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Aripiprazole in the Treatment of Irritability in Children and Adolescents With Autistic Disorder

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KEY WORDS
aripiprazole, autistic disorder, pediatrics

ABBREVIATIONS
EPS—extrapyramidal symptom
ADI-R—Autism Diagnostic Interview–Revised
CGI-S—Clinical Global Impression–Severity
ABC—Aberrant Behavior Checklist
ECG—electrocardiogram
CGI-I—Clinical Global Impression–Improvement
PedsQL—Pediatric Quality of Life Inventory
CGSQ—Caregiver Strain Questionnaire
AE—adverse event
ANCOVA—analysis of covariance
LOCF—last observation carried forward
TD—treatment difference
df—degrees of freedom
CI—confidence interval

This trial has been registered at www.clinicaltrials.gov (identifier NCT00332241).

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WHAT'S KNOWN ON THIS SUBJECT: Autistic disorder is often associated with serious behavioral disturbances, such as irritability, that represent a significant burden to individuals and families.

WHAT THIS STUDY ADDS: Aripiprazole is effective at reducing irritability in children and adolescents with irritability associated with autistic disorder and is well tolerated.

abstract

OBJECTIVE: The objective of this study was to evaluate short-term efficacy and safety of aripiprazole in the treatment of irritability in children and adolescents with autistic disorder who were manifesting behaviors such as tantrums, aggression, self-injurious behavior, or a combination of these.

METHODS: This 8-week, double-blind, randomized, placebo-controlled, parallel-group study was conducted of children and adolescents (aged 6–17 years) with autistic disorder. Patients were randomly assigned (1:1) to flexibly dosed aripiprazole (target dosage: 5, 10, or 15 mg/day) or placebo. Efficacy outcome measures included the Aberrant Behavior Checklist irritability subscale and the Clinical Global Impression–Improvement score (CGI-I). Safety and tolerability were also assessed.

RESULTS: Ninety-eight patients were randomly assigned to receive placebo ($n = 51$) or aripiprazole ($n = 47$). Mean improvement in Aberrant Behavior Checklist irritability subscale score was significantly greater with aripiprazole than with placebo from week 1 through week 8. Aripiprazole demonstrated significantly greater global improvements than placebo, as assessed by the mean CGI-I score from week 1 through week 8; however, clinically significant residual symptoms may still persist for some patients. Discontinuation rates as a result of adverse events (AEs) were 10.6% for aripiprazole and 5.9% for placebo. Extrapyramidal symptom-related AE rates were 14.9% for aripiprazole and 8.0% for placebo. No serious AEs were reported. Mean weight gain was 2.0 kg on aripiprazole and 0.8 kg on placebo at week 8.

CONCLUSIONS: Aripiprazole was efficacious in children and adolescents with irritability associated with autistic disorder and was generally safe and well tolerated. *Pediatrics* 2009;124:1533–1540

Autistic disorder is a neurodevelopmental disorder characterized by qualitative impairments in social interaction, communication, and restricted and repetitive behaviors.[1] It is estimated to affect 2.2 children in 1000.[2,3] Many patients with autistic disorder also experience irritability, which may be manifest as aggression, tantrums, rapidly changing moods, and self-injurious behavior. These dysfunctional behaviors can profoundly impair functioning and cause substantial individual and family burden.[4] Although the prevalence of these behaviors specifically in autistic disorder has not been as systematically evaluated, a recent study demonstrated that ~20% of individuals with pervasive developmental disorder experienced moderate to severe irritability.[5]

Although there is little evidence for pharmacologic treatments that target the core qualitative social and communicative impairments of autistic disorder, atypical antipsychotic agents may be useful for the treatment of aggression, self-injury, irritability, and other associated maladaptive behaviors.[6] Only risperidone has been approved by the US Food and Drug Administration for the symptomatic treatment of irritability (including symptoms of aggression toward others, deliberate self-injuriousness, temper tantrums, and quickly changing moods) in children and adolescents with autistic disorder on the basis of the results from 2 large, randomized, controlled trials.[7,8] Aripiprazole is an atypical antipsychotic agent that has been shown to be efficacious and generally well tolerated in children and adolescents with schizophrenia or bipolar mania.[9–12] Here, we report the results of a double-blind, randomized, placebo-controlled study that examined the efficacy and safety of flexibly dosed aripiprazole in reducing symptoms of irritability in children and adolescents with autistic disorder.

METHODS

Study Design and Treatments

This was an 8-week, double-blind, randomized, placebo-controlled, parallel-group, multicenter study to assess the efficacy, safety, and tolerability of flexibly dosed aripiprazole in children and adolescents with irritability associated with autistic disorder. The study was conducted at 20 study centers in the United States. Patients were enrolled from June 2006 until February 2008. The last patient visit was in April 2008. The study was conducted in accordance with the Declaration of Helsinki, and the institutional review board at each site approved the protocol. A guardian or caregiver provided written informed consent, and patients provided written informed assent when possible.

The study consisted of a screening phase followed by an 8-week treatment phase. During the screening phase, patients attended a screening visit, had a washout period and interim screening visit when applicable, and a baseline visit within 6 weeks. Study visits were conducted at the end of treatment weeks 1, 2, 3, 4, 5, 6, and 8 or at the time of early termination. Telephone contact occurred during week 7 to assess patients' well-being and medication tolerability.

At the baseline visit, eligible patients were randomly assigned (1:1) to either flexibly dosed aripiprazole or placebo according to a computer-generated randomization schedule prepared by Bristol Myers Squibb using a permuted block design. Investigational sites accessed a call-in interactive voice response system when patients were ready to be randomly assigned. The system assigned a medication bottle number to each patient. Aripiprazole was initiated at 2 mg/day, with a target dosage of 5, 10, or 15 mg/day (maximum dosage: 15 mg/day). All dosage increases, when deemed appropriate by the investigator, occurred at the weekly study visits and were incremental from the current dosage level to the next (dosage level: 2, 5, 10, or 15 mg/day). No dosage increases were to occur after week 6. The dosage could be adjusted downward for tolerability at the discretion of the investigator at any time, ideally remaining stable for the final 2 weeks of treatment.

All psychotropic medications (including antipsychotic, psychostimulant, antidepressant, anxiolytic, mood stabilizer, and neuroleptic agents) were prohibited and were discontinued at least 4 days before the interim screening visit. Depot antipsychotic agents were discontinued for at least 1 full cycle plus 1 week before the interim screen visit. Fluoxetine or olanzapine/fluoxetine was discontinued for at least 4 weeks before the interim screen visit. Lorazepam or alprazolam, for anxiety related to medical/study procedures, and sleep aids (diphenhydramine, melatonin, or nonbenzodiazepine hypnotics) could be administered at the investigator's discretion. Diphenhydramine up to 50 mg/day could be administered for serious behavior problems. Benztropine or propranolol, on the basis of investigator judgment, were permitted for the treatment of extrapyramidal symptoms (EPSs) but not within 12 hours before administration of movement rating scales.

Study Population

Patients were 6 to 17 years of age; met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* criteria for autistic disorder; and demonstrated behaviors such as tantrums, aggression, self-injurious

behavior, or a combination of these. Diagnosis was corroborated by the Autism Diagnostic Interview–Revised (ADI-R),[13] which was administered by an experienced interviewer who had been previously trained and approved as "research reliable" on the ADI-R or who had been approved after successful completion of a 2-day rater training course conducted by an ADI-R–certified trainer. Patients were also required to have a Clinical Global Impression–Severity (CGI-S) score ≥4 and Aberrant Behavior Checklist (ABC)[14] irritability subscale score of ≥18 at screening and baseline. The ABC irritability subscale contains 15 items that rate symptoms such as "injures self," "aggressive to other children and adults," "irritable," "temper outbursts," "depressed mood," "mood changes," and "yells or screams inappropriately" on a scale ranging from 0 (not at all a problem) to 3 (severe).

Exclusion criteria were a current diagnosis of bipolar disorder, psychosis, schizophrenia or major depression, or fragile X syndrome or a diagnosis of another disorder on the autism spectrum including pervasive developmental disorder–not otherwise specified, Asperger syndrome, Rett syndrome, or childhood disintegrative disorder. Additional exclusion criteria were history of neuroleptic malignant syndrome; a significant risk for committing suicide; seizure in the past year; history of severe head trauma or stroke; history or current evidence of any unstable medical conditions; or a laboratory test, vital sign, or electrocardiogram (ECG) result considered clinically significant. Patients who were considered to be treatment resistant to antipsychotic medication or had a known allergy or hypersensitivity to aripiprazole were also excluded. All patients were required to weigh ≥15 kg. Nonpharmacologic therapy (eg, behavior modification) was required to be stable before screening and consistent throughout the study.

Assessments

Efficacy and safety assessments were performed at each study visit and, when applicable, at the time of early termination. Analyses reported here are those that had been specified a priori. The primary efficacy outcome measure was the mean change from baseline to end point in the caregiver-rated ABC irritability subscale score. The key secondary efficacy outcome measure was the mean clinician-rated Clinical Global Impression–Improvement (CGI-I) score at end point. Additional secondary efficacy outcomes included the mean change in other ABC subscale scores (hyperactivity, stereotypy, inappropriate speech, and lethargy/social withdrawal), response rate (≥25% reduction in ABC irritability subscale score and CGI-I score of 1 [very much improved] or 2 [much improved] at end point), mean change in the Children's Yale-Brown Obsessive Compulsive Scale (compulsion scale only, weeks 0, 4, and 8 only),[15] and CGI-S scores.[16] Quality-of-life analyses included mean change in the Pediatric Quality of Life Inventory (PedsQL)[17] and the Caregiver Strain Questionnaire (CGSQ).[18] The PedsQL scores were computed as the sum of all item scores divided by the number of items answered. The CGSQ global score is presented as the sum of the 3 subscales, which were calculated as the averages of the corresponding individual items. These outcomes were assessed at baseline and at week 8.

Safety evaluations were based on reports of adverse events (AEs), vital signs, ECG findings, weight and laboratory assessments, and structured assessment of extrapyramidal symptoms by using the Simpson-Angus Scale,[19] the Barnes Akathisia Rating Scale,[20] and the Abnormal Involuntary Movement Scale.[21] Relationship of AEs to study treatment was assigned by the investigators, who were unaware of whether the participants were receiving aripiprazole or placebo treatment, as the events occurred. Prolactin levels were considered potentially clinically relevant when they were above the upper limit of normal for the child's age and gender.

Statistical Analyses

The study planned to randomly assign 100 patients to obtain at least 90 assessable patients (45 per group). This sample size would provide 93% power to differentiate between placebo and aripiprazole when the true difference in mean change from baseline in ABC irritability subscale score was 7.0. This assumed an SD of 9.42 and a 2-sided test at the 0.05 level of significance.

The randomized sample included all patients who were randomly assigned to double-blind treatment. The primary population for safety assessments comprised all patients in the randomly assigned sample who reported taking at least 1 dose of study medication during the double-blind treatment phase. The primary population for efficacy assessments comprised all patients in the safety sample who had at least 1 postrandomization efficacy evaluation and corresponding baseline value (assessable population). For continuous measurements, change scores were evaluated by analysis of covariance (ANCOVA). The ANCOVA models for last observation carried forward (LOCF) data sets included the baseline measure as a covariate and baseline body weight (≥40 kg or <40 kg), study center, and treatment as a priori main effects. *P* values that were generated from the ANCOVA model tested the least squares means differences, whereby the test statistic follows a "*t*" distribution with degrees of freedom

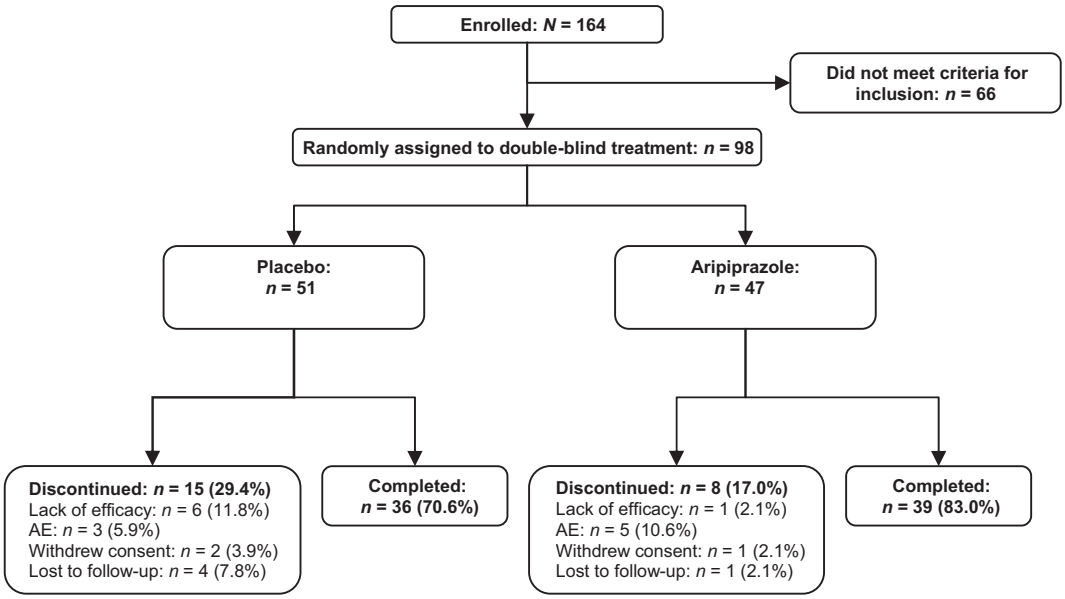

FIGURE 1
Subject disposition.

equal to the error degrees of freedom from the ANCOVA model. The effect size for the treatment difference (TD) in the primary end point was calculated by dividing the difference of treatment-specific mean estimates by the square root of the mean square error from the corresponding ANCOVA model. Categorical measures were analyzed within the framework of the generalized Cochran-Mantel-Haenszel procedure, controlling for treatment and study center. Change from baseline in weight, BMI, and EPS ratings were evaluated by using the analytical approaches described for the efficacy analyses. For response rate comparisons, the test statistic follows a "χ^2" distribution with degrees of freedom (df) = 1. Weight change was also evaluated by ANCOVA by using the observed case data set. Mean changes from baseline in Fridericia's correction ($QT_{cF} = QT/RR^{0.33}$) and Bazett's correction ($QT_{cB} = QT/RR^{0.5}$) of the QT interval were evaluated by ANCOVA, controlling for treatment and baseline value. All analyses were performed at the 5% significance level.

RESULTS

Patient Disposition and Characteristics

In total, 164 patients were enrolled and 98 patients were randomly assigned to receive treatment with placebo (n = 51) or aripiprazole (n = 47). Seventy-five (76.5%) patients completed the randomized, double-blind treatment phase; patient disposition is shown in Fig 1. All randomly assigned patients were included in the safety sample except for 1 patient in the placebo group, who was lost to follow-up before entering the double-blind treatment phase. Two patients were excluded from the efficacy sample; 1 patient in the placebo group withdrew consent, and 1 patient in the aripiprazole group discontinued on day 2 because of vomiting, both before completing a post-baseline efficacy evaluation.

Baseline characteristics were similar between treatment groups (Table 1). The mean age of the randomly assigned patients was 9.3 years, and most patients were younger than 12 years.

TABLE 1 Baseline demographics

Demographic	Placebo (N = 51)	Aripiprazole (N = 47)
Age, mean (SD), y	8.8 (2.6)	9.7 (3.2)
Age group, *n* (%)		
6–12 y	46 (90.2)	37 (78.7)
13–17 y	5 (9.8)	10 (21.3)
Male, *n* (%)	44 (86.3)	42 (89.4)
Race, *n* (%)		
White	41 (80.4)	32 (68.1)
Black	7 (13.7)	11 (23.4)
Asian	0 (0.0)	2 (4.3)
Other	3 (5.9)	2 (4.3)
Weight, mean (SD), kg	40.6 (18.9)	43.9 (19.2)
Weight group, <40 kg, *n* (%)	32 (62.7)	26 (55.3)
ABC irritability subscale score at baseline, mean (SD)	30.2 (6.5)	29.6 (6.4)

Of the patients in the safety sample, 50 (51.5%) were recorded as having received previous psychotropic medication. The most commonly received medications were antipsychotic agents (placebo: 30.0%; aripiprazole: 17.0%), psychostimulant agents (placebo: 26.0%; aripiprazole: 17.0%), anxiolytic agents (placebo: 16.0%; aripiprazole: 17.0%), and antidepressant agents (placebo: 10.0%; aripiprazole: 6.4%).

Study Medications

The distribution of aripiprazole dosing during the last week of treatment (n = 39) was as follows: 2 mg/day, n = 2 (5%); 5 mg/day, n = 13 (33%); 10 mg/day, n = 16 (41%); and 15 mg/day, n = 8 (21%). The prescription pattern of placebo during the last week of treatment (n = 36) was as follows: 2 mg/day, n = 1 (3%); 5 mg/day, n = 4 (11%); 10 mg/day, n = 5 (14%); and 15 mg/day, n = 26 (72%).

A total of 35 (36.1%) patients received at least 1 concomitant central nervous system medication during the trial (placebo: 36.0%; aripiprazole: 36.2%). The most commonly used central nervous system medications were analgesic and antipyretic agents (placebo: 22.0%; aripiprazole: 19.1%), followed by hypnotic and sedative agents (placebo: 12.0%; aripiprazole: 2.1%).

Efficacy Outcomes

At week 8, the mean decrease from baseline in the caregiver-rated ABC irritability subscale score was significantly greater for patients who received aripiprazole (−12.9) than placebo (−5.0; least-squares mean TD −7.9 [95% CI: −11.7 to −4.1]; $P <$ .001). This produces an effect size of −0.87. Significant TDs in favor of aripiprazole were observed as early as the first week of treatment, during which all patients who were on active medication were receiving aripiprazole 2 mg/day (Fig 2). At week 8, aripiprazole showed statistically significantly greater improvement in mean clinician-rated CGI-I scores compared with placebo beginning at week 1 ($P <$ .001) through week 8 (2.2 vs 3.6; TD: −1.4 [95% CI: −1.9 to −1.0]; $P <$ .001). Distribution of CGI-I scores at week 8 is shown in Fig 3.

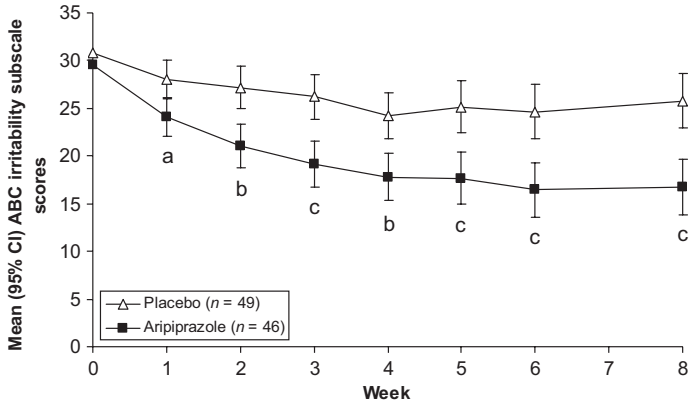

FIGURE 2
Mean ABC irritability subscale score according to week (LOCF; efficacy sample). [a] $P <$ .05, [b] $P <$ .005, and [c] $P <$ .001 versus placebo.

Significantly more aripiprazole-treated patients responded to treatment (as defined by ≥25% reduction in ABC irritability subscale score and CGI-I score ≤2) starting from week 2 (30.4% vs 4.1%; $P <$ .001) through week 8 (52.2% vs 14.3%; $P <$ .001). Table 2 shows the results for other secondary end points. Patients who received aripiprazole demonstrated improvement versus placebo on the PedsQL combined scales total score (TD 11.4 [95% CI: 6.1 to 16.8] and on the CGSQ global score (TD: −1.9 [95% CI: −2.7 to −1.2]).

Safety and Tolerability Outcomes

During the study, 36 (72.0%) patients in the placebo group and 43 (91.5%) in the aripiprazole group experienced at least 1 AE. AEs that occurred at an incidence ≥5% in any treatment group are shown in Table 3. Most AEs were mild to moderate in severity in both treatment groups; no serious AEs were reported during the study or within 30 days of discontinuing study treatment. No deaths were reported. Discontinuation from study treatment as a result of AEs occurred for 3 (6.0%) patients in the placebo group and 5 (10.6%) patients in the aripiprazole group. Reasons for dis-

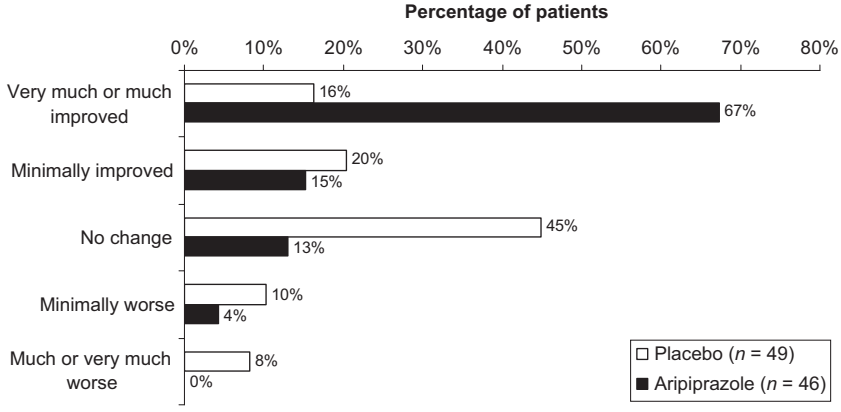

FIGURE 3
Distribution of CGI-I score at week 8 (LOCF; efficacy sample).

TABLE 2 Secondary Efficacy End Points (Week 8 LOCF, Efficacy Sample)

Variable	Placebo ($N = 49$)		Aripiprazole ($N = 46$)		TD (95% CI)[a]
	Mean Baseline	Mean Change From Baseline	Mean Baseline	Mean Change From Baseline	
ABC irritability subscale	30.8	−5.0	29.6	−12.9	−7.9 (−11.7 to −4.1)[b]
ABC hyperactivity subscale	34.7	−2.8	34.1	−12.7	−9.9 (−13.8 to −5.9)[b]
ABC stereotypy subscale	10.7	−2.0	11.9	−4.8	−2.9 (−4.5 to −1.2)[b]
ABC inappropriate speech subscale	7.0	−0.4	7.0	−2.5	−2.0 (−3.1 to −1.0)[b]
ABC lethargy/social withdrawal subscale	18.1	−6.2	19.9	−7.9	−1.7 (−4.8 to 1.3)
CGI-S[c]	4.8	−0.4	4.9	−1.2	−0.8 (−1.2 to −0.4)[b]
CY-BOCS (compulsions only)[d]	13.7	−0.8	12.8	−3.8	−3.0 (−4.3 to −1.6)[b]

CY-BOCS indicates Children's Yale–Brown Obsessive Compulsive Scale.

[a] Difference in adjusted treatment mean changes: aripiprazole-placebo ($df = 75$ for the ABC subscales; $df = 60$ for the CGI-S; and $df = 67$ for the CY-BOCS).

[b] $P < .001$ versus placebo.

[c] Placebo: $n = 40$; aripiprazole: $n = 40$.

[d] Placebo: $n = 44$; aripiprazole: $n = 43$

TABLE 3 Treatment-Emergent AEs

AE	Placebo ($N = 50$), n (%)	Aripiprazole ($N = 47$), n (%)
Occurring in ≥5% of any group		
Any AE	36 (72.0)	43 (91.5)
Headache	8 (16.0)	3 (6.4)
Somnolence	2 (4.0)	8 (17.0)
Sedation	1 (2.0)	5 (10.6)
Drooling	0 (0.0)	4 (8.5)
Tremor	0 (0.0)	4 (8.5)
Diarrhea	5 (10.0)	4 (8.5)
Vomiting	2 (4.0)	7 (14.9)
Insomnia	4 (8.0)	3 (6.4)
Aggression	4 (8.0)	1 (2.1)
Fatigue	2 (4.0)	10 (21.3)
Pyrexia	1 (2.0)	4 (8.5)
Upper respiratory tract infection	5 (10.0)	1 (2.1)
Nasopharyngitis	3 (6.0)	2 (4.3)
Nasal congestion	1 (2.0)	3 (6.4)
Increased appetite	5 (10.0)	7 (14.9)
Enuresis	4 (8.0)	3 (6.4)
EPSs		
Any EPS event[a]	4 (8.0)	7 (14.9)
Tremor	0 (0.0)	4 (8.5)
Extrapyramidal disorder	0 (0.0)	1 (2.1)
Muscle rigidity	0 (0.0)	1 (1.2)
Muscle spasms	1 (2.0)	0 (0.0)
Akathisia	1 (2.0)	0 (0.0)
Psychomotor hyperactivity	2 (4.0)	1 (2.1)
Hypokinesia	0 (0.0)	1 (2.1)
Hyperkinesia	1 (2.0)	0 (0.0)

[a] Patients with multiple EPS events were counted only once toward the total.

continuation from placebo treatment included 1 case of mania, negativism, and psychomotor hyperactivity; 1 case of aggression, hyperkinesia, impulsive behavior, and irritability; and 1 case of insomnia. Reasons for discontinuation from aripiprazole treatment included 1 case of fatigue, 1 case of vomiting, 1 case of weight and appetite increase, 1 case of intentional self-injury, and 1 case of psychomotor hyperactivity and aggression. Suicide-related AEs were reported by 3 patients in the placebo group (2 reports of self-injurious behavior and 1 report of self-injurious ideation, all judged as moderate in intensity and possibly/probably related to study treatment) and 1 patient in the aripiprazole group (intentional self-injury, mild in intensity and not related to study treatment).

EPS AEs are shown in Table 3. Of the 8 EPS events reported with aripiprazole treatment, 3 were reported as possibly related to study treatment, 4 were reported as probably related to study treatment, and 1 was reported as certainly related to study treatment. No placebo-treated patients received concomitant medication for the potential treatment of EPS; 1 aripiprazole-treated patient received benztropine. During treatment, minimal mean changes from baseline were seen at end point (LOCF) on the Simpson-Angus Scale (placebo: −0.5; aripiprazole: −0.6; $P = .763$), Abnormal Involuntary Movement Scale (placebo: −0.5; aripiprazole: −1.1; $P = .115$), and Barnes Akathisia Rating Scale (placebo: −0.1; aripiprazole: −0.1; $P = .699$).

Mean serum prolactin levels at baseline were 6.8 ng/mL for placebo and 9.8 ng/mL for aripiprazole. Aripiprazole was associated with a significant decrease in serum prolactin levels compared with placebo at end point (−6.3 vs 1.6 ng/mL; $P < .001$). Three (6.8%) patients in the placebo group and 1 (2.4%) patient in the aripiprazole group experienced potentially clinically relevant prolactin elevation.

Aripiprazole treatment was associated with significantly greater mean weight change compared with placebo at end point (LOCF: 2.0 vs 0.8 kg [$P < .005$]; observed case: 1.9 vs 0.5 kg [$P < .01$]). Aripiprazole was also associated with a greater incidence of clinically significant weight gain (≥7% increase from baseline) than placebo (LOCF: 28.9% vs 6.1%; $P < .01$). Numerically greater changes in BMI were observed in the aripiprazole group than in the placebo group, although these changes were

statistically significant only in the observed case analysis (0.7 vs 0.1 kg/m^2; $P < .05$) and not the LOCF analysis (0.7 kg/m^2 for aripiprazole and 0.3 kg/m^2 for placebo; $P = .07$). One patient on aripiprazole discontinued because of weight gain.

After treatment, the incidence of patients with fasting triglycerides ≥120 mg/dL (girls) and ≥160 mg/dL (boys) was similar between aripiprazole and placebo (13.6% vs 10.0%). One patient in the aripiprazole group experienced fasting low-density lipoprotein level ≥160 mg/dL and fasting total cholesterol values ≥240 mg/dL; no patients in the placebo group experienced increases above these values. Fasting high-density lipoprotein values ≤30 mg/dL were experienced by 1 patient in the placebo group only. No patients experienced fasting serum glucose values ≥115 mg/dL. There were no statistically significant differences (all $P > .05$) in the median change from baseline to end point for fasting triglycerides, low-density lipoprotein, total cholesterol, high-density lipoprotein, or serum glucose levels.

No patient discontinued from the study as a result of an ECG abnormality, and there was no pattern of vital sign abnormalities in the 2 treatment groups. The mean change in QT_{cF} interval from baseline to end point was similar between aripiprazole (LOCF: 0.6 milliseconds; mean baseline: 377.6 milliseconds) and placebo (4.5 milliseconds; mean baseline: 376.3 milliseconds; $P = .381$). No patient had a QT_{cF} >450 milliseconds. Similar mean changes from baseline to end point were observed using the Bazett's correction (QT_{cB}). Although 3 aripiprazole-treated patients experienced a QT_{cB} interval >450 milliseconds, all 3 had heart rates >100 beats per minute (QT_{cB} may overcorrect for heart rate >60) and all 3 had a QT_{cF} <440 milliseconds.

DISCUSSION

This 8-week, randomized, multicenter, double-blind, placebo-controlled study demonstrated that flexibly dosed aripiprazole was effective in reducing irritability in children and adolescents who had autistic disorder and were manifesting a variety of irritable behaviors, such as tantrums, aggression, and self-injurious behavior. Aripiprazole was significantly more efficacious than placebo at treating irritability, as measured on the caregiver-rated ABC irritability subscale, as early as week 1, when patients were on 2 mg, with continued improvement through week 8. Aripiprazole also produced significant improvements over placebo on the key secondary efficacy measure, the clinician-rated CGI-I score from week 1 through week 8. In addition, there were significantly more responders in the aripiprazole group than in the placebo group (52.2% vs 14.3%; $P < .001$). Although there was a statistically significant reduction in symptoms of irritability (as measured by the ABC irritability subscale) that was also clinically significant (as measured by the CGI-I), it is important to note that at end point, clinically significant residual symptoms may still persist for some patients, because the mean ABC irritability subscale at end point was only slightly lower than the minimum entrance criteria. The positive results for aripiprazole on the ABC hyperactivity, stereotypy, and inappropriate speech subscales suggest additional beneficial effects of aripiprazole in this population, although it should be cautioned that these subscales do not fully capture the core symptom domains seen in autistic disorder. Aripiprazole also produced greater improvement than placebo in measures of quality of life at week 8, as measured on the PedsQL and CGSQ scales.

Aripiprazole was generally well tolerated; discontinuations as a result of AEs were low, and no patients experienced serious AEs. Fatigue and somnolence were the most commonly reported AEs, although rarely of severity that led to discontinuation. Few aripiprazole-treated patients experienced EPS-related AEs; only 1 aripiprazole-treated patient required concomitant medication for the treatment of EPS. Weight gain was observed with aripiprazole treatment in this study; clinicians who treat children and adolescents with aripiprazole should be aware of the potential for weight gain and monitor weight change and provide appropriate advice when necessary. The decrease in serum prolactin levels with aripiprazole treatment reported here has been observed previously,[10] although the clinical consequences are unknown.

The findings of this study are strengthened by the use of both a parent/caregiver-based rating (ABC irritability subscale) and a clinician-based rating (CGI-I scale), both of which demonstrated consistent improvements. This study's titration strategy provides an appropriate treatment approach for the use of aripiprazole in this population. During the last full week of the study, the majority of patients were receiving either 5 mg/day or 10 mg/day, suggesting that dosing at 15 mg/day is not required for all patients.

Conclusions regarding the relative benefits of aripiprazole compared with other antipsychotic agents in this population cannot be drawn from the findings of this study; additional studies that include active comparator treatment arms would be required. There are several limitations to this study. The study included only patients with irritability associated with autistic disorder; generalizability of these results to irritability associated with other pervasive developmental disorders is unknown. The relatively short study duration limits conclusions as to the longer-term efficacy or safety in this population, and additional evaluation

of the effects of aripiprazole on metabolic parameters is warranted. Longer-term studies are under way. Furthermore, the flexible-dosing paradigm cannot accurately identify a minimally effective dosage or a maximally tolerated dosage.

CONCLUSIONS

During an 8-week period, aripiprazole was efficacious and generally well tolerated in the treatment of irritability associated with autistic disorder in children and adolescents who may be experiencing tantrums, aggression, self-injurious behavior, or a combination of these symptoms. Additional long-term controlled trials to evaluate the efficacy and safety of aripiprazole in this population may be warranted, along with studies to compare aripiprazole with other agents.

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Aripiprazole in the Treatment of Irritability in Children and Adolescents With Autistic Disorder

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