JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 21, Number 4, 2011

Pp. 345–351
DOI: 10.1089/cap.2010.0102

# An Open-Label Study of Aripiprazole in Children with a Bipolar Disorder

Robert L. Findling, M.D.,[1] Nora K. McNamara, M.D.,[1] Eric A. Youngstrom, Ph.D.,[2] Robert J. Stansbrey, M.D.,[1] Thomas W. Frazier, Ph.D.,[3] Jacqui Lingler, B.S.,[1] Benjamin D. Otto, B.A., Christine A. Demeter, M.A.,[1] Brieana M. Rowles, M.A.,[1] and Joseph R. Calabrese, M.D.[1]

## Abstract

***Objective:*** The purpose of this open-label study was to describe the effectiveness of aripiprazole (APZ) in the treatment of children with bipolar disorders suffering from manic symptomatology.
***Method:*** Symptomatic outpatients (Young Mania Rating Scale [YMRS] score $\geq$15) meeting strict, unmodified, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, diagnostic symptom criteria for a bipolar disorder, ages 4–9 years, were eligible. Subjects were treated prospectively with flexible doses of APZ (maximum daily dose of 15 mg/day), for up to 16 weeks or until *a priori* response criteria were met. Outcome measures included the YMRS, Clinical Global Impressions Scale-Severity, Children's Global Assessment Scale (CGAS), and the Children's Depression Rating Scale-Revised (CDRS-R). *A priori* response criteria consisted of 3 of 4 consecutive weeks with (1) CDRS-R $<$29; (2) YMRS $<$10; and (3) CGAS $>$50.
***Results:*** Ninety-six children (62 males; mean age of 6.9 (SD = 1.7), received APZ for an average length of treatment of 12.5 (SD = 3.9) weeks. Significant improvements in YMRS, CDRS-R, CGAS, and Clinical Global Impressions Scale-Severity scores ($p < 0.001$) were noted at the end of study participation. Sixty of the subjects (62.5%) met *a priori* response criteria at study's end. The most common side effects noted were stomachache, increased appetite, and headache. Two subjects were removed from the study due to side effects [epistaxis ($n = 1$); akathisia ($n = 1$)]. Subjects experienced an average weight gain of 2.4 (SD = 1.9) kg.
***Conclusion:*** APZ may be effective in the acute treatment of symptoms of children with bipolar illnesses.

## Introduction

In recent multi-site, pharmaceutical industry-sponsored studies, the treatment of manic and mixed states in pediatric bipolar disorder has generally focused on patients between the ages of 10–17 years (DelBello et al. 2007, 2008; Tohen et al. 2007; Findling et al. 2009b; Haas et al. 2009). The selection of this age range for these trials was likely the result of implementing the recommendations that were generated as part of a consensus meeting that suggested this age range be used in industry-sponsored research studies in this patient population (Carlson et al. 2003).

However, in research populations that have included children younger than age 10, pediatric bipolar disorders have been shown to be serious illnesses (Wozniak et al. 1995; Findling et al. 2001; Geller et al. 2004; Axelson et al. 2006). For these reasons, recent treatment guidelines have supported the judicious use of pharmacological treatment for these younger children (Kowatch et al. 2005).

Aripiprazole (APZ) is an atypical antipsychotic that has been reported to have both acute (Tramontina et al. 2009; Findling et al. 2009b) and long-term (Wagner et al. 2007) efficacy in the treatment of children (aged 8 to 17 years) with manic or mixed states. In 2008, the U.S. Food and Drug Administration (FDA) approved the use of APZ for the acute treatment of manic or mixed states in pediatric patients (aged 10 to 17 years). Additionally, use of APZ as either maintenance therapy or as an adjunct to treatment with lithium or valproate for manic or mixed episodes associated with bipolar I disorder (BP-I) is FDA-approved in this population, based on extrapolation from adult efficacy data. Past pediatric research that has included patients under the age of 10 has suggested that APZ might be a reasonable treatment option in this age group. In a prospective, open-label study that included 12 children (ages 6–12 years) with conduct disorder, APZ was found to be effective and reasonably well tolerated (Findling et al. 2009a). Additionally, retrospective reviews of APZ monotherapy and APZ as adjunctive therapy have reported symptom amelioration in children and adolescents aged 4 to 19 years with bipolar and bipolar spectrum disorders (Barzman et al. 2004; Biederman et al. 2005).

Based on the extant evidence when this study was designed, it appeared that APZ was a compound worthy of further investigation

[1]Department of Psychiatry, University Hospitals Case Medical Center, Case Western Reserve University, Cleveland, Ohio.
[2]Departments of Psychology and Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.
[3]Center for Pediatric Behavioral Health and Center for Autism, Cleveland Clinic Children's Hospital, Cleveland, Ohio.

in symptomatic children younger than age 10 years suffering from bipolar illnesses. The purpose of this study was to describe the safety and effectiveness of APZ in children 4 to 9 years of age with bipolar illnesses who were currently suffering from elevated symptoms of mania. It was hypothesized that APZ monotherapy would be generally well tolerated and associated with symptom reduction in this patient population.

## Methods

The University Hospitals Case Medical Center Institutional Review Board for Human Investigation approved the procedures of this outpatient, single-site study. Written informed consent was provided by all parents/guardians of study participants. Oral assent was provided by all children participating in the study.

After the baseline visit, youth were seen weekly for the first 4 weeks, then biweekly thereafter. The length of study participation could last up to 16 weeks. Once participants met *a priori* stabilization criteria (treatment with APZ for a minimum of 6 weeks and 3 of 4 consecutive weeks with: Children's Depression Rating Scale-Revised (CDRS-R) $< 29$; Young Mania Rating Scale (YMRS) $<10$; and Children's Global Assessment Scale (CGAS) $>50$) these children were withdrawn from this protocol and were offered enrollment in an ongoing randomized, double-blind, placebo-controlled discontinuation trial that was examining the efficacy of APZ in this patient population. Youth who participated in the present trial but (1) did not meet *a priori* response criteria; (2) were unable to tolerate the study medication; or (3) withdrew from this trial for any other reason were not eligible for enrollment into the aforestated discontinuation study.

### *Subjects*

Outpatient children aged 4–9 years meeting *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, criteria (American Psychiatric Association 2000) for a diagnosis of BP-I, BP-II, Bipolar Disorder NOS (BP-NOS), or Cyclothymia were eligible to enroll. Children who experienced spontaneous, dysfunctional manic episodes that did not meet full criteria for any other mood disorder were given the diagnosis of BP-NOS, as we have done in our prior work (Findling et al. 2005). The decision to include children with BP-NOS and cyclothymia was informed by finding that youth who suffer from these diagnoses who are seen at this center have substantial mood symptomatology and impairment (Findling et al. 2005), consistent with other studies (Axelson et al. 2006).

Patients were initially screened by highly trained interviewers completing the Schedule for Affective Disorders and Schizophrenia for School-Age Children interview (K-SADS-PL; Kaufman et al. 1997). Doctor's-level, master's-level, or bachelor's-level interviewers administered the K-SADS interviews. Inter-rater reliability on the K-SADS was assessed with the kappa ($\kappa$) statistic. Before leading a K-SADS interview, all interviewers demonstrated adequate inter-rater reliability ($\kappa \geq 0.85$) and diagnostic assessment agreement based on the results of five K-SADS interviews. Subsequently, inter-rater reliability was maintained ($\kappa \geq 0.85$) by conducting joint assessments. A previous study of the inter-rater reliability of K-SADS diagnoses reported high reliability ($\kappa = 1.00$) in children aged 4 to 10 years (Frazier et al. 2007).

Youth also received a separate clinical evaluation by a board-certified or board-eligible child and adolescent psychiatrist to confirm the bipolar diagnosis obtained based on the results of the K-SADS assessment. Further, all enrolled youth had an YMRS score of $\geq 15$ at the baseline visit, indicative of clinically significant manic symptomatology (Young et al. 1978).

Children were excluded from participating in this trial if they had a history of intolerance to APZ at doses of 0.1 mg/kg/day or were allergic to APZ. Children who experienced a manic episode with 0.2 mg/kg/day of APZ monotherapy were excluded. Those youth who in the clinical judgment of the evaluating physician had a pervasive developmental disorder, mental retardation, or a general medical or neurological condition for which treatment with APZ would be contraindicated were excluded. In addition, youth taking psychotropics within 1 week of baseline, or psychostimulants within 3 days of baseline, were not included in this study.

### *Screening period*

Before the baseline assessment, patients received a physical examination, an electrocardiogram (ECG), and screening laboratories (see below). During the screening process, information about subject demographics and clinical characteristics was obtained. For some subjects, screening and baseline occurred on the same day. For the sake of convenience, screening and baseline procedures could be split among more than one visit to reduce subject/family burden. The pretreatment screening period did not last longer than 4 weeks.

### *Pharmacotherapy*

Results from a previous open-label study of APZ informed the dosing design utilized in the present study (Findling et al. 2009a). All youth received an initial APZ dose of $\sim 0.1$ mg/kg/day, and were titrated, per protocol, in a flexible-dose manner based upon tolerability and effectiveness. The entire dose of APZ was to be administered at bedtime. However, morning or BID dosing was permissible to maximize clinical benefits while minimizing side effects. APZ could be increased to $\sim 0.15$ mg/kg/day at end of week 1, and could again be increased to the maximum dose of $\sim 0.2$ mg/kg/day at the end of week 2. After 3 weeks of treatment, patients with residual symptomatology and no intolerable side effects could have their dose increased to a total daily dose of $\sim 0.25$ mg/kg/day. Patients tolerating $\sim 0.25$ mg/kg/day could have their dose increased to a total daily dose of $\sim 0.3$ mg/kg/day at the end of week 4 if clinically indicated. However, the maximum total daily dose was set at 15 mg/day for all patients. APZ could be lowered at any time due to safety or tolerability issues. Those youth who experienced significant adverse effects at an APZ dose of 0.05 mg/kg/day were considered intolerant to APZ, and were removed from the study.

Youth who had received APZ for at least 6 weeks, and were determined to be responders as defined by the *a priori* criteria, yet still met *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, criteria for attention-deficit/hyperactivity disorder (ADHD) (American Psychiatric Association 2000) could be offered adjunctive psychostimulants. Youth could be treated in an open-label fashion with either methylphenidate-based preparations or amphetamine-based preparations at FDA-approved dosages for children, at the discretion of the treating physician. Treatment with other psychotropic medications was not permitted in this study.

### *Outcome measures*

Youth were evaluated by a child and adolescent psychiatrist and trained rater at every visit. The clinical rating scales used included the YMRS (Young et al. 1978); CDRS-R (Poznanski et al. 1985);

Clinical Global Impressions Scale-Severity (CGI-S) (NIMH 1985b); and the CGAS (Shaffer et al. 1983). Master's-level or bachelor's-level interviewers administered the YMRS and CDRS-R. Before leading a YMRS or CDRS-R interview independently, all raters needed to rate along with a qualified interviewer for five interviews and lead five interviews while demonstrating exact agreement with the experienced interviewer on at least 50% of the items with the other 50% of items differing by no more than one point. Both the YMRS and CDRS-R have demonstrated strong reliability and measure symptoms consistently across a wide range of ages (4 to 17 years) in pediatric bipolar disorder (Frazier et al. 2007).

### *Safety monitoring*

Monitoring of side effects occurred at each visit by open-ended inquiry of physical, emotional, behavioral, and cognitive changes noted by both subject and parent/guardian. In addition, each youth at every visit was evaluated using the Abnormal Involuntary Movement Scale (NIMH 1985a), the Barnes Akathisia Scale (BAS) (Barnes 1989), and the Neurological Rating Scale (NRS) (Simpson and Angus 1970). The NRS was supplemented with three additional items to assess cogwheeling, acute dystonic reaction, and subjective sense of stiffness.

Before study medication initiation, each youth received a physical examination, ECG, weight, height, blood pressure, and pulse measurements. Laboratory tests before dosing included urinalysis, research chemistry panel including fasting glucose and fasting lipid profile, complete blood count with platelets and differential, lead level, prothrombin time/partial thromboplastin time, prolactin concentration, and thyroid-stimulating hormone. Laboratory measures (except for the lead level, prothrombin time/partial thromboplastin time, and thyroid-stimulating hormone) were repeated at week 6 and week 16/end of study (EOS) participation. Weight, blood pressure, and pulse were assessed at each visit, whereas height and ECG measurements were repeated at week 6 and week 16/EOS participation.

### *Statistical analysis*

Analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS, version 16.0). Averages are presented as mean (standard deviation) unless otherwise noted. The data were considered adequately close to normally distributed if both skewness and kurtosis of the data were $<3.0$. Skewness measures the symmetry of the score distribution and indicates whether there were extreme high or low scores; kurtosis indicates whether the distribution was normal shaped versus having thicker tails or more bunching in the mid-range. Using an intent-to-treat analysis with last observation carried forward, paired samples *t*-tests were used to compare YMRS, CGAS, and CGI-S scores at baseline with end of week 6 and EOS participation scores. CDRS-R scores at baseline, week 6, and EOS CDRS-R scores as well as EOS weight was compared with baseline weight using the Wilcoxon Signed Ranks Sum Test because the data were not normally distributed. Fisher's Exact Tests were used to determine differences in the occurrences of side effects between those patients that were considered responders and those patients who did not meet response criteria. In addition, fasting glucose, fasting cholesterol, triglycerides, and prolactin levels at baseline and EOS were compared using paired samples *t*-tests.

A chi-square analysis was used to detect differences in the distribution of males and females who met response criteria. Also, age, bipolar diagnosis, comorbid diagnosis, age at onset of symptoms, length of illness, length of treatment, and baseline symptom severity were compared in patients considered responders at the EOS and nonresponders using independent sample *t*-tests. Standardized effect sizes were calculated using Cohen's d (Cohen 1988). The level of significance was set at 0.05 for all analyses. Due to the exploratory nature of this trial, the alpha level for statistical significance was not adjusted for the multiple comparisons performed.

## Results

### *Subjects*

One hundred forty subjects were screened for possible participation in this treatment study between May of 2004 and November of 2008. Of these subjects, 96 were enrolled, prescribed study medication, and returned after at least 1 week of treatment (Fig. 1). Fourty-four of the 140 screened patients did not receive study medication due to not meeting study inclusion/exclusion criteria ($n = 19$); withdrawing consent before dosing ($n = 14$); and study nonadherence (i.e., lost to follow-up) ($n = 11$). Demographics for the 96 subjects who were prescribed study medication are described in Table 1. Of the 96 participating subjects, 83 (86.5%) met diagnostic criteria for comorbid ADHD.

These 96 subjects participated in the study for a mean of 12.5 weeks (SD = 3.9), with a range of 2.0–18.1 weeks. Three participants remained in the study for approximately one additional week and another child for two additional weeks owing to scheduling difficulties.

### *Symptom response*

Baseline mood states of these 96 subjects are listed in Table 2. Subjects who presented as mixed at baseline did not differ in length of time in study compared with children who were manic or hypomanic at baseline ($t = 1.56$, df = 94, $p = 0.12$). Significant decreases in the YMRS, CDRS-R, CGI-S, and CGAS were found after 6 weeks of treatment with APZ and at the EOS (all *p*-values $<0.001$; See Table 3). The effect size of the change in YMRS, CDRS-R, CGI-S, and CGAS scores after 6 weeks of treatment with APZ and at the EOS are also included in Table 3. Overall effects were very large ($d > 2.00$) for YMRS, CGI-S, and CGAS outcomes and medium to large ($d = 0.68$–$0.69$) for CDRS-R outcomes at 6-weeks and EOS.

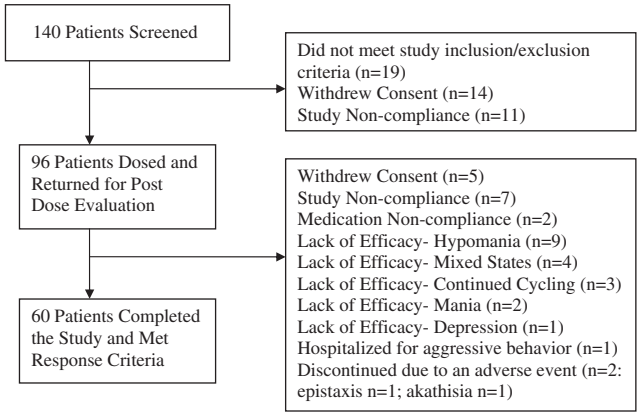


**FIG. 1.** Subject accountability flowsheet.

Table 1. Patient Demographics and Clinical Characteristics

| | *All subjects (n = 96)* | *Responders (n = 60)* | *Nonresponders (n = 36)* |
|---|---|---|---|
| Males (%) | 62 (65%) | 42 (70%) | 20 (56%) |
| Mean age (SD) | 6.9 (1.7) | 6.9 (1.6) | 6.9 (1.8) |
| Primary diagnosis | | | |
| Bipolar I | 41 (43%) | 21 (35%) | 20 (56%) |
| Cyclothymia | 8 (8%) | 6 (10%) | 2 (6%) |
| Bipolar disorder not otherwise specified | 47 (49%) | 33 (55%) | 14 (39%) |
| Comorbid diagnoses | | | |
| Attention-deficit/ hyperactivity disorder | 83 (87%) | 54 (90%) | 29 (81%) |
| Oppositional defiant disorder | 20 (21%) | 11 (18%) | 9 (25%) |
| Conduct disorder | 2 (2%) | 1 (2%) | 1 (3%) |
| Mean age at onset of bipolar symptoms (years) | 3.7 (1.8) | 3.6 (1.7) | 3.9 (1.9) |

SD = standard deviation.

### *Study participation and clinical response*

Of the 96 subjects who received study medication, 60 (62.5%) completed participation in the trial and were considered responders. The average length of treatment for these responders was 14.3 (2.6) weeks, with a range of 5.9–17.1 weeks. The average treatment duration for the 36 (37.5%) subjects who did not meet response criteria at EOS was 9.6 weeks (3.9), with a range of 2.0–18.1 weeks.

### *Medication dosing at EOS participation*

The average dose of APZ for the entire cohort at EOS was 6.5 mg/day (2.3 mg/day). Youth considered responders received a mean dose of APZ 6.4 mg/day (2.1 mg/day) and those youth who were nonresponders received a mean APZ dose of 6.8 mg/day (2.6 mg/day) during their last week of participation. Thirty-two (34.4%) of the 93 subjects who completed 6 weeks of study participation received treatment with an adjunctive psychostimulant.

### *Medication tolerability*

No subjects experienced/reported suicidal ideation or made a suicidal gesture/attempt, and there were no deaths fron any cause. One study participant discontinued the medication due to epistaxis and another subject discontinued after developing akathisia. The most common adverse events experienced by the study participants were stomachache ($n = 40$), headache ($n = 38$), and increased appetite ($n = 38$) (Table 4). In addition, there was no difference in the occurrence of the most commonly reported adverse events between the children who were considered responders and those considered nonresponders (all $p$-values $>0.05$, Table 4).

Three subjects scored a "1" on the NRS, indicative of mild severity (two subjects at week 1 and one subject at weeks 2 and 3). In addition, one subject who scored a "1" on the NRS at week 1 scored a "1" on the additional cogwheeling item on the NRS. Another subject scored a "1" on the BAS, indicative of mild intensity, at week 12. Finally, the subject that discontinued the study due to akathisia had a BAS total score of 7 three days before ending study and a BAS total score of 5 at EOS. All other subjects scored "0" on all items of the SARS, BAS, and Abnormal Involuntary Movement Scale throughout the course of the entire study.

Weight changed by a mean of 2.4 kg (1.9 kg), ranging from −0.68 to 7.7 kg. The children treated in this study had a significant increase in weight at the end of the study (mean predose weight = 26.9 kg (8.7), EOS weight = 29.3 kg (9.6); $p < 0.001$). No significant differences between baseline and EOS fasting glucose ($t = 1.31$, df = 73, $p = 0.194$) and fasting cholesterol ($t = 0.83$, df = 74, $p = 0.408$) (Table 5) were found. In addition, no clinically significant changes in laboratory measures, pulse, blood pressure, or QTc measurements on ECG were noted. Prolactin levels decreased at EOS compared with baseline levels ($t = 10.82$, df = 83, $p < 0.001$) and fasting triglyceride levels ($t = 2.67$, df = 74, $p < 0.01$) (Table 5) were found to increase.

### *Factors associated with response*

Sex, age, and the number of patients with BP-I were not significantly different between the responder and nonresponder groups. Age at symptom onset and mean duration of symptoms were not statistically different between responders compared with nonresponders. Responders were found to be enrolled in the study for a longer period than the nonresponders ($t = 7.15$, df = 94, $p < 0.001$).

Baseline CDRS-R scores significantly differed between responders [mean = 23.4 (4.8)] and nonresponders [mean = 28.0 (7.1); $t = 3.79$, df = 94, $p < 0.001$], with nonresponders having a significantly higher baseline CDRS-R score compared with the responders. Additionally, although baseline YMRS scores did not reach significance, a trend was found ($t = 1.94$, df = 94, $p = 0$ 0.06) for responders to have lower baseline YMRS scores [mean = 23.0 (4.9)] compared with the nonresponders [mean = 25.2 (5.6)]. However, CGI-S and CGAS scores were not significantly different between those patients that met response criteria and those patients that were considered nonresponders ($p$-values $> 0.05$). The mean weight adjusted APZ doses at EOS did not differ between responders [mean = 0.23 mg/kg (0.07)] and nonresponders [mean = 0.24 mg/kg (0.09): $t = 1.05$, df = 94, $p = 0.30$].

Table 2. Baseline Mood States

| *Mood state* | *n (%)* | *Mean (SD) length of study participation* | *Number achieving remission* |
|---|---|---|---|
| Mixed[a] | 23 (24%) | 11.4 (4.4) | 8 (35%) |
| Manic/hypomanic[b] | 73 (76%) | 12.9 (3.6) | 52 (71%) |

[a]Children's Depression Rating Scale-Revised (CDRS-R) >28 and Young Mania Rating Scale (YMRS) ≥12

[b]Manic = CDRS-R ≤28 and YMRS ≥16 ($n = 69$); Hypomanic = CDRS-R ≤28 and YMRS 12–15 ($n = 4$).

## Discussion

These preliminary data suggest that there are children aged 4–9 years with bipolar illness and elevated symptoms of mania who may acutely benefit from APZ therapy. Both mania (YMRS) and depression (CDRS-R) rating scales scores decreased significantly.

Overall, APZ was found to be generally safe and well tolerated. The extrapyramidal side effects experienced in this study were found to be mild, with only one child discontinuing the study due to akathisia. Only one other child ended the study due to an adverse event, epistaxis. Other side effects were generally transient and of modest severity with the most frequently reported adverse events experienced in this study being stomachache, increased appetite,

Table 3. Outcome Measure Results

| Measure | Baseline Score M (SD) | EOW 6 M (SD) | Effect Size Cohen's d Change at EOW6 compared with baseline | EOS M (SD) | Effect Size Cohen's d change at EOS compared with baseline |
|---|---|---|---|---|---|
| YMRS | | | | | |
| Overall | 23.8 (5.3) | 8.1 (4.9) | 3.07 | 8.5 (6.6) | 2.57 |
| Responders | 23.0 (4.9) | 6.4 (4.3) | 3.62 | 4.9 (3.7) | 4.22 |
| Nonresponders | 25.2 (5.6) | 11.0 (4.7) | 2.74 | 14.6 (6.0) | 1.82 |
| CDRS-R | | | | | |
| Overall | 25.2 (6.1) | 21.2 (5.2) | 0.69 | 21.4 (5.0) | 0.68 |
| Responders | 23.4 (4.8) | 20.0 (3.3) | 0.85 | 19.4 (2.6) | 1.09 |
| Nonresponders | 28.0 (7.1) | 23.3 (6.9) | 0.68 | 24.7 (6.0) | 0.50 |
| CGAS | | | | | |
| Overall | 53.3 (5.5) | 66.7 (6.6) | 2.20 | 67.9 (8.7) | 2.07 |
| Responders | 53.0 (4.9) | 68.0 (6.4) | 2.65 | 72.1 (6.2) | 3.44 |
| Nonresponders | 53.7 (6.5) | 64.2 (6.5) | 1.62 | 60.5 (7.4) | 0.99 |
| CGI-S | | | | | |
| Overall | 4.0 (0.7) | 1.9 (0.7) | 2.94 | 1.9 (0.9) | 2.54 |
| Responders | 3.9 (0.7) | 1.7 (0.7) | 3.21 | 1.5 (0.6) | 3.74 |
| Nonresponders | 4.0 (0.6) | 2.2 (0.8) | 2.68 | 2.7 (0.9) | 1.81 |

M = Mean; EOW 6 = End of Week 6; EOS = End of Study; CGAS = Children's Global Assessment Scale; CGI-S = Clinical Global Impressions Scale-Severity.

headache, sedation, and emesis. Using two or more study visits as a metric of persistence, 24 subjects experienced persistent sedation, and 7 subjects experienced persistent nausea/emesis.

Fasting glucose and cholesterol did not change significantly during the course of this study. No clinically significant cardiovascular effects, in the treating physicians' clinical judgment, were observed. However, fasting triglycerides were found to significantly increase, whereas prolactin levels were found to decrease, at the EOS in comparison to pretreatment levels. In addition, significant weight gain was found in this sample. Because of these tolerability concerns and the relative paucity of data about APZ in this patient population, whether or not the risk/benefit ratio associated with APZ treatment justifies prescribing this medication to an individual patient deserves careful consideration by the treating clinician.

### Nonresponse

Despite significant clinical benefit for the sub-cohort of youths who completed the protocol, 38% of the sample was nonresponders, most commonly due to medication noncompliance and/or continued symptomatology. There are several factors that may account for this nonresponse rate. Nonresponders remained in the study for less time due to study noncompliance and continued symptomatology. Also, those who did not respond had significantly more depressive symptoms and, although not statistically significant, more severe manic symptomatology compared with those who responded.

Further, dosing may have been inadequate in the nonresponder group. Although the mean final doses of APZ that were prescribed to responders were not significantly lower than the doses prescribed to nonresponders, it is quite possible that if a higher maximum total daily dose of medication were permitted per protocol, some of the nonresponders might have responded. Data from a retrospective study of APZ in youth with symptoms of mania reported doses of $16 \pm 7.9$ mg in youth ages $11.4 \pm 3.5$ years (Biederman et al. 2005). Similarly, higher APZ doses were found to be effective and reasonably well tolerated in a group of youths between the ages of 10 and 17 years in which treatment with APZ was initiated at 2 mg/day, and then, using a forced titration scheme, increased every 2 days for up to 12 days to achieve a maximum dose of 20, 25, or 30 mg/day (Findling et al. 2008). Additionally, a 30 mg/day APZ dose was both effective and generally well tolerated in a randomized, double-blind, placebo-controlled study in pediatric patients (ages 10 to 17) with BP-I, currently experiencing a manic or mixed episode (Findling et al. 2009b).

Table 4. Most Commonly Reported Adverse Events

| Adverse events | Overall, n (%) | Responders, n = 60 | Nonresponders, n = 36 | p |
|---|---|---|---|---|
| Stomachache | 40 (42%) | 24 (40%) | 15 (42%) | 1.000 |
| Increased appetite | 38 (40%) | 26 (43%) | 12 (33%) | 0.392 |
| Headache | 38 (40%) | 25 (42%) | 13 (36%) | 0.669 |
| Sedation | 33 (34%) | 24 (40%) | 9 (25%) | 0.183 |
| Emesis | 33 (34%) | 22 (37%) | 9 (25%) | 0.267 |
| Cold symptoms | 24 (25%) | 18 (30%) | 6 (17%) | 0.223 |
| Weight gain | 18 (19%) | 12 (20%) | 6 (17%) | 0.791 |
| Cough | 17 (18%) | 14 (23%) | 3 (8%) | 0.096 |
| Fever | 16 (17%) | 12 (20%) | 4 (11%) | 0.397 |
| Nasal congestion | 16 (17%) | 12 (20%) | 3 (8%) | 0.156 |
| Musculoskeletal pain | 12 (13%) | 9 (15%) | 3 (8%) | 0.526 |

Table 5. Mean Physiologic Measurements for Subjects

| Measure | Pretreatment | EOS |
|---|---|---|
| Prolactin (μg/L), n = 84 | 5.7 μg/L (3.7) | 1.2 μg/L (1.1) |
| Fasting glucose (mg/dL), n = 74 | 82.6 mg/dL (8.9) | 84.2 mg/dL (13.1) |
| Fasting cholesterol (mg/dL), n = 75 | 166.2 mg/dL (28.1) | 163.9 mg/dL (28.4) |
| Fasting triglyceride (mg/dL), n = 75 | 52.6 mg/dL (29.4) | 63.3 mg/dL (35.9) |

The results from both these studies were not available when this current trial was designed. However, in this preliminary safety study of young children, the APZ dose was kept intentionally within the extant evidence to minimize subject risks. In short, treatment with higher doses of APZ than used in the current study might be indicated in this patient population; however, this remains an empiric question that deserves further study.

## Limitations

This study has several limitations besides the dosing considerations noted above. It was the intention to include common comorbidites (e.g., ADHD and oppositional defiant disorder) in this study in an effort to allow this sample to be reasonably generalizable. However, the sample enrolled needed to meet explicit inclusion and exclusion criteria, and so may not fully represent the clinical diversity seen in general practice. Further, the open-label design lacks the methodological stringency of a randomized, double-blind, placebo-controlled trial. For these reasons, these data should be considered preliminary. The very large effect sizes suggest potentially promising efficacy, but a more rigorous trial will be needed to make stronger inferences and clinical recommendations. In addition, this trial had a limited sample size. As such, it is possible that uncommon medication-related adverse events might not have been observed. Also, assertions about the long-term tolerability and effectiveness of APZ cannot be made due to the study's brevity.

## Clinical Implications

To our knowledge, this is the first reported prospective study evaluating the effectiveness and safety of APZ that specifically treated children under the age of 10 years with bipolar illness. Although this report provides information in an area of critical need, more investigation into the use and safety of atypical antipsychotics in treating pediatric bipolar disorder would further inform clinical practice. These findings suggest that, using the dosing strategy employed in this trial, APZ monotherapy may be a safe and effective acute treatment option for bipolar disorder in a population of 4–9-year-old children. Further clinical research including studies that incorporate randomized, double-blind, placebo-controlled designs appear to be indicated. Studies that examine APZ dosing strategies, which might include higher APZ doses than employed herein, should also be considered to determine the most effective dosing paradigm for these children.

## Disclosures

Dr. Findling receives or has received research support, acted as a consultant, and/or served on a speaker's bureau for Abbott, Addrenex, AstraZeneca, Biovail, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Johnson & Johnson, KemPharm Lilly, Lundbeck, Neuropharm, Novartis, Noven, Organon, Otsuka, Pfizer, Sanofi-Aventis, Sepracore, Schering-Plough, Shire, Solvay, Supernus Pharmaceuticals, Validus, and Wyeth. Dr. Youngstrom has received travel support from Otsuka/Bristol-Meyers Squibb. Dr. Frazier has acted as a consultant to Shire Development Inc. Dr. Calabrese has received federal funding or research support from, acted as a consultant to/served on advisory boards for, or provided CME lectures to the Department of Defense, Health Resources Services Administration, National Institute of Mental Health, Abbott, Adamed, AstraZeneca, Bristol-Myers Squibb, Cephalon, Cleveland Foundation, Dainippon Sumitomo, Eli Lilly, EPI-Q, Inc., Eisai, Elan, Forest, France Foundation, Genaissance, GlaxoSmithKline, Janssen, Johnson and Johnson, Jazz Pharmaceuticals, JDS Pharmaceuticals, Lundbeck, Merck, Memory Pharmaceuticals, NARSAD, Neurosearch, Novartis, Organon, OrthoMcNeil, Otsuka, Pfizer, Repligen, Sanofi Aventis, Schering-Plough, Servier, Solvay, Stanley Medical Research Institute, Supernus, Synosia, Takeda, Tikvah, and Wyeth. The other authors have no financial ties to disclose.

## Acknowledgments

This work was primarily supported by a Clinical Research Center Grant and a Clinical Trials grant from the Stanley Medical Research Institute. It was also supported, in part, by NIMH P20 MH-66054, Bristol-Myers Squibb, and Otsuka Pharmaceuticals. Clinical trials registration no.: NCT00194077.

## Statistical Consultants

Eric A. Youngstrom, Ph.D. (University of North Carolina at Chapel Hill), Thomas W. Frazier, Ph.D. (Center for Pediatric Behavioral Health and Center for Autism, Cleveland Clinic Children's Hospital).

## References

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000.

Axelson D, Birmaher B, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan N, Leonard H, Hunt J, Iyengar S, Bridge J, Keller M: Phenomenology of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry 63:1139–1148, 2006.

Barnes TRE: A rating scale for drug-induced akathisia. Br J Psychiatry 154:672–676, 1989.

Barzman DH, DelBello MP, Kowatch RA, Gernert B, Fleck DE, Pathak S, Rappaport K, Delgado SV, Campbell P, Strakowski SM: The effectiveness and tolerability of aripiprazole for pediatric bipolar disorders: A retrospective chart review. J Child Adolesc Psychopharmacol 14:593–600, 2004.

Biederman, J, McDonnell MA, Wozniak J, Spencer T, Aleardi M, Falzone R, Mick E: Aripiprazole in the treatment of pediatric bipolar disorder: A systematic chart review. CNS Spectr 10:141–148, 2005.

Carlson GA, Jensen PS, Findling RL, Meyer RE, Calabrese J, DelBello MP, Emslie G, Flynn L, Goodwin F, Hellander M, Kowatch R, Kusumakar V, Laughren T, Leibenluft E, McCracken J, Nottelmann E, Pine D, Sachs G, Shaffer D, Simar R, Strober M, Weller EB, Wozniak J, Youngstrom EA: Methodological issues and controversies in clinical trials with child and adolescent patients with bipolar disorder: Report of a consensus conference. J Child Adolesc Psychopharmacol 13:13–27, 2003.

Cohen J: Statistical Power Analysis for the Behavioral Sciences, Second Edition. Hillsdale, NJ: Erlbaum Associates; 1988.

DelBello MP, Findling RL, Earley WR, Stankowski J: Efficacy of Quetiapine in Children and Adolescents with Bipolar Mania: A 3-week, Double-Blind, Randomized, Placebo-Controlled Trial. Boston, MA: American Academy of Child and Adolescent Psychiatry (AACAP) Annual Meeting, 2007 (abstract).

DelBello MP, Versavel M, Ice K, Keller D, Miceli J: Tolerability of oral ziprasidone in children and adolescents with bipolar mania, schizophrenia, or schizoaffective disorder. J Child Adolesc Psychopharmacol 18:491–499, 2008.

Findling RL, Gracious BL, McNamara NK, Youngstrom EA, Demeter CA, Branicky LA, Calabrese JR: Rapid, continuous cycling and

psychiatric co-morbidity in pediatric bipolar I disorder. Bipolar Disord 3:202–210, 2001.

Findling R, Kauffman R, Sallee FR, Salazar DE, Sahasrabudhe V, Kollia G, Kornhauser DM, Vachharajani NN, Assuncao-Talbott S, Mallikaarjun S, Iwamoto T, McQuade RD, Boulton DW, Blumer J: An open-label study of aripiprazole: Pharmacokinetics, tolerability, and effectiveness in children and adolescents with conduct disorder. J Child Adolesc Psychopharmacol 19:431–439, 2009a.

Findling RL, Kauffman RE, Sallee FR, Carson WH, Nyilas M, Mallikaarjun S, Shoaf SE, Forbes RA, Boulton DW, Pikalov A: Tolerability and pharmacokinetics of aripiprazole in children and adolescents with psychiatric disorders: An open-label, dose-escalation study. J Clin Psychopharmacol 28:441–446, 2008.

Findling RL, McNamara NK, Youngstrom EA, Stansbrey R, Gracious BL, Reed MD, Calabrese JR: Double-blind 18-month trial of lithium versus divalproex maintenance treatment in pediatric bipolar disorder. J Am Acad Child Adolesc Psychiatry 44:409–417, 2005.

Findling RL, Nylias M, Forbes RA, McQuade RD, Jin N, Iwamoto T, Ivanova S, Carson WH, Chang K: Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry 70:1441–1451, 2009b.

Frazier TW, Demeter CA, Youngstrom EA, Calabrese JR, Stansbrey RJ, McNamara NK, Findling RL: Evaluation and comparison of psychometric instruments for pediatric bipolar spectrum disorders in four age groups. J Child Adolesc Psychopharmacol 17:853–866, 2007.

Geller B, Tillman R, Craney JL, Bolhofner K: Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. Arch Gen Psychiatry 61:459–467, 2004.

Haas M, DelBello MP, Pandina G, Kushner S, Van Hove I, Augustyns I, Quiroz J, Kusumaker V: Risperidone for the treatment of acute mania in children and adolescents with bipolar disorder: A randomized, double-blind, placebo-controlled study. Bipolar Disord 11:687–700, 2009.

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N: Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 36:980–988, 1997.

Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M: Treatment guidelines for children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 44:213–235, 2005.

[NIMH] National Institute of Mental Health: Abnormal Involuntary Movement Scale (AIMS). Psychopharmacol Bull 21:1077–1080, 1985a.

[NIMH] National Institute of Mental Health: Clinical Global Impressions Scale. Psychopharmacol Bull 21:839–843, 1985b.

Poznanski EO, Freeman LN, Mokros HB: Children's depression rating scale-revised. Psychopharmacol Bull 21:979–989, 1985.

Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, Aluwahlia S: A Children's Global Assessment Scale (CGAS). Arch Gen Psychiatry 40:1228–1231, 1983.

Simpson GM, Angus JWS: A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 212:11–19, 1970.

Tohen M, Kryzhanovskaya L, Carlson G, DelBello M, Wozniak J, Kowatch R, Wagner K, Findling R, Lin D, Robertson-Plouch C, Xu W, Dittmann RW, Biederman J: Olanzapine versus placebo in the treatment of adolescents with bipolar mania. Am J Psychiatry 164:1547–1556, 2007.

Tramontina S, Zeni CP, Ketzer CR, Pheula GF, Narvaez J, Rohde LA: Aripiprazole in children and adolescents with bipolar disorder comorbid with attention-deficit/hyperactivity disorder: A pilot randomized clinical trial. J Clin Psychiatry 70:756–764, 2009.

Wagner KD, Nyilas M, Johnson B, Aurang C, Forbes A, Marcus R, Carson WH, Iwamoto T, Carlson GA: Long-Term Efficacy of Aripiprazole in Children (10–17 Years Old) with Mania. Boston, MA: American Academy of Child and Adolescent Psychiatry (AACAP) Annual Meeting, 2007 (abstract).

Wozniak J, Biederman J, Kiely K, Ablon S, Faraone S, Mundy E, Mennin D: Mania-like symptoms suggestive of childhood onset bipolar disorder in clinically referred children. J Am Acad Child Adolesc Psychiatry 34:867–876, 1995.

Young RC, Biggs JT, Ziegler VE, Meyer DA: A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 133:429–435, 1978.

Address correspondence to:
*Robert L. Findling, M.D.*
*Department of Psychiatry*
*University Hospitals Case Medical Center*
*Case Western Reserve University*
*10524 Euclid Ave.*
*Cleveland, OH 44106*

*E-mail:* robert.findling@uhhospitals.org