Combination Lithium and Divalproex Sodium in Pediatric Bipolarity

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ABSTRACT

Objective: Lithium carbonate (Li) or divalproex sodium (DVPX) may be effective for some juveniles with bipolar disorder. Many youths with bipolar disorder do not respond to DVPX or Li monotherapy. An open-label study was conducted to examine the effectiveness of combination DVPX and Li therapy with youths diagnosed with bipolar disorder. **Method:** Patients meeting *DSM-IV* criteria for bipolar I or bipolar II disorder, ages 5 to 17 years, were treated prospectively for up to 20 weeks with DVPX + Li. Assessments included the Young Mania Rating Scale (YMRS), Children's Depression Rating Scale–Revised (CDRS-R), and the Children's Global Assessment Scale (CGAS). The a priori definition of clinical remission utilized included four contiguous weekly ratings of YMRS ≤12.5, CDRS-R ≤40, CGAS ≥51, clinical stability, and no evidence of mood cycling. **Results:** Ninety patients (66 males, 24 females) were treated. Significant improvement ($p < .0001$) in all outcome measures was observed by week 8 as well as at the end of study. The mean time in study was 11.3 weeks. Forty-seven percent ($n = 42$) met a priori criteria for remission. **Conclusions:** Symptoms of mania and depression in juvenile bipolar disorder may be safely and effectively treated acutely with DVPX + Li. *J. Am. Acad. Child Adolesc. Psychiatry*, 2003, 42(8):895–901. **Key Words:** bipolar disorder, lithium, divalproex.

Monotherapies with either lithium carbonate (Li) or divalproex sodium (DVPX) are the most established treatments for adults with bipolar disorder, with both having proven therapeutic efficacy in this population (Bowden et al., 1994). There is evidence that Li monotherapy may be effective in the acute and maintenance treatment of juvenile bipolarity (Davanzo and McCracken, 2000). There are also data to suggest that DVPX may be useful in the treatment of pediatric bipolarity (see review by Chang and Ketter, 2001). However, because of the modest sample sizes used and the methodological limitations of the available studies, there are no agents with proven efficacy in the treatment of juvenile bipolar disorder.

Although either Li or DVPX may have salutary effects for some youths with bipolar illness, there is also evidence that monotherapy with Li or DVPX may not be particularly effective for the treatment of the majority of children and teenagers with this condition (Kowatch et al., 2000). There is also preliminary evidence to suggest that combination therapy with DVPX and Li (DVPX + Li) may be an effective treatment strategy for adults who do not optimally respond to monotherapy with either agent (Young et al., 2000). As many juveniles do not seem to respond to Li or DVPX monotherapy (Chang and Ketter, 2001; Kowatch et al., 2000) and DVPX + Li treatment may be effective in adults, it is possible that DVPX + Li early in the treatment of pediatric bipolarity may be a rational pharmacological approach for youths with bipolar disorder. Furthermore, there already is evidence that combination therapy may be a rational treatment approach for young patients with bipolar disorder. In a study of 28 adolescents with bipolar disorder and psychotic features,

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combination therapy with lithium and an antipsychotic agent was found to be an effective therapeutic strategy (Kafantaris et al., 2001).

The purpose of this study was to examine the effectiveness of combination therapy with DVPX and Li (DVPX + Li) in the treatment of juveniles with bipolar disorder. It was hypothesized that DVPX + Li would be a safe, effective treatment for these patients.

METHOD

The University Hospitals of Cleveland Institutional Review Board for Human Investigation approved the procedures of this outpatient study. The parents/guardians of all study subjects provided written informed consent. All youths provided written assent before participation in this trial. Subjects were seen weekly while they were enrolled in the study.

These results were collected during an initial stabilization portion of a multiphase study that has been previously described (Findling et al., 2000). The first phase of the study, which is described herein, comprised of open-label treatment with both Li and DVPX as the primary form of intervention. Patients who achieved clinical remission for 4 consecutive weeks could then be randomized to receive either Li or DVPX monotherapy in a double-blind, placebo-controlled fashion. These data reflect results from the initial phase of this larger body of work. The goal of this initial portion of this multiphase trial was to obtain rapid syndromal remission in a heterogeneous cohort of outpatient youths similar to those typically encountered in clinical practice. This was done to identify responders who could be randomized to receive monotherapy with either Li or DVPX.

Subjects

Youths between the ages of 5 and 17 years were eligible. To be enrolled, subjects had to have experienced at least one hypomanic or manic episode (American Psychiatric Association, 1994) within the prior 3 months. All subjects met diagnostic symptom criteria for a lifetime diagnosis of bipolar disorder type 1 (BP I) or 2 (BP II) based upon results of the Schedule for Affective Disorders and Schizophrenia for School-Age Children, either K-SADS-PL (Kaufman et al., 1997) or K-SADS-E (Orvaschel, 1994). In addition, all subjects met a lifetime diagnosis BP I or BP II based on the results of a clinical assessment by a child and adolescent psychiatrist.

Patients with a history of intolerance to Li levels of 0.6 mmol/L or a history of intolerance to DVPX levels of 50 μg/mL were not enrolled. Youths who had experienced a manic episode with documented Li levels of ≥1.0 mmol/L or had experienced a manic episode with a documented DVPX level >80 μg/mL were excluded. Other exclusionary criteria included active neurological/medical disorders, a substance abuse disorder within the 6 months prior to enrollment, and evidence of mental retardation or a pervasive developmental disorder. Females who were pregnant, nursing, were at risk of becoming pregnant, or intended to become pregnant were also excluded.

Pharmacotherapy

Patients began combination treatment with both Li and DVPX at baseline. Doses of each were administered so that targets of 20 mg/kg per day of DVPX and 30 mg/kg per day of Li were achieved by the end of week 2. To remain enrolled in the trial, youths had to be able to tolerate a minimum DVPX plasma level of 50 μg/mL and a minimum Li level of 0.6 mmol/L. Medication doses were adjusted so that patients' DVPX levels were between 50 and 100 μg/mL and Li levels between 0.6 and 1.2 mmol/L. Levels of Li and DVPX were obtained at week 2, week 4, and every 4 weeks thereafter. Physicians raised the doses of both Li and DVPX until either the maximum permitted blood levels were reached or until drug related side effects precluded further dose increases. Adherence with treatment was also assessed with direct patient/guardian query and pill counts. Patients entering the study who were currently being prescribed a psychostimulant, antipsychotic, or an antidepressant were tapered off of their current medications by the study physician as rapidly as possible and as clinically tolerated/indicated.

For patients with psychosis or other symptoms of bipolar disorder that did not seem to optimally respond to combination DVPX + Li treatment, transient antipsychotic pharmacotherapy was permitted up to maximum FDA-approved adult doses with risperidone, olanzapine, or quetiapine. For patients with depressive symptoms, adjunctive antidepressants could also be transiently prescribed.

Patients with attention deficit hyperactivity disorder (ADHD) during periods of euthymia were permitted adjunctive treatment with psychostimulants at FDA-approved doses. Clonidine at doses of up to 6 μg/kg per day could also be prescribed for these subjects. If the patients' mood episodes were not responding adequately to DVPX + Li treatment, adjunctive ADHD treatments were discontinued in order to ensure that these adjunctive agents were not interfering with thymoleptic therapy.

Outcome/Safety Measures

Patients were seen by a child/adolescent psychiatrist at all treatment visits. Symptoms of mania were assessed by an experienced rater with the Young Mania Rating Scale (YMRS) (Young et al., 1978), depression with the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski et al., 1985), overall illness severity and improvement with the Clinical Global Impressions Scale (CGI) (NIMH, 1985), and global functioning with the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1985) at each visit. The majority of the assigned scores from their measures were reviewed by the child and adolescent psychiatrist who saw the patient at the study visit. Prior to receiving study medication, a physical examination, an electrocardiogram, a urine toxicology screen, a chemistry profile, a thyroid-stimulating hormone level, a hematology profile, a coagulation profile, and a urinalysis were performed. Post-menstrual females received a urine pregnancy test. Patients also had their height and weights measured. These same safety measures were all obtained at end of the study. In addition, a hematology profile and a chemistry profile were obtained at weeks 4 and 12. A thyroid-stimulating hormone level was also obtained at week 8. Side effects were monitored by direct query from both a research assistant and a study physician at each visit.

Study Completion

At the end of study participation, patients were assigned to either one of two groups: "Remitters" or "Non-Remitters." Subjects were placed into the Remitters group if they tolerated combination DVPX + Li therapy at prescribed levels, were judged to be clinically stable, had no evidence of affective cycling, and did not require treatment with an antipsychotic, an antidepressant, or another mood stabilizer for 4 consecutive weeks. In addition, all Remitters met a priori criteria for clinical response. These criteria were as follows: a CDRS-R ≤40, a YMRS ≤12.5, and a CGAS ≥51 for 4 consecutive weeks. All other subjects were considered Non-Remitters. It should be noted

that the Non-Remitter group included subjects that ended the study due to nonadherence with study procedures, hospitalization, and persistent psychiatric symptomatology.

Participation in this initial stabilization phase could last up to 20 weeks. A patient's participation in this phase ended once he/she met criteria for inclusion into the Remitters group or once it became apparent that a patient would not be able to meet a priori criteria for inclusion in the Remitters group by the end of 20 weeks of treatment.

Statistical Analyses

Analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS, version 10.0, 1999). Averages are presented as mean (standard deviation) unless otherwise noted. Using an intent-to-treat analysis with last observation carried forward, paired samples *t* tests were used to compare YMRS, CDRS-R, CGAS, and CGI scores at baseline with end of week 8 and end of study scores.

Independent sample *t* tests were used to compare age at onset of symptoms, length of illness, baseline symptom severity, and end of study drug levels between the Remitters and Non-Remitters groups. The data were considered adequately close to normally distributed if both skewness and kurtosis of the data were <3.0.

Based on the prior work of Kafantaris et al. (2001) that reported that patients with mania and psychotic features might require treatment with an antipsychotic, χ^2 analyses were performed to examine whether individuals with a lifetime history of psychosis or psychotic symptoms at baseline were less likely to be considered a Remitter at end of study. A χ^2 analysis was also used to examine differences in the occurrences of the course modifier, rapid cycling, in the Remitter and Non-Remitter groups.

Additionally, an independent samples *t* test was performed to examine whether differences in mean drug levels of Li and DVPX existed between those patients who achieved clinical remission and those that did not.

A paired samples *t* test was performed comparing the average weight gain per week over the first 8 weeks to the average weight gain per week over the subsequent weeks in those subjects whose participation was 9 weeks or longer. This was done to examine whether the change in weight varied over time.

Because of the many analyses performed in this study, the reader may find it helpful to employ a Bonferroni corrected two-tailed α level of .0025 to ensure an overall α of <0.05 for the approximately 20 analyses.

RESULTS

Subjects

A total of 207 patients underwent a screening interview. After this interview, 56 did not meet diagnostic symptom criteria, 31 declined participation, and 11 others did not meet one or more of the other inclusion/exclusion criteria. A total of 109 patients were enrolled. Fifteen enrolled but were never dosed (most often due to study noncompliance). Of the 94 patients who received study medications, 4 did not return for an end of week 1 visit due to noncompliance (n = 2) or withdrawing consent (n = 2), and were not considered in the analyses. Ninety youths completed at least 1 week of treatment and were included in the statistical analyses.

TABLE 1
Baseline Mood States in 90 Children and Adolescents With Bipolar Disorder

Mood State	*N*	Overall (%)	Mean (SD) Length of Study Participation	No. (%) Achieving Remission
Mixed[a]	39	43.3	11.2 (4.9)	17 (43.6)
Manic[b]	34	37.8	11.5 (6.0)	16 (47.1)
Depressed[c]	8	8.9	12.3 (5.1)	5 (62.5)
Hypomanic[d]	5	5.6	11.1 (5.5)	2 (40.0)
Euthymic[e]	4	4.4	8.3 (3.5)	2 (50.0)

[a] Children's Depression Rating Scale–Revised (CDRS-R) > 28 and Young Mania Rating Scale (YMRS) ≥ 12.
[b] CDRS-R ≤ 28 and YMRS ≥ 16.
[c] CDRS-R > 28 and YMRS < 12.
[d] CDRS-R ≤ 28 and YMRS 12–15.
[e] CDRS-R ≤ 28 and YMRS < 12.

Those 90 patients ranged in age between 5 and 17 years with an average (SD) age of 10.9 (3.4) years. Sixty-six subjects were males and 86 met diagnostic criteria for BP I. Sixty percent exhibited the rapid cycling variant of bipolar disorder. The mean age of onset of bipolar symptoms was 7.2 (4.0) years with a mean length of illness of 167.8 (122.0) weeks.

Sixty-eight (75.6%) of the subjects also met diagnostic symptom criteria for one or more co-morbid psychiatric diagnoses. ADHD and the disruptive behavior disorders were the most common co-morbidities, with 64 of the subjects meeting diagnostic criteria for one or more of these conditions. Length of time participants were enrolled in the study ranged from 1 to 20 weeks with a mean (SD) length of treatment of 11.3 (5.3) weeks.

Symptomatic Response

Baseline mood states of these 90 subjects are listed in Table 1. There was a significant change from baseline values at both the end of week 8 and end of study on the YMRS (t = 12.4, df = 84, p < .0001 and t = 15.2, df = 88, p < .0001, respectively), the CDRS-R (t = 6.9, df = 84, p < .0001 and t = 7.3, df = 88, p < .0001, respectively), CGI-Severity score (t = 12.1, df = 86, p < .0001 and t = 13.8, df = 89, p < .0001, respectively), and CGAS (t = –10.5, df = 86, p < .0001 and t = –11.9, df = 89, p < .0001, respectively). Mean and standard deviations are summarized in Table 2.

TABLE 2
Outcome Measure Scores in 90 Children and Adolescents With Bipolar Disorder[a]

Measure	Baseline Score	EOW 8 Score	EOS Score
Young Mania Rating Scale	21.8 (8.2)	7.8 (9.0)	5.7 (8.5)
Children's Depression Rating Scale–Revised	31.7 (14.0)	20.9 (7.9)	21.0 (7.9)
Children's Global Assessment Scale	50.1 (7.2)	65.2 (12.9)	68.1 (13.5)
Clinical Global Impression Scale–Severity	4.1 (0.9)	2.3 (1.3)	2.0 (1.2)
Clinical Global Impression Scale–Improvement	NA	2.4 (1.1)	2.1 (1.2)

Note: NA = not applicable.
[a] Intent-to-treat analysis with last observation carried forward; data presented as mean (SD).

Clinical Remission

Of the 90 youths, 42 (46.7%) met a priori criteria for remission. Exit reasons for Non-Remitters to be withdrawn from the study included nonadherence with study procedures (n = 19), hospitalization (n = 3), and persistent psychiatric symptomatology (n = 11). Of the 11 (22.9%) Non-Remitters who exited the study due to persistent psychiatric symptoms, 7 discontinued because of psychosis and 4 patients discontinued because of persistent hypomania/mania or continued cycling. No patients were discontinued because of depressive symptoms. In summary, there were 42 Remitters and 48 Non-Remitters; of the 48 Non-Remitters, 11 subjects exited the study because of persistent psychiatric symptomatology. Table 3 shows demographic information of the Remitters, Non-Remitters, and Non-Remitters due to persistent symptomatology.

There was no significant difference in age at onset or length of illness (t = –1.4, df = 87, p = .17 and t = 1.4, df = 87, p = .16, both two-tailed) between the Remitters and the other subjects. In addition, a χ^2 analysis indicated that the proportion of patients with rapid cycling did not differ between the Remitter and Non-Remitter groups (χ^2 = 1.9, df = 1, p = .17, two-tailed). The average (SD) length of participation was 13.1 (4.1) weeks for the Remitters group and 9.6 (5.7) weeks for the Non-Remitters group. Either a lifetime history of psychosis or the presence of psychotic symptomatology at baseline was found to be more common in those patients who were Non-Remitters due to persistent psychiatric symptomatology (n = 11) than in those patients who were considered Remitters (n = 42) (χ^2 = 12.6, df = 1, $p \leq 0.0001$; χ^2 = 5.2, df = 1, p = .023, both two-tailed).

TABLE 3
Demographic Information by Remission Status in 90 Youths With Bipolar Disorder

	Remitters (N = 42)	All Nonremitters (N = 48)	Nonremitters due to Persistent Symptomatology (N = 11)
Gender			
Males [no. (%)]	29 (69.0)	37 (77.1)	8 (72.7)
Females [no. (%)]	13 (31.0)	11 (22.9)	3 (27.9)
Lifetime history of psychosis [no. (%)]	2 (4.8)	9 (18.8)	5 (45.5)
Lifetime history of rapid cycling [no. (%)]	22 (52.4)	32 (66.7)	6 (54.5)
Age (SD) (yr)	11.1 (3.6)	10.7 (3.2)	9.3 (2.2)
Age of onset (SD) (yr)	7.8 (4.3)	6.6 (3.8)	5.6 (2.8)
Baseline YMRS Score (SD)	19.6 (7.6)	23.8 (8.2)	21.4 (6.7)
Baseline CDRS-R Score (SD)	31.5 (12.8)	31.9 (15.1)	29.0 (9.8)
Baseline CGAS Score (SD)	51.0 (6.2)	49.4 (7.9)	52.5 (9.4)
End of Study YMRS Score (SD)	0.8 (2.2)	10.1 (9.7)	7.3 (5.0)
End of Study CDRS-R Score (SD)	18.1 (2.3)	23.5 (10.0)	17.8 (1.5)
End of Study CGAS Score (SD)	76.7 (6.9)	60.5 (13.3)	64.0 (10.2)
Any comorbid diagnosis (%)	29 (69.0)	39 (81.3)	10 (90.9)
Comorbid ADHD diagnosis (%)	25 (59.5)	35 (72.9)	10 (90.9)

Note: YMRS = Young Mania Rating Scale; CDRS–R = Children's Depression Rating Scale–Revised; CGAS = Children's Global Assessment Scale.

TABLE 4
Concomitant Medications Administered to 90 Children and Adolescents With Bipolar Disorder

Medication	Ever During Study [*N* (%)]	Study Entry [*N* (%)]	End of Study [*N* (%)]
Stimulant	53 (58.9)	32 (35.6)	47 (52.2)
α_2-adrenergic agonist	22 (24.4)	17 (18.9)	0 (0.0)
Atypical antipsychotic	19 (21.1)	8 (8.9)	13 (14.4)
SSRI	10 (11.1)	8 (8.9)	2 (2.2)
Other antidepressant	4 (4.4)	5 (5.6)	0 (0.0)
Tricyclic antidepressant	4 (4.4)	4 (4.4)	0 (0.0)
Anticonvulsant	3 (3.3)	4 (4.4)	0 (0.0)
Buspirone	2 (2.2)	2 (2.2)	2 (2.2)
Typical antipsychotic	2 (2.2)	2 (2.2)	1 (1.1)
Benzodiazepine	1 (1.1)	1 (1.1)	1 (1.1)

Note: SSRI = serotonin selective reuptake inhibitor.

TABLE 5
Most Common Adverse Events Reported in 90 Youths With Bipolar Disorder

Side Effect	*N*	%
Emesis	43	47.8
Enuresis	41	45.6
Stomach pain	41	45.6
Tremor	37	41.1
Increased thirst	33	36.7
Headache	31	34.4
Nausea	29	32.2
Sedation	28	31.1
Increased appetite	24	26.7
Diarrhea	22	24.4
Decreased appetite	15	16.7
Respiratory congestion	14	15.6
Fever with flu symptoms	13	14.4
Dizziness	11	12.2
Body ache	10	11.1

Medication Dosing

At the end of study, the mean (SD) total daily dose of DVPX was 862.5 (397.5) mg/day with an average end of study DVPX blood level of 79.8 (25.9) μg/mL. This corresponded to a weight-adjusted DVPX dose of 20.6 (8.7) mg/kg per day. The mean dose of Li that was prescribed at the end of study was 923.3 (380.2) mg/day with an average end of study Li level of 0.9 (0.3) mmol/L. The mean end of study dose of Li that was prescribed was 22.1 (8.7) mg/kg per day. There was no significant difference in DVPX levels at end of study between Remitters and Non-Remitters (mean ± SD, 80.0 ± 20.6 versus 79.6 ± 32.6, $t = -0.1$, $df = 67$, $p = .94$). However, Li levels at end of study in the Remitters ($n = 42$) and Non-Remitters ($n = 48$) were significantly different from each other (mean ± SD, 1.0 ± 0.3 versus 0.7 ± 0.3, respectively; $t = -3.3$, $df = 66$, $p = .002$).

In addition, when comparing the Non-Remitters due to persistent psychiatric symptomatology subgroup ($n = 11$) to the Remitters, a significant difference in end of study Li levels was found (mean ± SD, 0.8 ± 0.3 versus 1.0 ± 0.3, respectively; $t = 2.2$, $df = 49$, $p = .036$).

Concomitant medications that were taken by study subjects are shown in Table 4. Psychostimulants were the most common concomitant medications prescribed. Fifty-nine percent ($n = 53$) were prescribed a psychostimulant and 23.3% ($n = 21$) were prescribed clonidine at some time during study participation. Of the 11 patients that were Non-Remitters due to persistent symptomatology, 9 (81.8%) were treated with a stimulant, 7 (63.6%) received an atypical antipsychotic, 2 (18.2%) an SSRI, 1 (9.1%) with trazodone, and 1 (9.1%) with carbamazepine while enrolled in the study.

Medication Tolerability

Fifteen (16.7%) patients were withdrawn from this protocol due to medication intolerance. Twelve (80.0%) of the medication-related discontinuations were thought to be most likely attributable to Li. These included ataxia/neurological side effects ($n = 5$), persistent thyrotropin level >10.00 mU/L ($n = 3$), proteinuria ($n = 1$), enuresis ($n = 1$), emesis ($n = 1$), or dysphoria ($n = 1$). Two (13.3%) of the discontinuations were most likely attributable to probable DVPX-related side effects. These included increased transaminases ($n = 1$, 1.1% of all subjects) and worsening manic symptoms with increased DVPX doses ($n = 1$). One subject could not tolerate adjunctive treatment with psychostimulants for treatment of co-morbid ADHD and had to be removed. The remainder of the side effects noted in this trial were generally of mild severity and transient. A listing of the most common adverse events reported by study subjects/guardians at least once is shown in Table 5.

The mean (SD) baseline weight of study participants was 44.3 (22.2) kg and the mean (SD) weight at end of study was 47.3 (23.9) kg. Significant weight changes from baseline to end of study ($t = -6.4$, $df = 85$, $p < .0001$) were found. There were 55 youths whose study participation lasted longer than 8 weeks. This subset of subjects gained 0.3 (0.4) kg/week on average during the first 8 weeks. After week 8, these participants gained an aver-

age of 0.2 (0.5) kg/week. A comparison of these rates suggests that weight gain may diminish after the first 8 weeks of treatment ($t = 1.7$, $df = 54$, $p = .09$, two-tailed).

DISCUSSION

These preliminary data suggest that the combination of DVPX and Li may be useful in the treatment of juvenile bipolarity and that almost half of patients treated with this regimen achieve clinical remission.

Overall, therapy with DVPX and Li was well tolerated. Fifteen of the patients were withdrawn due to medication-related side effects. However, none of these adverse events was unexpected. Besides the relatively large sample size, other strengths of this study include the diagnostic homogeneity of the study cohort and the implementation of stringent, clinically meaningful criteria for remission.

The data reported in this paper suggest that the use of combination DVPX and Li pharmacotherapy may be a reasonable treatment option. In a recently reported study by Frazier et al. (2001), 23 youths meeting diagnostic symptom criteria for bipolar disorder, currently manic or mixed, were enrolled in an 8-week, open-label trial of olanzapine monotherapy. In that study, 61.0% of the subjects met those authors' responder criteria (defined as a ≥30% reduction in baseline YMRS total score and CGI-Severity score of ≤3 at 8 weeks). If the same response criteria were applied to this cohort, using intent-to-treat analysis (with the last observation carried forward), 75.3% of the subjects described herein would have met those authors' responder criteria at week 8.

In another prospective study, Kowatch et al. (2000) treated 42 youths with bipolar disorder, currently in a manic or mixed state, for up to 8 weeks with Li, DVPX, or carbamazepine monotherapy. One of those investigators' response criterion was defined as a ≥50% improvement in YMRS score from baseline. Another criterion was a score of 1 or 2 on the CGI–Improvement score for overall bipolar illness (implying the subjects were "much" or "very much" improved). The response rate based on the YMRS criterion for the patients seen in the study of Kowatch and colleagues was 38% for Li, 53% for DVPX, and 38% for carbamazepine. When applying this YMRS response criterion to the cohort described herein, using intent-to-treat analysis, a response rate of 70.6% was achieved in this trial. Based on the CGI response criterion of Kowatch et al. (2000), those investigators found a response rate of 46% for Li, 40% for DVPX, and 31% for carbamazepine. Using the same CGI response criterion, a response rate of 59.3% was observed for the DVPX + Li-treated subjects. In addition, when examining only those patients that were in a manic or mixed state at study entry and those not receiving an antidepressant or antipsychotic at week 8 ($n = 60$), these response rates were found to increase by ≤5%.

Kafantaris et al. (2001) initially reported that adjunctive treatment with an antispsychotic may be necessary in youths with psychotic symptoms to maintain overall symptom remittance. It is interesting to note that in this study subjects with either a lifetime history of psychosis or youths with psychotic symptoms at baseline were less likely to meet criteria for symptom remittance after Li and Dvpx combination treatment in this trial.

The results of this study provide information regarding potential developmental differences in the expression of bipolar disorder across the life cycle. Following initiation with DVPX + Li, depression was not a commonly observed mood state in this cohort. However, Calabrese et al. (2001) recently reported that when adults with rapid cycling bipolar disorders are treated with DVPX + Li, the most treatment recalcitrant mood state in that cohort was depression. The results of this study and that of Calabrese et al. (2001) extend the observations of Kraepelin (1921), who noted that as patients with manic-depressive disorder age, symptoms of depression become more manifest over time.

There are additional data to support that other developmental differences may exist between youths and adults who suffer from bipolar disorder. In this trial, almost half of the subjects had syndrome remission with DVPX + Li therapy. However, this response rate is about twice that of what was seen in the study of Calabrese et al. (2001). In that trial, approximately 25% of adult subjects experienced syndrome remission. These findings suggest that vigorous intervention early in the course of bipolar disorder may be of particular benefit.

Study Limitations

The study is limited by its open uncontrolled design and awaits replication in a randomized controlled trial. In addition, because of the relative brevity of this study, whether or not DVPX + Li is an optimal form of maintenance pharmacotherapy from the vantage points of both safety and effectiveness remains to be seen. Furthermore, permitting concomitant antipsychotic, antidepressant, and stimulant treatment during this trial may have contributed to the results observed in this study.

Therefore, comparison of this work to other previously reported trials with different methodologies should be made with caution.

Clinical Implications

Considering both the poor outcomes reported in juvenile bipolarity (Geller et al., 2001) and the paucity of therapeutic data in this population, the study of treatment for these vulnerable youths is an important unmet need. The findings of this study suggest that symptoms of both mania and depression may be safely and effectively treated over the short term with DVPX + Li treatment and suggest that the benefits of accurate and early detection and vigorous treatment of juvenile bipolarity may be substantial. Of note, this study did not directly compare acute treatment with Li or DVPX monotherapy to acute combination Li and DVPX treatment. Therefore, it should not be inferred that combination Li and DVPX therapy is superior to monotherapy in the acute treatment of youths with bipolar disorder. Although it is premature to recommend that patients be started on these two medications simultaneously, this does present promising results from a large cohort that includes patients commonly encountered in clinical practice. These data suggest that combination treatment of Li and DVPX is a clinical intervention worthy of further examination.

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