Aripiprazole in Children and Adolescents: Clinical Experience

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ABSTRACT

Despite few supportive data, aripiprazole was being administered to children and adolescents for management of mood instability, aggression, and psychosis. Using a retrospective review (n = 11) and prospective recruitment (n = 6), 17 children and adolescents received aripiprazole 5 to 20 mg/day. Only 4 of 16 bipolar and autistic subjects (25%) demonstrated reduced aggression without adverse events, and the symptoms of 2 of 4 psychotic subjects improved. Coadministration of sedative medications (particularly guanfacine or clonidine) and weight < 58 kg increased the risk of adverse events, such as increased lability and aggression. All three children < 8.6 years old, all four children < 34 kg, and all five children receiving α_2-agonists developed adverse events prior to clinical efficacy. Age > 11 years, weight > 58 kg, and absence of sedative medications were associated with a 56% (five of nine) success rate. Until larger, prospective studies are completed, caution is advised when considering aripiprazole for smaller children and children receiving sedative medications. (J Child Neurol 2005;20:603-610).

Antagonists of dopamine D_2 receptors are used as classic antipsychotics (such as haloperidol) and atypical antipsychotics (such as risperidone), although the latter also produce antagonism of serotonin 5-hydroxytryptamine 2A receptors. Both antipsychotic classes have been reported to be effective in managing disruptive and externalizing behaviors in children. However, these medications have significant adverse reactions, including extrapyramidal symptoms, prolongation of the Q-T interval, dizziness, hyperkinesia or mania, somnolence, drooling, tremor, nausea, hyperprolactinemia, increased appetite, and increased weight. Some antipsychotics can also have negative effects on glucose metabolism, possibly predisposing the patient to diabetes mellitus.

Aripiprazole (Abilify, Bristol-Meyers-Squibb, Princeton, NJ) has been approved by the US Food and Drug Administration for the treatment of adults with schizophrenia. As with other antipsychotic medications, the mechanism of action is unknown; however, the receptor interactions are different from other antipsychotics.

Aripiprazole is a partial agonist/antagonist of dopamine D_2, D_3, and D_4 receptors and of serotonin 5-hydroxytryptamine 1A and 2C receptors; it is also an antagonist at serotonin 5-hydroxytryptamine 2A receptors. It is primarily metabolized by the liver cytochrome CYP 3A4 and CYP 2D6 systems, although a small percentage is eliminated unchanged in the feces, with an elimination half-life between 75 and 94 hours.

Compared with other antipsychotics (classic and atypical), adult studies with aripiprazole reported fewer adverse events or side effects, specifically much less weight gain, no alterations of the Q-T-corrected interval, and no hyperprolactinemia. Extrapyramidal symptoms were similar to placebo (6% was reported for placebo and treatment groups), with akathisia being the most common. Other untoward events that were significantly greater than placebo included headache, insomnia, nausea, vomiting, light-headedness, somnolence, and constipation. Two cases of neuroleptic malignant syndrome occurred during premarketing experience with aripiprazole. In adult studies, subjects taking aripiprazole did not discontinue medicine owing to adverse events at a rate higher than that for placebo.

An open-label study of 23 children with conduct disorder ages 6 to 17 years old found the pharmacokinetics to be similar to that seen in adults. Doses ranging from 1 to 10 mg/day resulted in improvement in several observed scales: Clinical Global Impression of Severity scores, Rating of Aggression Against People and Property scale, and neuropsychologic tests. Because somnolence and vomiting were dose related (and notably more common in children than reported for adults), the authors of the study used lower doses of aripiprazole.
to mitigate these adverse events. Other reported adverse events included increased appetite, headache, and dyspepsia, but none of the adverse events were serious.

The primary objective of this study was to determine if aripiprazole improved disruptive behaviors in children with behavioral disorders, with an acceptable rate and severity of adverse events or side effects.

MATERIALS AND METHODS

Retrospective Review of Charts
Children receiving aripiprazole were identified using a computer search of prescriptions issued by the child neurologists, child psychiatrists, and neuropsychologists at the outpatient center of a children’s hospital specializing in neurodevelopmental, behavioral, and psychiatric disorders. These charts were then retrospectively reviewed for demographic data, diagnoses, documented target behaviors for the medication, medication doses, other medical treatments, treatment response in multiple environments (such as school, community or peer interactions, and home), adverse events, and follow-up. Clinical Global Impression of Severity scores (a 7-point Likert scale ranging from profoundly ill to no clinical symptoms) were retrospectively assigned prior to treatment and with treatment based on the degree to which the target behaviors resulted in disability in community or social, family or home, and educational environments. The Clinical Global Impression of Improvement scores (a 7-point Likert scale ranging from very much worse to no change to very much improved) were retrospectively assigned based on improvements seen in community or social, family or home, and educational environments at the time of optimal treatment. This retrospective review included 11 subjects (10 male and 1 female; 9 Caucasian, 1 Hispanic-American, and 1 African-American).

Prospective Evaluation of Subjects
After the study procedures were approved by a professional Institutional Review Board, children (4–18 years old) were identified from review of medical records at the developmental center and from sequential referral to the developmental center. Inclusion criteria included (1) a child or adolescent 4 to 18 years of age; (2) reliable transportation to and from the developmental center; (3) parent, teacher, or clinician concern that any or all of the following symptoms are disruptive enough to interfere regularly with daily individual or family functioning: aggression, agitation, anger, hyperactivity, and/or impulsivity; (4) an average Aberrant Behavior Checklist-Total score of > 63 for the irritability scale; and (5) a Clinical Global Impression of Severity score of "moderately ill" or higher (≥ 4). Exclusion criteria were (1) acute illness; (2) chronic gastrointestinal disorder that involves chronic or relapsing pain or emesis; (3) a known adverse reaction to any antipsychotic medication (including but not limited to haloperidol, chlorpromazine, thioridazine, pimozide, risperidone, quetiapine, ziprasidone); (4) a sexually active female patient unwilling or unable to appropriately use acceptable methods of contraception to prevent pregnancy or any female patient with urine, blood, or physical examination evidence of pregnancy; (5) known liver disease or serum hepatic enzyme levels > 1.5 times the upper limit of normal; (6) changes in any psychoactive medication over the past 90 days; (7) acute neurologic or medical instability or deterioration; (8) acute psychosis, acute suicidal ideation, or any acute psychiatric condition that might require emergent intervention; and (9) administration of any medication with a significant risk of unacceptable drug-drug interactions.

Physician specialists in neurodevelopmental disabilities, child neurology, or child psychiatry at the children’s hospital referred eligible subjects to the study. The six subjects who were referred for this open-label study consisted of newly referred sequential children to the children’s hospital and established patients who met the eligibility criteria. Informed consent was obtained from the legal guardian; informed assent was obtained from the subject when the investigator determined that the mental age was > 5 years old and when the subject was capable of understanding and communicating assent. The subjects continued medications administered for behavior control and medications required to manage chronic medical conditions (eg, anticonvulsants for seizure disorder, bronchodilators for asthma, antihistamines for allergic rhinitis or sinusitis). After obtaining informed consent or assent, screening data were recorded: height, weight, resting blood pressure, resting heart rate, resting respiratory rate, age, gender, diagnoses (primary and secondary), Aberrant Behavior Checklist score from parents, Aberrant Behavior Checklist score from teachers, the Clinical Global Impression of Severity score, a teacher questionnaire, and a parent questionnaire. If the subject qualified for a diagnosis of autism spectrum disorder, a Childhood Autism Rating Scale Score was also obtained. The primary diagnosis of autism spectrum disorder was assigned when the Childhood Autism Rating Scale score was > 30. If not objectively documented within the past 90 days, the subject also provided 12-hour fasting blood and urine samples for a complete chemistry profile, relevant blood levels of administered medications, a complete blood count, and urinalysis. Given that no menstruating or Turner ≥ 3 female patients were recruited for this study, no pregnancy evaluations were required.

All 6 referred subjects (5 male and 1 female, all Caucasian) were eligible and therefore participated in the study. No fixed dose titration schedule was used; aripiprazole was administered using an open-label, variable-titration protocol. All dose adjustments were made with the approval of the guardian and with the approval of the subject, when competent to make medical decisions. Tablets consisted of 5, 10, or 15 mg of aripiprazole. Subjects were started with half of a 5 mg tablet once a day except the first enrolled patient (a 16.3-year-old male patient with autism), who was started with one quarter of a 5 mg tablet. Evaluations (either on the telephone or in the office) were initially repeated no less frequently than every 14 days and consisted of assigning the Clinical Global Impression of Improvement score, recording adverse events or side effects, and completing a parent questionnaire form. The Clinical Global Impression of Improvement score was assigned using prearipiprazole behavior and function as a baseline; other reports were based on observations during the interval since the previous visit. If a clinical concern existed, then an office evaluation was held as quickly as feasible. Under any circumstance, an office evaluation was held at least monthly. The dose of aripiprazole was titrated according to the following protocol:

If a subject developed a serious adverse event or acute illness or whenever the subject or caretaker requested withdrawal from the study, the medication was immediately discontinued and the subject was immediately withdrawn from the study. If any had developed, serious adverse events would have been reported to the US Food and Drug Administration and the Institutional Review Board.

If a subject developed a moderate adverse event that regularly and significantly disrupted daily activity, the dose was reduced to the maximum tolerated dose and the subject was reevaluated no more than 1 week later. If the adverse event persisted or if the maximum tolerated dose was less than 2.5 mg/day, the medication was discontinued and the subject was withdrawn from the study.

If a minor adverse event occurred, the symptoms were medically managed as appropriate to the situation. If the treatment required any exclusion medication or if administration of any treatment medication was longer than 10 days, the dose was reduced to the maximum tolerated dose and the subject was reevaluated no more than 1 week later. If the minor
adverse event persisted for more than one additional week or if the maximum tolerated dose was less than 2.5 mg/day, the medication was discontinued and the subject was withdrawn from the study.

Complete data for the end of the open-label study were obtained only if evaluations did not interfere with the discontinuation of the medication or with administration of appropriate treatment, only if treatment did not involve administration of a psychoactive or exclusion medication, and only if the caretaker and subject agreed to continue treatment until the data could be obtained.

If the subject demonstrated an inadequate response to the administered dose of aripiprazole (as judged clinically by the treating physician specialist using primarily the Clinical Global Impression of Improvement score but also considering the Aberrant Behavior Checklist scores, questionnaire data, interview, and physical examination) without adverse events or with resolution of minor adverse events, the medication titration proceeded with an increase of half of a 5 mg tablet per day administered as a once-daily dose. The subjects were then reevaluated within 14 days. The maximum dose allowed was 30 mg/day.

In the absence of adverse events, the titration ended when the clinician or family chose to discontinue upward titration or when the maximal dose had been reached. The clinician decision to discontinue upward titration was primarily determined by evaluating the Clinical Global Impression of Improvement score while also considering the Aberrant Behavior Checklist scores, questionnaire data, interview, and physical examination. Specifically, when the Clinical Global Impression of Improvement score demonstrated that the patient was "much improved" (2) or "very much improved" (1), upward titration was discontinued. Once the final dose had remained stable for at least 30 days, the following data were obtained: age, height, weight, resting blood pressure, resting heart rate, resting respiratory rate, Aberrant Behavior Checklist score, Clinical Global Impression of Severity score, Clinical Global Impression of Improvement score, a teacher questionnaire, a parent questionnaire, a 12-hour fasting blood sample for complete chemistry profile, relevant blood levels of administered medication, complete blood count, lipid profile, and urinalysis.

In addition to descriptive statistics, data analysis included the Fisher exact test, Mann-Whitney-U-test, Spearman rank correlation, single-factor analysis of variance, and Student's t-test, assuming unequal variances.

**RESULTS**

The average age of the 17 subjects was 11.4 years (SD 3.9) with a range from 5.1 to 17.9 years. Seven subjects had bipolar disorder: six subjects were comorbid with attention-deficit hyperactivity disorder (ADHD) and two subjects had psychotic features, such as hallucinations and delusions. Nine other subjects had autism spectrum disorder (with one subject demonstrating psychotic features). For these 16 bipolar and autistic subjects, the aripiprazole was administered to improve aggression: 4 demonstrated self-directed physical aggression, 12 demonstrated physical aggression toward others, and 2 others demonstrated verbal aggression toward others. One additional subject had neither bipolar disorder nor autism: a nonaggressive female subject was diagnosed as having psychotic disorder not otherwise specified comorbid with ADHD and for this subject, the aripiprazole was administered to reduce psychotic features. When considering the target symptoms, assessment with the initial Clinical Global Impression of Severity resulted in a range from 4 to 7 (with 4 = moderately ill, 5 = markedly ill, 6 = severely ill, and 7 = among the most extremely ill) and an average score of 5.8 (SD 0.9).

On average, the subjects started with an aripiprazole dose of 7.3 mg/day (SD 4.2), and each subject was titrated to an average final dose of 12.8 mg/day (SD 4.5; range 5–20 mg/day), administered once daily. These final doses represented a daily dose of 0.28 mg/kg (SD 0.16; range 0.11–0.66 mg/kg/day).

At the time of writing, the average duration of aripiprazole administration was 106.6 days (SD 75.5; range 14–210 days). Five subjects (8.6–16.3 years old) were still receiving aripiprazole at the time of this article; this group had been receiving the medication for an average of 157 days (SD 59). These subjects showed clinical efficacy at once-daily doses ranging from 10 mg (n = 5) to 15 mg (n = 2); these doses represented an average dose of 0.28 mg/kg/day (SD 0.16; range 0.11–0.40 mg/kg/day). Of all 17 subjects in this study, only 8 (47%) continued aripiprazole beyond 100 days and only 4 (23%) beyond 160 days.

The remaining 12 subjects discontinued the aripiprazole: 10 subjects (9 male and 1 female) developed adverse events before or concomitant with improvement with target symptoms, 1 was discontinued at the physician's recommendation (owing to noncompliance and admitted alcohol use), and 1 was discontinued when the caretaker requested a different treatment (no reduction in aggression despite aripiprazole 15 mg/day, 0.39 mg/kg/day). These subjects discontinued the aripiprazole while taking an average daily dose of 13.1 mg (SD 5.1; range 5–20 mg), which corresponds to an average daily dose of 0.30 mg/kg/day (SD 0.16; range 0.11–0.66 mg/kg/day).

**Adverse Events**

Although only one parent expressed concerns with weight gain, aripiprazole use was associated with significant weight gain. For the 14 subjects with accurately measured pretreatment and treatment weights (13 male and 1 female), the average weight increased from 51.6 kg (SD 20.5; range 28.5–91.6 kg) to 55.5 kg (SD 22.1; range 28.3–105.2 kg). Similarly, the body mass index increased from 23.8 kg/m² (SD 4.5) to 25.5 kg/m² (SD 5.2). Put another way, the subjects taking aripiprazole increased their body weight by 3.9 kg (7.6%) and increased their body mass index by 7.1%.

There is some evidence to suggest that subjects taking aripiprazole longer and subjects with higher mg/kg/day doses are more likely to gain weight than those subjects with shorter durations and lower mg/kg/day doses. The Spearman rank correlation demonstrated a positive correlation between the percentage of weight gain and the duration of aripiprazole (rs statistic = .62; P = .018) and between the change in body mass index and the duration of aripiprazole treatment (rs statistic = .70; P = .005). Confirming this association, significantly more subjects gained < 4% weight when the duration was < 110 days than when the duration was > 110 days (Fisher exact test P = .03). Conversely, significantly more subjects gained > 10% weight when the duration was > 110 days than when the duration was < 110 days (Fisher exact test P = .05).

On the other hand, no significant correlation between the percentage of weight gain and the maximum mg/kg/day dose of aripiprazole or between a change in the body mass index and the maximum dose of aripiprazole was demonstrated with Spearman rank correlation. However, significantly more subjects with doses > 0.375 mg/kg/day gained > 10% body weight (all four patients) than subjects receiving < 0.375 mg/kg/day (only 2 of 10 patients; Fisher exact test P = .01).
When compared with standard gender- and age-based tables of average weight growth\(^9\) (applied to each subject individually), the expected average weight gain of this population would have been 1.5 kg (2.9%) and the expected 90th percentile weight gain would have been 2.3 kg (4.5%). Overall, 9 of 14 subjects gained more weight than expected for 90% of the same-age and same-gender peers. The overall average weight gain of the 14 subjects was greater than expected for 90% of the same-age and same-gender peers.

Adverse events included increased emotional lability and increased aggression (35%) in six subjects; five of these six subjects were autistic (Figure 1). When considering that only four autistic subjects were included in the 11 subjects without aripiprazole-mediated behavioral exacerbation, this overrepresentation of autism spectrum disorders did not reach statistical significance (Fisher exact test \(p = .09\)). Additionally, 4 of the 6 subjects with increased lability and aggression were coadministered \(\alpha_2\)-agonists (clonidine and guanfacine) compared with only 1 of the other 11 subjects; this difference is statistically significant (Fisher exact test \(p = .03\)). Overall, 5 of the 6 subjects with increased lability and aggression were coadministered medications with > 15% incidence of sedation\(^9-11\) (mirtazepine, guanfacine, clonidine, cetrizine, divalproex, trazodone, chlorpromazine, diazepam, olanzepine, oxcarbazepine) compared with 3 of the other 11 subjects; this difference was also statistically significant (Fisher exact test \(p = .04\)). Although the total daily dose for these six behaviorally exacerbated subjects tended to be higher than for the nonexacerbated group (14.2 mg/day, SD 4.9 vs 12.0 mg/day, SD 4.3 and 0.35 mg/kg/day SD 0.20 vs 0.24 mg/day, SD 0.12), this difference did not reach statistical significance. Neither gender, age, weight, nor initial Clinical Global Impression of Severity was different between these 6 subjects with increased lability and aggression compared with the other 11 subjects.

In addition to weight gain and lability or aggression, adverse events included two autistic subjects with nausea and emesis (12%) and one subject each (6%) with staring episodes and listlessness, coarse tremors, and sedation. Adverse events necessitated discontinuation of aripiprazole for 10 of 17 subjects, at an average duration of 79 days (SD 73; range 14-242 days). Of particular note, all subjects < 8.6 years (\(n = 3\); Fisher exact test \(p = .17\)), all subjects < 34 kg (\(n = 4\); Fisher exact test \(p = .08\)), six of seven subjects < 10.5 years old (Fisher exact test \(p = .08\)), and eight of nine subjects < 58 kg (Fisher exact test \(p = .01\)) developed adverse reactions before improvement of target symptoms. All five subjects receiving the \(\alpha_2\)-noradrenergic agonists clonidine and guanfacine developed adverse events (emotional lability or increased aggression or coarse tremors) prior to efficacy (Fisher exact test \(p = .04\)). Seven of eight subjects coadministered highly sedative medications (as defined previously) along with aripiprazole developed adverse events before efficacy; this overrepresentation of sedative medications was statistically significant (Fisher exact test \(p = .04\)). As seen in Figure 2 (comparing 10 subjects with adverse events with 7 subjects without adverse events), the following were found to be statistically significantly associated with the development of adverse events: weight < 58 kg, coadministered sedative medications, and coadministered \(\alpha_2\)-agonists. There was no association between adverse events and administration of stimulants (methylphenidate and mixed amphetamine salts) or administration of risperidone.

Adverse events could not be explained by coadministration with CYP 2D6 or CYP 3A4 inhibitors because coadministration of these medications\(^9\) (bupropion, chlorpromazine, fluvoxamine, venlafaxine) was not different for the group of subjects with adverse events (2 of 10) and the group of subjects without adverse events (1 of 7; Fisher exact test \(p = .64\)).

### Comparing Nonresponders With Responders

Nonresponders were defined as subjects who developed adverse events that necessitated aripiprazole discontinuation and/or subjects who did not show a significant improvement in the primary target behaviors (ie, Clinical Global Impression of Improvement score ≥ 4) with aripiprazole administration. Conversely, responders showed significant improvement in the primary target behavior (ie, Clinical Global Impression of Improvement score ≤ 3) without significant adverse events. For 16 subjects, improvement in the primary target behavior was defined as a reduction in the frequency and intensity of aggression. Although a decrease in psychotic features was observed in 1 of these 16 subjects, the parent requested discontinuation of aripiprazole owing to weight gain and a lack of efficacy in reducing aggression; this individual was included as a nonresponder. The one subject who was not demonstrating aggression showed significant improvement in her psychotic features; therefore, she was included as a responder.

When comparing the 11 nonresponders (10 males and female with an average initial Clinical Global Impression of Severity score of 6.7, SD 0.9) with the 6 aripiprazole responders (5 males and 1 female with an average initial Clinical Global Impression of Severity score of 5.8, SD 1.0), no significant differences existed for gen-
der, initial Clinical Global Impression of Severity score, or dose (13.4 mg/day, SD 5.3 vs 11.7 mg/day, SD 2.6 and 0.32 mg/kg/day, SD 0.16 vs 0.20 mg/kg/day, SD 0.13). Although the nonresponders tended to be younger (10.4 years, SD 3.9 vs 13.3 years, SD 3.4; \( P = .05 \)), the difference did not quite reach statistical significance using non-parametric measures (Mann-Whitney U-test \( P = .07 \)). Nonresponders nonetheless had significantly lower initial weights (47.1 kg, SD 17.7 vs 67.6 kg, SD 20.6; Mann-Whitney U-test \( P = .03 \)) than those who responded to aripiprazole without adverse events.

**DISCUSSION**

Although prior reports suggested that atypical antipsychotics such as clozapine and risperidone are effective and tolerated for treatment of aggression in children,\(^2\,^4\,^5\,^23\) this study showed mixed results when aripiprazole was used as a treatment for children with aggression. Overall, only 4 of 16 (25%) aggressive subjects showed clinical improvement without significant adverse events. In contrast, two of four subjects with psychotic features (50%) showed clinical improvement prior to the onset of adverse events, although one of these two subjects still discontinued the aripiprazole owing to a lack of efficacy for aggression. These are success rates significantly below those published for other atypical antipsychotics used for the treatment of tantrums, escalation, and aggression.\(^2\,^4\,^5\,^23\)

The most frequent adverse event related to aripiprazole administration was increased lability and aggression (behavioral exacerbation) in 6 of 17 subjects (35%), although 10 of 17 subjects (58%) developed one of several adverse events (including nausea and emesis, tremors, sedation, staring episodes with listlessness). In this study, the coadministration of aripiprazole with sedative medications, particularly the \( \alpha_2 \)-agonists clonidine and guanfacine, increased the risk of adverse events (particularly behavioral exacerbation): only one of eight subjects (13%) receiving these medications showed a reduction in the intensity and frequency of aggression without significant adverse events. No similar exacerbation of symptoms was seen when aripiprazole was coadministered with stimulants or risperidone (for which the incidence of sedation was only 3 to 8%). Conversely, aripiprazole was efficacious in five of nine subjects (56%) without these sedative medications. The association between sedative medications (especially \( \alpha_2 \)-agonists) and adverse events was not adequately explained by cytochrome CYP 2D6 and 3A4 inhibition, resulting in toxic levels of aripiprazole, because the prevalence of CYP-inducing medications was no different for subjects with adverse events and subjects without adverse events.

The smaller (\(< 58 \) kg) subjects were more prone to adverse events owing to aripiprazole than were the larger subjects, as evidenced by the significant difference in average weight (smaller subjects tending to be less likely to demonstrate efficacy without side effects) and the statistically significant difference in the rates of adverse events below and above 58 kg. Specifically, only one of eight subjects \(< 58 \) kg (13%) showed clinical improvements without adverse events with aripiprazole administration. Although only one of seven subjects \(< 10.5 \) years old demonstrated improvement without adverse events, this trend did not reach statistical significance. Although not statistically significant, it is notable that all three subjects below 8.6 years old developed adverse events prior to efficacy. Any potential association between age and adverse events is likely to be related to the weight–adverse event association. Decreased tolerance could not be explained by either a greater daily dose or per kilogram daily dose because these were not significantly different for the two groups. This finding is consistent with a previous study that demonstrated a greater sensitivity of younger individuals to adverse events from aripiprazole.\(^1\) Conversely, 56% of the subjects over 11 years old and 56% of the subjects over 58 kg (five of nine subjects each) showed clinical improvement without adverse events.

There was a tendency for autistic subjects receiving aripiprazole to demonstrate more emotional lability or aggression and nausea or emesis than nonautistic subjects, although this did not reach statistical significance. Any potential association can be partly explained by the tendency of children with autism in this study to have more administration of sedative medications: six of nine autistic subjects received sedative medications compared with two of eight nonautistic subjects (Fisher exact test \( P = .05 \)). On the other hand, any potential association between autism and adverse events cannot be explained by association with weight: six of nine subjects \(< 58 \) kg were autistic and three of eight subjects \( > 58 \) kg were autistic (Fisher exact test \( P = .24 \)).

Although age and weight were likely linked variables associating with the emergence of adverse events, they were separate from the variable defined as coadministration of sedative medications: sedative medications were administered to five of nine subjects \(< 58 \) kg and four of eight subjects \( > 58 \) kg (Fisher exact test \( P = .60 \)).

Although it could be considered that the reduced efficacy observed in subjects who are smaller and for subjects who are using sedative-combined pharmacotherapy relate to a greater severity of symptoms or a more severe disorder, this theory was not substantiated by the similar initial Clinical Global Impression of Severity scores for responders and nonresponders (5.7 compared with 5.8). This conclusion lends further credence to the hypothesis that the increased tendency for younger or smaller subjects to develop adverse events is more directly related to the immaturity of the central nervous system or to the smaller physical size or more immature physical proportions.
Aripiprazole resulted in greater weight gain than would be expected for age and gender, based on standardized growth velocity charts, with a longer duration resulting in greater weight gain and a greater increase in body mass index. There might be an increase in body mass index. There might be an association between weight gain and the maximum dose of aripiprazole: doses above 0.375 mg/day are associated with a statistically significantly greater weight gain, but the relationship between maximum dose and weight gain might not be linear. The weight gain that occurred with aripiprazole administration was 70% greater than the weight gain seen at the 90th percentile for same-age and same-gender children. Overall, 9 of 14 subjects (64%) gained weight faster than 90% of their peers. Although this is a finding seen with other atypical antipsychotics, the relationship with aripiprazole is clouded by coadministration of other weight-increasing medications in six of the subjects (divalproex in two subjects, risperidone in two subjects, mirtazapine in one subject, olanzapine in one subject). When removing these 6 subjects from the 14 subjects with accurate pretreatment and treatment weights, the remaining 8 subjects still demonstrated a weight increase greater than that for the 90th percentile on average: the initial weight was 53.5 kg and the standard deviation was 21.7; the final weight was 57.9 kg and the standard deviation was 24.9; and the calculated expected final weight was 56.5 kg if the weight gain was assumed to be at the 90th percentile for gender and age. Four of eight of these subjects (50%) still gained more weight than expected for 90% of same-age and same-gender peers. The average weight gain with aripiprazole administration, even in the absence of coadministered medications with a known adverse event of weight gain, was 8.2% compared with the expected 5.0% weight gain if growing with a velocity equal to that at the 90th percentile. In other words, aripiprazole still caused a 47% greater weight gain than would be seen if growth was at the 90th percentile and a 69% greater weight gain than would be seen if growth was at the 50th percentile. This represents an average of an additional 1.4 kg over an average duration of 136 days (SD 74) if growth occurred at the 90th percentile and an average of an additional 1.8 kg over the same duration if growth occurred at the 50th percentile.

A previous study evaluating the efficacy and tolerability of aripiprazole in children and adolescents (6 to 12 years old) demonstrated positive effects on the symptoms of conduct disorder, particularly

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<th>Age (yr)/Gender</th>
<th>Weight (kg)</th>
<th>Primary Diagnosis</th>
<th>Medications</th>
<th>Aripiprazole Dose</th>
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<td>7.2/M</td>
<td>30.90</td>
<td>Autism</td>
<td>Citirizine</td>
<td>7.5</td>
<td>0.24</td>
<td>Staring episodes, listlessness, Somnolence</td>
</tr>
<tr>
<td>8.9/M</td>
<td>45.45</td>
<td>Autism</td>
<td>Clonidine, divalproex</td>
<td>15</td>
<td>0.51</td>
<td>Increased aggression</td>
</tr>
<tr>
<td>9.2/M</td>
<td>38.30</td>
<td>Bipolar disorder, ADHD</td>
<td>Methylphenidate</td>
<td>15</td>
<td>0.33</td>
<td>Weight gain, lack of efficacy at 15 mg</td>
</tr>
<tr>
<td>9.5/M</td>
<td>29.40</td>
<td>Autism</td>
<td>Clonidine, divalproex</td>
<td>15</td>
<td>0.39</td>
<td>Lack of efficacy at 15 mg</td>
</tr>
<tr>
<td>11.1/M</td>
<td>65.00</td>
<td>Bipolar disorder, ADHD*</td>
<td>Methylphenidate, risperidone</td>
<td>20</td>
<td>0.31</td>
<td>Increased aggression, lack of efficacy</td>
</tr>
<tr>
<td>11.8/F</td>
<td>46.14</td>
<td>Bipolar disorder</td>
<td>Clonidine</td>
<td>5</td>
<td>0.11</td>
<td>Increased aggression, lack of efficacy</td>
</tr>
<tr>
<td>13.3/M</td>
<td>69.55</td>
<td>Autism spectrum disorder*</td>
<td>Mixed salts of amphetamine, clonidine, trazodone</td>
<td>10</td>
<td>0.14</td>
<td>Increased aggression, nausea, lack of efficacy</td>
</tr>
<tr>
<td>16.3/M, SD 3.9</td>
<td>77.73</td>
<td>Bipolar disorder, ADHD*</td>
<td>Methylphenidate, venlafaxine, divalproex, chlorpromazine</td>
<td>20</td>
<td>0.26</td>
<td>Increased aggression</td>
</tr>
<tr>
<td>16.6/M, SD 3.9</td>
<td>57.05</td>
<td>Autism</td>
<td>Clonidine, diazepam, olanzapine</td>
<td>10</td>
<td>0.18</td>
<td>Increased aggression</td>
</tr>
<tr>
<td>10.4, SD 3.9</td>
<td>47.1, SD 17.7</td>
<td></td>
<td></td>
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</tr>
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</table>

ADHD = attention-deficit hyperactivity disorder, CGI-S = Clinical Global Impression of Severity.
*Subject demonstrated psychotic features such as hallucinations and/or delusions.
with respect to aggression (using the Rating of Aggression Against People and/or Property scale). When these authors noted a high incidence of enuresis and somnolence initially, the doses of aripiprazole were decreased to improve tolerability. This study found a greater degree of problematic emotional lability or increased aggression and less efficacy than the study by Findling et al. It is conceivable that some of the exacerbated mood lability and aggression observed in this study is related to the same physiology that causes sedation, in much the same way that most people are more irritable when tired. Additionally, some differences in design (using different rating scales, retrospective review inclusion versus exclusion, duration of administration averaging 106 days versus 15 days, different strategies of data analysis) and in population (autism and bipolar predominance versus conduct disorder and oppositional defiant disorder) might account for some of the differences. Because this study involved many children with autism and was conducted at a developmental center rather than at a psychiatry department, there is a significant possibility that this study included more children with intellectual deficits than the study of children with conduct disorders. In addition, this study was conducted with most patients receiving combination medication treatment, particularly with sedative medications. Also to be considered is the degree to which a ratio of "impulsive-reactive-hostile-affective" aggressive subjects to "controlled-proactive-instrumental-predatory" aggressive subjects in children and adolescents < 8.6 years old and all four children and adolescents. Notable but not statistically significant are the findings that all three subjects < 8.6 years old and all four subjects < 34 kg developed adverse events prior to efficacy. Conversely, 50% of subjects over 11 years old and 56% of subjects over 58 kg demonstrated symptom improvement with adequate tolerance. As with other atypical antipsychotics, weight gain (greater than that expected for typical growth) is associated with aripiprazole administration. Prospective studies with larger numbers of subjects will be needed to further delineate these risks and determine more accurately the risk-benefit analysis of aripiprazole use in children. Until those studies are completed, caution is advised when prescribing aripiprazole for younger or smaller children and when prescribing aripiprazole along with sedative medications (particularly clonidine and guanfacine).

Acknowledgment
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References


