-1986 that provides detailed information on affective symptoms in children, including data regarding cycling patterns. The WASH-U-KSADS has been shown to reliably distinguish ADHD from bipolar disorder in child populations[33,34] and maintain a 6-month stability in bipolar diagnosis.[35]

Subjects were evaluated by either a child psychiatrist or a trained research assistant who was aware of parental status. Interrater reliability was established by rating videotaped interviews, observing trained rater interviews, and performing interviews with observation by a trained rater, as described by Geller et al.[34] Both the parents and children were interviewed. Symptoms were positively rated if endorsed by either parent or child, based on interviewer decision (e.g., if a child seemed to be exaggerating a symptom, the interviewer had the option to use the parent's report instead). Diagnostic decisions were ultimately made by a child psychiatrist (K.D.C.), based on review of the structured-interview data, clinical history, and videotapes of the interview if the research assistant (K.D.) performed the interview.

### Measures

In addition to the HAM-D and YMRS, ratings included the Clinical Global Impressions-Improvement (CGI-I) and Clinical Global Impressions-Severity (CGI-S),[36] the Child Behavior Checklist (CBCL),[37] and the Revised Children's Manifest Anxiety Scale (RCMAS).[38]

### Procedures

Subjects were assessed at baseline, on their current medication regimen. Medications then were tapered and discontinued to achieve a 2-week medication-free period, after which subjects were reassessed. If no improvement was noted by the CGI-I, then the subject was begun at week 0 with open divalproex treatment. Divalproex was begun at 125–250 mg/day and increased by 125–250 mg/day every 4 to 7 days as necessary and as tolerated. Target final doses were 15–20 mg/kg, with serum target levels of 50–120 μg/mL to be reached by week 4. Titration continued past week 4 if necessary, based on clinical response and serum level. No additional psychotropic medications were allowed. Subjects were allowed to continue psychotherapy that had been initiated at least 2 months prior to beginning divalproex.

Subjects were assessed weekly for 4 weeks, then every 2 weeks until week 12. The HAM-D, YMRS, CGI-I, CGI-S, and an adverse events form were completed at each meeting. RCMAS scores were obtained every 4 weeks. CBCLs were filled out by parents at weeks 0 and 12. Ratings were performed by a board-eligible child psychiatrist or a masters-level research assistant. After suitable rater training, 2 independent raters achieved 100% concordance on 3 consecutive patients.

### Determination of Response

Primary measure for response was a 1 or 2 on the CGI-I ("very much improved" or "much improved") at week 8 or 12. Secondary measures were a 50% decrease from baseline in YMRS or HAM-D scores.

## RESULTS

### Baseline Characterizations

Sixty-four percent of children (N = 15) had 1 parent with bipolar I disorder, 36% (N = 9) had 1 parent with bipolar II disorder. Subjects had an average of 47% of evaluable first-degree relatives with a mood disorder by FH-RDC.

Fifty-eight percent had a diagnosis of ADHD, 29% cyclothymia, 21% major depressive disorder, and 8% dysthymic disorder. Thirteen (57%) of 23 completers had prior exposure to psychotropic medications, including antidepressants, stimulants, and antipsychotics (Table 1). At baseline, YMRS scores for the sample ranged from 0 to 27 (mean = 14.5, SD = 7.6), HAM-D scores ranged from 1 to 26 (mean = 14.2, SD = 8.0), and CBCL total scores (by parent report) ranged from 53 to 83 (mean = 70, SD = 7) (Table 2).

**Table 2. Outcome Measures in Divalproex-Treated Child and Adolescent Offspring of Parents With Bipolar Disorder**

| Subject | CGI-S Week 0 | CGI-S Week 12 | CGI-I Week 12 | CBCL Total Week 0 | CBCL Total Week 12 | YMRS Week 0 | YMRS Week 12 | HAM-D Week 0 | HAM-D Week 12 | VPA Dose Final (mg/day) | VPA Level Final (μg/mL) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 4 | * | * | * | * | 21 | * | 17 | * | * | * |
| 2 | 2 | 0 | 2 | 73 | 59 | 7 | 3 | 12 | 7 | 500 | 51 |
| 3 | 3 | 2 | 2 | 75 | ... | 7 | 2 | 21 | 24 | 1000 | 67 |
| 4 | 3 | 1 | 1 | 76 | 73 | 18 | 3 | 16 | 1 | 750 | 62 |
| 5 | 3 | 1 | 2 | 72 | ... | 9 | 2 | 13 | 6 | 1000 | 84 |
| 6 | 4 | 3 | 3 | 74 | 73 | 26 | 11 | 5 | 4 | 1500 | 99 |
| 7 | 4 | 3 | 2 | 70 | ... | 17 | 3 | 13 | 2 | 1000 | 83 |
| 8 | 3 | 2 | 3 | 63 | ... | 20 | 6 | 5 | 1 | 375 | 128 |
| 9 | 3 | 3 | 2 | ... | ... | 25 | 14 | 9 | 6 | 750 | 111 |
| 10 | 4 | 0 | 1 | 59 | 57 | 5 | 1 | 26 | 3 | 1000 | 71 |
| 11 | 4 | 3 | 3 | 74 | ... | 22 | 23 | 4 | 5 | 750 | 100 |
| 12 | 3 | 3 | 4 | 70 | 80 | 13 | 11 | 1 | 9 | 1250 | 116 |
| 13 | 3 | 2 | 2 | 73 | ... | 11 | 3 | 26 | 5 | 625 | 93 |
| 14 | 4 | 1 | 1 | 72 | ... | 27 | 6 | 23 | 4 | 1000 | 92 |
| 15 | 5 | 3 | 2 | 69 | ... | 17 | 9 | 22 | 14 | 750 | 92 |
| 16 | 4 | 2 | 2 | 74 | ... | 19 | 7 | 6 | 4 | 750 | 87 |
| 17 | 3 | 2 | 3 | 64 | 71 | 0 | 0 | 19 | 11 | 1000 | 69 |
| 18 | 2 | 0 | 1 | 53 | ... | 12 | 0 | 6 | 0 | 1000 | 92 |
| 19 | 4 | 1 | 2 | 68 | 60 | 18 | 3 | 14 | 9 | 625 | 104 |
| 20 | 3 | 2 | 2 | 56 | ... | 19 | 6 | 2 | 6 | 875 | 76 |
| 21 | 3 | 1 | 1 | 69 | ... | 15 | 0 | 16 | 0 | 500 | 104 |
| 22 | 3 | 0 | 1 | 71 | 63 | 2 | 0 | 21 | 2 | 1000 | 38 |
| 23 | 5 | 2 | 2 | 72 | ... | 16 | 14 | 25 | 5 | 375 | 42 |
| 24 | 3 | 0 | 1 | 83 | ... | 12 | 0 | 20 | 2 | 1000 | 85 |

Symbols: * = dropped out, ... = information not obtained.
Abbreviations: CBCL = Child Behavior Checklist, CGI-I = Clinical Global Impressions-Improvement, CGI-S = Clinical Global Impressions-Severity, HAM-D = 28-item Hamilton Rating Scale for Depression, VPA = valproate, YMRS = Young Mania Rating Scale.

**Response**

One subject (male) withdrew from the study before week 3 due to lack of perceived improvement in symptoms.

Among the sample of 23 subjects who completed the study, mean YMRS and HAM-D scores were significantly lower at week 12 compared with week 0 (YMRS: paired samples $t = 6.97$, $df = 22$, $p < .0001$; HAM-D: $t = 4.56$, $df = 22$, $p = .0002$). Moreover, mean YMRS and HAM-D scores were significantly lower as early as week 2 compared with week 0 (YMRS: paired samples $t = 3.14$, $df = 17$, $p = .006$; HAM-D: $t = 4.46$, $df = 17$, $p = .0003$). The changes in mean YMRS and HAM-D scores over time are presented in Figure 1.

At week 12, 18 subjects (78%) were responders by primary criteria, and 19 subjects (83%) were responders by secondary criteria. CGI-I scores are provided in Table 2, and CGI-S scores are provided in Table 2 and Figure 2.

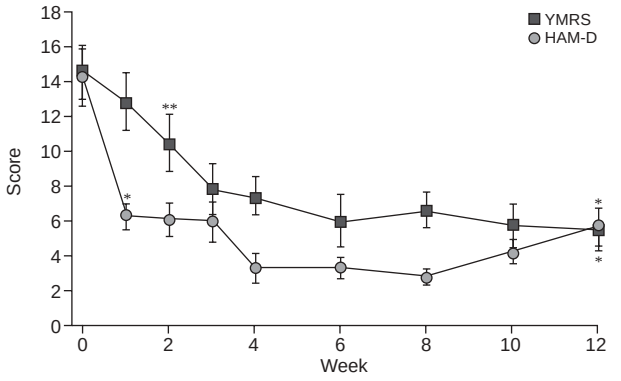
The small number of nonresponders limited the power of categorical statistical comparisons of responders and nonresponders. However, 7/7 females (100%), but only 11/16 males (69%), who completed the study were responders. Ten (83%) of the 12 subjects with a primary diagnosis of a mood disorder (major depressive disorder, dysthymic disorder, or cyclothymia) responded (Table 2). Six (86%) of 7 subjects considered to have had "marked improvement" (CGI-I score = 1) at week 12 had a mood disorder, but this small sample size also precluded further statistical analysis of the group.

According to secondary criteria, time until response as measured by the HAM-D ranged from 1 to 4 weeks. The median time to 50% reduction for HAM-D scores was 2 weeks. As measured by YMRS, time until response ranged from 1 to 12 weeks; the median was 3 weeks.

In order to explore predictors of response rate, we fit individual regression lines to each subject's data across the 12 weeks of the study, yielding slopes for HAM-D, YMRS, and CGI-I scores. Simple linear regression analyses were then conducted to see whether demographic factors, diagnosis, and baseline CBCL scores were related to slopes. Gender, presence of mood disorder, and age did not significantly correlate with CGI-I slopes. Baseline score on the CBCL social problems scale correlated with rate of reduction of CGI-I ($rho = .49$, $p = .02$).

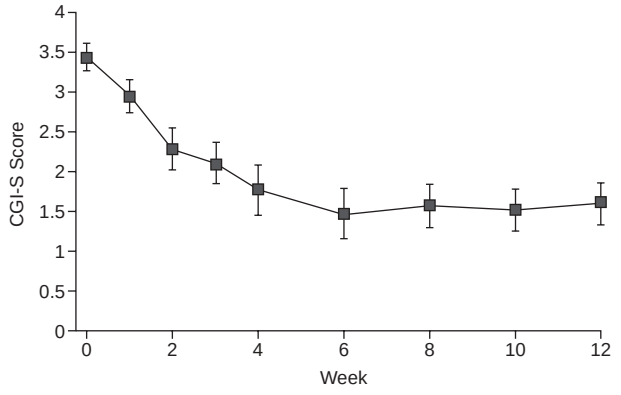
Female subjects showed a significantly greater decrease in HAM-D scores across the study period compared with males ($F = 6.9$, $p = .02$), but this relationship was attenuated after accounting for their higher baseline HAM-D score ($F = 2.3$, $p = .14$). Subjects with mood disorders had rates of reduction on the HAM-D similar to those of non–mood disordered subjects. Age was not related to HAM-D slope. Baseline scores on the Anxious/Depressed scale of the CBCL significantly correlated

**Figure 1. Change in Mean Young Mania Rating Scale (YMRS) and Hamilton Rating Scale for Depression (HAM-D) Scores Over 12 Weeks of Open Divalproex Treatment (N = 23)[a]**




[a]Means are based on last-observations-carried-forward analysis, and ranges are standard errors.
*p < .001, compared with week 0.
**p < .01, compared with week 0.

**Figure 2. Change in Clinical Global Impressions-Severity (CGI-S) Score Over 12 Weeks of Divalproex Treatment (N = 23)[a]**




[a]Ranges are standard errors.

with the rate of reduction in HAM-D score (Spearman rho = –.50, p = .02), indicating a more robust response when baseline mood problems were reported as high. However, all subjects with the exception of 4 (17%) were rated as having improved mood at exit.

Gender, presence of mood disorder, age, and baseline CBCL scores did not significantly correlate with YMRS slopes.

Mean final divalproex dose was 821 mg/day, and final serum valproate level was 79.0 ± 26.8 μg/mL. Adverse effects were minimal except for a mean weight gain of 3.7 ± 1.6 kg (8.2 ± 3.5 lb) over the course of the study (range, 0.9–5.5 kg [2.0–12.1 lb]). There were no laboratory abnormalities in liver transaminases or thyroid function tests during the study. No subjects withdrew due to adverse effects.

## DISCUSSION

To our knowledge, this is the first study of mood stabilizer treatment of bipolar offspring with affective symptoms, a strategy in line with preventive intervention. In this open trial, children and adolescents at risk for bipolar disorder improved after 12 weeks of divalproex treatment, with significant response by 2 weeks and more robust improvement for subjects who were more symptomatic at baseline. There were only 4 (5 by primary response criteria) nonresponders, predominantly males with only ADHD. Divalproex was well tolerated with the main adverse effect being mild-to-moderate weight gain.

Geller and colleagues[20] reported that lithium was no better than placebo in alleviating major depression in children who had strong family histories of bipolar disorder. In that study, 40% of subjects had a parent with bipolar disorder, but the other 40% had a more distant relative (aunt, uncle, or cousin) with bipolar disorder and 20% had a family history of major depression only (without mania). This heterogeneity of familial risk may have decreased the response rate to lithium. Furthermore, the treatment period was only 6 weeks. The authors also did not indicate a global response rate; rather, they reported that final Clinical Global Assessment of Severity scores, while improved, were still below 60, indicating continuing clinical problems. There was a large standard deviation, however, indicating a wide distribution of subjects who responded well and subjects who responded poorly. It is difficult to use this study for comparison to our study, as the Geller et al. study was a placebo-controlled study of a slightly different population. Nevertheless, while it is unclear how many subjects would have been considered responders by our criteria (CGI-I), it appears that this number would be less than 50%. It is possible that lithium may be less effective than divalproex in treating mood symptoms in bipolar offspring. Although both lithium and divalproex are effective antimanic agents, their range of efficacy through the bipolar spectrum may differ. Adults with rapid-cycling bipolar disorder are generally more resistant to lithium and more responsive to divalproex.[39] Furthermore, adolescents with bipolar disorder who had prepubertal onset of psychiatric problems have been reported to be lithium-resistant.[40]

However, while divalproex is increasingly being used as a treatment for pediatric bipolar disorder, there is little experience with its use in childhood depression and ADHD. Thus, the efficacy of divalproex in this study may be due to treatment of a brain state that is more similar to bipolar disorder than depression or ADHD. Retrospective histories of adults with bipolar disorder have reported prodromal symptoms of hyperactivity, depression, suicid-

ality, abrupt mood changes, and anger dyscontrol occurring during childhood, 9 to 12 years before the first diagnosis of bipolar I disorder.[41,42] With the added genetic risk factor in our cohort, it is highly likely that our subjects were in the prodromal stages of bipolar disorder.

It is possible that divalproex not only relieves acute prodromal symptoms but also attenuates progression to fully developed bipolar disorder. Divalproex has been proposed to be an antikindling agent[22] and has been shown to prevent the kindling of seizures in laboratory rats given repeated subthreshold electrical stimuli. In other animal studies, both lithium and valproate have been shown to inhibit glycogen synthase kinase-3β,[43] an enzyme that may be involved in activating proteins involved in neuronal death. Valproate also increases frontal cortex Bcl-2,[44,45] a neurotrophic and neuroprotective protein that may be the downstream agent of endogenous nerve growth factors. Valproate further activates mitogen-activated protein kinases, which mediate the effects of these neurotrophic factors to stimulate neural dendritic growth.[44,46] Taken together, these findings are consistent with the possibility that valproate has neuroprotective qualities and thus potentially will be effective in reducing risk for development of bipolar disorder in vulnerable populations. From a theoretical and preclinical point of view, these findings provide a substantive basis for our proposed intervention. However, data regarding kindling and stimulation of neurotrophic factors are limited in humans, and therefore the clinical relevance of these findings is currently unknown.

We did not identify a predictor of response to divalproex, including gender, age, or presence of mood disorder, perhaps due to the sample size or the small number of nonresponders. Although it appeared that presence of a mood disorder may have numerically favored a more robust response than presence of only ADHD, this observation was not statistically significant.

The majority of responders improved within the first 4 weeks of treatment and retained their response through week 12. Depressive symptoms appeared to resolve especially rapidly, with mean HAM-D scores achieving the endpoint mean by week 1. This rate of response may have been due to placebo response, receiving support from an academic institution, being in a study, and having regular visits to a physician. However, this placebo response would have been carried throughout the 12 weeks of the study. Also, as our subjects were subsyndromal for bipolar disorder, they might have had a less severe expression of the disorder (supported by their low-to-moderate mood scale scores) and might therefore have been more responsive to a single medication intervention compared with subjects with fully developed bipolar disorder and higher symptom severity. Finally, there are adult data reporting a rapid (1 week) response of depressive symptoms to divalproex in adults with bipolar II depression[19]; our subjects had a similar response in this study.

**Limitations**

Foremost, this was an open study, without a placebo arm and without blinded raters. This limitation raises the possibilities of placebo effects and rater biases. This trial was longer than many acute clinical trials to offset possible initial placebo-effect responses. Furthermore, 56% of responders had had previous trials of stimulants and/or antidepressants without satisfactory clinical effects. Finally, despite our careful characterization of both parents and subjects by means of semistructured interviews, our subject population was still a heterogeneous group. Although all bipolar offspring, the subjects differed in primary diagnoses, gender, and pubertal state. Thus, considerable caution needs to be taken when considering the significance or generalizability of our findings.

While these are preliminary data, an important implication from this study is the possibility that divalproex may relieve emotional and behavioral symptoms in bipolar offspring. On a case-by-case basis, if bipolar offspring present to the clinician with subsyndromal symptoms of bipolar disorder, divalproex therapy could be considered. However, randomized, controlled, acute, and longitudinal trials are needed to support this approach before adopting it on a regular basis for any symptomatic child or adolescent at high risk for bipolar disorder.

*Drug name:* divalproex (Depakote).

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