

Combination Lithium and Divalproex Sodium in Pediatric Bipolar Symptom Restabilization

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ABSTRACT

Objective: It has been reported that bipolar disorder may become less responsive to previously effective treatment with each symptomatic relapse. The primary goal of this study was to assess the rate of restabilization after the resumption of lithium (Li^+) plus divalproex (DVPX) following relapse on either agent as monotherapy. **Method:** This is a prospective, 8-week, open-label outpatient Li^+ /DVPX combination therapy trial. Patients ages 5 to 17 years with bipolar disorder type I or II, who had achieved symptom remission with Li^+ /DVPX combination therapy and subsequently relapsed during treatment with Li^+ or DVPX monotherapy were enrolled between January 1999 and January 2003. **Results:** Thirty-eight patients with a mean age of 10.5 years entered the study. Thirty-four (89.5%) patients responded to treatment with Li^+ /DVPX mood stabilizer therapy alone, but four patients required adjunctive antipsychotic treatment to address residual symptomatology. Overall, reinitiation of Li^+ /DVPX combination therapy was well tolerated with no subjects discontinuing because of a medication-related adverse event. **Conclusions:** It appears that most youths with bipolar disorder who stabilize on combination Li^+ /DVPX therapy and subsequently relapse during monotherapy can safely and effectively be restabilized with the reinitiation of Li^+ /DVPX combination treatment. *J. Am. Acad. Child Adolesc. Psychiatry*, 2006;45(2):142–148. **Key Words:** bipolar disorder, lithium, divalproex sodium, treatment.

During the past several years, there has been a growing body of evidence to support the assertion that treatment with more than one thymoleptic medication may be a rational therapeutic strategy in the short-term management of children and adolescents with bipolar

disorder (BP; Findling et al., 2003; Kafantaris et al., 2001; Kowatch et al., 2003). It has been unclear whether patients who stabilized on combination drug therapy continued to benefit from receiving more than one drug.

To address this question, a recently completed randomized, double-blind trial was conducted at the University Hospitals of Cleveland. In this study, a group of patients who had achieved syndromal remission with combination lithium (Li^+) and divalproex (DVPX) treatment (Findling et al., 2003) were randomized to receive Li^+ or DVPX monotherapy (Findling et al., 2005) for up to 76 weeks. Results of that study indicated that despite the complex cycling patterns seen in youths with BP (Findling et al., 2001; Geller et al., 1995), DVPX was not superior to Li^+ as a maintenance treatment in this patient cohort.

In adults, some investigators have noted that patients with bipolar disorder may become less responsive to previously effective Li^+ therapy after Li^+ discontinuation (Post et al., 1992). Others have not observed this phenomenon, however (Coryell et al., 1998).

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Unfortunately, there are no randomized studies that have definitely addressed this issue. Thus, it was not clear whether the pediatric study patients who had initially remitted with combination drug therapy could safely and effectively be restabilized with the reinitiation of the same combination drug treatment if they relapsed during medication monotherapy. In the absence of any such prospective data in pediatric bipolarity, based on our clinical experience, we hypothesized that youths who had achieved syndromal remission with Li⁺/DVPX combination therapy and relapsed during Li⁺ or DVPX monotherapy would respond in a satisfactory fashion to the reinitiation of Li⁺/DVPX combination treatment.

METHOD

The University Hospitals of Cleveland Institutional Review Board for Human Investigation approved the procedures of this outpatient protocol. The parents/guardians of all of the study subjects provided written informed consent and all youths provided written assent before participation. During the 8-week trial, patients were seen initially weekly for 4 weeks, then biweekly for the remaining 4 weeks.

The results reported herein were collected as part of the final portion of a multiphase study (Findling et al., 2000, 2003, 2005). As illustrated in Figure 1, all patients participated in an initial open-label stabilization phase lasting up to 20 weeks during which time they received Li⁺/DVPX combination therapy. Those who achieved biphasic symptom remission for 4 consecutive weeks entered a subsequent double-blind randomized maintenance phase during which time they received Li⁺ or DVPX monotherapy for up to 76 weeks. Patients who experienced mood symptom relapse during the blinded monotherapy phase were eligible to enroll in this open-label 8-week study in which subjects again received combination Li⁺/DVPX.

Subjects

Youths ages 5 to 17 years, meeting *DSM-IV* (American Psychiatric Association, 2000) criteria for a lifetime diagnosis of BP type I

(BPI) or II (BPII), based on a Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS) interview (Ambrosini, 2000; Kaufman et al., 1997; Orvaschel, 1994), were eligible for enrollment in the initial study phase (Findling et al., 2003) and could receive open-label Li⁺/DVPX. All of the participants also met criteria for BPI or BPII as per a separate clinical assessment by a child and adolescent psychiatrist.

A history of intolerance to therapeutic levels of Li⁺ or DVPX, occurrence of a manic episode while at a therapeutic level of Li⁺ or DVPX, or existence of a neurological or other medical disorder for which Li⁺ or DVPX would be contraindicated was exclusionary. Patients with evidence of mental retardation, a pervasive developmental disorder, an inability to swallow pills, a history of alcohol or other substance abuse or dependence within 6 months before enrollment, or an active neurological or other medical condition suspected to contribute to the expression of mood symptoms were also excluded from participation. In addition, pregnant females or those who intended to become pregnant, as well as those females who were sexually active and were on an inadequate form of birth control were not permitted to participate.

Pharmacotherapy

Throughout this multiphase trial, patients were dosed to meet target serum concentrations of 0.6 to 1.2 mmol/L for Li⁺ and 50 to 100 µg/mL for DVPX, and patient tolerability at these serum concentrations was required to remain enrolled. During the randomized monotherapy phase, serum concentrations were monitored by an unblinded physician. If subjects developed symptoms of mood relapse during the blinded monotherapy phase, then they were enrolled in this restabilization study based on the treating physician's clinical judgment. At the onset of enrollment into the restabilization study, patients were treated with the doses of both Li⁺ and DVPX at which earlier stabilization had occurred. If necessary, dose adjustments were made to again achieve optimal therapeutic doses. Serum DVPX and Li⁺ levels were obtained at baseline and at weeks 2, 4, 6, and 8. Pill counts and direct query of parent/guardian were used to assess for patient adherence to medication treatment. During this restabilization trial, patients were able to be prescribed a psychostimulant at a U.S. Food and Drug Administration–approved dose, as well as clonidine at a maximum daily dose of 6 µg/kg/day if residual symptoms of ADHD were present. Adjunctive treatment with other mood-stabilizing medications was also permissible during this

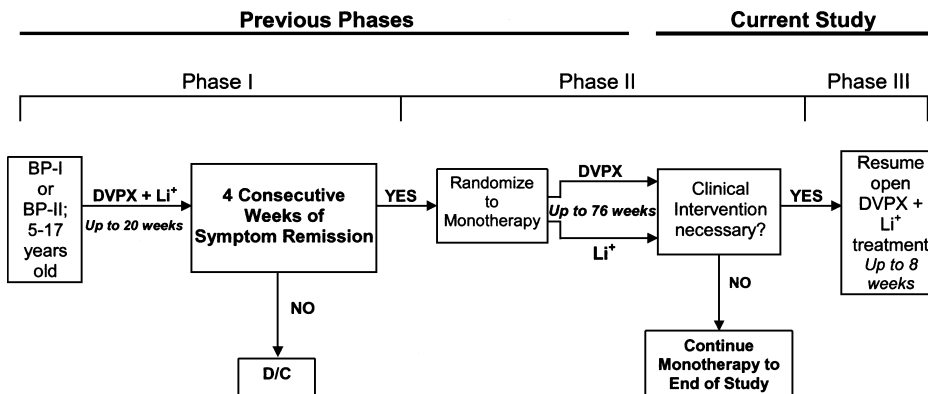


Fig. 1 Study design.

rehabilitation trial, at the treating physician's discretion, if it was felt that the response to the reinstatement of Li^+ and DVPX was inadequate.

Outcome/Safety Measures

Outcome measures of specific mood state included the Children's Depression Rating Scale-Revised (CDRS-R; Poznanski et al., 1985), which assesses the presence and severity of symptoms of depression, and the Young Mania Rating Scale (YMRS; Young et al., 1978), which provides a rating for 11 distinct symptoms of mania. The Clinical Global Impressions Scale (CGI; National Institute of Mental Health, 1985) was used to assess overall bipolar symptom severity (CGI-S). In addition, the Children's Global Assessment Scale (CGAS; Shaffer et al., 1983) was used to provide an assessment of overall functioning at home, with peers, and in school. The above outcome measures were completed at each study visit. Patients and their parents/guardians were also queried at each visit regarding adverse events. Patients underwent a physical examination and electrocardiography at the initiation and end of this rehabilitation phase. Safety laboratory tests were also performed at the beginning and the end of this rehabilitation study and included a urine toxicology screen, a thyroid-stimulating hormone blood level, chemistry and hematology profiles, a coagulation profile, and a urinalysis. Female patients who had reached menarche received a urine pregnancy test at baseline and at the end of study participation. In addition, vital signs and patient weight were documented at each visit.

Statistical Analyses

Analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS, version 11.5, 2002). Averages are presented as mean (standard deviation) unless otherwise noted. The α level for statistical significance was set at $p \leq .05$.

Paired-samples t tests using last observation carried forward were used to compare YMRS, CDRS-R, CGI-S, and CGAS scores at baseline of the reinitiation phase with those at the end of week 4 and at the end of study participation. In addition, paired-samples t tests were used to compare mean DVPX and Li^+ levels at the start of this rehabilitation phase, with the DVPX and Li^+ levels measured at the end of study participation. A paired-samples t test was also conducted to determine whether there was significant change in the mean weight of patients during the course of participation in this 8-week rehabilitation trial.

RESULTS

Subjects

Two hundred eighty-seven subjects were screened for participation and 161 subjects were enrolled in the multiphase protocol. A complete description of subject accountability throughout the protocol is shown in Figure 2.

Forty patients were initially enrolled in this rehabilitation study between January 1999 and January 2003, and 38 patients completed at least 1 week of treatment and were included in the statistical analyses. Of the two

patients who were not included in the analyses, one patient withdrew consent and was not dosed, and the other patient did not return after baseline. Thirty-five (92.1%) patients completed all 8 weeks of the study. Three patients did not complete the study because of withdrawal of consent ($n = 2$) and loss to follow-up ($n = 1$).

The 38 patients ranged in age between 5 and 17 years with an average age of 10.5 (3.62) years at the start of the reinitiation of DVPX and Li^+ treatment. Additional demographic information is provided in Table 1. Sixteen subjects (42.1%) exhibited the rapid cycling variant of the disorder, exhibiting at least four distinct mood episodes during the course of 1 year. The mean age at onset of bipolar symptoms was 6.4 (3.9) years, with a mean length of illness at enrollment of the reinitiation phase of 185.1 (131.5) weeks at the onset of DVPX and Li^+ treatment.

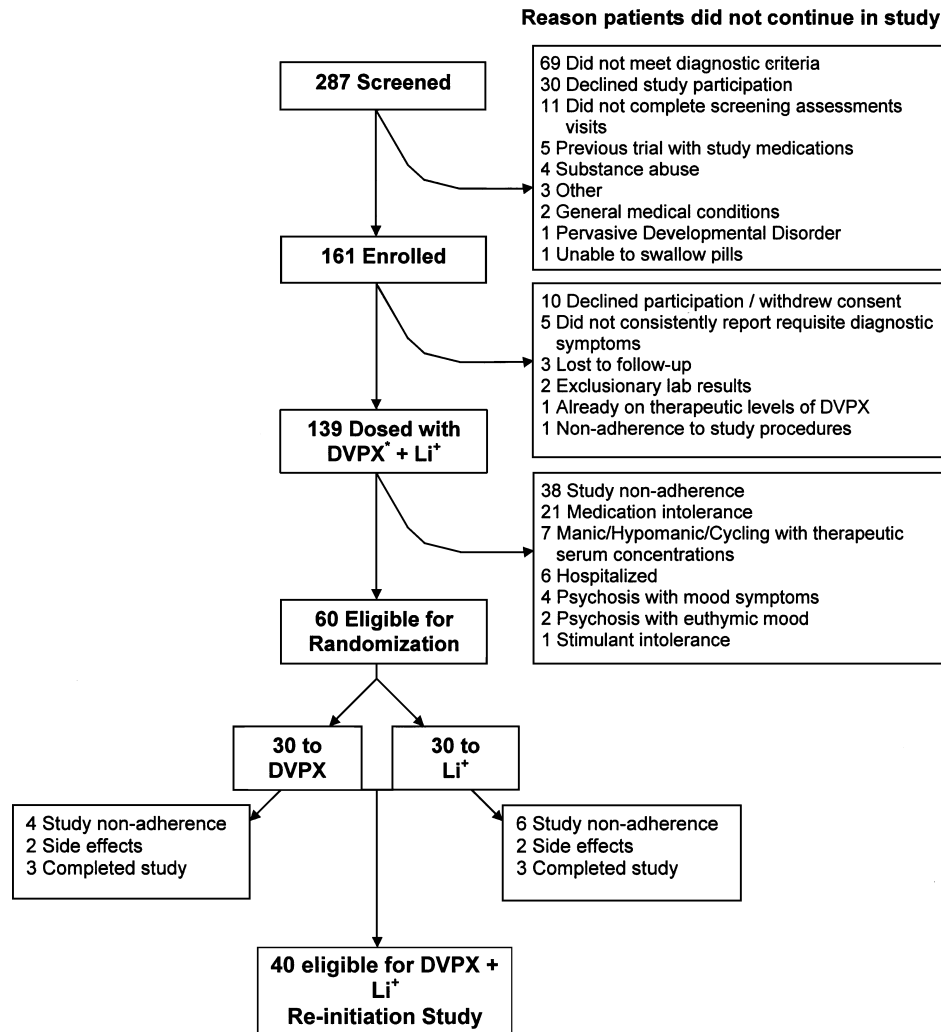
Thirty (78.9%) of the subjects also met diagnostic symptom criteria for one or more comorbid psychiatric diagnoses. ADHD ($n = 25$, 65.8%), oppositional defiant disorder ($n = 10$, 26.3%), conduct disorder ($n = 3$, 7.9%), and encopresis ($n = 3$, 7.9%) were the most common psychiatric comorbidities.

Nineteen patients (50%) received Li^+ monotherapy and 19 patients (50%) received DVPX monotherapy during the randomized maintenance monotherapy trial. Table 1 shows demographic and length-of-treatment information in previous phases of this study.

Symptomatic Response

The mean psychometric outcome scores at baseline of the reinitiation phase, week 4, and end of study are shown in Table 2. There was a significant decline in symptoms during the course of the study on the YMRS ($t = 6.6$, $df = 34$, $p < 0.01$), CDRS-R ($t = 2.4$, $df = 34$, $p < 0.05$), CGAS ($t = 7.2$, $df = 34$, $p < 0.01$), and the CGI-S ($t = 8.8$, $df = 34$, $p < 0.01$) measures.

At the start of this rehabilitation phase, mean Li^+ and DVPX serum concentrations were 0.87 mmol/L (0.18 mmol/L) and 85.2 $\mu\text{g}/\text{mL}$ (20.2 $\mu\text{g}/\text{mL}$) respectively. The end of study mean Li^+ and DVPX serum concentrations were 0.83 mmol/L (0.28 mmol/L) and 75.5 $\mu\text{g}/\text{mL}$ (18.9 $\mu\text{g}/\text{mL}$), respectively. A comparison of mean serum concentrations at the beginning and end of this rehabilitation phase revealed no significant difference for DVPX ($t = 0.94$, $df = 17$, $p = .36$) or Li^+



* DVPX = divalproex sodium, Li⁺ = lithium

Fig. 2 Subject accountability.

($t = 0.47$, $df = 18$, $p = .64$). The end of study average total daily Li⁺ dose was 872 mg (22.2 mg/kg) and the mean total daily DVPX dose was 833 mg (21.0 mg/kg).

Twenty-five (65.8%) patients were prescribed a stimulant medication during the study. Twelve (31.6%) patients were prescribed one or more other psychotropic medication(s). These concomitant medications are listed in Table 3.

Four subjects received adjunctive treatment with an atypical antipsychotic for treatment of either residual mood symptomatology ($n = 3$) or aggression ($n = 1$). These antipsychotics included risperidone and olanzapine, at doses ranging between 0.25 and 1 mg, and 2.5 and 5 mg, respectively. These antipsychotics were

initiated within the first 3 weeks of treatment, and their use was continued for the remainder of the trial.

Medication Tolerability

Overall, the study medications were generally well tolerated, with none of the patients ending participation in the study because of medication intolerance. In addition, no occurrences of discontinuation of study participation were related to abnormal laboratory results or adverse events. The most commonly reported adverse events were emesis ($n = 10$), enuresis ($n = 8$), and headache ($n = 8$). Adverse events reported in $\geq 10\%$ of the subjects are listed in Table 4. The mean (SD) weight of study participants at the start of the reinitiation phase

TABLE 1
Demographics of the 38 Trial Participants

	Li ⁺ (n = 19)	DVPX (n = 19)	Overall (N = 8)
Gender, no. (%)			
Males	15 (78.9)	12 (63.2)	27 (71.1)
Females	4 (21.1)	7 (36.8)	11 (28.9)
Diagnosis, no. (%)			
BPI	17 (89.5)	18 (94.7)	35 (92.1)
BPII	2 (10.5)	1 (5.3)	3 (7.9)
Age at onset of bipolar illness, yr (SD)	6.1 (4.0)	6.8 (3.9)	6.4 (3.9)
Age at entry in reinitiation trial, yr (SD)	10.3 (3.7)	10.7 (3.7)	10.5 (3.6)
Length of illness at onset of reinitiation trial, wk (SD)	195.2 (134.4)	174.9 (131.3)	185.1 (131.5)
Time to initial stabilization with combination Li ⁺ /DVPX treatment, wk (SD)	12.9 (4.3)	13.6 (3.8)	13.3 (4.0)
Time to relapse during Li ⁺ /DVPX combination therapy, wk (SD)	13.5 (12.1)	10.6 (10.3)	12.0 (11.2)

Li⁺ = lithium; DVPX = divalproex; BPI/II = bipolar disorder type I/II.

was 43.0 (23.8) kg and mean weight at the end of study participation was 44.2 (24.3) kg. A statistically significant weight change from baseline to the end of the study ($t = 3.8$, $df = 37$, $p < .0001$) was found.

DISCUSSION

These data suggest that most youths with BP who initially stabilize on combination Li⁺/DVPX drug therapy and who subsequently experience recurrence of symptoms while receiving Li⁺ or DVPX monotherapy can be effectively retreated with the reinitiation of combined Li⁺/DVPX treatment. In addition to a relatively large sample size, other strengths of this study include a prospective study design and diagnostic homogeneity of the study sample.

This study is novel in that it is the first to specifically address the issue of restabilization of children and adolescents following symptom relapse associated with medication discontinuation. It should be noted, however, that reinitiation of combination drug therapy

occurred upon clinically significant symptom relapse at the treating physician's discretion, and patients did not need to meet all of the diagnostic symptom criteria for either a manic or depressive episode before the reinitiation of Li⁺/DVPX treatment. Therefore, it can be inferred that these findings may be most applicable for treating youths who may be early in relapse rather than those with significant duration and/or marked severity of symptoms.

Limitations

One limitation of this study is its open-label design. The use of a randomized and blinded design may have provided more methodologically rigorous evidence pertaining to the effectiveness of the reinitiation of combination drug treatment. Because it has not been established whether juvenile-onset BP is the same condition as adult-onset BP, these results may not be generalizable to older-onset patients. In addition, these results may not be applicable to young patients with

TABLE 2
Mean (SD) Scores of Psychometric Measures at Baseline, End of Week 4,
and End of the Restabilization Trial

Scale	Baseline	End of Week 4	End of Study
Young Mania Rating Scale	12.2 (7.8)	3.5 (4.4) ^a	2.8 (3.2) ^a
Children's Depression Rating Scale-Revised	23.9 (8.1)	18.9 (3.8) ^a	20.4 (5.6) ^a
Children's Global Assessment Scale	60.1 (8.4)	71.3 (7.9) ^a	73.2 (6.9) ^a

^a Using intent-to-treat analyses with the last observation carried forward.

TABLE 3
Number of Subjects Prescribed Concomitant Psychotropic Medications

Sequence of Concurrent Therapy	Mixed Amphetamine Salts ^a	Methylphenidate ^b	Olanzapine	Risperidone	Clonidine
Initiated before onset of reinitiation trial					
Discontinued before end of study	0	1	0	0	0
Continued through end of study	10	8	0	0	5
Initiated after onset of reinitiation trial					
Discontinued before end of study	0	0	1	0	0
Continued through end of study	1	5	0	4	3

^a Adderall ($n = 9$), Adderall XR ($n = 2$).

^b Concerta ($n = 2$), immediate-release methylphenidate ($n = 12$).

atypical presentations of bipolarity. It should also be noted that the sample in this study was predominately composed of young males with a high rate of comorbid ADHD who were allowed to receive concomitant pharmacotherapy. For these reasons, this sample may not be entirely generalizable and symptom remittance may have been facilitated by these other compounds. Furthermore, although symptom remittance occurred in almost all of the patients enrolled, the relative brevity of this 8-week study prevents definitive conclusions to be made regarding the durability of symptom response. In addition, because this was a relatively brief trial, no statements can be made pertaining to the long-term safety and tolerability of the medication regimens prescribed herein.

Clinical Implications

There is evidence that young people with bipolar illness may benefit greatly from combination drug therapy. After acute combination drug therapy has successfully been implemented, limited data exist to suggest

whether attempting to treat patients with drug monotherapy was safe (in terms of sequelae associated with symptom relapse) or if after an unsatisfactory monotherapy trial those patients would benefit from their previous thymoleptic regimen. These data suggest that, for youths who stabilize on drug combination therapy, if carefully monitored and promptly addressed, the sequelae associated with symptomatic relapse may be effectively managed without serious consequences such as hospitalization and the development of serious suicidal behaviors. These results also suggest that if patients are treated early in the course of symptomatic relapse, then most will respond to their prior medication regimen. It should be noted, however, that some patients may not respond to previously effective treatment.

In summary, these data provide the basis to begin the characterization of the risks associated with a drug monotherapy trial for patients who had responded to combination drug therapy. The results suggest that the likelihood of adequate benefit with the reinitiation of previously effective combination drug therapy is high. In youths who achieve syndromal remission with Li⁺/DVPX therapy, it appears symptom reductions may generally be achieved relatively quickly and safely upon the reinitiation of combination Li⁺/DVPX treatment should they relapse during treatment with Li⁺ or DVPX monotherapy.

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TABLE 4

Side Effects Reported by At Least 10% of Study Subjects

Side Effect	No.	%
Emesis	10	26.3
Enuresis	8	21.1
Headache	8	21.1
Nausea	7	18.4
Diarrhea	6	15.8
Tremor	6	15.8
Stomach pain	4	10.5
Sedation	4	10.5
Increased thirst	4	10.5

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