Acute Treatment of Pediatric Bipolar I Disorder, Manic or Mixed Episode, With Aripiprazole: A Randomized, Double-Blind, Placebo-Controlled Study

Robert L. Findling, MD; Margaretta Nyilas, MD; Robert A. Forbes, PhD; Robert D. McQuade, PhD; Na Jin, MS; Taro Iwamoto, PhD; Svetlana Ivanova, PhD; William H. Carson, MD; and Kiki Chang, MD

Objectives: To determine the efficacy and safety of aripiprazole for the treatment of pediatric bipolar I disorder, manic or mixed episode, with or without psychotic features.

Method: Subjects were enrolled between March 2005 and February 2007 in a randomized, multicenter, double-blind 4-week study of aripiprazole 10 mg/d, aripiprazole 30 mg/d, and placebo. Subjects (n = 296) were 10 to 17 years old with a *DSM-IV* diagnosis of bipolar I disorder with current manic or mixed episodes, with or without psychotic features, and a Young Mania Rating Scale (YMRS) score ≥ 20. The primary efficacy variable was change from baseline in the YMRS total score.

Results: Both doses of aripiprazole were superior to placebo on the YMRS total score beginning at week 1 and continuing through week 4. Aripiprazole 10 mg and 30 mg were more effective than placebo on global improvement, mania, and overall bipolar illness outcome measures. Response (≥ 50% reduction in YMRS total score) at week 4 was achieved by 44.8%, 63.6%, and 26.1% of subjects in the aripiprazole 10 mg, aripiprazole 30 mg, and placebo groups, respectively ($P < .01$ both doses vs placebo). Both doses were generally well tolerated. The most common adverse events were extrapyramidal disorder and somnolence; rates were higher for aripiprazole 30 mg compared with aripiprazole 10 mg. Average weight gain was not significantly different between the aripiprazole 10 mg (+0.82 kg) or 30 mg (+1.08 kg) groups compared with the placebo group (+0.56 kg) ($P = .35$ and $P = .13$, respectively).

Conclusions: Aripiprazole in daily doses of 10 mg or 30 mg is an effective and generally well-tolerated acute treatment for pediatric subjects with bipolar I mania or mixed episodes.

Trial Registration: clinicaltrials.gov Identifier: NCT00110461

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Corresponding author: *Robert L. Findling, MD, Department of Psychiatry, Division of Child and Adolescent Psychiatry, University Hospitals Case Medical Center, Case Western Reserve University, 10524 Euclid Ave–1st Floor, Cleveland, OH 44106 (robert.åndling@uhhospitals.org).*

Pediatric bipolar disorder is a severe, disabling psychiatric condition that is increasingly diagnosed and treated.[1,2] Although the diagnosis of pediatric-onset bipolar disorder may be seen as controversial to some, an increasing body of systematic research has helped confirm the validity of this syndrome and has demonstrated the chronicity of the disorder.[3–7] Diagnosis rates for bipolar disorder in children and adolescents increased 40-fold from 1994 to 2003 in one large, nationally representative sample of youth seen in office-based settings. During the period between 1999 and 2003, 48% of the pediatric subjects in this cohort who received a diagnosis of bipolar disorder were prescribed an antipsychotic agent,[8] and atypical antipsychotic agents, along with mood stabilizers, are generally considered the first line of treatment.[9,10]

Despite the dramatic rise in recognition of pediatric bipolar disorder and use of antipsychotic agents, there is a lack of data from randomized, placebo-controlled trials to guide treatment. Most published data on atypical antipsychotic use are from small, open-label, non–placebo-controlled studies.[11–15] Data from published and presented randomized, double-blind, placebo-controlled trials of atypical antipsychotics in adolescents with bipolar disorder have demonstrated that quetiapine was more effective than placebo as an adjunct to divalproex[16] and that quetiapine[17] and risperidone[18] were generally well tolerated and superior to placebo on improvement on mania scores in subjects aged 10 to 17 years with bipolar mania. Olanzapine has also been shown to be superior to placebo in adolescents 13–17 years of age with an acute manic or mixed episode.[19] Risperidone is approved for the short-term treatment of children and adolescents aged 10–17 years who have acute manic or mixed episodes associated with bipolar I disorder, adolescents aged 13–17 years with schizophrenia, and children

and adolescents aged 5–16 years who have irritability associated with autistic disorder.

Aripiprazole is a next-generation atypical antipsychotic with partial-agonist activity at D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors.[20,21] Aripiprazole is approved by the US Food and Drug Administration for the acute and maintenance treatment of manic or mixed episodes associated with bipolar I disorder in adults. Aripiprazole is also approved in the United States for the treatment of bipolar I disorder in pediatric patients (10–17 years of age). Here, we report results of a randomized, double-blind, placebo-controlled, 4-week trial to evaluate the efficacy and safety of aripiprazole in daily doses of 10 mg and 30 mg in youths with bipolar I disorder currently experiencing either a manic or mixed episode with or without psychotic features. This study was the basis for the approval of aripiprazole for use in pediatric mania.

METHOD

Patients

This 4-week multicenter, double-blind, randomized, placebo-controlled study enrolled outpatients and hospitalized, or partially hospitalized, subjects from 59 sites in the United States between March 2005 and February 2007. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice guidelines. Institutional review boards at each site approved methods and informed consent/assent procedures.

Subjects were aged 10 to 17 years with a confirmed *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) diagnosis of bipolar I disorder with current manic or mixed episodes, with or without psychotic features, and a Young Mania Rating Scale (YMRS)[22] total score ≥ 20 at baseline. Board-certified or board-eligible child and adolescent psychiatrists made the diagnosis after obtaining written informed consent from the parent or legal guardian and written informed assent from the patient. Trained interviewers confirmed the primary diagnosis using the Schedule for Affective Disorders and Schizophrenia for School Aged Children: Present and Lifetime Version (K-SADS-PL).[23] Subjects with comorbid attention-deficit/hyperactivity disorder (ADHD), conduct disorder, oppositional defiant disorder, or anxiety disorders (except posttraumatic stress disorder or obsessive-compulsive disorder) were eligible.

Mood stabilizers and other psychotropics were tapered and discontinued at least 5 half-lives before day 1. Benzodiazepine and anticholinergic therapy was permitted as rescue medication and for extrapyramidal symptom relief, although not within 4 or 12 hours of efficacy or safety assessments, respectively.

Subjects who had not initiated aripiprazole use within 7 days of screening, but who had used aripiprazole within 3 months prior to screening, were considered eligible for enrollment upon mutual agreement of the investigator and sponsor, provided that they had met all inclusion criteria. All subjects were required to complete a 3-day medication washout period prior to randomization, including those who had received aripiprazole within 7 days of screening. Eight subjects had used aripiprazole prior to randomization (n = 3, placebo; n = 5, aripiprazole).

Exclusionary criteria were bipolar II disorder, bipolar disorder not otherwise specified, a pervasive developmental disorder, schizophrenia, schizoaffective disorder, psychosis due to other medical condition or concomitant medication, mental retardation (ie, documented IQ < 70 or clinical/social/school history suggestive of mental retardation), *DSM-IV* substance or alcohol use disorder, positive drug screen for cocaine or other substances of abuse during screening, sexual activity without contraceptive use, pregnancy, lactation, or other medical reason as determined by the investigator. Noncompliance with medication washout, inability to swallow tablets whole, or a history of antipsychotic treatment resistance (ie, failed courses of 2 different antipsychotic agents of adequate dose and duration) or neuroleptic malignant syndrome also excluded enrollment. Subjects who attempted suicide in the past 6 months, had a score > 3 on the Suicidal Ideation item of the Children's Depression Rating Scale-Revised (CDRS-R),[24] or were determined by the investigator to be at risk of suicide were excluded. Other reasons for exclusion included clinically important laboratory test results, vital sign, or electrocardiogram (ECG) abnormalities; diabetes mellitus; abnormally elevated serum glucose levels; epilepsy; history of severe head trauma; stroke; unstable thyroid pathology requiring treatment; other unstable medical conditions; prior participation in an aripiprazole study; allergy or hypersensitivity to aripiprazole; or participation in an investigational drug trial in the past month.

Treatment/Dosing

After screening and medication washout, subjects were randomly assigned to target doses of aripiprazole (10 mg or 30 mg) or matching placebo once daily for 4 weeks. Study medication could be administered at any time of day without regard for meals. Aripiprazole dosing started with 2 mg/d (days 1 and 2), 5 mg/d (days 3 and 4), and 10 mg/d on day 5. Subjects in the 10 mg group remained at that target dose, and titration continued for the 30 mg group with 10 mg/d (days 5 and 6), 15 mg/d (days 7 and 8), 20 mg/d (days 9 and 10), and 25 mg/d (days 11 and 12) and concluded with the target dose of 30 mg/d on day 13. Matching placebo was administered according to the same titration schedule. Study medication was dispensed at weekly visits in child-resistant blister cards containing a 1-week supply.

Efficacy Assessments and Schedule

The primary efficacy endpoint was change from baseline (ie, randomization day 1) to week 4 in the YMRS total score.

Secondary efficacy variables were change from baseline scores on the Children's Global Assessment Scale (CGAS)[25]; Clinical Global Impressions Scale-Bipolar Version (CGI-BP) severity of mania, depression, and overall bipolar illness[26]; CDRS-R[24]; an abbreviated version of the General Behavior Inventory[27,28] (GBI; 20-items with 2 subscales that assessed symptoms of mania/hypomania and depression which was completed by both parents/guardians and subjects); and the parent questionnaire on home behaviors version of the ADHD Rating Scale-Version IV (ADHD-RS-IV).[29] Primary and secondary efficacy variables were assessed at screening, at baseline, and at each scheduled weekly visit through week 4. The Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q)[30] was administered at baseline and week 4. Other efficacy variables were response (≥ 50% reduction from baseline YMRS total score) and time to discontinuation. A post hoc analysis defined remission as a YMRS total score ≤ 12 and CGI-BP severity score for mania ≤ 2.

Safety Assessments and Schedule

An independent data safety monitoring board prospectively reviewed adverse events throughout the study and was informed weekly of serious adverse events. An adverse event was considered "serious" if it was fatal, life-threatening, persistently or significantly disabling or incapacitating; required the subject to be hospitalized; or prolonged a youth's hospitalization.[31] In addition, any other medically significant event requiring medical or surgical intervention to prevent one of the outcomes listed above was also considered "serious." Adverse events were patient/guardian-reported, elicited at each visit using open-ended questions about new medical problems and exacerbation of existing medical problems. Investigators recorded self-injurious behaviors and documented any relationship to suicide attempts. Vital signs and measurements of height and weight were obtained at screening and baseline and at each scheduled visit. Other assessments obtained at baseline and week 4 were physical examinations, ECGs, and laboratory tests, the latter of which included assessment of body mass index (BMI), serum prolactin, fasting serum glucose, fasting total cholesterol, fasting triglycerides, and fasting high-density lipoprotein (HDL) cholesterol. Extrapyramidal-related symptoms were assessed at screening and baseline and at each visit using the Simpson-Angus Scale (SAS),[32] the Abnormal Involuntary Movement Scale (AIMS),[33] and the Barnes Akathisia Rating Scale (BARS).[34] Medication adherence and well-being were also monitored during a telephone interview on day 4.

Statistical Analysis

Sample size considerations. This study was designed to have 85% power to detect a difference between aripiprazole and placebo of a −5.1 point change from baseline YMRS total score at week 4. The mean difference of −5.1 points was estimated from 2 bipolar mania trials in adults,[35,36] using a pooled standard deviation of 11.1. On the basis of these estimates and using a 2-sided α of .05, 87 subjects per treatment arm with a total of 261 subjects were required to yield 85% power.

Data analysis. Efficacy and safety analyses were conducted using data from baseline through week 4 visits. Analyses of safety and tolerability parameters included data from all randomized subjects who had taken at least 1 dose of study medication (safety sample). The efficacy sample included all patients in the safety sample who had at least 1 postbaseline efficacy assessment. All analyses were conducted in the last-observation-carried-forward data set.

An overall *F*-test for the mean change from baseline in YMRS total score was performed at a significance level of .05 (2-tailed) for the aripiprazole 10 mg, aripiprazole 30 mg, and placebo groups. Since this hypothesis was rejected at the .05 level, each of the aripiprazole 10 mg versus placebo, and aripiprazole 30 mg versus placebo comparisons were tested at a 2-sided .05 significance level. Change scores from baseline were analyzed using analysis of covariance (ANCOVA) with treatment as a factor and baseline score as a covariate at each timepoint. The least squares (LS) means obtained from a type III analysis using SAS were used for the treatment comparisons. Two-tailed Student *t* tests were used to test differences between the LS means within the ANCOVA model. The proportion of responders was analyzed using a χ^2 test. Adverse events are summarized using descriptive statistics. The proportion of patients with clinically significant weight gain (≥ 7% increase from baseline) was evaluated using the Fisher exact test.

RESULTS

Patients

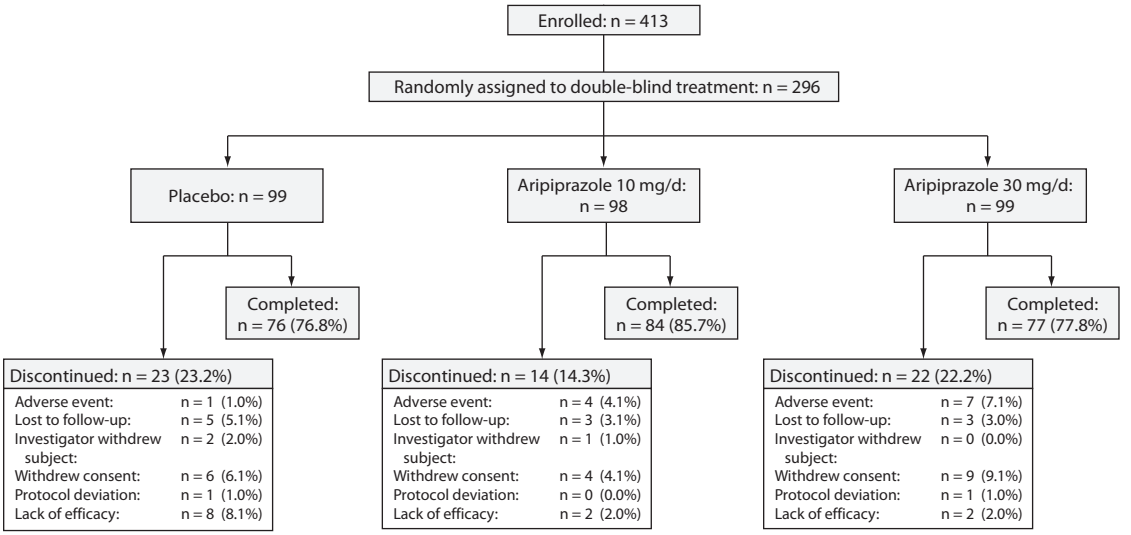
A total of 413 subjects were screened and 296 eligible subjects randomly assigned to aripiprazole 10 mg/d (n = 98), aripiprazole 30 mg/d (n = 99), or placebo (n = 99). Two hundred thirty-seven subjects (80%) completed the 4-week study; subject disposition is shown in Figure 1. Two subjects randomly assigned to placebo were excluded from the safety population as they did not receive at least 1 dose of study medication.

Demographic and clinical characteristics, including information on comorbidities, are shown in Table 1 and were similar for all 3 groups. The overall mean age was 13.4 years, and the majority (78.0%) of subjects were aged 12–17 years. Slightly more than half of subjects were male, and roughly two-thirds were white. The overall mean BMI was 23.8 kg/m^2, and 28.6% of subjects exceeded the 95th percentile BMI adjusted for age and gender at baseline. The mean age at onset of bipolar disorder was 12.1 years, with a mean duration of bipolar illness of 1.3 years (Table 1).

Efficacy

Primary efficacy measure. Aripiprazole 10 mg and 30 mg were superior to placebo on the primary efficacy variable

Figure 1. Subject Disposition (randomized sample)



at the week 4 timepoint (Figure 2). At the 4-week endpoint, mean changes from baseline on the YMRS total score were significantly greater for aripiprazole 10 mg compared with placebo (–14.2 vs –8.2; $P < .0001$) and aripiprazole 30 mg compared with placebo (–16.5 vs –8.2; $P < .0001$). Statistically significant differences between both doses of aripiprazole and placebo occurred as early as week 1 for the 10 mg (–9.0 vs –5.6; $P = .002$) and 30 mg groups (–9.4 vs –5.6; $P < .001$) and were sustained through week 4.

Secondary efficacy measures. Mania/overall bipolar illness. Treatment with aripiprazole 10 mg or 30 mg resulted in statistically significant changes from baseline to week 4 compared to placebo on CGI-BP severity of mania and the GBI total scores on parent/guardian and patient version of mania/hypomania (all $P < .05$) (Table 2). Treatment with aripiprazole 10 mg or 30 mg also resulted in statistically significant changes from baseline to week 4 compared to placebo on CGI-BP overall bipolar illness scores ($P < .0001$). Both dose groups of aripiprazole demonstrated statistical superiority to placebo at the week 1 visit on CGI-BP severity scores for mania and overall bipolar illness and GBI total score on the parent/guardian version for mania (data not shown).

Depression. As shown in Table 2, there were no statistically significant differences in change from baseline to week 4 scores on the clinician-rated CGI-BP severity of depression scale or the CDRS-R for either aripiprazole dose compared to placebo. Aripiprazole 10 mg resulted in significantly greater improvement than placebo on the GBI total score on the parent/guardian version of depression ($P = .0430$), although improvement with aripiprazole 30 mg was not significantly different than with placebo at week 4. No statistically significant differences in change from baseline to week 4 scores on the GBI total scores on the patient-completed measure of depression were observed.

Response and remission. Beginning at week 1 and continuing through week 4, the percentage of responders in both aripiprazole treatment groups was significantly higher than in the placebo group. At week 4, the response criterion was met by 44.8% of subjects in the aripiprazole 10 mg group ($P = .0074$ vs placebo), 63.6% in the 30 mg group ($P < .0001$ vs placebo), and 26.1% in the placebo group. Remission was achieved by 25% of subjects in the aripiprazole 10 mg group ($P = .0002$ vs placebo), 47.5% in the 30 mg group ($P < .0001$ vs placebo), and 5.4% in the placebo group at week 4. Remission rates separated from placebo as early as week 1 for both aripiprazole groups.

Additional outcomes. Treatment with aripiprazole 10 mg or 30 mg resulted in statistically significant changes in CGAS score from baseline to week 4 compared to placebo. While small improvements on the P-QLES-Q total score occurred in each treatment group, there were no significant differences between aripiprazole and placebo at week 4. Treatment with aripiprazole 10 mg or 30 mg also resulted in statistically significant changes from baseline to week 4 compared to placebo on the ADHD-RS-IV total scores (both $P < .0001$).

Safety

Aripiprazole was generally well tolerated. There were no deaths or suicides during the study. At least 1 serious adverse event occurred in 5.1% (n = 5) of subjects in the aripiprazole 10 mg group, 2.0% (n = 2) in the aripiprazole 30 mg group, and 5.2% (n = 5) in the placebo group. Serious adverse events in the aripiprazole 10 mg group included the following: 1 subject with accidental overdose, grand mal seizure, and respiratory arrest, all judged by the study investigator

Table 1. Demographic and Baseline Clinical Characteristics of All Randomized Subjects in a Study of Pediatric Bipolar I Disorder Treated With Aripiprazole 10 mg, Aripiprazole 30 mg, or Placebo

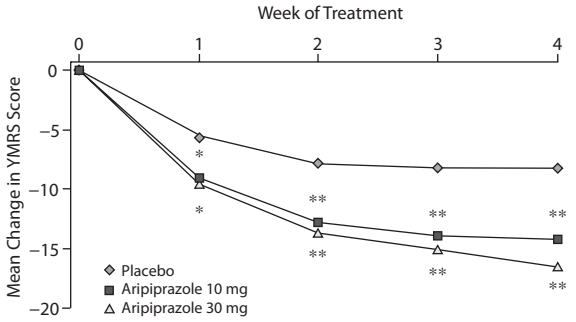
Baseline Characteristic	Aripiprazole 10 mg (n = 98)	Aripiprazole 30 mg (n = 99)	Placebo (n = 99)	Total (n = 296)
Age, mean ± SD, y	13.7 ± 2.2	13.3 ± 2.3	13.3 ± 2.1	13.4 ± 2.2
Age group, n (%)				
10–11 y	18 (18.4)	26 (26.3)	21 (21.2)	65 (22.0)
12–17 y	80 (81.6)	73 (73.7)	78 (78.8)	231 (78.0)
Height, mean ± SD, cm	161.1 ± 12.5	158.4 ± 12.2	158.7 ± 11.6	159.4 ± 12.1
Weight, mean ± SD, kg	63.8 ± 20.1	60.5 ± 21.5	60.5 ± 17.3	61.6 ± 19.7
BMI, mean ± SD, kg/m^2	24.2 ± 5.4	23.7 ± 6.7	23.7 ± 5.0	23.8 ± 5.7
BMI > 95th percentile, n (%)	27 (27.6)	27 (27.3)	30 (30.9)[a]	84 (28.6)
Sex, % male	53.1	51.5	56.6	53.7
Race, % white	66.3	68.7	60.6	65.2
Ethnicity, % non-Hispanic/Latino	93.9	89.9	84.9	89.5
Age at onset, mean ± SD, y	12.5 ± 3.2	12.0 ± 3.0	11.9 ± 3.0	12.1 ± 3.0
Duration of bipolar disease, mean ± SD, y	1.3 ± 2.2	1.3 ± 2.5	1.4 ± 1.9	1.3 ± 2.2
YMRS total score, mean ± SD	29.8 ± 6.5	29.5 ± 6.3	30.7 ± 6.8	30.0 ± 6.5
Current episode, n (%)[b]				
Mixed	43 (43.9)	39 (39.4)	43 (43.4)	125 (42.2)
Manic	41 (41.8)	40 (40.4)	38 (38.4)	119 (40.2)
Unknown	14 (14.3)	20 (20.2)	18 (18.2)	52 (17.6)
Rapid cycling (*DSM-IV* criteria), n (%)[b]				
Yes	17 (17.4)	13 (13.1)	15 (15.2)	45 (15.2)
No	49 (50.0)	46 (46.5)	51 (51.5)	146 (49.3)
Unknown	32 (32.7)	40 (40.4)	33 (33.3)	105 (35.5)
Psychotic features in previous episode, n (%)[b]				
Yes	2 (2.0)	6 (6.1)	7 (7.1)	15 (5.1)
No	67 (68.4)	62 (62.6)	65 (65.7)	194 (65.5)
Unknown	29 (29.6)	31 (31.3)	27 (27.3)	87 (29.4)
Psychotic features in current episode, n (%)[b]				
Yes	7 (7.1)	4 (4.0)	3 (3.0)	14 (4.7)
No	58 (59.2)	58 (58.6)	64 (64.7)	180 (60.8)
Unknown	33 (33.7)	37 (37.4)	32 (32.3)	102 (34.5)
Current or past history of ADHD, n (%)[b]				
Yes	48 (49.0)	50 (50.5)	55 (55.6)	153 (51.7)
No	34 (34.7)	25 (25.3)	18 (18.2)	77 (26.0)
Unknown	16 (16.3)	24 (24.2)	26 (26.3)	66 (22.3)
Current or past history of ODD, n (%)[b]				
Yes	28 (28.6)	34 (34.3)	31 (31.3)	93 (31.4)
No	48 (49.0)	39 (39.4)	41 (41.4)	128 (43.2)
Unknown	22 (22.5)	26 (26.3)	27 (27.3)	75 (25.3)
Treatment with antipsychotics within past month, n (%)	12 (12.2)	10 (10.1)	14 (14.1)	36 (12.2)
Prior aripiprazole treatment, n (%)				
Within past month	0	2 (2.0)	1 (1.0)	3 (1.0)
Prior to past month	2 (2.0)	1 (1.0)	2 (2.0)	5 (1.7)
Treatment-naive, %[c]	41.8	49.5	36.4	42.6
Family history of bipolar I disorder, n (%)	44 (44.9)	35 (35.4)	52 (52.5)	131 (44.3)
CDRS-R suicidal ideation score, mean ± SD	1.1 ± 0.4	1.1 ± 0.5	1.2 ± 0.5	1.2 ± 0.5

[a]Based on the placebo safety intent-to-treat population, n = 97.
[b]Data relating to these clinical characteristics were collected post hoc; capturing data on comorbid diagnoses was not required by investigators, and thus there is a high percentage of missing data.
[c]No prior treatment for bipolar illness.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BMI = body mass index, CDRS-R = Children's Depression Rating Scale-Revised, ODD = oppositional defiant disorder, YMRS = Young Mania Rating Scale.

as not related to aripiprazole treatment; 1 subject each with aggression judged not related to treatment; 1 subject with oppositional defiant disorder judged not related to treatment; 1 subject with suicidal ideation, not likely related to aripiprazole treatment; and 1 subject with aggression and fatigue, judged as probably related to aripiprazole treatment. Both serious adverse events in the aripiprazole 30 mg group and all 5 serious adverse events in the placebo group were "exacerbation of bipolar disorder"; all were judged by the study investigator as unrelated or not likely related to study medication.

Adverse events occurring in at least 5% of subjects are summarized in Table 3. Twelve subjects (aripiprazole 10 mg, n = 4; aripiprazole 30 mg, n = 7; placebo, n = 2) discontinued treatment due to adverse events before completing the full 4 weeks of treatment. An additional 4 subjects (aripiprazole 10 mg, n = 2, aripiprazole 30 mg, n = 1; placebo, n = 1) completed the week 4 study visit, and were counted as acute phase completers, but discontinued due to adverse events before entering the extension phase. Adverse events resulting in study discontinuation in the 10 mg group were fatigue (n = 2), sedation (n = 2), akathisia (n = 1), aggression (n = 1),

Figure 2. Mean Change From Baseline in YMRS Total Score (LOCF) Weeks 1 Through 4 for Aripiprazole 10 mg, Aripiprazole 30 mg, and Placebo (efficacy sample)[a]



[a]Baseline YMRS scores (efficacy sample): aripiprazole 10 mg, 29.8; aripiprazole 30 mg, 29.5; placebo, 31.1.
*$P < .05$.
**$P < .0001$.
Abbreviations: LOCF = last observation carried forward, YMRS = Young Mania Rating Scale.

and suicidal ideation (n = 1). In the 30 mg group, extrapyramidal disorder (n = 3), exacerbation of bipolar disorder (n = 2), vomiting (n = 1), dystonia (n = 1), and somnolence (n = 1) led to study withdrawal (1 subject discontinued because of aggression and fatigue). Anxiety (n = 1) and exacerbation of bipolar disorder (n = 1) were adverse events leading to discontinuation in the placebo group.

Laboratory analyses, vital signs, ECG. There were no relevant trends observed in the incidence of potentially clinically significant heart rate or blood pressure abnormalities. No trends were observed for any potentially clinically significant changes in ECG parameters, including QT_{cB}. Abnormal QT_{cB} values (≥ 420 msec for subjects 10–17 years and a ≥ 10% increase from baseline or ≥ 450 msec for subjects ≥ 18 years at the time of measurement and a ≥ 10% increase from baseline) occurred in 4 subjects in the aripiprazole 10 mg group (4.4%), 2 in the aripiprazole 30 mg group (2.3%), and 7 in the placebo group (8.4%). Abnormalities in laboratory values appeared to be isolated findings and showed no clinically meaningful trends as assessed by an independent data safety monitoring board.

EPS-related symptoms. EPS-related adverse events were categorized under 5 separate category headings (dystonic, Parkinsonian, akathisia, dyskinetic, and residual events) (Table 3). The most common EPS-related adverse events (more than 5% incidence) were extrapyramidal disorder, akathisia, and dystonia. Extrapyramidal events were reported by 23 of the aripiprazole 10 mg patients, 39 of the aripiprazole 30 mg patients, and 7 of the placebo patients (Table 3). Of these, 11 of the aripiprazole 10 mg patients, 17 of the aripiprazole 30 mg patients, and 4 of the placebo patients received medication for the treatment of EPS. The majority of EPS events were Parkinson-like in nature and were classified as mild to moderate as evidenced by a low rate of adverse event–related discontinuation. Discontinuations occurred in patients who experienced akathisia (aripiprazole 10 mg, 1.0%), dystonia (aripiprazole 30 mg, 1.0%), and extrapyramidal disorder (aripiprazole 30 mg, 3.0%). Change from baseline on the physician-rated BARS and AIMS did not differ from placebo at week 4. Change in SAS scores at week 4 indicated relative worsening from baseline in aripiprazole patients compared to placebo (aripiprazole 10 mg, LS mean change 0.6 vs –0.1 for placebo, $P = .0338$; aripiprazole 30 mg, 1.2 vs –0.1, $P < .0001$).

Metabolic parameters and weight change. Changes in metabolic parameters and weight over the course of the study are shown in Table 4. Mean weight change from baseline to week 4 in the aripiprazole 10 mg (+0.82 kg) and the aripiprazole 30 mg (+1.08 kg) groups was not significantly different from placebo (+0.56 kg) ($P = .35$ and $P = .13$, respectively). The incidence of clinically significant weight gain (≥ 7% increase from baseline) at week 4 was not significantly different between aripiprazole 10 mg (4.0%) or aripiprazole 30 mg (12.3%) and placebo (4.6%) ($P = 1.00$ and $P = .14$, respectively). Mean change in BMI from baseline to week 4 was also comparable between both aripiprazole treatment groups and placebo ($P = .4425$ and $P = .1212$, respectively). Overall, there were no clinically meaningful changes from baseline in fasting serum glucose, total cholesterol, triglycerides, or HDL-cholesterol or meaningful trends in the incidence of abnormalities in these parameters.

Serum prolactin levels decreased from baseline to week 4 in both aripiprazole groups, and changes were more pronounced for males. Low prolactin levels (females, < 3 ng/mL; males, < 2 ng/mL) occurred in 22 subjects in the aripiprazole 10 mg group (25.3%), 35 in the 30 mg group (39.3%), and 2 in the placebo group (2.4%).

DISCUSSION

This is the first randomized, double-blind, placebo-controlled trial of aripiprazole treatment of bipolar I disorder in pediatric subjects with a manic or mixed episode. Results of this study indicate that aripiprazole is effective and well tolerated for the treatment of pediatric mania. Reduction in mania, as measured by change from baseline in YMRS total score, was significantly greater with aripiprazole than placebo at week 4 for the 10 mg/d dose and the 30 mg/d dose. Onset of action was rapid, with statistically significant improvement in mania symptoms observed at week 1 and sustained through endpoint for both doses.

Aripiprazole also showed statistically significant improvements on several other key indicators of clinical efficacy. Remission, which was stringently defined as a YMRS total score ≤ 12 and CGI-BP severity score ≤ 2, was achieved by significantly more subjects in the aripiprazole 10 mg (25%) and the aripiprazole 30 mg (48%) groups compared with placebo (5%) at week 4. Response rates (≥ 50%

Table 2. Mean Change From Baseline (day 1 visit) to End of Week 4 for Efficacy Variables in Pediatric Subjects With Bipolar I Disorder Treated With Aripiprazole 10 mg, Aripiprazole 30 mg, or Placebo (efficacy sample, LOCF dataset)[a,b]

				Comparison of Aripiprazole and Placebo (*P* Value)	
Efficacy Rating Scale	Aripiprazole 10 mg	Aripiprazole 30 mg	Placebo	Aripiprazole 10 mg	Aripiprazole 30 mg
YMRS total score					
Baseline	29.8 (n = 96)	29.5 (n = 99)	31.1 (n = 94)		
LS mean change at week 4	−14.2 (n = 96)	−16.5 (n = 99)	−8.2 (n = 92)		
Treatment difference at week 4 (95% CI)	−5.99 (−8.49 to −3.50)	−8.26 (−10.7 to −5.77)		< .0001	< .0001
CGAS score					
Baseline	46.9 (n = 96)	47.5 (n = 99)	45.5 (n = 94)		
LS mean change at week 4	15.1 (n = 96)	17.3 (n = 99)	5.8 (n = 92)		
Treatment difference at week 4 (95% CI)	9.30 (5.77 to 12.84)	11.51 (7.99 to 15.03)		< .0001	< .0001
CGI-BP severity score—mania					
Baseline	4.7 (n = 96)	4.6 (n = 99)	4.9 (n = 94)		
LS mean change at week 4	−1.6 (n = 96)	−2.1 (n = 99)	−0.8 (n = 92)		
Treatment difference at week 4 (95% CI)	−0.81 (−1.15 to −0.48)	−1.26 (−1.59 to −0.93)		< .0001	< .0001
CGI-BP severity score—depression					
Baseline	2.9 (n = 96)	2.9 (n = 99)	2.8 (n = 94)		
LS mean change at week 4	−0.9 (n = 96)	−0.9 (n = 99)	−0.6 (n = 92)		
Treatment difference at week 4 (95% CI)	−0.25 (−0.54 to 0.04)	−0.26 (−0.55 to 0.03)		.0878	.0752
CGI-BP severity score—overall bipolar illness					
Baseline	4.7 (n = 96)	4.6 (n = 99)	4.8 (n = 94)		
LS mean change at week 4	1.6 (n = 96)	−2.0 (n = 99)	−0.8 (n = 92)		
Treatment difference at week 4 (95% CI)	−0.83 (−1.16 to −0.51)	−1.18 (−1.51 to −0.86)		< .0001	< .0001
CDRS-R score					
Baseline	35.2 (n = 91)	34.1 (n = 94)	33.8 (n = 86)		
LS mean change at week 4	7.2 (n = 91)	−6.1 (n = 94)	−4.9 (n = 85)		
Treatment difference at week 4 (95% CI)	−2.28 (−4.81 to 0.25)	−1.19 (−3.69 to 1.32)		.0767	.3515
GBI total scores—parent/guardian (mania)					
Baseline	17.7 (n = 95)	17.4 (n = 96)	19.1 (n = 93)		
LS mean change at week 4	9.9 (n = 95)	−9.5 (n = 96)	−4.0 (n = 91)		
Treatment difference at week 4 (95% CI)	−5.88 (−8.02 to −3.73)	−5.46 (−7.60 to −3.32)		< .0001	< .0001
GBI total scores—parent/guardian (depression)					
Baseline	13.4 (n = 95)	12.4 (n = 96)	13.4 (n = 93)		
LS mean change at week 4	5.9 (n = 95)	−4.1 (n = 96)	−3.8 (n = 91)		
Treatment difference at week 4 (95% CI)	−2.13 (−4.20 to −0.07)	−0.31 (−2.37 to 1.76)		.0430	.7696
GBI total scores—patient (mania)					
Baseline	15.1(n = 96)	14.8 (n = 96)	14.8 (n = 93)		
LS mean change at week 4	6.4 (n = 96)	−6.6 (n = 96)	−4.6 (n = 91)		
Treatment difference at week 4 (95% CI)	−1.85 (−3.67 to −0.03)	−2.03 (−3.85 to −0.20)		.0468	.0296
GBI total scores—patient (depression)					
Baseline	12.1 (n = 96)	11.3 (n = 96)	10.5 (n = 93)		
LS mean change at week 4	3.4 (n = 96)	−3.3 (n = 96)	−3.4 (n = 91)		
Treatment difference at week 4 (95% CI)	0.07 (−1.73 to 1.86)	0.19 (−1.61 to 1.98)		.9418	.8377
ADHD-RS-IV total score					
Baseline	31.5 (n = 95)	32.1 (n = 97)	35.7 (n = 91)		
LS mean change at week 4	12.5 (n = 95)	−11.9 (n = 97)	−3.7 (n = 90)		
Treatment difference at week 4 (95% CI)	−8.86 (−12.3 to −5.43)	−8.23 (−11.6 to −4.83)		< .0001	< .0001

[a]Variation in n numbers reflects rating scales not completed for all subjects.
[b]Positive change on the CGAS signifies improvement; for all other scales, negative change signifies improvement.
Abbreviations: ADHD-RS-IV = ADHD Rating Scale-Version IV, CDRS-R = Children's Depression Rating Scale-Revised, CGAS = Children's Global Assessment Scale, CGI-BP = Clinical Global Impressions Scale-Bipolar Version, GBI = General Behavior Inventory, LOCF = last observation carried forward, LS = least squares, YMRS = Young Mania Rating Scale.

reduction from baseline YMRS total score) at week 4 were also significantly greater with aripiprazole than placebo. As with the primary efficacy variable, statistically significant response and remission rates were observed with both doses of aripiprazole relative to placebo from week 1 through week 4. It is worth noting that in addition to investigator-rated improvement in the symptoms of mania, as measured by YMRS total scores, both subjects and parents/caregivers noted significant improvement in mania symptoms on the GBI scale. It should be noted that aripiprazole did not produce significant improvements in depressive symptoms in this patient group. Data supporting the use of aripiprazole as an adjunct to antidepressant therapy in adults with major depressive disorder should not be extrapolated to this pediatric population.

The results reported here confirm findings from previous open-label and retrospective studies which have previously described that aripiprazole treatment is effective and well tolerated for the treatment on mania in youth with bipolar disorder.[37–39]

Current guidelines for the treatment of children and adolescents with bipolar mania recommend first-line treatment

Table 3. Treatment-Emergent Adverse Events in Pediatric Subjects With Bipolar I Disorder Treated With Aripiprazole 10 mg, Aripiprazole 30 mg, or Placebo (safety sample), N (%)[a]

Adverse Event	Aripiprazole 10 mg (n = 98)	Aripiprazole 30 mg (n = 99)	Placebo (n = 97)
Occurring in ≥ 5% of any group			
Any adverse event	72 (73.5)	75 (75.8)	57 (58.8)
Extrapyramidal disorder	12 (12.2)	27 (27.3)	3 (3.1)
Somnolence	19 (19.4)	26 (26.3)	3 (3.1)
Fatigue	13 (13.3)	9 (9.1)	4 (4.1)
Headache	17 (17.3)	19 (19.2)	16 (16.5)
Akathisia	8 (8.2)	11 (11.1)	2 (2.1)
Nausea	9 (9.2)	12 (12.1)	4 (4.1)
Vomiting	8 (8.2)	7 (7.1)	9 (9.3)
Blurred vision	8 (8.2)	8 (8.1)	0
Salivary hypersecretion	3 (3.1)	8 (8.1)	0
Decreased appetite	6 (6.1)	3 (3.0)	3 (3.1)
Dizziness	5 (5.1)	5 (5.1)	1 (1.0)
Increased appetite	2 (2.0)	5 (5.1)	3 (3.1)
Upper abdominal pain	4 (4.1)	5 (5.1)	3 (3.1)
Dystonia	0	5 (5.1)	0
Exacerbation of bipolar disorder	0	3 (3.0)	5 (5.2)
Extrapyramidal symptom categories (reported events)[a]			
Dystonic event (dystonia and muscle spasms)	0	7 (7.0)	2 (2.0)
Parkinsonism event (extrapyramidal disorder, bradykinesia and tremor)	14 (14.2)	29 (29.2)	4 (4.1)
Dyskinetic event	2 (2.0)	0	0
Residual event (muscle twitching)	1 (1.0)	1 (1.0)	0
Akathisia event (akathisia and psychomotor activation)	8 (8.1)	12 (12.1)	2 (2.0)
Any extrapyramidal symptom event	23 (23.5)	39 (39.4)	7 (7.2)

[a]Reported as preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). Categories include the following events.
Dystonic event: dystonia, emprosthotonos, muscle contractions involuntary, muscle rigidity, muscle spasms, muscle spasticity, myotonia, nuchal rigidity, oculogyration, opisthotonos, pleurothotonus, risus sardonicus, torticollis, trismus.
Parkinsonism event: akinesia, asterixis, athetosis, bradykinesia, cogwheel rigidity, essential tremor, extrapyramidal disorder, freezing phenomenon, hypertonia, hypokinesia, hypokinesia neonatal, intention tremor, masked facies, Parkinson's disease, parkinsonian crisis, parkinsonian gait, parkinsonian rest tremor, parkinsonism, tremor, tremor neonatal.
Akathisia event: akathisia, hyperkinesia, psychomotor hyperactivity, hyperkinesia neonatal.
Dyskinetic event: ballismus, buccoglossal syndrome, choreoathetosis, clumsiness, dyskinesia, dyskinesia neonatal, dyskinesia esophageal, fumbling, on-and-off phenomenon, tardive dyskinesia, head titubation.
Residual event: chorea, Huntington's chorea, muscle twitching, myoclonus, clonus.
Subjects with multiple adverse event terms within the same category were counted only once toward the total. Subjects with extrapyramidal symptom events within multiple categories were counted only once toward the total.

with atypical antipsychotics or mood stabilizers.[9] At the time, this recommendation was based on the approval of these agents for bipolar disorder in adults, as evidence of the efficacy for these agents in children and adolescents was sparse. Results from our study now provide evidence from a methodologically stringent, randomized clinical study supporting the use of aripiprazole in this patient population. Indeed, since the publication of the American Academy of Child and Adolescent Psychiatry guidelines,[9] aripiprazole has been approved by the US Food and Drug Administration for the treatment of pediatric patients with bipolar disorder 10 to 17 years of age. Interestingly, the baseline disease characteristics of the pediatric subjects included in this study differ slightly from similar trials with aripiprazole conducted in adults.[35,40] Here, a similar proportion of subjects were experiencing current manic or mixed episodes (both ~40%), whereas in adult studies a higher proportion of subjects were being treated for manic episodes.[35,40] The proportion of subjects with rapid-cycling bipolar mania reported here was slightly lower than reported in adult aripiprazole studies (15% vs 18%–23%).[35,40]

Aripiprazole was generally well tolerated in this population. Somnolence and extrapyramidal symptoms were more commonly reported by subjects in the aripiprazole 30 mg group compared with aripiprazole 10 mg. In this short-term study, changes from baseline in measures of BMI, body weight, increased fasting glucose and lipids, and ECG abnormalities were similar to those observed with placebo and were not deemed clinically meaningful by an independent data safety monitoring board. Weight gain with aripiprazole reported here is similar to previous findings in adolescents with schizophrenia[41]; in that study, neither active treatment group (aripiprazole 10 mg or aripiprazole 30 mg) exhibited substantial weight gain over the 6-week treatment period, although change in weight differed from placebo due to weight loss in the placebo group. Clinicians treating children and adolescents with aripiprazole should be aware of the potential for weight gain and routinely monitor patients longer-term.[42] Weight gain appeared to be less with aripiprazole 10 mg compared to aripiprazole 30 mg and may be a reason to consider 10 mg over 30 mg when dosing.

Decreases in serum prolactin concentrations were observed in both males and females during the course of aripiprazole treatment, although further study is needed to establish whether these changes will dissipate over time. Mean decreases in prolactin levels have previously been

Table 4. Changes in Baseline Metabolic Parameters for Pediatric Subjects With Bipolar I Disorder Treated With Aripiprazole 10 mg, Aripiprazole 30 mg, or Placebo (safety sample)

	Aripiprazole 10 mg		Aripiprazole 30 mg		Placebo	
Metabolic Parameter	Total N	Value	Total N	Value	Total N	Value
BMI						
Change from baseline, mean (SD), kg/m^2	75	0.2 (0.8)	72	0.3 (1.1)	65	0.1 (0.8)
Subjects with BMI > 95th percentile for age and gender, n (%)						
Baseline	98	27 (27.6)	99	27 (27.3)	97	30 (30.9)
Week 4	75	22 (29.3)	72	24 (33.3)	65	18 (27.7)
Subjects with BMI change from normal at baseline to abnormal (> 95th percentile) at week 4, n (%)	53	1 (1.9)	48	0	46	2 (4.3)
Body weight						
Change from baseline, mean (SD), kg	75	0.82 (1.69)	73	1.08 (2.27)	65	0.56 (2.14)
Subjects with weight > 95th percentile for age and gender, n (%)						
Baseline	98	25 (25.5)	99	25 (25.3)	97	21 (21.6)
Week 4	75	21 (28.0)	73	24 (32.9)	65	13 (20.0)
Subjects with weight change from normal at baseline to abnormal (> 95th percentile) at week 4, n (%)	55	3 (5.6)	50	2 (4.0)	52	0
Fasting serum glucose level—clinically meaningful elevation (≥ 110 mg/dL), n (%)						
Baseline	83	2 (2.4)	86	3 (3.5)	76	1 (1.3)
Week 4	65	1 (1.5)	64	2 (3.1)	53	1 (1.9)
Fasting total cholesterol level—clinically meaningful elevation (≥ 170 mg/dL), n (%)						
Baseline	83	34 (41.0)	83	32 (37.2)	83	17 (35.5)
Week 4	65	27 (41.5)	65	28 (43.8)	65	11 (20.8)
Fasting triglyceride level—clinically meaningful elevation (≥ 110 mg/dL), n (%)						
Baseline	83	31 (37.3)	83	33 (38.4)	83	29 (38.2)
Week 4	65	22 (33.8)	65	22 (34.4)	65	15 (28.3)
Fasting HDL cholesterol level—clinically meaningful elevation (≤ 40 mg/dL), n (%)						
Baseline	83	16 (19.3)	83	9 (10.5)	83	8 (10.5)
Week 4	65	10 (15.4)	65	9 (14.1)	65	12 (22.6)
Prolactin level, mean (SD), ng/mL						
Males						
Baseline	52	5.42 (3.39)	51	5.92 (3.89)	54	6.65 (5.70)
Change at week 4	37	−3.35 (3.49)	31	−4.23 (4.47)	37	−0.11 (6.35)
Females						
Baseline	46	12.2 (12.9)	48	7.7 (4.0)	43	10.6 (11.3)
Change at week 4	31	−5.74 (13.78)	37	−1.59 (5.21)	26	−2.69 (12.58)
Low serum prolactin levels at week 4, n (%)						
Males (< 2 ng/mL)	45	18 (40.0)	44	20 (45.5)	47	2 (4.3)
Females (< 3 ng/mL)	42	4 (9.5)	45	15 (33.3)	38	0

Abbreviations: BMI = body mass index, HDL = high-density lipoprotein.

observed in adults with bipolar mania being treated with aripiprazole.[35,40] Clinicians should be mindful of the potential for lowered prolactin levels in children and adolescents and monitor patients accordingly. Reduction in prolactin levels may be related to the dopamine partial agonist properties of aripiprazole, which is thought to mimic the inhibitory action of dopamine on pituitary prolactin secretion. This is in contrast to the well-established action of D_2 antagonists in the tuberoinfundibular pathway, which are known to increase prolactin secretion. The clinical relevance of low prolactin levels is unknown, with few published data on the putative consequences of lowered prolactin levels in children and adolescents or in adults. However, while speculative, possible consequences could include failure to lactate in childbearing females, possible decrease in pubic hair, and, in extreme cases, possible fertility impairment.[43–45]

Study completion rates were high, and rates of discontinuation due to adverse events were low. A gradual forced-dose titration schedule that began with 2 mg and brought subjects to the 10-mg target dose by day 5 and the 30-mg dose by day 11 was used on the basis of results of a prior study[46] in a pediatric population which showed that this titration schedule successfully minimized the incidence of adverse events. The present study also provides support for exploration of the adult 30-mg dose when treating children and adolescents.[46] Using an identical titration schedule, the efficacy and safety of aripiprazole 10 mg and 30 mg were examined in a randomized, double-blind, placebo-controlled trial[41] in 302 adolescents with schizophrenia. Rates of study completion and discontinuation due to adverse events were similar to this study of youths with bipolar illness.

This study allowed inclusion of subjects with comorbid psychiatric diagnoses such as ADHD and disruptive behavior disorders. For those subjects for whom information on comorbid conditions was available, just over half had a current or past history of ADHD, and just over 30%

had a current or past history of oppositional defiant disorder. However, it should be noted that data on some clinical characteristics were missing for nearly a quarter of subjects. Given that bipolar disorder in children and adolescents is frequently associated with comorbid psychiatric conditions, the inclusion of patients with these conditions provides evidence to support the clinical relevance and generalizability of these findings.

The findings reported here should, however, be considered in light of several limitations. First, as information on some clinical characteristics was missing for nearly a quarter of subjects, this prevents definitive conclusions regarding the generalizability of the dataset. Second, the lack of an active comparator precludes conclusions regarding the relative benefits of aripiprazole compared with other agents for the treatment of children and adolescents with bipolar mania. While the short-term nature of the study does not allow for conclusions to be drawn as to the longer-term safety and efficacy of aripiprazole treatment, results of the subsequent long-term extension phase that subjects could enter after participation in this clinical trial will help to clarify the role of aripiprazole as a long-term treatment in this population.

In conclusion, aripiprazole doses of 10 mg or 30 mg have demonstrated both safety and efficacy in the acute treatment of pediatric subjects with bipolar I disorder suffering from a manic or mixed episode, with or without psychotic features. We observed a rapid onset of improvement in mania symptoms by the first week of treatment that was sustained through the 4-week endpoint. In addition, rates of response and remission were significantly greater than placebo as early as week 1. Using a gradual upward dose titration, aripiprazole was generally well tolerated in this population, and retention rates through the 4-week study were reasonably high.

Drug names: aripiprazole (Abilify), divalproex (Depakote and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).
Author affiliations: Department of Psychiatry, University Hospitals Case Medical Center/Case Western Reserve University, Cleveland, Ohio (Dr Findling); Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, New Jersey (Drs Nyilas, Forbes, McQuade, Iwamoto, and Carson and Ms Jin); Otsuka America Pharmaceutical Inc., Rockville, Maryland (Dr Ivanova); and Department of Child Psychiatry, Stanford University School of Medicine, Stanford, California (Dr Chang).
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