Aripiprazole in Children and Adolescents With Bipolar Disorder Comorbid With Attention-Deficit/Hyperactivity Disorder: A Pilot Randomized Clinical Trial

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Objective: To assess response to treatment with aripiprazole in children and adolescents with bipolar disorder comorbid with attention-deficit/hyperactivity disorder (ADHD).

Method: Children and adolescents were extensively assessed according to *DSM-IV* criteria for bipolar disorder comorbid with ADHD (n = 710). Those with this comorbidity who were acutely manic or in mixed states were randomly assigned in a 6-week double-blind, placebo-controlled trial to aripiprazole (n = 18) or placebo (n = 25). Primary outcome measures were assessed weekly and included the Young Mania Rating Scale; the Swanson, Nolan, and Pelham Scale-Version IV; and weight. Secondary outcome measures were the Clinical Global Impressions-Severity of Illness scale, the Child Mania Rating Scale-Parental Version (CMRS-P), the Children's Depression Rating Scale-Revised, the Kutcher Adolescent Depression Scale, and adverse events. The trial was conducted at the Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brazil, from January 2005 to November 2007.

Results: The group receiving aripiprazole showed a significantly greater reduction in YMRS scores ($P = .02$, effect size [ES] = 0.80), CMRS-P scores ($P = .02$; ES = 0.54), and CGI-S scores ($P = .04$; ES = 0.28) from baseline to endpoint than the placebo group. In addition, higher rates of response ($P = .02$) and remission ($P = .01$) were found for the aripiprazole group. No significant between-group differences were found in weight, ADHD symptoms, and depressive symptoms. Adverse events significantly more frequent in the aripiprazole group were somnolence and sialorrhea.

Conclusions: Aripiprazole was effective in reducing manic symptoms and improving global functioning without promoting severe adverse events or weight gain. No significant treatment effect in ADHD symptoms was observed. Studies are needed to assess psychopharmacologic interventions for improving ADHD symptoms in juvenile bipolar disorder comorbid with ADHD.

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Dr Tramontina has been a member of the speakers/advisory board for Abbott for the past year. Dr Rohde was on the speakers bureaus and/or acted as consultant for Eli Lilly, Janssen-Cilag, and Novartis in the last 3 years. Currently, his only industry-related activity is taking part of the speakers bureau/advisory boards for Eli Lilly and Novartis (less than US$ 10,000 per year and reflecting less than 5% of his gross income per year). The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last 3 years: Abbott, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Novartis, and Shire. Drs Zeni and Pheula received travel awards from Abbott to attend a national meeting. Dr Ketzer and Ms Narvaez report no additional financial or other relationship relevant to the subject of this article.

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Bipolar disorder has been increasingly recognized in children and adolescents.[1] Epidemiologic studies in adolescents and data from adult studies estimate the prevalence of bipolar disorder in children and adolescents to be around 1%.[2–4]

The high recurrence of mood episodes (around 50% of the patients present with a new episode within a year) and high rates of interepisodic symptoms make juvenile bipolar disorder associated with severe developmental impairment, disruptions in family and peer relations, substance abuse, and suicide risk.[5–7] High rates of comorbidity are observed in clinical samples of youths suffering from the disorder. A recent meta-analysis found attention-deficit/hyperactivity disorder (ADHD) present in over 60% of patients with juvenile bipolar disorder.[8,9]

The presence of ADHD in subjects with juvenile bipolar disorder may predict a chronic rather than an episodic course of bipolar disorder, with an irritable rather than an elated mood, higher rates of other disruptive disorders, and a greater psychosocial impairment.[10] Strober et al[11] reported that adolescents with juvenile bipolar disorder and ADHD had a lower response to lithium in manic symptoms than adolescents with only juvenile bipolar disorder. A meta-analysis including children and adolescents from 5 to 19 years old (n = 273) also reported a better response in those who did not present comorbid ADHD.[12] Together, these findings warrant specific studies in this population.

Available algorithms[13,14] for the treatment of juvenile bipolar disorder published in the literature clearly suggest a role for psychopharmacologic interventions. Nevertheless, few rigorous methodological investigations have been published in the field. Although these algorithms have proposed the use of atypical antipsychotics[15] as potential treatment of the disorder, only 2 randomized clinical trials (RCTs) have been published with atypical antipsychotics—one with quetiapine[16] and another with olanzapine.[17] Both trials have presented positive findings. Some other industry trials have been conducted in the field, but results are not available for public scrutiny yet.

Aripiprazole has shown efficacy and safety in investigations in adult samples with bipolar disorder.[18,19] Despite differences in characteristics of clinical presentation, course of illness, and response to treatment, findings from studies in adult bipolar disorder provide a rationale for studies in children and adolescents. The proposed mechanism of action of aripiprazole, ie, stabilization of dopaminergic transmission, seems promising for the treatment of comorbid bipolar disorder and ADHD.[20] Biederman et al.[21] found clinically and statistically significant reduction of manic symptoms and also good tolerability in a sample of children and adolescents with juvenile bipolar disorder. No significant weight gain was observed. Tramontina et al[22] conducted a 6-week open trial with aripiprazole in juvenile bipolar disorder comorbid with ADHD (n = 10), reporting that aripiprazole was effective in improving mania and ADHD symptoms. Although an overall positive tolerability was reported, small but significant weight gain was observed.

Recently, aripiprazole was approved by the US Food and Drug Administration for bipolar I disorder, mixed or manic episodes, in children aged 10 years and older.[23] However, findings from RCTs supporting this indication have not been published in peer-reviewed journals yet. A large (n = 296) multicenter study found that adolescents with bipolar disorder (10–17 years old) showed significant reductions in manic symptoms with the use of aripiprazole 10 or 30 mg.[24] Moreover, trials from pharmaceutical companies might be strongly associated with proindustry results,[25] and there are few trials investigating response to medication for bipolar disorder in adolescents outside the United States. This fact is especially relevant in children under age 10. These younger children may not share the same response to pharmacologic agents as adolescents, and they have been poorly studied. This scenario makes more data urgently needed.

Because of its associated higher risk for type 2 diabetes mellitus and cardiovascular disease, weight gain is a major concern when treating children and adolescents. Unfortunately, weight gain is a frequent occurrence with atypical antipsychotics.[15,26,27] Moreover, weight gain may impose negative effects on the physical and emotional development and self-esteem of children and adolescents.[27,28] In a recent RCT comparing olanzapine and placebo in a sample of children and adolescents with juvenile bipolar disorder,[17] significant increases in weight and body mass index (BMI) were detected even in that short 3-week trial.

Thus, we conducted an independent double-blind, placebo-controlled, randomized trial to assess the efficacy and tolerability of aripiprazole in children and adolescents with bipolar I or II disorder comorbid with ADHD. We chose to include only patients with this comorbidity because of the high prevalence of ADHD in juvenile bipolar disorder, worse response to treatment in this population, and because the proposed mechanism of action of aripiprazole suggests that it might work for both conditions. Our hypotheses were (1) that patients would show a better response in manic and ADHD symptoms with aripiprazole than with placebo and (2) that aripiprazole would not be associated with clinically significant weight gain.

METHOD

Design

A randomized, double-blind, parallel-group design was used. Patients were randomly assigned, based on a computer-derived algorithm (Epi Info, U.S. Centers for Disease Control and Prevention, Atlanta, Georgia), to a 6-week trial of aripiprazole or placebo. Participants and investigators were blind to the treatment status. Group allocation was performed by an independent third party who also provided the weekly pill package for each patient, identified by ID and dosage. The trial was conducted at the Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brazil, from January 2005 to November 2007.

Subjects

Inclusion criteria were (1) age from 8 to 17 years; (2) *DSM-IV* bipolar I or II disorder comorbid with DSM-IV ADHD[29] (bipolar II disorder was included to be consistent with protocols in previous studies[30,31]); (3) clear reports of ADHD symptom onset preceding any mood symptomatology; and (4) acutely manic or mixed state, defined as a Young Mania Rating Scale score ≥ 20 at the baseline visit. Exclusion criteria were (1) estimated IQ lower than 70, assessed using the Wechsler Intelligence Scale for Children,

Third Edition,[32] by a trained psychologist; (2) use of any medication 4 weeks prior to entering the study; (3) diagnoses of pervasive developmental disorder, schizophrenia, or substance abuse or dependence; (4) severe suicide/homicide risk contraindicating outpatient treatment; (5) previous use of aripiprazole; (6) any other acute or chronic disease that might interfere in the study; or (7) pregnancy.

Sample Size

Since there had been no previously published RCT for the treatment of juvenile bipolar disorder when the current study was conceptualized, and considering logistic issues, we based our sample size computation on the expectation of at least a moderate effect size (ES) for aripiprazole. Thus, we stipulated an ES = 0.7, an expected between-group difference of 30% in the change from baseline to endpoint in YMRS scores, with SDs in both groups of half of the size of the change from baseline to endpoint in YMRS scores. A sample size of 50 subjects was estimated based on this computation. Because of the unexpected, extremely long enrolling period (Figure 1), we needed to stop data collection after 34 months of recruiting patients.

Assessment

Recruitment was performed in the community through press releases. The initial assessment comprised a telephone interview conducted by a child psychiatrist for identification of eligible candidates. After primary caregivers had endorsed symptoms of bipolar disorder and ADHD according to *DSM-IV* criteria in their children and exclusion criteria had been ruled out, children, adolescents, and parents together underwent a confirmatory 3-stage process: (1) evaluation with a semistructured interview (the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version [K–SADS-E]; see Figure 1), modified to assess *DSM-IV* criteria, as has been done by others.[31,33] Parents were interviewed by trained research assistants.[21,31] The K-SADS-E training process consisted in seminars about general child psychopathology and the structure of the instrument, live observation of 5 interviews performed by trained interviewers, and live administration of the K-SADS-E interview in 5 patients in the presence of trained observers. Finally, research assistants performed reliability analyses based in previous K-SADS-E interviews recorded on videotape. κ Coefficient was calculated as 0.93 for mood disorders and 0.94 for disruptive behavior disorders[34]; (2) review of each diagnosis derived through the K-SADS-E in a clinical committee chaired by an experienced child psychiatrist (L.A.R.); (3) clinical evaluation of ADHD, bipolar disorder, and comorbid conditions using *DSM-IV* criteria performed with both parents and their children by an experienced child psychiatrist who had previously received the results of the K-SADS-E. It is important to note that, if a diagnostic disagreement occurred in this 3-stage process, priority was always given to the final clinical diagnoses formulated at the end by an experienced child psychiatrist.

Parental written informed consent and children's verbal assent were obtained. This study was approved by the ethical committee of the Hospital de Clínicas de Porto Alegre.

Treatment Protocol

Patients initially received a weekly supply of aripiprazole or placebo based on their weight. Subjects weighing more than 50 kg received a 5 mg starting dose, while those weighing less received a 2 mg dose. Patients were assessed weekly for 6 weeks after the baseline evaluation, and doses were increased 5 mg/weekly according to clinical response and to the onset of adverse events, until a maximum dose of 20 mg/d was reached. Both placebo and aripiprazole were enclosed in capsules of the same color, shape, smell, and taste, especially constructed to not interfere with normal absorption. No concomitant medication was allowed during the study period. Compliance was checked by counting the remaining pills in the blister packs returned at the end of each week.

Efficacy and Adverse Events Measures

The primary outcome measures were changes from baseline to the endpoint in dimensional scores of the Young Mania Rating Scale[35] (YMRS); the Swanson, Nolan, and Pelham Scale- Version IV [36] (SNAP-IV); and weight. The YMRS[35] is the instrument used most often for measuring manic symptoms in clinical trials with children and adolescents with juvenile bipolar disorder. It is an 11-item scale, and the Portuguese version has been validated (κ = 0.32–0.91, intraclass correlation coefficient = 0.8).[37] Treatment responders were defined as those who presented at least 50% improvement in the YMRS scores. Juvenile bipolar disorder remission was defined as a YMRS score ≤ 12. Changes in ADHD symptoms were assessed with the SNAP-IV.[36] The SNAP-IV is a revision of the original SNAP questionnaire, and its items are rated on a scale from 0 to 3. This measure has been frequently used in ADHD investigations, including those designed to assess clinical interventions. It is also validated in Portuguese, and the internal consistency of the SNAP-IV varies from good to excellent (Cronbach coefficient = 0.74).[38] Weight was assessed by the principal investigator (PI) of the study (S.T.) weekly in the same weighing machine—Filizola Personal Model 4897, calibrated by Filizola Balanças Industriais S/A.

Secondary outcome measures were changes from baseline to the endpoint in the scores of (1) the Child Mania Rating Scale-Parent Version[39] (CMRS-P), a parental report of severity of manic symptoms. Its internal consistency and test-retest reliability are each 0.96. Since there was no validated Portuguese version of the CMRS-P when the study was conceptualized, we oversaw a process of

translation and back-translation of the instrument by independent teams, and the final version was approved by the authors of the scale; (2) the Clinical Global Impressions-Severity of Illness scale[40] (CGI-S). This scale was applied to rate severity of patients' clinical presentation. Scores ranged from 1 (not at all ill) to 7 (extremely ill); (3) the Brazilian version of the Children's Depression Rating Scale-Revised (CDRS-R).[41,42] This instrument is a 17-item clinician-administered scale that assesses presence and severity of depressive symptoms; (4) the Kutcher Adolescent Depression Scale[43] (KADS). This scale is an 11-item self-report instrument to detect and monitor depression in adolescents. Its mean correlation with clinician-administered depression rating scales is 0.69. Since no validated Portuguese version of the KADS was available, we again oversaw a process of translation and back-translation of the instrument by independent teams, and the final version was approved by the authors of the scale.

Adverse events were assessed using a checklist of all 49 adverse events associated with the use of aripiprazole described in the literature. Also, an open question ("Have you felt anything different since last week?") was included as suggested by Greenhill et al.[44] Laboratory tests performed did not show any significant change, and the results of these tests will be detailed in a separate manuscript.

Statistical Analyses

Statistical analyses were performed using the SPSS for Windows, software version 15 (SPSS Inc, Chicago, Illinois). Clinical and demographic characteristics were considered covariates[45] when associated with both the independent factor (aripiprazole use) and the outcome measure for a flexible *P* value of .2 using *t* tests (continuous data) or Fisher exact tests (categorical data). Remission and response were compared between groups using Fisher exact tests.

Changes between baseline and endpoint scores in primary outcome measures were analyzed using analysis of covariance (ANCOVA) models, which included terms for baseline scores and covariables. Patients with baseline and at least 1 postbaseline measurement were included in the analysis using last observation carried forward. Other missing data in the middle of the protocol (8 of 2,193 possible measures) were extrapolated from curve estimation.[46]

Estimates of ES were calculated for dimensional changes between baseline and endpoint scores, and so was number needed to treat for rates of response and remission. All tests of hypotheses used a 2-sided $\alpha = .05$.

RESULTS

The screening process is detailed in Figure 1. Basically, from the 710 subjects who made an initial phone contact with our program, 360 children and adolescents and their parents were scheduled for direct interviews. After the final interview with the PI of this investigation, bipolar disorder and ADHD were confirmed in 43 subjects who were invited to start the clinical trial. Demographics and baseline measures are presented in Table 1. Significant differences between the aripiprazole and the placebo group were found regarding socioeconomic status (*P* = .02).

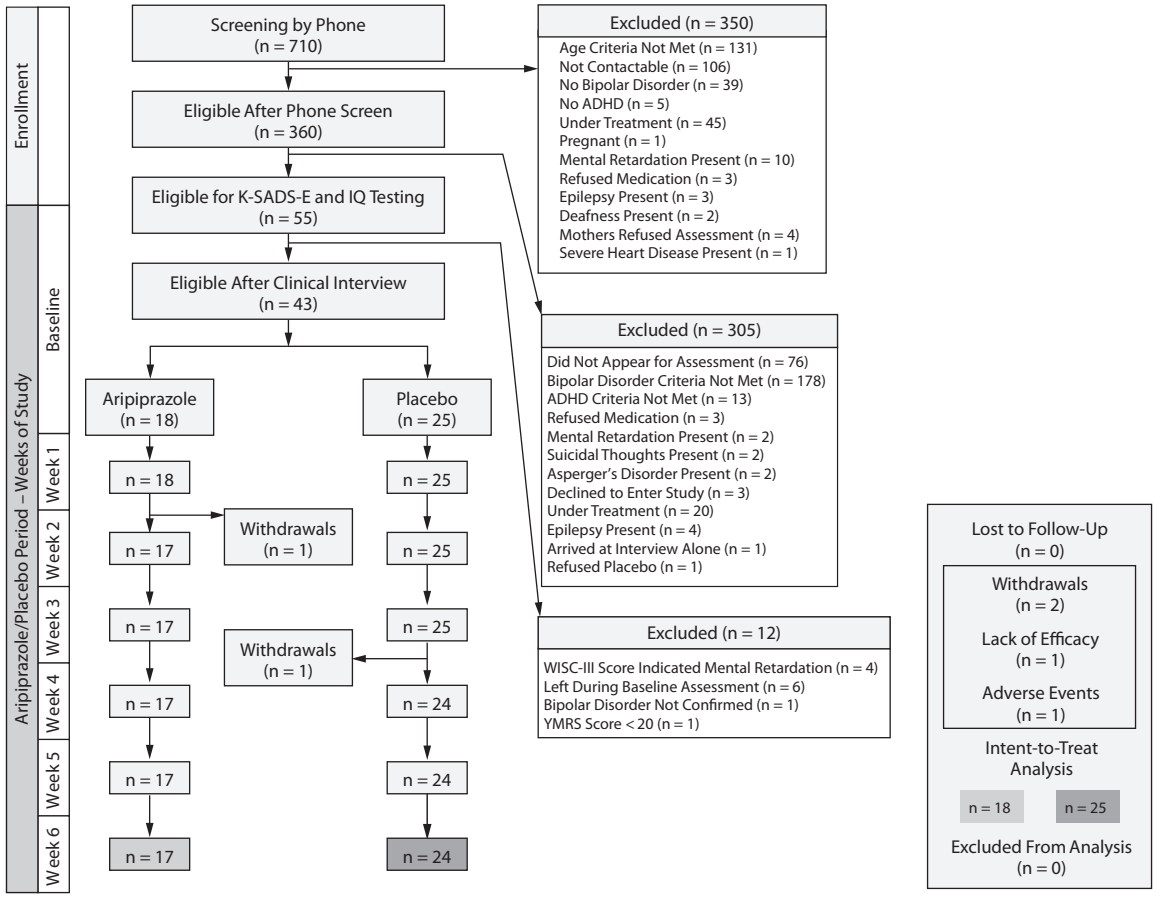
Regarding *DSM-IV* criterion A, 80% of the patients presented elated or expansive mood and 85.7% presented irritability (20% presented with irritability alone, 14.3% presented with euphoria alone, and 65.7% presented with both criteria). Rates of criterion B symptoms were as follows: grandiosity/inflated self-esteem = 82.9%; decreased need for sleep = 68.6%; pressured speech = 71.4%; racing thoughts = 71.4%; distractibility = 94.3%; increased goal-directed energy: (1) socially = 65.7%, (2) at work or school = 25.7%, (3) sexually = 34.3%, or (4) psychomotor agitation = 91.4%; and excessive involvement in pleasurable activities that have a high potential for painful consequences = 77.1%. Significant differences in the rates of *DSM-IV* criterion B symptoms were detected when we compared patients presenting with irritability alone to patients presenting with elated or expansive mood accompanied or not by irritability. Patients with irritability alone presented with less grandiosity/inflated self-esteem (*P* = .01) and less distractibility (*P* = .05)

Two patients discontinued the trial. One patient who was taking placebo refused to continue in the study at the fourth week; aripiprazole was discontinued during the second week for 1 patient who was taking aripiprazole 5 mg/d and presented with severe extrapyramidal symptoms. Mean ± SD daily aripiprazole and placebo final doses were 13.61 ± 5.37 mg (range = 5–20 mg) and 15 ± 3.22 mg (range = 10–20 mg), respectively. Only 20 of the 250 blister packs were returned with unused pills. Ten of these were from 9 subjects in the aripiprazole group, and the other 10 were from 8 subjects in the placebo group. No significant between-group difference was detected in the number of blister packs with unused pills (*P* = .34).

Primary Efficacy Measures

YMRS. Patients taking aripiprazole showed a significant reduction in YMRS scores from baseline to endpoint compared to the placebo group (27.22 vs 19.52, $F_{1,42}$ = 5.87; *P* = .02; effect size = 0.80; 95% CI = 0.15 to 1.41). The covariables retained in the final model were YMRS baseline scores and ADHD type. Findings did not change significantly when only completers were included in analyses. Significantly higher rates of response and remission were found in the patients in the aripiprazole group than in those in the placebo group (response = 88.9% vs 52%, *P* = .02, NNT 2.70; remission = 72% vs 32%, *P* = .01, NNT = 2.50). Figure 2 shows YMRS score changes during the trial.

Figure 1. Study Phases and Patient Disposition



Abbreviations: ADHD = attention-deficit/hyperactivity disorder; BD = bipolar disorder; K-SADS-E = Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version; MR = mental retardation; WISC-III = Wechsler Intelligence Scale for Children, Third Edition; YMRS = Young Mania Rating Scale.

SNAP-IV total score. No significant differences were found between patients taking aripiprazole or placebo in change from baseline to endpoint in SNAP-IV total scores (respectively, 0.79 vs 0.55; $F_{1,39} = 0.74$; $P = .39$. The covariates in this model were baseline SNAP-IV score and type of ADHD.

Weight and BMI. Weight gain was not significantly different between aripiprazole and placebo groups (1.2 kg vs 0.72 kg; respectively; $F_{1,38} = 1.36$; $P = .25$; effect size = 0.35; 95% CI = 0.26 to 0.96). Baseline weight, socioeconomic status, type of ADHD, and conduct disorder comorbidity were covariates included in this analysis. BMI changes were also not significantly different between groups ($F_{1,38} = 0.48$; $P = .49$). Covariates included in the analyses were baseline BMI, type of ADHD, and socioeconomic status.

Secondary Efficacy Measures

CMRS-P. Patients taking aripiprazole showed a significant reduction in CMRS-P scores from baseline to endpoint compared to placebo (21.16 vs 15.52; $F_{1,39} = 5.51$; $P = .02$; ES = 0.54). Findings did not change significantly when only completers were included in analyses. The covariates retained in the final model were CMRS-P baseline scores and IQ. Figure 3 shows CMRS-P score changes during the trial.

CGI-Severity. Patients taking aripiprazole showed a significant reduction in CGI-S scores from baseline to endpoint (2.05 vs 1.64; $F_{3,43} = 4.38$; $P = .04$, ES = 0.28). Covariates were baseline CGI-S scores and IQ.

No significant between-group differences were detected in any measure for depression—CDRS-R: (aripiprazole = 16.33 vs placebo = 14.04, $F_{1,40} = 0.3$; $P = .59$; covariate included in the final model = baseline CDRS-R score) and KADS: (aripiprazole = 6.72 vs placebo = 5.48; $F_{1,40} = 1.78$; $P = .19$; covariate included in the final model = baseline KADS score).

Adverse Events

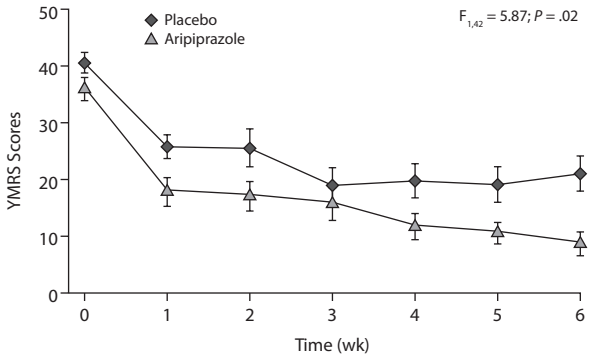
No significant differences were found between patients taking aripiprazole and placebo in the change from baseline to endpoint in adverse events count;

Table 1. Demographic Data, Clinical Data, and Rating Scale Scores at Baseline[a]

Characteristic	Aripiprazole (n = 18)	Placebo (n = 25)	*p*
Demographic data			
Age, mean (SD), y	11.72 (2.71)	12.16 (2.75)	.6
Sex, male, n (%)	6 (33.3)	14 (56)	.21
Race/ethnicity, white, n (%)	15 (83.3)	24 (96)	.31
Socioeconomic status, n (%)			
Top fifth	0 (0)	0 (0)	.02
Upper middle	4 (22.2)	15 (60.0)	
Middle	10 (55.6)	9 (36.0)	
Lower middle	4 (22.2)	1 (4.0)	
Bottom fifth	0 (0)	0 (0)	
Clinical data			
Bipolar disorder type, n (%)			
I	15 (83.3)	20 (80)	.55
II	3 (16.7)	5 (20)	
Age at onset, mean (SD), y			
Bipolar disorder	7 (3)	8.64 (3.54)	.11
ADHD	4.39 (1.82)	4.64 (2.30)	.30
ADHD combined type, n (%)	15 (83.3)	19 (76)	.16
Psychosis, n (%)	8 (44.4)	8 (32)	.52
Disruptive behavioral disorders, n (%)	15 (83.3)	20 (80)	1
Anxiety disorders, n (%)	8 (44.4)	13 (52)	.76
IQ, mean (SD)	93.38 (14.56)	100.24 (15.62)	.14
Weight, mean (SD), kg	48.24 (17.46)	51.34 (18.92)	.58
Rating scale scores, mean (SD)			
YMRS	35.94 (8.55)	40.56 (9.01)	.09
SNAP-IV	2.21 (0.53)	2.02 (0.46)	.24
CGI-S	4.05 (1.21)	4.40 (1.19)	.36
CMRS-P	33.33 (11.30)	33.16 (10.79)	.96
CDRS-R	49.27 (13.82)	49.32 (13.91)	.99
KADS	11.61 (6.65)	13.40 (9.37)	.46

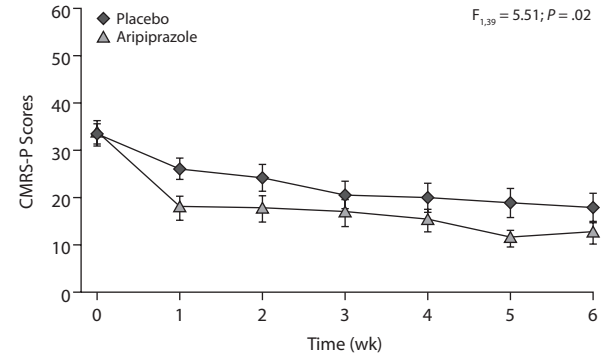
[a]Comparison between groups using *t* tests (continuous data) or Fisher exact tests (categorical data).
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CDRS-R = Children's Depression Rating Scale-Revised; CGI-S = Clinical Global Impressions-Severity of Illness scale; CMRS-P = Child Mania Rating Scale-Parent Version; KADS = Kutcher Adolescent Depression Scale; SNAP-IV = Swanson, Nolan, and Pelham Scale–Version IV; YMRS = Young Mania Rating Scale.

Figure 2. Changes in YMRS Scores During the Trial[a,b]



[a]ANCOVA (dependent variable = change from baseline to endpoint in YMRS score; independent variable = aripiprazole use; covariables = baseline YMRS score and ADHD type).
[b]Error bars represent ± SE at each assessment.
Abbreviation: YMRS = Young Mania Rating Scale.

Figure 3. Changes in CMRS-P Scores During the Trial[a,b]



[a]ANCOVA (dependent variable = change from baseline to endpoint in CMRS-P score; independent variable = aripiprazole use; covariables = baseline CMRS-P score and IQ).
[b]Error bars represent ± SE at each assessment.
Abbreviations: ANCOVA = analysis of covariance, CMRS-P = Child Mania Rating Scale-Parent version.

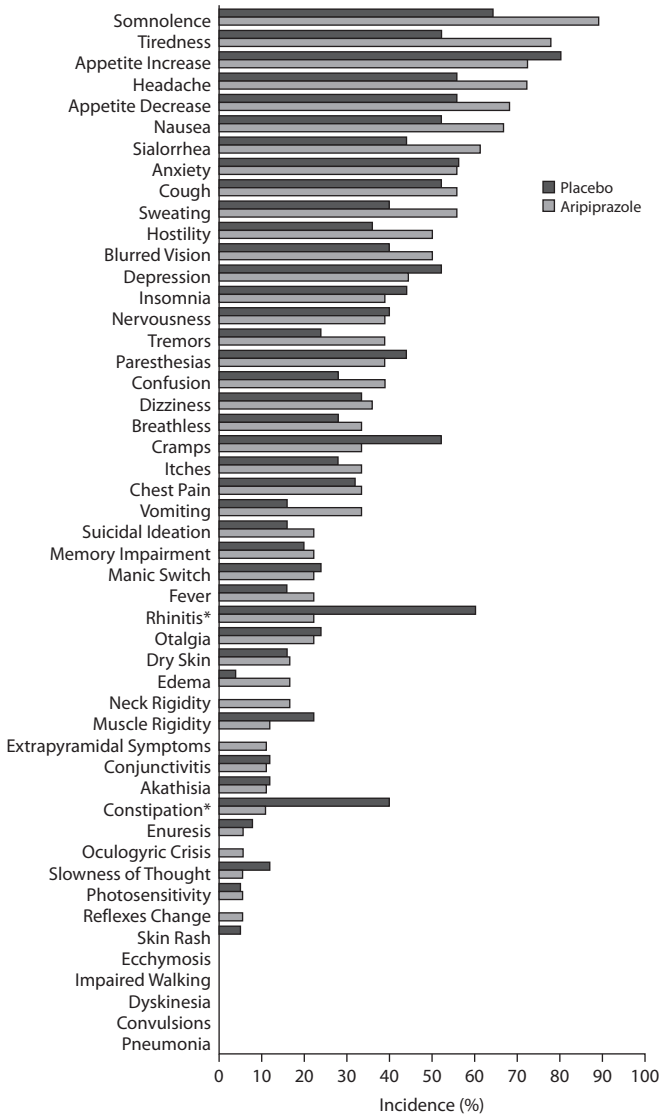
(3.76 vs 4.83, respectively; $F_{1,36} = 0$; $P = .99$, covariables: baseline adverse events count, school failure, and baseline YMRS score). Figure 4 shows the incidence of treatment-emergent adverse events (events that emerged after a negative baseline assessment, and events that were present in the baseline assessment, disappeared, and then reappeared along the trial). All the comparisons of the 49 symptoms between groups at each assessment point of the study are available on request.

Although socioeconomic status did not fulfill the formal definition of confounding variable,[45] it was clearly unequally distributed between groups (see Table 1). Thus, we ran additional analyses including socioeconomic status as a covariable for all models with significant findings. Positive findings for aripiprazole (ANCOVA) remained significant. Further analyses were also performed adjusting ANCOVA models for age stratified at a 10-year threshold, since FDA approval of aripiprazole extends only to children aged 10 years and older. Again, positive findings for aripiprazole remained significant, and no effect was found for stratified age in any primary measure. In addition, no significant difference emerged in comparisons between patients under 10 years old on one hand and older subjects on the other in the frequency of symptoms according to DSM-IV A or B criteria.

DISCUSSION

We have observed significantly greater improvements in manic symptoms (according to 2 different instruments) with aripiprazole compared to placebo in a sample of children and adolescents with juvenile bipolar I or II disorder

Figure 4. Incidence of Treatment-Emergent Adverse Events at Any Time in Children and Adolescents With Bipolar Disorder and Attention-Deficit/Hyperactivity Disorder Treated With Aripiprazole (5–20 mg/d) or Placebo



*$P \leq .05$.

comorbid with ADHD. Response to pharmacologic treatment was detected in almost 90% of the subjects receiving medication, and remission was observed in 72% of these individuals. However, neither significant reduction in ADHD symptoms nor significant changes in depressive symptoms were observed with the medication. In addition, we were not able to detect significant differences in weight between patients receiving aripiprazole and placebo. We are not aware of other double-blind, placebo-controlled, randomized trials assessing effects of aripiprazole in children and adolescents with juvenile bipolar I or II disorder comorbid with ADHD in the literature.

There is a great debate concerning the most appropriate clinical phenotype for juvenile bipolar disorder in the literature,[5,6,47] as well as on the borders between juvenile bipolar disorder and ADHD phenotypes.[48] To deal with these 2 relevant clinical issues, we only included subjects (1) with bipolar I or II disorder in our study diagnosed only after an extensive clinical assessment including 4 stages at study intake: phone assessment, interview with child and adolescent psychiatrists, semistructured interview, and final diagnosis by the PI who is an experienced child psychiatrist; and (2) for whom parents clearly described a history of ADHD symptom onset occurring before any bipolar disorder symptoms (eg, mood swings).

Our results are in accordance with recent findings suggesting a role for atypical antipsychotics in the treatment of mania in juvenile bipolar disorder, even though the ES of the response in manic symptoms had a wide confidence interval, probably because of the small sample size in our study. However, all previous chart reviews,[49–51] the 2 prospective open-label studies, and the unpublished RCT mentioned above also report positive response to aripiprazole.[21,22,24] In addition, olanzapine was effective in reducing manic symptoms in the only randomized clinical trial[17] comparing atypical antipsychotics and placebo for bipolar disorder in adolescents published in the literature. High rates of study completion and low discontinuation rates were observed in that investigation. The findings from the olanzapine study differ from ours, especially in one outcome: weight gain (3.66 kg in 3 weeks in the olanzapine study vs 1.2 kg in 7 weeks in our study). The weight change was even lower in 13- to 17-year-old subjects from our sample (the age range of the subjects who received olanzapine in the previous protocol) during the first 3 weeks. (Patients lost 0.03 kg in our study.)

One clinical aspect of the mechanism of action of aripiprazole that might be relevant for the treatment of patients presenting with bipolar disorder comorbid with ADHD is its potential dopaminergic stabilization.[20] However, we did not detect significant between-group differences in ADHD symptoms. Our findings are in accordance with others suggesting that additional medications might be needed for treatment of ADHD after mood stabilization in patients with juvenile bipolar disorder.[14] However, it is important to note that it is always difficult to disentangle effects of medication on ADHD symptoms in patients presenting these dual diagnoses (juvenile bipolar disorder + ADHD). In other words, detected reductions of potential core ADHD symptoms like hyperactivity—even measured by standard ADHD rating scales—might be simply reflecting a halo effect of the reduction of bipolar disorder symptoms. It is important to note that ours is one of the only

investigations in the field of psychopharmacologic interventions for juvenile bipolar disorder in which a standard assessment scale for ADHD was part of the protocol. Replication in a larger sample could disentangle the role of aripiprazole in children and adolescents with juvenile bipolar disorder and ADHD.

Aripiprazole was well tolerated and did not promote a significant weight change in this study when compared to placebo. Only 2 patients dropped out of the study, one in the placebo group and one in the aripiprazole group. Adverse events rates and weight ESs may have not been precisely estimated because of the small sample size, but our results are in accordance with those from all previous chart reviews[49–51] and the open trial by Biederman et al[21] in which overall good tolerability and no significant weight gain were detected. The same findings are reported in studies in adults with bipolar disorder,[18,19] in which no significant weight gain is observed in acute treatment. In addition, this is the first psychopharmacologic trial for bipolar disorder in children and adolescents conducted outside the United States, and one of only a few international studies presenting clinical data about this population using standard instruments. The clinical profile of our patients was similar to those found in samples from other countries (for a review, see Soutullo et al, 2005),[52] except for the preponderance of females in our study. Since disruptive boys would have a higher likelihood of being under treatment, this may have occurred due to the exclusion of medicated patients.

Our study should be understood in the context of some limitations. First, no correction for multiple comparisons was performed. Thus, we cannot rule out type I error. Nevertheless, even with the observation of a robust and rapid (see Figure 2) response to placebo (characteristic of acute juvenile bipolar disorder trials),[17] we documented significant improvement in manic symptoms in the 3 independent instruments used for assessing juvenile bipolar disorder (one of them chosen a priori as a primary outcome measure). Our sample size might not have allowed us to detect associations between aripiprazole treatment and changes in both ADHD and depression measures. However, studies in adults with bipolar disorder have reported similar findings regarding depressive symptoms.[19] Despite the fact that our findings suggested no impact of age on the efficacy measures assessed, we cannot rule out different response rates among children and adolescents. We also did not assess moderator effects of exposure to environmental factors, such as levels of expressed emotion or family functioning. Although the assessment of efficacy measures was always implemented before the assessment of adverse event measures, these assessments were performed by the same experienced child psychiatrist—the PI of this study—in this protocol. This strategy might have created problems for the integrity of the protocol blindness, but we found only minimal between-group differences in adverse events, making a correct guess of patient treatment status by an investigator improbable. Breakdown of the blinding occurred after the last endpoint assessment for each subject, since this protocol was followed by a crossover study to assess psychopharmacologic interventions for those who improved in bipolar disorder symptoms but not in ADHD scores. This strategy might have made it easier for investigators to discern the treatment status of subsequent patients. However, this strategy has a potential for causing such problems when block or stratified randomized enrollment are used,[53] and that was not the case in our study (eg, 58.1% of our patients were randomly assigned to placebo).

In sum, aripiprazole was effective in reducing manic symptoms and improving global functioning without promoting serious adverse events or weight gain. Due to the absence of a significant change in ADHD symptoms, highly prevalent in patients with juvenile bipolar disorder, trials are needed to assess response to other agents in combination with aripiprazole for patients with both conditions. Again, replication of these findings in a larger sample is imperative so that a more definite conclusion can be drawn about the response to aripiprazole in this group of children and adolescents.

Drug names: aripiprazole (Abilify), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel).

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