Safety and Tolerability of Aripiprazole for Irritability in Pediatric Patients With Autistic Disorder: A 52-Week, Open-Label, Multicenter Study

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ABSTRACT

Objective: Evaluate the long-term safety and tolerability of aripiprazole in the treatment of irritability in pediatric subjects (6–17 years) with autistic disorder.

Method: A 52-week, open-label, flexibly dosed (2–15 mg/d) study of the safety and tolerability of aripiprazole in outpatients with a *DSM-IV-TR* diagnosis of autistic disorder who either had completed 1 of 2 antecedent, 8-week randomized trials or were enrolled de novo (ie, not treated in the randomized trials). Safety and tolerability measures included incidences of adverse events, extrapyramidal symptoms, weight, metabolic measures, vital signs, and other clinical assessments.

Results: Subjects were enrolled between September 2006 and June 2009. Three hundred thirty subjects entered the treatment phase: 86 de novo, 174 prior aripiprazole, and 70 prior placebo. A total of 199 (60.3%) subjects completed 52 weeks of treatment. Adverse events were experienced by 286/330 subjects (86.7%). Common adverse events included weight increase, vomiting, nasopharyngitis, increased appetite, pyrexia, upper respiratory tract infection, and insomnia. Discontinuations due to adverse events occurred in 35/330 randomized subjects (10.6%)—most commonly aggression and weight increase. One patient discontinued from the study due to a laboratory-related adverse event (moderately increased alanine transaminase and aspartate transaminase). Nine subjects experienced serious adverse events—most frequently aggression. Extrapyramidal symptoms–related adverse events occurred in 48/330 subjects (14.5%)—most commonly tremor (3.0%), psychomotor hyperactivity (2.7%), akathisia (2.4%), and dyskinesia (not tardive, 2.4%). At > 9 months' aripiprazole exposure (n = 220), mean change in body weight *z* score was 0.33 and body mass index *z* score was 0.31. The percentages of subjects with clinically significant fasting metabolic abnormalities at > 9 months were 2% for glucose, 5% for total cholesterol, 7% for low-density lipoprotein cholesterol, 30% for high-density lipoprotein cholesterol, and 5% for triglycerides.

Conclusions: Aripiprazole was generally safe and well tolerated in the long-term treatment of irritability associated with autistic disorder in pediatric subjects. Weight should be proactively monitored during long-term treatment.

Trial Registration: clinical trials.gov Identifier: NCT00365859

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Autistic disorder is characterized by impaired social interaction and communication, as well as restricted, repetitive, and stereotyped patterns of behaviors, activities, or interests.[1] Additionally, behavioral problems such as aggression toward others, deliberate self-injuriousness, temper tantrums, and quickly changing moods, may be present.[2] These problems not only can be detrimental to the affected individual's social interaction and communication but also can have a significant impact on the individual and his or her family's quality of life.[2]

Treatment of secondary behavioral symptoms may involve a combination of behavioral and pharmacologic approaches, including the use of atypical antipsychotics.[3] Risperidone and aripiprazole are approved by the US Food and Drug Administration for the treatment of pediatric patients with irritability associated with autistic disorder, including symptoms of aggression toward others, deliberate self-injuriousness, temper tantrums, and quickly changing moods.[4,5] Recently, results from two 8-week, multicenter, randomized, double-blind, placebo-controlled studies have demonstrated that the atypical antipsychotic aripiprazole is efficacious and generally safe and well tolerated for the treatment of pediatric patients aged 6–17 years with irritability associated with autistic disorder.[6,9]

Although the short-term trials provided important safety and tolerability information regarding aripiprazole in this subject population, there is a need for additional long-term safety data.[7] The primary aim of this study was to assess the longer-term safety and tolerability of aripiprazole in the treatment of irritability associated with autistic disorder. Results relating to long-term efficacy are reported elsewhere.[8]

METHOD

Study Design and Subjects

A 52-week, open-label study was conducted at 53 centers in the United States (clinicaltrials.gov identifier: NCT00365859). Subjects were enrolled between September 2006 and June 2009. Subjects who had previously completed 1 of the 2 antecedent 8-week double-blind, randomized, placebo-controlled studies[6,9] were eligible for inclusion, as were de novo subjects who had not participated in the prior 8-week studies.

Subjects were eligible for inclusion to the original, placebo-controlled studies if they met the following entry criteria: aged 6–17 years, inclusive, at the time of enrollment; a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*) diagnosis of autistic disorder,[1] which was also confirmed using the Autism Diagnostic Interview-Revised (ADI-R)[10]; the presence of serious behavioral problems,

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specifically irritability, agitation, self-injurious behavior, or a combination of these; a mental age of ≥ 18 months; and a Clinical Global Impressions-Severity of Illness scale (CGI-S) score of ≥ 4 and an Aberrant Behavior Checklist irritability subscale (ABC-I)[11] score ≥ 18 at screening and baseline. De novo subjects had to demonstrate current behavioral problems or were required to have a history of behavioral problems that were currently being treated with psychotropic medication; there was no requirement of a minimum ABC-I or CGI-S score. Nonpharmacologic therapy (such as behavior modification) was required to be stable before screening and consistent throughout the study.

The study was conducted in compliance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. Institutional review board/independent ethics committee approval was received at each site prior to study initiation. All parents/guardians provided written informed consent to participate, and subjects provided written, informed assent when possible.

Dosing

All subjects started therapy with aripiprazole at 2 mg/d, with a target daily dose of 5, 10, or 15 mg/d. Dose increases occurred no more frequently than every 4 days, and dosage could be adjusted downward based on tolerability. All subjects who had received placebo in the antecedent study were switched to aripiprazole during the current study, and all subjects who had previously received aripiprazole had their dose retitrated, starting at 2 mg/d.

A washout period was required for de novo subjects receiving concomitant medications. Long-acting (depot) neuroleptics, clonidine, guanfacine, guanabenz, carbamazepine, and other antipsychotics were prohibited. Use of all other psychotropic and nonpsychotropic medications was permitted unless there was a potential safety risk or a subject had the potential for an adverse drug interaction with aripiprazole. Anticholinergic therapy was washed out for a minimum of 4 days prior to the interim screening visit.

Assessments

Subjects had study visits at the end of weeks 1, 2, and 4 (± 2 days from the baseline visit) and at the end of weeks 8, 14, 20, 26, 34, 42, and 52 (± 7 days from the end of baseline visit). Monitoring for adverse events, serious adverse events, vital signs, weight, and height were performed at each visit. Clinical laboratory evaluations were conducted during screening visits and at weeks 8, 26, and 52. Electrocardiograms were conducted during screening and at weeks 8, 26, and 52. Vital signs were designated as being potentially clinically significant using a predefined criterion value or a change from baseline. Clinicians also assessed extrapyramidal symptoms–related adverse events at each study visit. Severity of extrapyramidal symptoms was assessed using the Simpson-Angus Scale (SAS),[12] the Barnes Akathisia Rating Scale (BARS),[13] and the Abnormal Involuntary Movement Scale (AIMS)[14] at baseline and weeks 8, 26, and 52.

Clinical Points

- For chronic conditions such as irritability associated with autistic disorder, a need exists for long-term safety data to help inform clinical decision making.
- Aripiprazole was generally well tolerated in this 1-year study, although it is important to be aware of the potential for weight gain in some patients.

Statistical Analysis

Subjects were categorized into 3 groups: (1) subjects from the antecedent placebo-controlled trials who had received aripiprazole (prior aripiprazole), (2) subjects from the antecedent placebo-controlled trials who had received placebo (prior placebo), and (3) de novo subjects who had not been enrolled in the placebo-controlled studies.

For prior aripiprazole subjects, for the parameters of demographics, disposition, and adverse events, baseline was defined as the start of the open-label study. For the parameters of weight, *z* score, metabolic measures, and prolactin levels, baseline was defined using measurements from the start of the antecedent placebo-controlled trial (ie, prior to the first aripiprazole exposure; comprising part of the "total aripiprazole exposure" data set). For prior placebo and de novo subjects, baseline was defined using measurements from the start of the open-label study for all parameters (ie, prior to the first aripiprazole exposure).

Summary statistics for safety data are presented, including mean, standard deviation, median, and ranges for continuous variables and frequency and percentage frequency for categorical variables. For prior aripiprazole and placebo subjects, adverse events with onset during open-label treatment were included in the summary tables; adverse events with onset during double-blind treatment that continued into open-label treatment were not included. Rating scale scores are presented as mean change from baseline. No formal statistical testing was planned a priori.

Changes in weight, body mass index (BMI), and metabolic measures were analyzed using the "total aripiprazole exposure" data set, which used those values obtained prior to the first aripiprazole exposure as baseline. The percentage of subjects experiencing a shift in their percentile body weight category from baseline to the end of study was calculated using the observed cases data set using predefined body weight percentile categories.[15]

RESULTS

Subject Disposition and Demographics

Baseline demographic characteristics of subjects in the safety sample are shown in Table 1. The mean (standard error) time on study therapy for the entire population was 44.1 (1.2) weeks (prior aripiprazole subjects, 44.8 [1.7] weeks;

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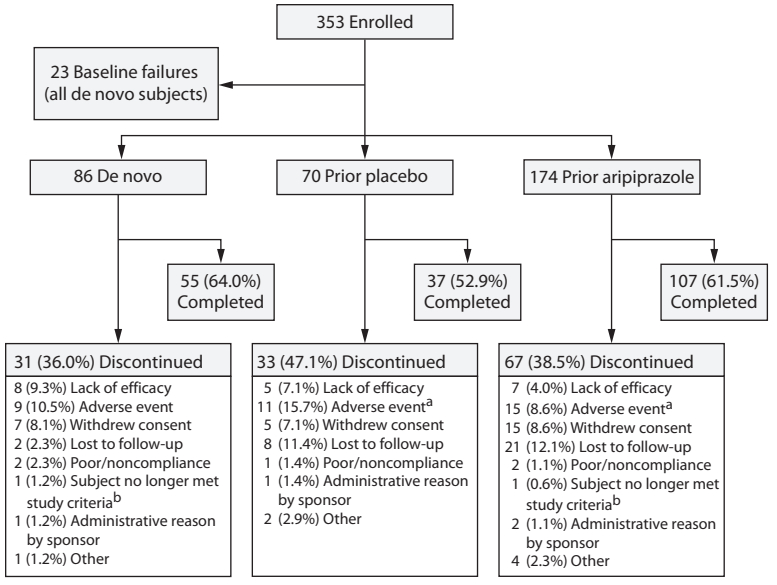
Table 1. Subject Demographic Characteristics at Baseline[a]

Characteristic	De Novo (n = 86)	Prior Placebo (n = 70)	Prior Aripiprazole (n = 174)	Total (n = 330)
Age, mean (SD), y	9.7 (3.1)	9.6 (3.0)	9.5 (3.0)	9.6 (3.0)
Age group, n (%), y				
6–12	69 (80.2)	56 (80.0)	138 (79.3)	263 (79.7)
13–17	17 (19.8)	14 (20.0)	36 (20.7)	67 (20.3)
Male subjects, n (%)	70 (81.4)	62 (88.6)	155 (89.1)	287 (87.0)
Race, n (%)				
White	65 (75.6)	53 (75.7)	117 (67.2)	235 (71.2)
Black/African American	14 (16.3)	12 (17.1)	44 (25.3)	70 (21.2)
Other	7 (8.1)	5 (7.1)	13 (7.5)	25 (7.6)
Weight, mean (SD), kg	42.2 (23.0)	44.8 (20.4)	45.3 (21.8)	44.4 (21.8)
Weight group < 40 kg, n (%)	54 (62.8)	36 (51.4)	93 (54.7)[b]	183 (56.1)
ABC-I score, mean (SD)	23.4 (9.0)	21.6 (9.8)	15.0 (9.1)	18.7 (10.0)
Prior CNS medication use, n (%)	67 (77.9)	31 (44.3)	93 (53.4)	191 (57.9)
Most commonly used prior CNS medications, n (%)				
Antipsychotics	28 (32.6)	16 (22.9)	37 (21.3)	81 (24.5)
Psychostimulants	29 (33.7)	8 (11.4)	22 (12.6)	59 (17.9)
Anxiolytics	16 (18.6)	13 (18.6)	29 (16.7)	58 (17.6)
Antidepressants	29 (33.7)	4 (5.7)	22 (12.6)	55 (16.7)

[a]For prior aripiprazole/placebo subjects, baseline measurements were derived from the original baseline assessments from either of the antecedent studies, except for the ABC-I. For de novo subjects, baseline measurements were derived during a visit at week 0.
[b]n = 170; baseline weight was missing for 4 subjects.
Abbreviations: ABC-I = Aberrant Behavior Checklist irritability subscale, CNS = central nervous system.

Figure 1. Subject Disposition, Enrolled Sample



[a]For 2 subjects from the antecedent studies, adverse events leading to discontinuation started prior to the start of open-label treatment.
[b]Reasons for no longer meeting study criteria included receiving prohibited concomitant medication (de novo subject) and request for subject to be given stimulant medication to treat attention (prior aripiprazole subject).

prior placebo subjects, 38.0 [2.4] weeks; de novo subjects, 43.3 [2.3] weeks).

Subject disposition is shown in Figure 1. Of the 330 subjects entering open-label treatment, 199 (60.3%) completed 52 weeks of treatment. All subjects who received at least 1 dose of study medication were included in the safety sample (n = 330).

Dosing

The mean daily dose of aripiprazole during the final week of treatment (week 52) for subjects who remained on treatment (n = 200) was 10.6 mg/d (range, 1.1–15.0). The mean daily dose of aripiprazole on the last day of dosing for all subjects, including those who discontinued prematurely, was 9.6 mg/d (range, 1.1–15.0). The proportion of subjects receiving each aripiprazole dose (0, 2, 5, 10, or 15 mg/d) in week 52 of the study in each dosing category was as follows: 0 mg/d, n = 1 (0.5%); 2 mg/d, n = 10 (5.0%); 5 mg/d, n = 35 (17.5%); 10 mg/d, n = 64 (32.0%); and 15 mg/d, n = 90 (45.0%).

Overall, 64.2% of subjects received concomitant central nervous system (CNS) medications during the study. The most commonly used central nervous system concomitant medications were analgesics and antipyretics (35.5%), anxiolytics (15.8%), psychostimulants (15.8%), and antidepressants (15.2%).

Adverse Events

Of the 330 subjects (from all subgroups) who were included in the safety sample, 286 (86.7%) experienced an adverse event. Adverse events occurring in ≥ 5% of subjects are presented in Table 2. Weight increase was the most frequently reported adverse event across all subgroups.

Thirty-three subjects (10.0%) in the safety sample (n = 330) discontinued due to an adverse event: 9 de novo subjects (10.5%), 10 prior placebo subjects (14.3%), and 14 prior aripiprazole subjects (8.0%). The most frequent adverse events leading to discontinuation in > 2% of subjects were aggression (2.1%) and weight increase (2.1%) in the overall population. Aggression (3.5%) in de novo subjects and aggression (2.9%) and weight increase (5.7%) in prior placebo subjects occurred at an incidence of > 2%. No adverse events leading to discontinuation occurred at a rate of > 2% in prior aripiprazole subjects.

Serious adverse events were reported in 9 subjects (2.7%): 3 de novo subjects (3.5%), 1 prior placebo subject (1.4%), and 5 prior aripiprazole subjects (2.9%). The most

Table 2. Treatment-Emergent Adverse Events[a] Occurring in ≥ 5% of Subjects in Any Subgroup, Safety Sample

Adverse Event, n (%)	De Novo (n = 86)	Prior Placebo (n = 70)	Prior Aripiprazole (n = 174)	Total (n = 330)
Weight increased	20 (23.3)	16 (22.9)	40 (23.0)	76 (23.0)
Vomiting	17 (19.8)	11 (15.7)	34 (19.5)	62 (18.8)
Nasopharyngitis	12 (14.0)	10 (14.3)	22 (12.6)	44 (13.3)
Increased appetite	16 (18.6)	8 (11.4)	19 (10.9)	43 (13.0)
Pyrexia	6 (7.0)	10 (14.3)	23 (13.2)	39 (11.8)
Upper respiratory tract infection	11 (12.8)	11 (15.7)	16 (9.2)	38 (11.5)
Insomnia	8 (9.3)	8 (11.4)	17 (9.8)	33 (10.0)
Headache	7 (8.1)	7 (10.0)	18 (10.3)	32 (9.7)
Cough	10 (11.6)	6 (8.6)	15 (8.6)	31 (9.4)
Diarrhea	7 (8.1)	8 (11.4)	15 (8.6)	30 (9.1)
Aggression	8 (9.3)	6 (8.6)	15 (8.6)	29 (8.8)
Sedation	8 (9.3)	10 (14.3)	9 (5.2)	27 (8.2)
Fatigue	7 (8.1)	7 (10.0)	9 (5.2)	23 (7.0)
Drooling	3 (3.5)	3 (4.3)	16 (9.2)	22 (6.7)
Agitation	8 (9.3)	2 (2.9)	11 (6.3)	21 (6.4)
Epistaxis	8 (9.3)	3 (4.3)	10 (5.7)	21 (6.4)
Ear infection	3 (3.5)	2 (2.9)	15 (8.6)	20 (6.1)
Nasal congestion	10 (11.6)	0	10 (5.7)	20 (6.1)
Sinusitis	7 (8.1)	2 (2.9)	10 (5.7)	19 (5.8)
Constipation	6 (7.0)	4 (5.7)	7 (4.0)	17 (5.2)
Irritability	4 (4.7)	1 (1.4)	10 (5.7)	15 (4.5)
Decreased appetite	6 (7.0)	2 (2.9)	7 (4.0)	15 (4.5)
Rash	5 (5.8)	3 (4.3)	7 (4.0)	15 (4.5)
Enuresis	5 (5.8)	4 (5.7)	6 (3.4)	15 (4.5)
Gastroenteritis viral	5 (5.8)	1 (1.4)	8 (4.6)	14 (4.2)
Anxiety	3 (3.5)	0	10 (5.7)	13 (3.9)
Somnolence	4 (4.7)	6 (8.6)	3 (1.7)	13 (3.9)
Lethargy	7 (8.1)	1 (1.4)	2 (1.1)	10 (3.0)
Nausea	3 (3.5)	4 (5.7)	2 (1.1)	9 (2.7)
Dyskinesia	5 (5.8)	0	3 (1.7)	8 (2.4)
Tic	0	6 (8.6)	2 (1.1)	8 (2.4)
Respiratory tract congestion	1 (1.2)	4 (5.7)	2 (1.1)	7 (2.1)
Vaginal infection[b]	1 (6.3)	0	1 (5.3)	2 (4.7)
Dysmenorrhea[b]	1 (6.3)	0	0	1 (2.3)

[a]Adverse events for prior aripiprazole and placebo subjects include all adverse events with onset during open-label treatment; adverse events with onset during double-blind treatment that continued into open-label treatment are not included.
[b]Adverse event rates have been adjusted for gender.

frequently reported serious adverse event was aggression (prior aripiprazole subjects, n = 1 [0.6%]; de novo subjects, n = 1 [1.2%]), whereas all other serious adverse events were reported by only 1 subject each. These included impulsive behavior, acute otitis media, pharyngotonsillitis, sinusitis, dysphagia, cholecystitis, cholelithiasis, and asthma in prior aripiprazole subjects; suicidal ideation and skin infection in de novo subjects; and 1 case of convulsion in a prior placebo subject. The convulsion occurred in a 6-year-old male subject, was considered by the investigator to be severe, and was possibly related to study drug. It led to drug discontinuation and resolved on the day of onset.

There was 1 report of suicidal ideation in a 13-year-old male subject from the de novo group, which resulted in hospitalization. Extreme family stresses, with the subject coping poorly, and aggressive behavior had been reported prior to hospital admission. This case was considered by the investigator to be most likely not related to study medication, but treatment was discontinued, and the serious adverse event resolved.

Of note, one 6-year-old male subject from the prior aripiprazole group experienced development of sparse, pigmented pubic hair at the base of the scrotum. Subsequent referral to a pediatric endocrinologist assessed the event as unrelated to study drug.

Body Weight and Metabolic Abnormalities

The mean change in body weight from baseline to end point (last observation carried forward [LOCF]) was 6.3 kg in the total population (n = 322; observed cases weight gain = 8.1 kg, [n = 178]). Following > 9 months' aripiprazole exposure (n = 220), the mean (SD) change in body weight *z* score was 0.33 (0.50), and the mean (SD) change in BMI *z* score was 0.31 (0.74). Of note, at baseline, 27.9% of subjects had a body weight in the > 95th percentile. Percentile body weight categorical shift data are presented in Table 3.

The proportion of subjects with a clinically relevant fasting metabolic abnormality and the median percentage change in metabolic parameters by time period are shown in Table 4. No subjects discontinued due to metabolic abnormalities, and increased triglycerides was the only metabolic abnormality reported as adverse event (n = 3; 0.9%). Four subjects (1.2%) received a blood glucose–lowering medication, and 19 subjects (5.8%) received a cholesterol and triglyceride reducer during the study.

Prolactin

Aripiprazole treatment was associated with a decrease in serum prolactin. At baseline, mean serum prolactin was 7.4 ng/mL and the mean change in prolactin levels was –5.6, –5.4, –6.0, and –6.3 ng/mL following total exposure times of ≤ 3 months, 3–6 months, 6–9 months, and > 9 months, respectively.

Assessment of Extrapyramidal Symptoms

Extrapyramidal symptoms–related adverse events occurred in 48 of the 330 subjects (14.5%) included in this study. The most frequently reported extrapyramidal symptoms–related adverse events (> 2% of subjects) were tremor (3.0%), psychomotor hyperactivity (2.7%), akathisia (2.4%), and dyskinesia (2.4%). There were no reports of tardive dyskinesia. Extrapyramidal symptoms–related adverse events leading to discontinuation included extrapyramidal disorder (n = 2) and 1 case each of akathisia, masked facies, psychomotor hyperactivity, and tremor. Concomitant medications for the potential treatment of extrapyramidal symptoms included anticholinergic agent, 3.9%; β-blocking agent, 0.9%; and dopaminergic agent, 0.3%. The mean AIMS, SAS, and BARS baseline scores for the total population were 0.6, 10.8, and 0.2, respectively, and the mean change values from baseline to end point (LOCF) were –0.3, –0.0, and 0.0, respectively.

Other Safety Measurements

No subjects discontinued from the study because of an electrocardiogram or vital sign abnormality; however, 1 aripiprazole subject discontinued the study due to blood

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Table 3. Shift From Baseline to End Point (observed cases) in Percentile Distribution of Body Weight: Total Aripiprazole Exposure Data, Safety Sample[a]

End Point Percentile Category (observed cases)	Baseline Percentile Category, n (%)							
	≤5	5–10	10–25	25–50	50–75	75–90	90–95	>95
≤5	5 (62.5)	1 (25.0)	1 (5.0)	1 (6.7)	0	0	0	0
5–10	0	0	0	0	0	0	0	0
10–25	3 (37.5)	1 (25.0)	7 (35.0)	1 (6.7)	0	0	0	0
25–50	0	2 (50.0)	8 (40.0)	3 (20.0)	3 (7.5)	0	0	0
50–75	0	0	4 (20.0)	6 (40.0)	16 (40.0)	4 (12.5)	0	0
75–90	0	0	0	4 (26.7)	14 (35.0)	12 (37.5)	2 (20.0)	1 (2.0)
90–95	0	0	0	0	4 (10.0)	6 (18.8)	1 (10.0)	2 (4.1)
>95	0	0	0	0	3 (7.5)	10 (31.3)	7 (70.0)	46 (93.9)

[a]Body weight percentile categories: ≤5th percentile, 5th–10th percentile, 10th–25th percentile, 25th–50th percentile, 50th–75th percentile, 75th–90th percentile, 90th–95th percentile, >95th percentile.[14]

Table 4. Fasting Metabolic Laboratory Abnormalities by Time Period: Total Aripiprazole Exposure Data, Safety Sample

Laboratory test	Criteria	≤3 mo[a]	3–6 mo	6–9 mo	>9 mo
Subjects with potentially clinically significant laboratory abnormalities, n/n (%)					
Serum glucose	≥115 mg/dL	3/189 (1.6)	1/106 (0.9)	2/141 (1.4)	3/154 (1.9)
HDL cholesterol	<40 mg/dL	25/188 (13.3)	23/106 (21.7)	31/141 (22.0)	46/153 (30.1)
LDL cholesterol	≥130 mg/dL	9/188 (4.8)	6/105 (5.7)	9/141 (6.4)	10/153 (6.5)
Total cholesterol	≥200 mg/dL	14/188 (7.4)	6/107 (5.6)	8/141 (5.7)	8/153 (5.2)
Triglycerides	≥200 mg/dL	6/188 (3.2)	7/106 (6.6)	7/141 (5.0)	7/153 (4.6)

	Baseline[b]			Median Percent Change		Median Percent Change		Median Percent Change
	n	Median	n		n		n		n	
Change from baseline in fasting metabolic laboratory measurements[c]										
Serum glucose, mg/dL	188	88.0	156	1.6	89	0.0	121	0.0	119	2.1
HDL cholesterol, mg/dL	187	51.0	154	0.0	88	−2.1	120	−2.7	118	−4.1
LDL cholesterol, mg/dL	187	87.0	154	−1.8	87	−6.8	120	−2.1	118	−4.5
Total cholesterol, mg/dL	188	154.0	155	0	90	−3.3	121	−1.9	119	−3.4
Triglycerides, mg/dL	188	66.5	155	5.3	89	2.6	121	2.0	119	2.4

[a]For prior aripiprazole subjects, time point ≤3 months includes an additional 8 weeks of aripiprazole therapy.
[b]For metabolic laboratory abnormalities, baseline for prior aripiprazole/placebo subjects was defined using measurements from the start of the antecedent placebo-controlled trial (ie, prior to the first aripiprazole exposure; comprising part of the "total aripiprazole exposure" data set).
[c]In order to be included in the period evaluation, patients must have had a baseline measurement and at least 1 laboratory measurement within the time period that was assessed within 30 days of the last known day of study medication.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

chemistry abnormalities, increased aspartate transaminase levels (≥3 × upper limits of normal), as well as elevated alanine transaminase levels (≥3 × upper limits of normal).

There were few potentially clinically relevant electrocardiogram abnormalities with aripiprazole treatment, and no single electrocardiogram abnormality occurred in >2% of subjects across all time points during the study. One de novo subject had a clinically relevant Fredericia-corrected QT abnormality (479 milliseconds on day 57). A clinically relevant increase and decrease in sitting systolic blood pressure was observed in 10/94 (10.6%) and 32/94 (34.0%) subjects, respectively, while a clinically relevant increase and decrease in sitting diastolic blood pressure was observed in 5/94 (5.3%) and 31/94 (33.0%) subjects, respectively. A clinically relevant increase in sitting heart rate (beats per minute) was seen in 2/93 subjects (2.2%); no clinically relevant decreases were observed. A clinically relevant Bazett-corrected QT interval (milliseconds) abnormality was observed in 3/300 subjects (1.0%). Potentially clinically relevant laboratory abnormalities at any time point included abnormal hematocrit, which was found in 0.7% of subjects; hemoglobin (g/dL), 1.7%; leukocytes ($\times 10^3/\mu L$), 1.7%; platelet count ($\times 10^9/L$), 0.3%; eosinophils (relative percent), 1.3%; and neutrophils (relative percent), 0.3%. Creatine kinase–level elevation was the only potentially clinically relevant blood chemistry abnormality observed in >5% of subjects in any 1 subgroup; this abnormality was seen in 6.0% of prior placebo subjects.

DISCUSSION

Atypical antipsychotics are used to treat some of the behavioral symptoms associated with autistic disorder in pediatric patients, yet there is a need for additional data on the long-term safety and tolerability of specific agents. This study investigated the safety and tolerability of aripiprazole for the longer-term treatment of irritability, manifested as aggression toward others, deliberate self-injuriousness, temper tantrums, and quickly changing moods, in children and

adolescents aged 6–17 years with autistic disorder. In this study, aripiprazole was generally well tolerated. As would be expected, the rate of discontinuation due to adverse events was lower in subjects from the prior aripiprazole group, as they had previously received treatment with aripiprazole for 8 weeks and were retitrated to aripiprazole at the start of open-label treatment. The most common adverse events for the group overall were weight increase, vomiting, nasopharyngitis, increased appetite, pyrexia, upper respiratory tract infection, and insomnia. Aggression was reported in 9% of subjects, although it is important to note that this is also a component of the symptoms of irritability for which the subjects were receiving treatment.

Weight gain was the most commonly reported adverse event in this study and, after at least 9 months of exposure to aripiprazole, subjects' mean weight *z* scores increased by approximately 0.3 standard deviations, as did BMI *z* scores, indicating that weight is an important parameter to monitor in this population. Many subjects also demonstrated a shift to a higher weight percentile category; however, increased weight gain and BMI appear to plateau over time in patients who continued treatment. It is interesting to note that nearly one-third of subjects had a body weight above the 95th percentile for their age at baseline, suggesting that this population is already at risk of being overweight. All pediatric patients receiving treatment with atypical antipsychotics should be monitored for weight gain, and this should be proactively managed if it occurs.[16] Further analysis is warranted to determine if pediatric patients who gain weight are at an elevated risk for metabolic problems, although it should be noted that 30% of subjects experienced a potentially clinically significant decrease in high-density lipoprotein cholesterol levels.

During this long-term study, 48/330 subjects (14.5%) experienced extrapyramidal symptoms–related adverse events, and 15 subjects received concomitant medications for the treatment of extrapyramidal symptoms–related adverse events. However, only 6 subjects discontinued treatment due to extrapyramidal symptoms–related adverse events, indicating that although these symptoms can occur with some frequency, they are generally tolerable or manageable.

Decreases in serum prolactin levels with aripiprazole treatment have previously been observed during short-term treatment with aripiprazole in this population,[6,9] and as in these short-term studies, longer-term aripiprazole treatment was also associated with an overall mean decrease in serum prolactin levels. Although the clinical consequences of increased prolactin levels have been documented,[17] the clinical consequences of decreased serum prolactin levels are unknown.

Electrocardiogram abnormalities were infrequent with aripiprazole therapy and there were no discontinuations due to electrocardiogram-related adverse events. There was no overall pattern of hematologic abnormalities with aripiprazole treatment. In terms of other laboratory findings, however, it should be noted that 1 subject did discontinue the study due to increased aspartate transaminase/alanine transaminase levels.

The findings of this study are noteworthy due to the large overall subject population who remained on aripiprazole for up to 1 year. However, one of the limitations of the study is its open-label study design. It should also be taken into account that this study included only subjects with irritability associated with autistic disorder, and the generalizability of these results to irritability in the context of other disorders cannot be determined from this study. Furthermore, all subjects were retitrated to aripiprazole at entry into open-label treatment, and this treatment decision may have had an impact on adverse events for subjects who were previously receiving a stable dose of aripiprazole during the antecedent studies—the impact of this was not evaluated. It should also be considered that 64% of subjects received concomitant central nervous system medications at some point during the study, and the contribution of these medications to the safety parameters reported is unknown. Conclusions regarding the relative safety and tolerability of aripiprazole compared with other antipsychotics in this population cannot be drawn from the data generated in this study.

In conclusion, aripiprazole was generally well tolerated in the treatment of irritability and associated with autistic disorder in pediatric patients over 52 weeks of treatment. Weight gain is a common adverse event to consider during the long-term use of aripiprazole in this population. In agreement with consensus guidelines, all patients receiving atypical antipsychotics should undergo routine monitoring of weight, waist circumference, blood pressure, fasting plasma glucose level, and fasting lipid profile.[18]

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), clonidine (Catapres, Duraclon, and others), guanfacine (Intuniv, Tenex, and others), risperidone (Risperdal and others).

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