Double-Blind, Randomized, Placebo-Controlled Long-Term Maintenance Study of Aripiprazole in Children With Bipolar Disorder

Robert L. Findling, MD, MBA; Eric A. Youngstrom, PhD; Nora K. McNamara, MD; Robert J. Stansbrey, MD; Jaime L. Wynbrandt, MA; Clara Adegbite, BA; Brieana M. Rowles, MA; Christine A. Demeter, MA; Thomas W. Frazier, PhD; and Joseph R. Calabrese, MD

ABSTRACT

Background: This study evaluates the long-term efficacy of aripiprazole compared to placebo in children with bipolar disorders.

Method: Outpatients aged 4 to 9 years meeting *DSM-IV* criteria for a bipolar disorder (I, II, not otherwise specified, cyclothymia) were eligible to receive up to 16 weeks of open-label treatment with aripiprazole (phase 1). Patients were randomized into the 72-week double-blind phase of the study once they met a priori response criteria for stabilization (phase 2). During phase 2, patients either remained on their current aripiprazole regimen or began a double-blind taper with aripiprazole discontinued and switched to placebo. The primary outcome measure for phase 2 was time to discontinuation due to a mood event.

Results: Patients were recruited between May 2004 and November 2008. Following phase 1, in which 96 patients received aripiprazole, 30 patients (mean age = 7.1 years) were randomly assigned to continue aripiprazole and 30 patients (mean age = 6.7 years) were randomly assigned to placebo. The mean (SD) dose of aripiprazole prior to randomization for these patients was 6.4 (2.1) mg/d. Patients randomly assigned to aripiprazole were enrolled significantly longer until time to study discontinuation due to a mood event (6.14 median weeks, SE ± 11.88 weeks; $P = .005$) and discontinuation for any reason (including mood events) (4.00 median weeks, SE ± 3.91 weeks; $P = .003$) than those randomly assigned to placebo (mood event, 2.29 median weeks, SE ± 0.38 weeks; any reason, 2.00 median weeks, SE ± 0.31 weeks). Regardless of random assignment, both the aripiprazole and placebo groups showed substantial rates of withdrawal from maintenance treatment over the initial 4 weeks (15/30 [50%] for aripiprazole; 27/30 [90%] for placebo), suggesting a possible nocebo effect (ie, knowledge of possibly switching from active medication to placebo increasing concern about relapse). The most frequently reported adverse events during double-blind aripiprazole therapy included stomach pain (n = 10, 33%), increased appetite (n = 9, 30%), and headaches (n = 9, 30%).

Conclusions: Despite the possibility of a nocebo effect, these results suggest that aripiprazole may be superior to placebo in the long-term treatment of pediatric patients following stabilization with open-label aripiprazole.

Trial Registration: clinicaltrials.gov Identifier: NCT00194077

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Corresponding author: *Robert L. Findling, MD, MBA, Department of Psychiatry, University Hospitals, Case Medical Center, 10524 Euclid Ave, Cleveland, OH 44106 (robert.findling@uhhospitals.org).*

Aripiprazole is an atypical antipsychotic indicated by the US Food and Drug Administration (FDA) for the acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate in pediatric patients aged 10 to 17 years.[1] Aripiprazole has been found to be effective, when compared to placebo, in the short-term[2] and long-term[3] treatment of youths 10 years and older with bipolar I disorder.

A growing body of research has documented the validity, chronicity, and seriousness of a bipolar diagnosis in patients under 10 years of age.[4–18] Owing to the severity and persistence of bipolarity in this patient group, safe and effective long-term intervention strategies are needed. This study tested the maintenance efficacy of aripiprazole in children with a bipolar disorder.

METHOD

The University Hospitals Case Medical Center Institutional Review Board for Human Investigation approved all study procedures. Written informed consent was obtained from each patient's guardian and oral assent was obtained from each patient before any study-related procedures were performed. Patients could withdraw from the study at any time.

Study Design

This was a multiphase, single-site outpatient study. Phase 1 was a stabilization period in which patients were treated with open-label aripiprazole for up to 16 weeks, the results of which are contained in Findling et al.[19] Patients were seen weekly for the first 4 weeks and every 2 weeks thereafter. Once a priori response criteria (described below) were met, patients were randomized into the double-blind phase of the study (phase 2).

Phase 2, the primary focus of this report, was a double-blind trial in which 30 patients were randomly assigned to receive ongoing aripiprazole treatment and 30 patients were assigned to receive placebo for up to 72 weeks. Participation in phase 2 ended if the patient required clinical intervention other than what was provided as part of the trial or that did not adhere to study-related procedures. Patients were seen weekly for the first 4 weeks, every 2 weeks for the next 4 weeks, and every 4 weeks thereafter.

To be enrolled into phase 2, patients must have adhered to study-related procedures during phase 1, tolerated a minimum daily aripiprazole dose of 0.05 mg/kg/d for at least 6 weeks, and met a priori response criteria. Participants were considered responders if they met the following criteria for 4 consecutive weeks: (1) a Children's Depression Rating Scale-Revised (CDRS-R)[20] score < 29; (2) a Young Mania Rating Scale (YMRS)[21] score < 10; and (3) a Children's Global Assessment Scale (CGAS)[22] score > 50.

Clinical Points

- Prospective, randomized maintenance studies in pediatric patients with bipolar disorder are feasible.
- Aripiprazole is generally well tolerated and may be beneficial in the long-term treatment of young children with bipolar disorder.

Patients who were withdrawn from phase 2 were eligible to receive 8 weeks of open-label treatment with aripiprazole. Results from the aripiprazole reinitiation portion of this study will be described in a subsequent article.

Subjects

Patients were recruited between May 2004 and November 2008. Children aged 4 to 9 years who met *DSM-IV* criteria for a diagnosis of bipolar I disorder, bipolar II disorder, bipolar disorder not otherwise specified, or cyclothymia were eligible. Participants were initially screened by highly trained raters completing the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version interview (K-SADS-PL).[23] K-SADS interviews conducted at this site have shown high interrater diagnostic reliability across pediatric groups, including young children.[24] Patients also received a separate clinical evaluation by a child and adolescent psychiatrist to confirm the diagnostic impression of the K-SADS assessment.

Children were excluded from the study if there was evidence of a pervasive developmental disorder, Rett's syndrome, mental retardation, or a general medical or neurologic condition for which treatment with aripiprazole would be contraindicated. See Findling et al[19] for a detailed description of the rater training and diagnostic procedures, as well as inclusion and exclusion criteria for the study. The study is registered at clinicaltrials.gov (NCT00194077).

Medication Treatment

Phase 1: open stabilization. Aripiprazole was initiated at a dose of approximately 0.1 mg/kg/d upon entry into phase 1. Medication could be increased weekly, in a flexibly dosed manner, by approximately 0.05 mg/kg/d until the maximum allowed daily dose of 15 mg was reached. The decision to allow a maximum daily dose of 15 mg was based on a prior study that indicated that this dose of aripiprazole was safe and well tolerated by children.[25] However, it is worth noting that aripiprazole dose could be lowered at any time due to safety or tolerability issues.

Phase 2: double-blind maintenance phase. Phase 2 began with patients either remaining on their current medication regimen or beginning a double-blind taper to allow the participant to begin receiving placebo. For patients randomly assigned to placebo, a drug reduction schedule was generated so that the taper of the medication occurred over the course of the first 4 weeks of phase 2. For those patients randomly assigned to continued aripiprazole treatment, attempts were made to keep doses of aripiprazole consistent during the course of phase 2. Aripiprazole and the corresponding placebo were administered as identically appearing tablets.

Adjunctive Medications

If, after receiving aripiprazole for at least 6 weeks during phase 1, patients still met *DSM-IV* criteria for attention-deficit/hyperactivity disorder, adjunctive psychostimulants could be offered, as was done successfully in prior work.[25–27] Patients could be treated with open-label methylphenidate- or amphetamine-based preparations at dosages FDA-approved for children aged 6–12 years, at the discretion of the treating physician. Patients receiving coadministration of psychostimulants during phase 1 were able to continue on a stable dose of concomitant treatment during phase 2. Other psychotropic medications were not permitted in this study.

Safety Measures

At the end of phase 1/baseline of phase 2, patients underwent an electrocardiogram; weight, height, blood pressure, and pulse measurements; and laboratory tests. Laboratory tests included urinalysis, chemistry panel (including fasting glucose and lipid profile), complete blood count with platelets and differential, and prolactin level. Laboratory measures were repeated at weeks 16, 36, 52, and 72/early termination. Weight, blood pressure, and pulse were obtained at each study visit. Height was measured every 8 weeks and at end of study. Additionally, an electrocardiogram was collected at weeks 36 and 72/early termination.

Adverse events were ascertained by open-ended inquiry of physical, emotional, behavioral, and cognitive changes noted by the patient and the patient's guardian at each study visit. In addition, children were evaluated using the Abnormal Involuntary Movement Scale,[28] the Barnes Akathisia Scale,[29] and the Neurological Rating Scale for Extrapyramidal Side Effects (NRS)[30] at every visit. The NRS was supplemented with 3 additional items to assess cogwheeling, acute dystonic reaction, and subjective sense of stiffness.

Outcome Measures

Patients were evaluated by a child psychiatrist and an experienced rater at every visit. The rating scales used in this study included the CDRS-R,[20] YMRS,[21] CGAS,[22] and Clinical Global Impressions-Severity of Illness scale (CGI-S).[31] Prior research has shown that these instruments are appropriate for assessing pediatric patients across a wide age range, including children as young as 4 years.[17,24] The CGAS was obtained monthly, while all other instruments were administered at every visit.

The CDRS-R[20] 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

Table 1. Demographics of 60 Children Treated With Aripiprazole or Placebo for up to 72 Weeks

	Aripiprazole (n = 30)	Placebo (n = 30)	Overall (n = 60)	Statistic	*P* Value
Gender, n (%)					
Males	19 (63)	23 (77)	42 (70)	Fisher exact test	.40
Females	11 (37)	7 (23)	18 (30)		
Diagnosis, n (%)					
Bipolar disorder NOS	17 (57)	16 (53)	33 (55)	Fisher exact test	1.00
Bipolar I disorder	10 (33)	11 (37)	21 (35)	Fisher exact test	1.00
Cyclothymia	3 (10)	3 (10)	6 (10)	Fisher exact test	1.00
Comorbid diagnoses, n (%)					
Disruptive behavior disorder[a]	6 (20)	5 (17)	11 (18)	Fisher exact test	1.00
ADHD	27 (90)	27 (90)	54 (90)	Fisher exact test	1.00
Any anxiety disorder[b]	0	2 (7)	2 (3)	Fisher exact test	.49
Age, mean (SD), y	7.1 (1.5)	6.7 (1.7)	6.9 (1.6)	$t_{58} = 0.81$	.42
Weeks enrolled in phase 2, mean (SD)	25.9 (30.3)	3.0 (3.1)	14.5 (24.3)	$t_{58} = 4.12$	< .001
Concomitant stimulants, n (%)	12 (40)	13 (43)	25 (42)	Fisher exact test	1.00
YMRS score at randomization, mean (SD)	5.0 (3.5)	4.8 (4.0)	4.9 (3.7)	$t_{58} = 0.24$	.81
CDRS-R score at randomization, mean (SD)	19.7 (2.6)	19.0 (2.7)	19.4 (2.6)	$t_{58} = 1.03$	.31

[a]Includes conduct disorder, oppositional defiant disorder, and disruptive behavior disorder not otherwise specified.
[b]One child was diagnosed with posttraumatic stress disorder, and 1 child was diagnosed with obsessive-compulsive disorder.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CDRS-R = Children's Depression Rating Scale-Revised, NOS = not otherwise specified, YMRS = Young Mania Rating Scale.

using the YMRS,[21,32] an 11-item, clinician-rated scale with total scores ranging from 0 (no manic symptoms) to 60 (severely manic).

Overall bipolar illness severity was assessed using the CGI-S.[31] CGI-S items are rated from 1 (normal, not ill) to 7 (very severely ill). The CGAS[22] assessed child and adolescent overall functioning. This clinician-rated instrument has scores ranging from 0 to 100, with 100 being superior functioning at home, at school, and with peers.

Statistical Methods

Power analyses. For the primary analysis testing difference in length of time remaining in the maintenance protocol comparing aripiprazole to placebo, power was 0.80 to detect hazard ratios of 2.1 or larger with $\alpha = .05$ 2-tailed, 30 participants per arm, median survival of 4 weeks in one arm, and follow-up extending up to 72 weeks per protocol.[33] Prior maintenance studies with similar diagnoses but different compounds provided the basis for median survival time.[26,34] Power was similar or higher for the secondary analyses, based on *t* test and χ^2 analyses.

Analyses. Preliminary analyses examined the differences between the treatment groups on demographic, diagnostic, and symptom variables. Fisher exact tests evaluated differences in distribution between treatment groups in sex, diagnoses, and concomitant stimulant treatment. Independent *t* tests examined possible differences in treatment groups in age, weeks enrolled in the blinded portion of the study, and YMRS, CDRS-R, CGAS, and CGI-S scores at time of randomization.

Two separate Kaplan-Meier survival analyses examined treatment efficacy. One used "discontinuation for any reason" as the event of interest, and the other used "discontinuation as a result of development of a mood episode" to quantify risk of discontinuation.

Cox regression analyses examined the effects of possible covariates, including dose of aripiprazole at randomization, age at onset of bipolar disorder symptoms, YMRS and CDRS-R scores at randomization, and whether the child received stimulant medication in phase 2.

Fisher exact tests evaluated whether the number of individuals reporting adverse events differed across treatment arms. Subjects counted as "positive" if they reported having that adverse event at any time during phase 2. An independent *t* test compared mean weight-adjusted dose and weight gain at end of study across treatment groups. Because youth in this age range are expected to grow rapidly, a secondary analysis also compared rate of weight change adjusting for number of weeks in study.

Changes in fasting glucose, fasting cholesterol, fasting triglyceride levels, prolactin, pulse, and diastolic and systolic blood pressure between time of randomization and end of participation were examined with mixed-model analysis of variance to evaluate change over time between the 2 treatment groups. All analyses used a significance level (α) of .05, 2-tailed.

RESULTS

Patient Demographics

Table 1 presents demographic information and diagnostic status for the 60 study participants. No significant differences were observed between treatment groups at baseline in any symptom ratings or demographic or diagnostic characteristics (all *P* values > .05).

Thirty subjects were randomly assigned to aripiprazole after a mean of 14.3 (SD = 2.8) weeks of open-label treatment with aripiprazole, and 30 subjects were randomly assigned to placebo after 14.3 (SD = 2.5) weeks of treatment with open-label aripiprazole. The 2 groups did not significantly differ in the time until randomization in the initial study phase ($t_{58} = 0.15$, $P = .88$). Due to scheduling issues, 5 subjects were in phase 2 for over 72 weeks (76 weeks, n = 1; 74 weeks, n = 1; and 73 weeks, n = 3). Patients who received aripiprazole

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Figure 1. Patient Accountability

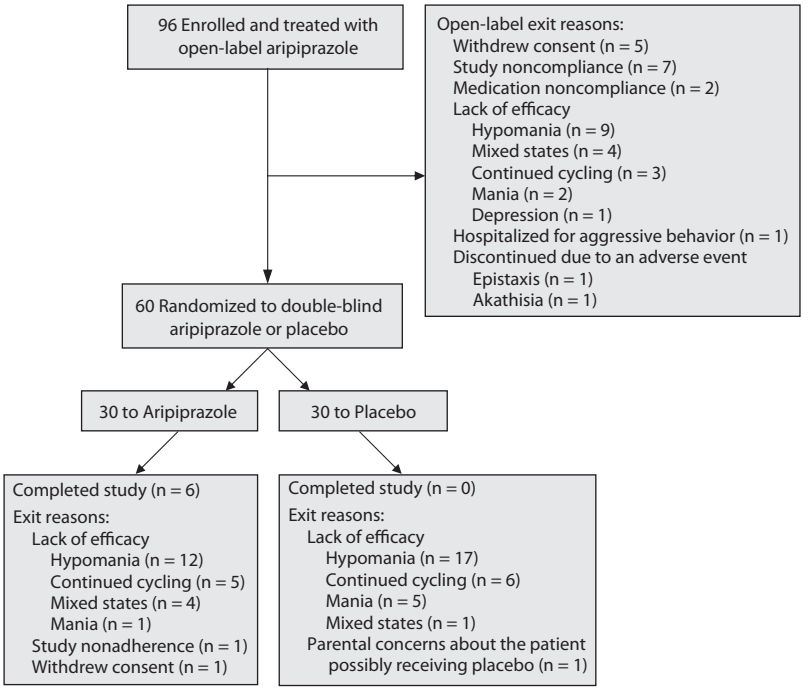
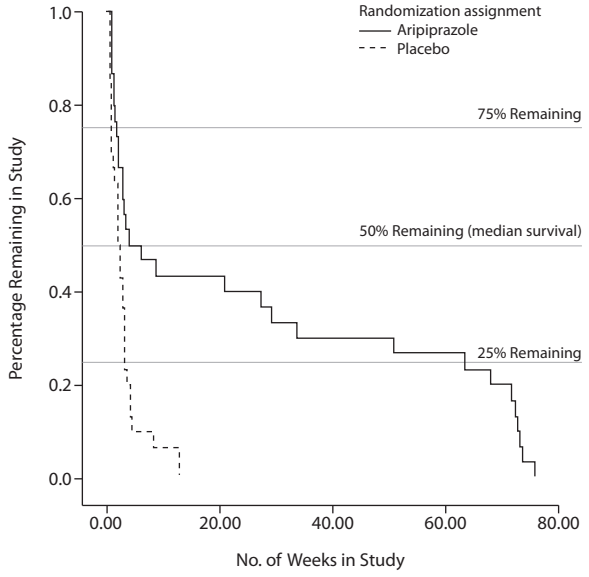


Figure 2. Discontinuation From Phase 2 for Any Event



during phase 2 who began concomitant stimulant therapy during phase 1 were treated with stimulants for a mean of 6.2 weeks prior to randomization. Patients who received placebo during phase 2 were treated with stimulants for a mean of 5.5 weeks during phase 1 prior to beginning participation in phase 2.

Figure 1 summarizes the study design and patient accountability. As shown, the most common reason for study discontinuation was lack of efficacy.

Medication Dosing

The mean (SD) dose of aripiprazole prior to randomization for these patients was 6.4 (2.1) mg/d. At randomization, the active medication group (mean = 0.23 mg/kg, SD = 0.07 mg/kg) did not significantly differ from the placebo group (mean = 0.22 mg/kg, SD = 0.07 mg/kg) in mean weight-adjusted total daily dose ($t_{58} = 0.47$, $P = .64$). At the end of study participation, the mean weight-adjusted dose did not significantly differ between treatment groups (aripiprazole, mean = 0.26 mg/kg, SD = 0.11 mg/kg; placebo, mean = 0.22 mg/kg, SD = 0.07 mg/kg; $t_{58} = 1.53$, $P = .13$). Twelve patients in the aripiprazole group and 13 patients in the placebo group were treated with stimulant medication. There was no significant difference in the number of patients receiving stimulant medication (Fisher exact test, $P = 1.00$).

Efficacy

Figure 2 presents the Kaplan-Meier curve indicating time in study prior to discontinuation for any reason ("Exit Reasons" in Figure 1). Patients randomly assigned to aripiprazole were enrolled significantly longer until time to study discontinuation for any reason (25.93 mean weeks, SE ± 5.53 weeks; 4.00 median weeks, SE ± 3.91 weeks) compared to those patients randomly assigned to placebo (3.00 mean weeks, SE ± 0.57 weeks; 2.00 median weeks, SE ± 0.31 weeks; Breslow $\chi^2_1 = 8.81$, $P = .003$). Similarly, time until discontinuation as a result of a mood event significantly differed between treatment groups (aripiprazole: 25.93 mean weeks, SE ± 5.81 weeks; 6.14 median weeks, SE ± 11.88 weeks; placebo: 3.10 mean weeks, SE ± 0.58 weeks; 2.29 median weeks, SE ± 0.38 weeks; Breslow $\chi^2_1 = 8.06$, $P = .005$).

Cox regression modeling time until discontinuation for any reason found that aripiprazole was significantly associated with longer maintenance on study protocol, even when controlling for dose of aripiprazole at randomization, age at onset of bipolar disorder symptoms, YMRS and CDRS-R scores at randomization, and treatment with stimulant medication ($\chi^2_6 = 14.81$, $P = .02$). None of the other covariates were significantly associated with time until study discontinuation (largest Wald, $\chi^2_1 = 0.59$, $P = .44$ for age at onset of bipolar disorder symptoms). Similar results were found when discontinuation due to a mood event was modeled. Covariates yielded a significant overall prediction of time until discontinuation (mood event, $\chi^2_6 = 15.37$, $P = .02$). Treatment with aripiprazole was significantly associated with time until mood event, either by itself or after controlling for all covariates (both $P < .05$). Dose of aripiprazole at randomization, age at onset of bipolar disorder symptoms, YMRS and CDRS-R scores at randomization, and treatment with stimulant medication were not significantly associated with time

Table 2. Adverse Events Reported in Greater Than 5% of Youths Treated With Aripiprazole (n = 30) or Placebo (n = 30)

Side Effect	Aripiprazole, n (%)	Placebo, n (%)	Overall, n (%)	*P*
Musculoskeletal pain	8 (27)	0	8 (13)	.005
Stomach pain	10 (33)	1 (3)	11 (18)	.006
Cold symptoms	8 (27)	2 (7)	10 (17)	.08
Coughing	5 (17)	1 (3)	6 (10)	.20
Increased appetite	9 (30)	13 (43)	22 (37)	.42
Headaches	9 (30)	6 (20)	15 (25)	.55
Enuresis	4 (13)	2 (7)	6 (10)	.67
Emesis	7 (23)	6 (20)	13 (22)	1.00
Weight gain	6 (20)	5 (17)	11 (18)	1.00
Sedation	3 (10)	2 (7)	5 (8)	1.00
Nasal congestion	2 (7)	2 (7)	4 (7)	1.00

Table 3. Mean Physiologic and Safety Measurements in Subjects

	Aripiprazole		Placebo			
Measurement	Prerandomization, Mean (SD)	End of Study,[a] Mean (SD)	Prerandomization, Mean (SD)	End of Study,[a] Mean (SD)	*F*	*P* Value[b]
Prolactin, μg/L[c]	1.2 (1.1)	0.9 (0.7)	1.2 (1.2)	3.5 (3.7)	19.76	< .001
Fasting triglyceride, mg/dL[d]	59.5 (27.3)	54.2 (18.8)	56.1 (28.5)	56.8 (48.0)	0.39	.54
Fasting cholesterol, mg/dL[d]	171.0 (28.4)	170.2 (26.1)	162.4 (18.8)	163.2 (16.4)	0.07	.80
Fasting glucose, mg/dL[d]	85.7 (8.5)	85.6 (11.9)	79.4 (18.7)	84.1 (4.7)	1.26	.27
Systolic blood pressure, mm Hg	108.1 (11.1)	107.6 (14.2)	104.8 (11.7)	107.6 (9.7)	1.36	.25
Diastolic blood pressure, mm Hg	64.3 (8.7)	64.5 (9.2)	62.9 (6.4)	63.3 (7.2)	0.01	.92
Pulse, beats per min	93.5 (11.4)	89.8 (14.5)	88.1 (12.5)	93.9 (14.9)	8.58	.01
Height, in[c,e]	47.4 (9.2)	50.1 (4.4)	49.3 (5.0)	49.2 (4.5)	1.33	.26

[a]End of phase 2.
[b]*P* value for time-by-treatment interaction.
[c]Aripiprazole (n = 29); placebo (n = 29).
[d]Aripiprazole (n = 20); placebo (n = 17).
[e]Corrected for time in study.

until study discontinuation (largest Wald, $\chi^2_1 = 0.98$, $P = .32$ for age at onset of bipolar disorder symptoms). The hazard ratio for aripiprazole versus placebo ranged from 0.32 to 0.41 for discontinuation due to mood or any event, indicating that aripiprazole decreased the odds of discontinuation by ~60% even after adjusting for all covariates.

Symptom Ratings

No significant between-group treatment effects on symptom ratings at randomization or changes over time were found for the YMRS, CDRS-R, CGAS, or CGI-S (all *P* values > .05).

Safety

No deaths occurred during this study. No patients discontinued due to adverse events. Table 2 presents adverse events that were reported in > 5% of study participants. Those children treated with aripiprazole were more likely to report both stomach and musculoskeletal pain than those subjects who received placebo (both $P < .01$).

Subjects randomly assigned to aripiprazole (mean 30.4 kg, SD = 10.0 kg) did not significantly differ in mean weight at randomization compared to subjects receiving placebo (mean = 28.7 kg, SD = 10.3 kg; $t_{58} = 0.62$, $P = .54$). There was a significant difference in weight gain from time of randomization between patients who received aripiprazole (mean = 2.61 kg, SD = 3.88 kg) and those who received placebo (mean = 0.42 kg, SD = 1.26 kg; $t_{35.04} = 2.94$, $P = .006$). As youngsters this age are growing, it is worth noting that the median time in phase 2 for the aripiprazole group was more than 8 times longer than for the placebo group. Adjusting for difference in time on protocol eliminated the significant difference in weight gain, although this adjustment could plausibly be an overcorrection, since both time on protocol and weight gain were correlated with the third variable of treatment status.

Two subjects had a score of 1 on the Neurological Rating Scale for Extrapyramidal Side Effects (NRS), indicative of mild severity (1 subject at week 3 on the glabella tap item and 1 subject at week 36 on the head rotation item). All other NRS scores were 0 for all other subjects at all other visits. In addition, all subjects scored 0 on the Barnes Akathisia Scale and Abnormal Involuntary Movement Scale throughout the course of the entire study.

Laboratory and safety measures are presented in Table 3. No significant time-by-treatment interactions in end-of-study fasting glucose, fasting cholesterol, fasting triglyceride levels, diastolic blood pressure, or systolic blood pressure were found (all *P* values > .05). A small nonsignificant increase in pulse in the placebo group and a small nonsignificant decrease in the aripiprazole group at the end of study, when combined, led to a significant time-by-treatment interaction ($P = .01$). However, there was a significant time-by-treatment interaction for prolactin levels ($P < .001$). Prolactin levels decreased at end of study compared to levels at time of randomization in the aripiprazole group, while prolactin levels at end of study in the placebo group increased compared to levels at time of randomization. No laboratory values were abnormal and clinically significant.

DISCUSSION

To our knowledge, this study is the first placebo-controlled trial to assess the efficacy of any medication specifically in children under age 10 with bipolarity. The study was designed to complement placebo-controlled studies in youth 10 years and older with bipolar I disorder,[2,35–39] many of which have led to FDA indications. These results suggest that aripiprazole may be beneficial in the long-term treatment of children with bipolar disorder. The data complement the results of placebo-controlled acute and maintenance treatment with aripiprazole in older youth with bipolarity[2,3] and further confirm the feasibility of prospective, randomized maintenance studies in this patient population.[26,40]

Similar to the discontinuation paradigms employed previously,[26,40] this study suggests the possibility of a nocebo effect early in the course of randomized, double-blind treatment. Both groups showed a high rate of withdrawal from the maintenance phase over the first 4 weeks, even though there was no dosing change for those who remained on aripiprazole treatment. More specifically, 42 of 60 (70%; 15/30, 50% for aripiprazole; 27/30, 90% for placebo) subjects withdrew during this initial 4-week period. The knowledge that the patient was shifting from open-label treatment to blinded therapy may have had the psychological effect of increasing concern about relapse or adverse events.

Notably, only 6 of the original 30 patients randomly assigned to treatment with aripiprazole completed 72 weeks of double-blind treatment. Even though aripiprazole maintenance was statistically superior to placebo maintenance, alone it was not sufficient to keep most youth stable for extended periods of time. These findings underscore the crucial need for studies that extend beyond acute stabilization and evaluate effectiveness and maintenance over longer terms.

Drug names: aripiprazole (Abilify), lithium (Lithobid and others), methylphenidate (Focalin, Daytrana, and others).

Author affiliations: Department of Psychiatry, Case Western Reserve University/University Hospitals Case Medical Center, Cleveland, Ohio (Drs Findling, Youngstrom, McNamara, Stansbrey, and Calabrese and Mss Wynbrandt, Adegbite, Rowles, and Demeter); Departments of Psychology and Psychiatry, University of North Carolina at Chapel Hill (Dr Youngstrom); and Center for Pediatric Behavioral Health and Center for Autism, Cleveland Clinic Children's Hospital, Cleveland, Ohio (Dr Frazier).

Author contributions: Drs Youngstrom and Frazier provided statistical consultation.

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