Double-Blind 18-Month Trial of Lithium Versus Divalproex Maintenance Treatment in Pediatric Bipolar Disorder

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ABSTRACT

Objective: To determine whether divalproex sodium (DVPX) was superior to lithium carbonate (Li^+) in the maintenance monotherapy treatment of youths diagnosed with bipolar disorder who had been previously stabilized on combination Li^+ and DVPX (Li^+/DVPX) pharmacotherapy. **Method:** Youths ages 5–17 years with bipolar I or II disorder were initially treated with Li^+ /DVPX. Patients meeting remission criteria for four consecutive weeks were then randomized in a double-blind fashion to treatment with either Li^+ or DVPX for up to 76 weeks. Study participation ended if the subject required additional clinical intervention or if the subject did not adhere to study procedures. **Results:** Patients were recruited between July 1998 and May 2002. One hundred thirty-nine youths with a mean (SD) age of 10.8 (3.5) years were initially treated with Li^+/DVPX for a mean (SD) duration of 10.7 (5.4) weeks. Sixty youths were then randomized to receive monotherapy with Li^+ (n = 30) or DVPX (n = 30). The Li^+ and DVPX treatment groups did not differ in survival time until emerging symptoms of relapse (p = .55) or survival time until discontinuation for any reason (p = .72). **Conclusions:** DVPX was not found to be superior to Li^+ as maintenance treatment in youths who stabilized on combination Li^+ /DVPX pharmacotherapy. *J. Am. Acad. Child Adolesc. Psychiatry,* 2005;44(5):409–417. **Key Words:** bipolar disorder, lithium, divalproex sodium.

Juvenile bipolar disorder can be a debilitating condition associated with significant psychosocial dysfunction and human suffering (Findling et al., 2001; Geller et al., 2000a; Wozniak et al., 1995). As it appears that juveniles with bipolar disorders have a chronic course (Carlson et al., 2002; Geller et al., 2002), long-term treatment is likely to be necessary for these vulnerable patients. In addition, children and adolescents diagnosed with bipolar disorders often have high rates of rapid cycling that includes complex cycling patterns (Findling et al., 2001; Geller et al., 1995), which often complicates the treatment of these patients.

Unfortunately, limited data are available describing the optimal maintenance treatment of bipolar disorder in pediatric-aged patients. Strober et al. (1990) studied 37 teenagers with bipolar I disorder who had responded to lithium (Li^+) treatment during a psychiatric hospitalization in a prospective, naturalistic fashion. Those investigators observed that the patients who continued with Li^+ therapy had a lower risk of relapse than patients who did not. Other than this report, we are not aware of any published randomized, double-blind clinical trials that have examined the maintenance pharmacotherapy of pediatric bipolar disorder.

Accepted December 7, 2004.

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The Stanley Medical Research Institute primarily supported this study. It was also supported in part by an NIMH Developing Centers for Interventions and Services Research Grant (P 20 MH-66054). Nursing and pharmacy activities were supported in part by NICHD Pediatric Pharmacology Research Unit (PPRU) contract HD 31323-05. Medications were provided in part by Abbott Laboratories.

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0890-8567/05/4405–0409©2005 by the American Academy of Child and Adolescent Psychiatry

DOI: 10.1097/01.chi.0000155981.83865.ea

Because the safety and efficacy of a psychotropic medication might differ between children and adults, there is a need to perform methodologically rigorous studies in young people with psychiatric illnesses so that clinicians will not be obligated to depend on information generated by research done in adults (Wiznitzer and Findling, 2003). To address the unmet need for randomized clinical trials in youths diagnosed with a bipolar disorder, we conducted a long-term, double-blind maintenance treatment study in juveniles with bipolar disorder. At the time that this study was initiated, the agents for which there were the greatest amount of data that pertained to the treatment of pediatric bipolar disorder were divalproex sodium (DVPX) and Li^+. At that time, there was also evidence that adults with the rapid cycling variant of bipolar disorder might respond better to treatment with DVPX than with Li^+ (Calabrese and Delucchi, 1990). When the fact that youths with bipolar disorder were frequently reported to have complex cycling patterns (Findling et al., 2001; Geller et al., 1995) was also considered, it was presumed that youths with bipolar disorder might have superior sustained treatment response to DVPX than to Li^+ monotherapy. Thus, the primary goal of this study was to determine whether DVPX was superior to Li^+ in the maintenance treatment of symptoms of bipolar I or II disorder in children and adolescents who have achieved syndromal remission after receiving open-label combination pharmacotherapy with DVPX and Li^+.

METHOD

The University Hospitals of Cleveland Institutional Review Board for Human Investigation approved all procedures in this study. Written informed consent was obtained from each subject's guardian and written assent was obtained from each subject before any study-related procedures were performed. A child and adolescent psychiatrist saw each patient and his or her guardian(s) at every treatment visit. Subjects could withdraw from the study at any time if the patient or their guardian no longer wanted to participate in the trial.

Study Design

This was a multiphase, single-site outpatient study, the schema of which is summarized in Figure 1. Phase 1 was a stabilization period in which subjects were treated with open-label combination Li^+ plus DVPX (Li^+/DVPX) for up to 20 weeks. Subjects were seen weekly while in phase 1. Subjects ended participation in phase 1 once they met entry criteria for phase 2 (see below). Subjects who were not eligible to enroll in phase 2 ended study participation on completion of enrollment in phase 1.

Phase 2 was a 76-week, randomized, double-blind clinical trial that employed a double-dummy substitution paradigm in which the subjects who were receiving combination Li^+/DVPX therapy on entry into phase 2 were randomized to receive either Li^+ or DVPX monotherapy. Subject participation in phase 2 ended if the patient required clinical intervention other than what was provided as part of the trial or did not adhere to study-related procedures. Patients were seen weekly for the first 4 weeks of phase 2, at weeks 6 and 8, and then every 4 weeks thereafter.

To be enrolled into phase 2, clinically stable subjects had to adhere to study-related procedures during phase 1, tolerate a minimum Li^+ serum concentration of ≥0.6 mmol/L and a minimum DVPX serum concentration level ≥50 μg/mL while in phase 1 and also achieve persistent bimodal syndromal remission for four consecutive weeks while receiving no other mood stabilizer, antipsychotic, or antidepressant. Syndromal remission was achieved if the subject met the following criteria for four consecutive weeks: (1) a Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski et al., 1985) score ≤40, (2) a Young Mania Rating Scale (YMRS) (Young et al., 1978) score ≤12.5, and (3) a Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983) score ≥51.

If during phase 2, subjects experienced a relapse in mood symptoms, treatment with open combination Li^+/DVPX was reinitiated at the treating physician's discretion for up to 8 weeks. Results from the Li^+/DVPX reinitiation portion of this study will be described in a subsequent article.

Subjects

Patients were recruited between July 1998 and May 2002. Medically healthy outpatient children and adolescents ages 5–17 years meeting unmodified diagnostic symptom criteria for a primary diagnosis of either bipolar I or II disorder (American Psychiatric Association, 1994) were eligible. In addition, to be eligible for entry into this trial, youths had to have experienced at least one manic or hypomanic episode (American Psychiatric Association, 1994) within the past 3 months. Diagnosis was based on the results of a semistructured diagnostic interview, the Schedule for Affective Disorders

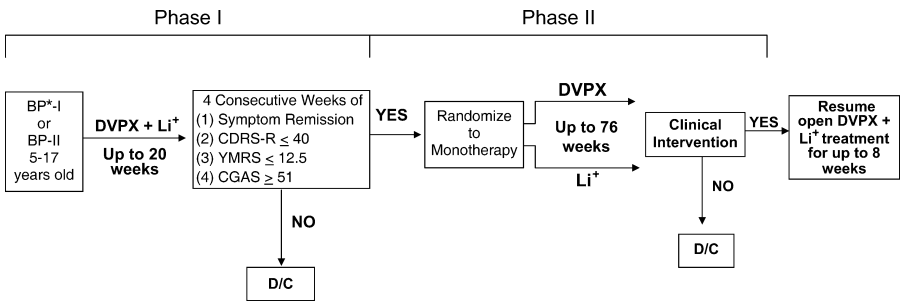

Fig. 1 The study design of a randomized, maintenance trial in pediatric bipolarity. BP* = bipolar disorder; DVPX = divalproex sodium; Li^+ = lithium; CDRS-R = Children's Depression Rating Scale-Revised; YMRS = Young Mania Rating Scale; CGAS = Children's Global Assessment Scale; D/C = discontinued from study.

and Schizophrenia for School-Age Children (Kaufman et al., 1997; Orvaschel, 1994), which was administered by a highly trained interviewer with acceptable interrater reliability and used unmodified *DSM-IV* criteria. These diagnostic procedures have been described in more detail elsewhere (Findling et al., 2001). In addition, all patients also had their diagnoses confirmed with a 90- to 120-minute clinical interview by a child and adolescent psychiatrist to be enrolled in this study.

Exclusion criteria included (1) a history of intolerance to Li^+ serum concentration of levels ≥0.6 mmol/L; (2) a history of a manic episode with a documented Li^+ serum concentration level ≥1.0 mmol/L; (3) a history of intolerance to a DVPX serum concentration ≥50 μg/mL; (4) a history of a manic episode with a documented DVPX serum concentration ≥80 μg/mL; (5) the presence of a substance abuse disorder within the previous 6 months; (6) females who were pregnant, at risk of becoming pregnant, or nursing; (7) the presence of a clinically significant abnormality on any baseline laboratory measure (thyrotropin blood level, comprehensive metabolic profile, complete blood count, prothrombin time/partial thromboplastin time, urinalysis, urine toxicology screen and electrocardiogram; (8) clinically significant abnormalities in pulse and blood pressure at study entry; and (9) clinical evidence of a pervasive developmental disorder or mental retardation.

Medication Treatment

Phase 1: Open Stabilization. Li^+ and DVPX were both initiated simultaneously at entry into phase 1. An immediate-release preparation of Li^+ was used in this trial. Drug serum concentrations were measured at weeks 2 and 4 and every 4 weeks thereafter. Medications were increased over the first 2 weeks so that target doses of 20 mg/kg/day of DVPX and 30 mg/kg/day of Li^+ could be achieved. Doses of Li^+ and DVPX were adjusted so that serum concentrations of Li^+ were maintained between 0.6 and 1.2 mmol/L and DVPX serum concentrations were between 50 and 100 μg/mL. The treating physicians increased the dosing of Li^+ and DVPX until either dose-limiting side effects occurred or maximum medication levels were surpassed. Patients who could not tolerate the minimum drug serum concentration of either compound were withdrawn from the trial.

Phase 2: Double-Blind Maintenance Phase. Patients randomized to a given treatment arm had their dose of that medication started at the same dosing level used at the end of phase 1. The other medication was gradually weaned over the initial 8-weeks to minimize the likelihood of discontinuation rebound relapse. Either the treating physician or the nonblind medical monitor could subsequently adjust doses of medication based on psychiatric symptoms, serum concentrations, or reported side effects (see below). Trough Li^+ and DVPX serum concentrations were obtained biweekly during the first 8 weeks of monotherapy and then every 4 weeks thereafter. The nonblind medical monitor could adjust doses of medications, as needed to ensure that Li^+ serum concentrations were maintained between 0.6 and 1.2 mmol/L and that DVPX serum concentrations were maintained between 50 and 100 μg/mL. Active agents and their corresponding placebos were administered as identically appearing tablets or capsules.

Adjunctive Medications

Patients who entered phase 1 who were currently being prescribed a psychostimulant, an antipsychotic, or an antidepressant were tapered off these medications as quickly as feasible and as clinically tolerated. For patients with symptoms of major depression that persisted despite Li^+/DVPX combination therapy, adjunctive antidepressants could be prescribed. Similarly, if patients had persistent symptoms of psychosis or mania that were not responding adequately to Li^+/DVPX, adjunctive treatment with an antipsychotic was allowed. Subjects who were unable to discontinue antidepressants or antipsychotics were not eligible to be enrolled into phase 2.

If youths had symptoms consistent with the diagnosis of attention-deficit/hyperactivity disorder (ADHD), adjunctive treatment with psychostimulants at U.S. Food and Drug Administration–approved doses was allowed before entry into phase 2. Similarly, clonidine could be prescribed at doses as high as 6 μg/kg/day. Subjects had to be on stable doses of these ADHD-related medications for at least 4 weeks before being eligible for randomization during phase 2.

Randomization

Subject randomization was stratified based on three factors: (1) age (ages 5–11 or 12–17 years), (2) the presence/absence of rapid cycling, and (3) whether the patient had comorbid ADHD. Youths eligible to enroll in phase 2 were then randomly assigned to receive either Li^+ or DVPX monotherapy with an equal numbers of subjects planned to be randomized to each arm.

Safety Measures

Phase 1. At study entry, subjects underwent a physical examination (with height and body weight measured), an electrocardiogram, a urine toxicology screen, a comprehensive metabolic profile, a thyrotropin blood level, a complete blood count, prothrombin time/partial thromboplastin time, and a urinalysis. Females of child-bearing potential received a urine pregnancy test. All these measures were also obtained when a subject's participation in phase 1 ended. An additional complete blood count and comprehensive metabolic profile were obtained at weeks 4 and 12. A thyrotropin blood level was obtained at week 8. Adverse events/side effects were ascertained by direct inquiry of the subject and their guardian at each study visit. Blood pressure and pulse were also monitored at each study visit.

Phase 2. In addition to the laboratory test results obtained at the end of phase 1 (which served as the baseline for phase 2), other safety measures were obtained throughout phase 2. A complete blood count, a comprehensive metabolic profile, a thyrotropin blood level, a urinalysis, a urine toxicology screen, and a urine qualitative pregnancy test (peri- and postpubertal females only) were performed at the end of week 4 and then every 12 weeks thereafter. Blood pressure, pulse, and body weight were recorded at each study visit. All baseline measures were also obtained at the end of phase 2 or when a patient prematurely discontinued participation while in phase 2.

To maintain the integrity of the blind during phase 2, all side effects and laboratory test results were reported to a study nurse who did not complete clinical outcome measures. The side effects and laboratory test results were reviewed by an unblinded physician medical monitor. Patients were withdrawn from phase 2 by the unblinded medical monitor if a significant side effect or adverse event occurred (such as abnormal laboratory test results or side effects) that would not be apparent to the treating child and adolescent psychiatrist.

Outcome Measures

Two primary outcome measures were used to assess the effectiveness of Li^+ and DVPX monotherapy. The first was time to premature discontinuation for treatment of emerging symptoms of relapse

(''relapse''). Mood state at time of emerging relapse was recorded in these subjects. The second outcome measure was premature discontinuation from the study for any reason. Reason for premature study discontinuation was noted for all patients.

Predictors of response analysis included gender, rapid cycling, age at entry into phase 2, age at onset of bipolar illness, duration of bipolar illness, entry YMRS score, entry CDRS-R score, age at entry into phase 2, comorbid diagnosis of ADHD, and concomitant ADHD medications while in phase 2.

Psychometric instruments that served as secondary outcomes measures included the CDRS-R, YMRS, the Clinical Global Impression Scale of Severity (CGI-S) and Improvement (CGI-I) (National Institute of Mental Health, 1985), and the CGAS. These instruments were administered at each study visit.

The CDRS-R (Poznanski et al., 1985) 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 symptomatology. Hypomania and mania were assessed using the YMRS (Young et al., 1978; Youngstrom et al., 2002). The YMRS is an 11-item, clinician-rated scale, with total scores ranging from 0 (no manic symptoms) to 60 (severely manic). Overall bipolar illness severity and improvement were assessed using the CGI-S and the CGI-I. CGI-S items are rated from 1 (normal, not ill) to 7 (very, severely ill). Symptom improvement items on the CGI-I are rated from 1 (very much improved) to 7 (very much worse). 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.

Statistical Methods

Before study initiation, the necessary sample size was determined to detect differences in the DVPX and Li^+ treatment groups. It was estimated that a minimum of 30 patients per treatment arm would be needed to detect a minimum hazard ratio of at least 0.36 at a power of 0.81 and an α level of .05.

Statistical analyses were performed using SPSS v11.5. Kaplan-Meier survival analyses and stepwise Cox regressions tested whether there were differences in time until the patient relapsed into a mood episode or discontinued the study for any reason depending on treatment arm or other covariates. Mixed analysis of variance and random effects models were used to examine changes in psychometric instrument scores over time. Chi-square tests or *t* tests, as appropriate, were used to examine whether there were demographic differences between those patients who were (1) randomized to monotherapy and those patients who were not randomized, (2) demographic differences in those patients who received DVPX monotherapy compared with subjects who received Li^+ monotherapy, or (3) differences in the occurrences of side effects between those randomized to Li^+ and those treated with DVPX. The level of significance was set at .05 for all analyses. Data are presented as mean (standard deviation) unless otherwise noted.

RESULTS

Subjects

Patients were enrolled into this trial from July 1998 through May 2002. Two hundred eighty-seven children and adolescents were screened for participation in this study, with 161 being enrolled. Subject participation through the course of the trial is summarized in Figure 2. The most common reasons that screened subjects were not enrolled included the following: (1) subjects did not meet diagnostic criteria (n = 69) and (2) subjects declined further study participation (n = 30). Of the 161 youths who were enrolled, 139 received treatment with study medication (Table 1). One hundred thirty-nine youths with a mean age of 10.8 (3.5) years were initially treated with Li^+/DVPX for a mean of 10.7 (5.4) weeks. Of these 139 youths, 60 were randomized into phase 2 with 30 randomized to the Li^+ monotherapy arm and 30 randomized to the DVPX monotherapy arm. The most common reason that youths were not randomized was nonadherence with study-related procedures (n = 38) and medication intolerance (n = 21). More detailed data regarding the first 90 youths who received treatment in phase 1 has been summarized elsewhere (Findling et al., 2003).

Demographic information is shown in Tables 2 and 3. Thirty-five of the patients (58.3%) treated with maintenance monotherapy were also prescribed concomitant psychostimulants for ADHD symptoms. At

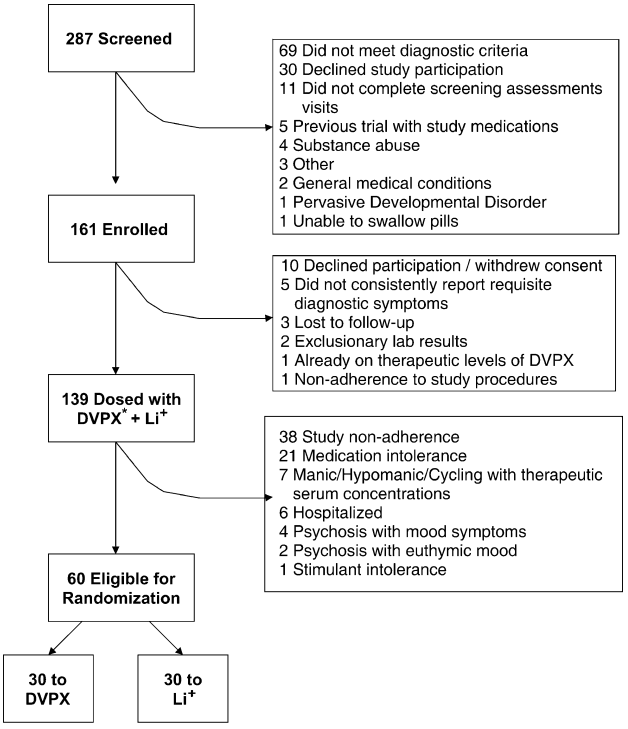

Fig. 2 Subject accountability in a randomized maintenance trial in pediatric bipolarity. DVPX* = divalproex sodium; Li^+ = lithium.

TABLE 1
Demographics of 139 Children and Adolescents Treated With Both Lithium and Divalproex Sodium For as Long as 20 Weeks (Phase 1)

	Randomized (n = 60)	Not-Randomized (n = 79)	Overall (N = 139)
Gender, no. (%)			
Males	39 (65.0)	54 (68.4)	93 (66.9)
Females	21 (35.0)	25 (31.6)	46 (33.1)
Diagnosis, no. (%)			
BP-I	55 (91.7)	76 (96.2)	131 (94.2)
BP-II	5 (8.3)	3 (3.8)	8 (5.8)
Course modifiers no. (%)			
Rapid cycling	30 (50.0)	52 (65.8)	82 (59.0)
Psychosis	2 (3.3)	10 (12.7)	12 (8.6)
Mixed states	4 (6.7)	4 (5.1)	8 (5.8)
Age, yr (SD)	10.7 (3.6)	10.8 (3.4)	10.8 (3.5)
Age at onset, yr (SD)	7.3 (4.1)	6.7 (3.9)	7.0 (3.9)
Duration of illness, wk (SD)	149.7 (115.4)	182.4 (117.3)	168.1 (117.2)
No. of weeks enrolled in phase 1[a] (SD)	13.4 (4.0)	8.6 (5.5)	10.7 (5.4)
Concomitant stimulants, no. (%)	38 (63.3)	33 (41.8)	71 (51.1)
Mean baseline YMRS score (SD)	19.1 (6.9)	21.2 (9.2)	20.3 (8.3)
Mean baseline CDRS-R score (SD)	29.5 (11.6)	30.4 (13.9)	30.0 (12.9)
Mean baseline CGAS score (SD)	50.5 (5.8)	50.4 (7.6)	50.4 (6.9)

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

[a]A t test indicated that a significant difference ($p < .01$) existed in the mean time in phase I between those patients who were randomized and those who were not on this variable. No other statistically significant differences were noted between the youths who were randomized to monotherapy and those who were not randomized based on the results of t tests or χ^2 analyses, as appropriate, on any other demographic variable.

randomization, CDRS-R, YMRS, and CGAS scores did not significantly differ among those patients randomized to Li^+ compared with those randomized to DVPX ($p > .05$, largest t value 0.89, with 58 df). Sixty-three percent ($n = 38$) of the youths exited the study due to mood-related reasons. Study exit reasons are shown in Table 4.

Survival Analyses

Time to mood relapse did not differ between the Li^+ and DVPX treatment groups (log-rank [1 df] = 0.35, $p = .55$). Furthermore, the two treatment groups did not differ in time until study discontinuation for any reason (log-rank [1 df] = 0.13, $p = .72$; Fig. 3).

The time to median survival for subjects who relapsed due to the presence of mood symptoms was 114 days, SE ±57.4 days for patients randomized to receive Li^+ and 112 days, SE ±56 days for patients treated with DVPX. For patients who prematurely discontinued the study for any reason, the median survival time was 91 days, SE ±30.1 days for Li^+ and 56 days, SE ±19.9 days for DVPX.

Post hoc analyses (stepwise Cox regressions) found that youths with a younger age at onset were more likely to relapse into a mood episode, $\chi^2_1 = 3.95$, $p = .047$. Similarly, youths with higher YMRS scores at study baseline were more likely to discontinue the study early $\chi^2_1 = 4.92$, $p = .027$. Controlling for either of these variables did not change the significance of the comparison between drugs. Age at randomization, comorbid ADHD, rapid cycling status (i.e., the three stratification variables), gender, duration of bipolar illness, baseline CDRS score, and concurrent use of ADHD medications were not associated with time until mood event or study discontinuation, nor did controlling for any or all of these covariates change the results for the drug comparison.

Psychometric Measures

Overall, both treatment groups indicated a decline in psychometric measures over the course of the study. Mixed analyses of variance (drug × time) using last observation carried forward scores indicated that YMRS

TABLE 2
Demographics of 60 Children and Adolescents Treated With Lithium or Divalproex Sodium Maintenance Monotherapy For as Long as 76 Weeks (Phase 2)[a]

	Lithium (n = 30)	DVPX (n = 30)	Overall (n = 60)
Gender, no. (%)			
Males	21 (70.0)	18 (60.0)	39 (65.0)
Females	9 (30.0)	12 (40.0)	21 (35.0)
Diagnosis, no. (%)			
BP-I	28 (93.3)	27 (90.0)	55 (91.7)
BP-II	2 (6.7)	3 (10.0‘)	5 (8.3)
Course modifiers, no. (%)			
Rapid cycling	13 (43.3)	17 (56.7)	30 (50.0)
Psychosis	1 (3.3)	1 (3.3)	2 (3.3)
Mixed states	3 (10.0)	1 (3.3)	4 (6.7)
Age, yr (SD)	10.3 (3.3)	11.2 (3.9)	10.7 (3.6)
Age at onset, yr (SD)	6.7 (4.0)	8.0 (4.1)	7.3 (4.1)
Duration of illness, wk (SD)	162.6 (117.9)	136.8 (113.4)	149.7 (115.4)
No. of weeks enrolled in phase 2 (SD)	21.1 (22.5)	20.0 (23.9)	20.6 (23.0)
Concomitant stimulants, no. (%)	18 (60.0)	17 (56.7)	35 (58.3)
Mean YMRS score (SD) at randomization	1.0 (2.2)	0.8 (1.8)	0.9 (2.0)
Mean CDRS-R score (SD) at randomization	17.5 (1.4)	18.6 (2.7)	18.0 (2.2)
Mean CGAS score (SD) at randomization	76.1 (7.2)	75.6 (6.2)	75.8 (6.7)

Note: DVPX = divalproex sodium;
YMRS = Young Mania Rating Scale; CDRS-R = Children's Depression Rating Scale-Revised; CGAS = Children's Global Assessment Scale.
[a]No statistically significant differences were noted between the youths who were randomized to Lithium monotherapy and those subjects who were randomized to DVPX monotherapy based on the results of t tests or χ^2 analyses, as appropriate, on any listed demographic variable.

scores increased significantly over the first 8 weeks of the study period ($F_{1,56}$ = 40.03, p < .00005, Cohen's d = 0.93 [where d = 0.80 is considered a large effect size]). Similarly, CDRS-R scores increased over time ($F_{1,56}$ = 24.23, p < .00005, Cohen's d = 0.65) and CGAS scores decreased over time ($F_{1,56}$ = 12.75, p = .001, Cohen's d = 0.48). There was no main effect for treatment on any of the three measures: $F_{1,56}$ = 0.28 for YMRS, 2.28 for CDRS, and 0.03 for CGAS scores, all p values >0.136. Likewise, change over time did not depend on treatment: $F_{1,56}$ = 0.44 for YMRS, 0.82 for CDRS, and 0.17 for CGAS, all p values >0.368. The largest effect size associated with treatment was d = 0.20 (where d = 0.20 is considered a small effect). Random effects models examining individual slopes over time (i.e., hierarchical linear models) produced results consistent with

TABLE 3
Comorbid Behavioral and Anxiety Disorders in 60 Children and Adolescents Treated With Lithium or Divalproex Sodium Maintenance Monotherapy For as Long as 76 Weeks

	Lithium (n = 30)	DVPX (n = 30)	Overall (n = 60)
Attention Deficit hyperactivity disorder, no. (%)	20 (66.7)	18 (60.0)	38 (63.3)
Oppositional defiant disorder, no. (%)	7 (23.3)	5 (16.7)	12 (20.0)
Conduct disorder, no. (%)	2 (6.7)	4 (13.3)	6 (10.0)
Posttraumatic stress disorder, no. (%)	0 (0.0)	1 (3.3)	1 (1.7)
Generalized anxiety disorder, no. (%)	0 (0.0)	1 (3.3)	1 (1.7)
Specific phobia, no. (%)	0 (0.0)	1 (3.3)	1 (1.7)

TABLE 4
Exit Reasons in 60 Youths Treated With Lithium or Divalproex Maintenance Monotherapy

	Randomization Assignment		
Exit Reason	Lithium (n = 30) No. (%)	DVPX (n = 30) No. (%)	Over all (n = 60) No. (%)
Mood related	18 (60.0)	20 (66.7)	38 (63.3)
Hypomania/mania/mixed states	15 (50.0)	19 (63.3)	34 (56.7)
Lack of efficacy/depression	3 (10.0)	1 (3.3)	4 (6.7)
Other reasons	7 (23.3)	5 (16.7)	12 (20.0)
Medication nonadherence	4 (13.3)	2 (6.7)	6 (10.0)
Side effects	2 (6.7)	3 (10.0)	5 (8.3)
Residual oppositionality	1 (3.3)	0	1 (1.7)
Completed study	3 (10.0)	3 (10.0)	6 (10.0)
Nonadherence with other study procedures	2 (6.7)	2 (6.7)	4 (6.7)

the last observation carried forward analyses: There was a significant worsening of manic and depressive symptoms as well as global functioning over time but no significant effects for treatment nor interactions between treatment and slope for the three outcomes.

Medication Dosing

At randomization, the mean Li^+ and DVPX serum concentrations were 0.94 mmol/L (0.26) and 81.1 μg/mL (20.5), respectively. The mean Li^+ and DVPX serum concentrations at end of participation in phase 2 were 0.84 (0.30) mmol/L and 75.3 (29.4) μg/mL, respectively.

Adverse Events/Side Effects

Seventy-five percent (n = 45) of the patients reported side effects after randomization. The most frequently reported side effects of those who received Li^+ monotherapy were emesis (n = 9, 30.0%) and enuresis (n = 9, 30%). There was a significant difference in the frequency with which patients reported emesis, increased thirst, and enuresis compared with those treated with DVPX (χ^2 = 3.75, p = .05, Fisher's exact test p = .05, and χ^2 = 5.46, p = .02, respectively). Furthermore, those treated with DVPX most frequently reported headache (n = 7, 23.3%) and stomach pain (n = 7, 23.3%) as adverse events. However, those treated with DVPX monotherapy did not report headache or stomach pain more frequently than those treated with Li^+ (χ^2 = 1.00, p = .32 and χ^2 = 1.92, p = .17, respectively). The most commonly reported side effects are listed in Table 5. Of note, weight gain was not a spontaneously reported adverse event during this maintenance study.

Five patients discontinued study participation due to adverse events. Alopecia led to the discontinuation of two patients (n = 1 DVPX, n = 1 Li^+) from the study. One patient randomized to DVPX was discontinued due to an increased thyrotropin blood level (12.86 mU/L). In addition, one patient was discontinued from the study after 20 weeks of DVPX monotherapy due to thrombocytopenia (platelet count = 51 $\times$ 10^9/L). One patient who was receiving Li^+ was discontinued from the study due to enuresis. Of note, no patients were discontinued from this trial due to a suicide attempt or the need for psychiatric hospitalization.

DISCUSSION

This study was successful in answering the proposed question of whether DVPX was superior to Li^+ in the

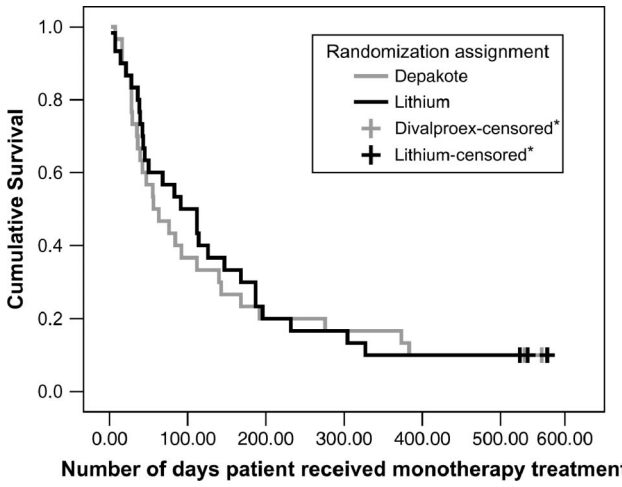

Fig. 3 Kaplan-Meier curve indicating overall time in study for 60 youths treated with either lithium or divalproex sodium. *Note:* Log-rank (1 *df*) = 0.13, p = .72. *Completed 72 weeks of treatment.

TABLE 5
Adverse Events Reported in >5% of 60 Youths Treated With Lithium or Divalproex Sodium Maintenance Monotherapy

Side Effect	Lithium (n = 30) No. (%)	DVPX (n=30) No. (%)	p
Emesis	9 (30.0)	3 (10.0)	.05[a]
Headache	4 (13.3)	7 (23.3)	.32[a]
Tremor	6 (20.0)	5 (16.7)	.74[a]
Enuresis	9 (30.0)	2 (6.7)	.02[a]
Stomach pain	3 (10.0)	7 (23.3)	.17[a]
Nausea	5 (16.7)	2 (6.7)	.42[b]
Diarrhea	4 (13.3)	2 (6.7)	.67[b]
Decreased appetite	3 (10.0)	3 (10.0)	1.00[b]
Increased thirst	5 (16.7)	0	.05[b]
Upper respiratory congestion	2 (6.7)	3 (10.0)	1.00[b]
Fever	4 (13.3)	1 (3.3)	.35[b]
Sore throat	1 (3.3)	3 (10.0)	.61[b]

[a]Frequency of reported side effects compared with χ^2 analysis.
[b]Frequency of reported side effects compared with Fisher's Exact Test.

maintenance treatment of bipolar disorder in children and adolescents. DVPX was not found to be superior to Li^+ monotherapy in the maintenance pharmacotherapy of youths with bipolar I or II disorder who achieved syndromal remission with Li^+ /DVPX treatment. This finding was consistent for analyses that considered time to symptomatic reemergence or overall time in study. In this trial, it was also observed that neither comorbidity with ADHD nor exposure to psychostimulants during the randomized phase of this trial was associated with earlier time to relapse.

The data generated in this study are comparable with those of the double-blind maintenance study of similar design performed in adults with rapid cycling bipolar disorder (Calabrese et al., 2003). As in this report, the study of Calabrese et al. also failed to demonstrate a difference between the two monotherapy treatment arms. In adults, the most common mood state associated with symptomatic relapse was depression, while in this pediatric trial, depression was rarely the mood state that led to relapse.

These data extend a recent report of Kafantaris et al. (2004) of a rapid rate of relapse in subjects who continued to receive active Li^+. This study, as well as the work of Kafantaris et al. (2004), suggests the possibility of a nocebo effect early in the course of studies that incorporate a discontinuation design.

There are novel aspects to this work. First, this study demonstrates that prospective, randomized maintenance studies in pediatric patients with bipolar disorder are feasible. In addition, the study subjects were not a rarified cohort but representative of youths with bipolar disorder who present for clinical care. As an example, a substantial number of subjects in this study had comorbid ADHD (Findling et al., 2001; Geller et al., 2000b). Anticipating high rates of ADHD comorbidity, this study permitted the concomitant use of psychostimulants.

This study had several inherent strengths including its randomized, double-blind design as well as the 76-week study length. The use of an initial stabilization phase that preceded randomization to maintenance medication therapy is also a positive aspect of this trial. Another strength of this study was the use of a blinded medical professional to monitor adverse events to maintain the integrity of the blind.

Limitations

This study has several noteworthy limitations. Although this study successfully achieved its a priori objective, it may be asserted that this trial was still relatively modest in size. Based on these data, 3,564 subjects would have needed to be randomized to detect a statistically significant overall between-group difference in survival time. These results suggest that if there is a difference between Li^+ and DVPX monotherapy, it is clinically insignificant. The results of this trial also suggest that this was not an underpowered study.

In retrospect, it may have been helpful if there were another randomization arm in which patients could have continued receiving combination Li^+/DVPX. A Li^+/DVPX treatment arm might have provided the information necessary to define the relative efficacy of continued Li^+/DVPX therapy when compared with continued treatment with either Li^+ or DVPX monotherapy.

Another shortcoming of this trial is that it was not placebo controlled. Also, these findings might only be generalizable to patients who stabilize on Li^+/DVPX. Last, patients and their families knew when they were entering the double-blind phase of the study, thus possibly resulting in a nocebo effect.

It may be asserted that a logical subsequent study to this one would be a trial in which stabilized youths are randomized to receive drug monotherapy (either Li^+ or DVPX) or placebo. However, due to the particularly

rapid median relapse times observed herein with drug monotherapy, possible randomization to placebo might not be well accepted by patients or their families or considered ethical by institutional review boards. Subsequent studies might include other comparisons between monotherapies or comparisons between drug monotherapy and combination therapy. Combination therapy arms could either consist of more than one drug or a single drug supplemented by an empirically proven psychosocial intervention.

Clinical Implications

In conclusion, DVPX was not found to be superior to Li^+ as maintenance treatment in youths who stabilized acutely on combination Li^+/DVPX pharmacotherapy. As pediatric bipolar disorder is chronic and debilitating, more research into the maintenance pharmacotherapy of this condition is needed.

Disclosure: Dr. Findling receives or has received research support, acted as a consultant, or served on a speaker's bureau for Abbott, AstraZeneca, Bristol-Myers Squibb, Celltech-Medeva, Forest, GlaxoSmithKline, Johnson & Johnson, Lilly, New River, Novartis, Otsuka, Pfizer, Shire, Solvay, and Wyeth. Dr. Youngstrom has received research support from Abbott. Dr. Gracious has received research support, acted as a consultant, or served on a speaker's bureau for Astra Zeneca, Bristol-Myers Squibb, Eli Lilly & Co, Janssen, Otsuka, and PsychCME, Inc. Dr. Reed has received research grant support, acted as a consultant, or served on a speaker's bureau for Abbott Laboratories, AstraZeneca, Aventis, Bayer, Bristol-Myers Squibb, Eli Lilly, Enzon, Forrest Laboratories, Glaxo SmithKline, HRSA, Janssen, Johnson & Johnson, Merck, Novartis, Organon, Pfizer, Roche, Schering, Somerset, and Wyeth-Ayerst. Dr. Calabrese has received research support, acted as a consultant, or served on a speaker's bureau for Abbott, AstraZeneca, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Merck, Otsuka, Pfizer, and Teva. The other authors have no financial relationships to disclose.

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