An Open-Label Study of the Efficacy and Tolerability of Aripiprazole for Children and Adolescents With Tic Disorders

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Objectives: This study aimed to investigate the efficacy and tolerability of aripiprazole, an atypical antipsychotic with dual agonist and antagonist actions toward dopaminergic imbalance and partial serotonin-2A receptor antagonism, for treating children and adolescents with tic disorders.

Method: Twenty-four outpatients aged 7 to 18 years with DSM-IV–diagnosed tic disorders were treated with aripiprazole using an open-label, flexible dosing schedule for 8 weeks from January 2005 to August 2006. The Korean versions of the Yale Global Tic Severity Scale (YGTSS), the Clinical Global Impressions-Improvement scale (CGI-I), and the CGI-Severity of Illness scale (CGI-S) scores were used to measure the drug efficacy. Side effects were assessed using an adverse effect checklist, the Extrapyramidal Symptom Rating Scale, height and weight measurements, laboratory tests, and electrocardiograms.

Results: Aripiprazole was prematurely discontinued in 6 (25%) of the 24 subjects due to intolerable adverse effects. After a mean of 9.8 ± 4.8 mg/day of aripiprazole for 8 weeks, there was a 52.8% reduction in the mean YGTSS Total Tic scores (from 26.7 ± 5.5 to 12.6 ± 7.6, $p < .001$). Nineteen patients (79.2%) showed either much improved or very much improved status according to the CGI-I. The CGI-S score was also reduced (from 5.5 ± 0.5 to 3.0 ± 1.4, $p < .001$). The initial dose of 5 mg/day aripiprazole for 2 weeks was also found to reduce tic symptoms significantly (Total Tic scores decreased from 26.7 ± 5.5 to 17.9 ± 8.7, $p < .001$). Fourteen subjects (58.3%) experienced unwanted side effects, the most common being hypersomnia (37.5%), nausea (20.8%), and headache (16.6%).

Conclusion: This open-label study suggests that aripiprazole is an efficacious and safe treatment for children and adolescents with tic disorders.

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Tics are defined as sudden, fast, repetitive, nonrhythmical, involuntary or semivoluntary, meaningless, and stereotyped motor movements (motor tics) and/or phonic productions (phonic tics) that involve discrete muscle groups. They can be easily confused with normal coordinated movements or vocalizations.[1] Tics are frequently described in terms of their complexity. Complexity refers to how simple or involved a movement or sound is, ranging from a brief, meaningless, abrupt fragment (simple tics) to ones that are longer and more involved and that have seemingly more purpose (complex tics).[2] Although tics are rather frequent phenomena, known to occur in approximately 12% of school-aged children,[3] chronic motor tics and Tourette's disorder develop in only 2% to 5%[1] and less than 1% of children, respectively.[4]

Although the standard tic treatments haloperidol and pimozide are both effective in reducing tics, they cause diverse adverse effects such as sedation, cognitive blunting, and extrapyramidal symptoms (EPS).[5] In addition, rare, severe adverse events such as tardive dyskinesia or QT prolongation have been reported to be associated with these anti-tic medicines.[1] To minimize such side effects of traditional neuroleptics, the atypical antipsychotics have been prescribed for patients with tic disorders as alternatives. Clozapine was found to have a low efficacy,[6] and while olanzapine did appear to be effective at reducing symptoms in its open trials and case reports, its use has been limited due to considerable adverse effects such as weight gain and sedation.[7–9] Ziprasidone was superior to placebo in children with tic disorders,[10] and quetiapine was also effective for controlling tics with minimal side effects.[11–15] Risperidone is the most widely

and intensively investigated drug in terms of efficacy and tolerability for tic disorders. Risperidone has been found to be efficacious and safe in children with tic disorders in 2 open studies,[16,17] double-blind studies also involving pimozide[18] and clonidine,[19] and a placebo-controlled study.[20] However, weight gain was reported as a significant side effect.[18]

Besides atypical antipsychotics, α_2-agonists such as clonidine and guanfacine were also effective on reducing tic symptoms with rather fewer metabolic adverse effects.[1] Clonidine, however, had other problematic side effects such as sedation and orthostatic hypotension,[19] and guanfacine is not available in Korea.

Aripiprazole is another emerging candidate atypical antipsychotic for children with tic disorders because it appears to not only cause fewer metabolic side effects such as weight gain and diabetes relative to other atypical antipsychotics[21,22] but also have a unique pharmacodynamic profile related to tic symptoms,[23] that is, a full dopaminergic receptor affinity but limited intrinsic activity.[23] Several case reports have already revealed effective and tolerable use of aripiprazole in patients with Tourette's disorder.[24–28]

To our knowledge, it appears there have been no clinical studies investigating the efficacy and safety of aripiprazole in patients with tic disorders. The present study was an 8-week open trial of aripiprazole in children and adolescents with transient and chronic tic disorders, including Tourette's disorder.

METHOD

Subjects

Twenty-four subjects (mean ± SD age = 11.8 ± 3.8 years; 19 males and 5 females; mean ± SD total IQ = 108.0 ± 13.8) were recruited in an outpatient clinic at the Asan Medical Center, Seoul, Korea, from January 2005 to August 2006 (Table 1). After informed consent was obtained from each parent and child, subjects were screened for eligibility. The protocol was reviewed and approved by the local institutional review board. The inclusion criterion was a DSM-IV diagnosis of tic disorders according to the Korean version of the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (KSADS-PL)[29] and a Total Tic score ≥ 22 on the Korean version of the Yale Global Tic Severity Scale (YGTSS)[30,31] corresponding to at least moderate severity as ascertained by a child psychiatrist.

Subjects with evidence of current mood disorders, generalized anxiety disorder, separation anxiety disorder, or psychotic symptoms were excluded using the KSADS-PL. However, we did not exclude the subjects with comorbid obsessive-compulsive disorder, which is the most frequent comorbid anxiety disorder with tic disorders. Subjects with an IQ of 70 or less (assessed by the Korean Educational Development Institute Wechsler Intelligence Scale for Children-Revised [KEDI-WISC-R[32]]), previous or current seizure episode, or abnormalities in a current electroencephalogram (EEG) were also excluded. In addition, patients with a history of aripiprazole use were excluded. Subjects were required to be free from psychotropic medication for at least 2 weeks before study entry and free from any significant medical problems.

Procedure

Baseline assessment included routine laboratory tests (i.e., hematology and chemistry), electrocardiogram (ECG), resting pulse and blood pressure while sitting, height and weight measurements, medical history taking, and physical and neurologic examinations. A child psychiatrist initially prescribed 5.0 mg/day of aripiprazole, and then increased the dose in 5-mg/day increments as tolerated at visits every 2 weeks. The dose was reduced by 2.5 to 5.0 mg upon the emergence of unbearable adverse effects. The maximum allowable dose was 20 mg/day. This dose schedule was based on our previous anecdotal report.[28] We did not prescribe any drugs to control the comorbid psychiatric symptoms during the study period. The final evaluation was undertaken at 8 weeks after commencement of the medication treatment.

Measures

The YGTSS is a semistructured clinical interview designed to measure current tic severity.[31] The multidimensional scales of the YGTSS yield 3 summary scores: Total Motor (0–25), Total Phonic (0–25), and Total Tic (sum of motor and phonic). The YGTSS also contains a separate (0–50) Impairment scale, which assesses the global burden of function due to tics. The study aimed to evaluate the efficacy of aripiprazole for tics, hence the Total Tic score was used as the primary outcome measure since the Impairment scale can be influenced by other components of tic disorders. The YGTSS was administered at each visit.

The Clinical Global Impressions-Improvement scale (CGI-I)[33] and the CGI-Severity of Illness scale (CGI-S)[34] scores were used as the secondary outcome measures. In terms of the CGI-I scores, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. Scores of 1 or 2 are regarded as a positive response. The CGI-S consists of 7 scores indicating the level of symptom severity: 1 = normal, not ill; 2 = minimally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = extremely severely ill. These scores were also determined at every visit.

Adverse effects of aripiprazole were assessed using an adverse effect checklist, which covered common side effects of aripiprazole and general inquiries regarding any health issues, medical appointments, intercurrent illness or injury, and concomitant medications. The

Table 1. Descriptive Data and Medication Information for 24 Children and Adolescents With Tic Disorders

Variable	Value
Gender, male/female, N (%)	19 (79.2)/5 (20.8)
Age, mean ± SD (range), y	11.8 ± 3.8 (7–18)
Total IQ, mean ± SD	108.0 ± 13.8
Type of tic disorder, N	
Tourette's disorder	17
Chronic motor and vocal tic disorder	4
Transient tic disorder	3
Comorbidity, N	
Attention-deficit/hyperactivity disorder	7
Oppositional defiant disorder	2
Obsessive-compulsive disorder	3
Duration of tic disorders, mean ± SD, y	4.3 ± 2.8
Previous drug history for controlling tic symptoms, N	
Risperidone	8
Pimozide	1
Aripiprazole dose, mean ± SD (range), mg/d	9.8 ± 4.8 (2.5–20.0)
Duration of aripiprazole treatment, mean ± SD (range), d	49.3 ± 13.9 (14.0–60.0)

Extrapyramidal Symptom Rating Scale (ESRS) was also used, which rates the severity of parkinsonism, akathisia, dystonia, and dyskinesia.[35] Height and weight were also measured at every visit. Physical and neurologic examinations, laboratory tests, and ECGs were completed at the study endpoint.

All tests were administered and scored by a psychiatrist different from the investigator who prescribed the drug. This evaluator was blinded only to dose changes, not to the intervention.

Statistical Analyses

The analysis of variance (ANOVA) for repeated measures with the last observation carried forward method was used to identify changes in clinical variables from baseline to endpoint. Multivariate post hoc analyses for planned comparisons were performed to determine any changes due to the initial dose (from baseline to 2 weeks) or due to the medication for the subsequent 6 weeks (from 2 weeks to endpoint). Statistical significance for all analyses was set at $\alpha = .0125$ (by the Bonferroni correction on 4 variables: the mean of the Total Tic score, the Total Motor score, the Total Phonic score, and the CGI-S score) for 2-tailed tests using the SPSS software version 11.0 (SPSS, Inc., Chicago, Ill.).

RESULTS

Of the 24 study subjects, 17 (70.8%) had Tourette's disorder. Ten subjects (41.7%) had other comorbid psychiatric disorders, the most common being attention-deficit/hyperactivity disorder (29.2%). The mean duration of tic disorders was 4.3 ± 2.8 years, and 9 subjects (37.5%) had a history of anti-tic medication. The mean dose and duration of aripiprazole medication was 9.8 ± 4.8 mg/day and 49.3 ± 13.9 days, respectively (Table 1).

After 8 weeks of aripiprazole treatment, the Total Tic score was found to decrease by 52.8% (26.7 ± 5.5 vs. 12.6 ± 7.6; $F = 34.4$, $p < .001$). In addition, there was a 50.6% decrease in the Motor Tic score (16.4 ± 5.3 vs. 8.1 ± 5.7; $F = 23.4$, $p < .001$) and a 56.3% decrease in the Phonic Tic score (10.3 ± 6.5 vs. 4.5 ± 4.6; $F = 16.3$, $p < .001$). The CGI-I scores showed 19 subjects (79.1%) had improved much or very much. In addition, the CGI-S score was lowered by aripiprazole treatment (5.5 ± 0.5 vs. 3.0 ± 1.4; $F = 31.4$, $p < .001$) (Table 2).

The Total Tic scores decreased between baseline and week 2 (26.7 ± 5.5 vs. 17.9 ± 8.7, $p < .001$) and between week 2 and endpoint (17.9 ± 8.7 vs. 12.6 ± 7.6, $p < .001$) (Table 2) (Figure 1). The Motor Tic and Phonic Tic scores also decreased between baseline and week 2 (16.4 ± 5.3 vs. 11.5 ± 5.9, $p < .001$, and 10.3 ± 6.5 vs. 6.4 ± 5.5, $p = .001$, respectively) and between week 2 and endpoint (11.5 ± 5.9 vs. 8.1 ± 5.7, $p < .001$, and 6.4 ± 5.5 vs. 4.5 ± 4.6, $p = .008$, respectively). The CGI-S scores also decreased between baseline and week 2 (5.5 ± 0.5 vs. 4.0 ± 1.5, $p < .001$) and between week 2 and endpoint (4.0 ± 1.5 vs. 3.0 ± 1.4, $p < .001$) (Table 2).

Six subjects (25%) were unable to complete the study protocol due to intolerable adverse effects such as nausea (4 subjects), sedation (4 subjects), headache (2 subjects), dizziness (1 subject), akathisia (1 subject), EPS (1 subject), and vomiting (1 subject). Fourteen children and adolescents (58.3%) experienced 1 or more unwanted side effects, and 8 patients had transient and/or tolerable adverse effects. The most common side effects of aripiprazole were hypersomnia (37.5%), nausea (20.8%), headache (16.6%), EPS (8.3%), and akathisia (8.3%) (Table 3). The ESRS rating showed that parkinsonism was observed in 11 subjects and akathisia or dystonia in 1 subject each. No subjects were shown to have dyskinesia. These positive findings by the ESRS never resulted in significant discomfort to decrease or discontinue the drug. There were no significant changes in body weight, height, and laboratory test results or ECG findings.

Table 2. Efficacy of Aripiprazole in 24 Children and Adolescents With Tic Disorders

Characteristic	Baseline	Week 2	Baseline vs. Week 2 t	Baseline vs. Week 2 95% CI	Endpoint*	Week 2 vs. Endpoint t	Week 2 vs. Endpoint 95% CI
Yale Global Tic Severity Scale score, mean ± SD							
Motor	16.4 ± 5.3	11.5 ± 5.9	–5.52†	–6.8 to –3.1	8.1 ± 5.7	–3.38‡	–5.2 to –1.6
Phonic	10.3 ± 6.5	6.4 ± 5.5	–3.76§	–6.1 to –1.8	4.5 ± 4.6	–2.90¶	–3.2 to –0.5
Total Tic score	26.7 ± 5.5	17.9 ± 8.7	–6.04†	–11.9 to –5.8	12.6 ± 7.6	–4.32‡	–7.7 to –2.8
CGI-I rating, N (%)							
Very much improved	…	6 (25.0)			9 (37.5)		
Much improved	…	7 (29.2)			10 (41.7)		
Minimally improved	…	4 (16.7)			2 (8.3)		
No change	…	7 (29.2)			2 (8.3)		
Minimally worse	…	0			1 (4.2)		
Much worse	…	0			0		
Very much worse	…	0			0		
CGI-S score, mean ± SD	5.5 ± 0.5	4.0 ± 1.5†	–5.09	–2.1 to –0.9	3.0 ± 1.4‡	–4.08	–1.4 to –0.5
CGI-S rating, N (%)							
Normal, not ill	0	2 (8.3)			3 (12.5)		
Minimally ill	0	1 (4.2)			7 (29.2)		
Mildly ill	0	7 (29.2)			6 (25.0)		
Moderately ill	0	4 (16.7)			3 (12.5)		
Markedly ill	13 (54.2)	6 (25.0)			4 (16.7)		
Severely ill	11 (45.8)	4 (16.7)			1 (4.2)		
Extremely severely ill	0	0			0		

*Regarding dropout cases, the last-observation-carried-forward method was applied.
†$p < .001$, significant changes between baseline and week 2.
‡$p < .001$, significant changes between week 2 and endpoint.
§$p = .001$, significant changes between baseline and week 2.
¶$p = .008$, significant changes between week 2 and endpoint.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = CGI-Severity of Illness scale.
Symbol: … = not applicable.

DISCUSSION

To our knowledge, this is the first open-label study to examine the efficacy and tolerability of aripiprazole for the treatment of children and adolescents with tic disorders. This pilot study suggests that less than 10 mg/day of aripiprazole is efficacious for children and adolescents with tic disorders (Table 1). The dose is comparable to doses reported for treating children and adolescents with developmental disabilities[36,37] and is either higher[38] or lower than in children and adolescents with bipolar disorders,[39,40] depending on the study.

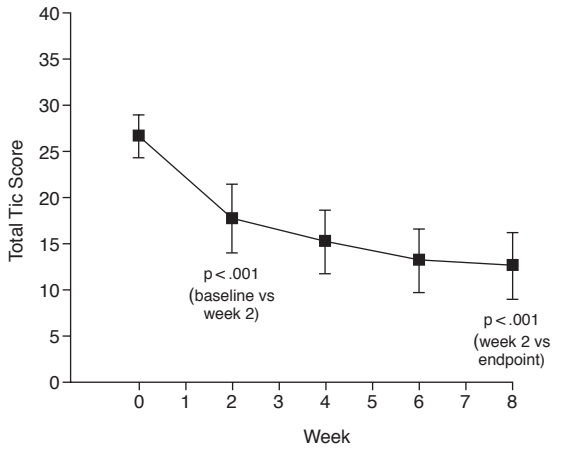
Although there is a tendency that the effect size in open-label studies is larger than that in double-blind studies, our result, a 53% reduction in tic symptoms, suggests a strong potency. Compared with typical antipsychotics such as haloperidol and pimozide, which can reduce tic symptoms by 65% and 60%, respectively,[41] atypical antipsychotics appear to have a lower potency for symptom reduction. For example, risperidone has been reported to reduce tic symptoms by 32% to 42%.[16,18,20] The present data indicating the strong potency of aripiprazole for tic disorders should be confirmed in head-to-head comparison studies using a well-controlled double-blind design.

Of particular note, the present study found that aripiprazole was efficacious at the initial dose of 5 mg and that 62.0% of the Total Tic score reduction was achieved within first 2 weeks of administration. Although there are no direct reports, the initial potency of the other atypical antipsychotics may be less than that of aripiprazole.[7,16,19,20]

While 75% of subjects were found to have good tolerance for aripiprazole in the current study, the adverse effects were similar to[38] or more common than in previous studies using aripiprazole to treat children and adolescents with bipolar disorders[40] or developmental disabilities[37] and compared with most studies in adult populations.[23] However, compared with the present side effect data for aripiprazole, the use of other atypical antipsychotics for tics has been reported to result in both greater[7,10] and fewer[7–9,13,16,19,20] side effects. One girl in the current study could not tolerate even 2.5 mg of aripiprazole due to serious hypersomnia and EPS. Adverse effect profiles of this drug should be reassessed in Korean children and adolescents.

Aripiprazole, unlike the second-generation antipsychotic predecessors with serotonin-2A (5-HT_{2A}) receptor antagonism and adequate blockade of dopamine-2 (D_2) receptors, is considered a partial dopaminergic agonist acting on both postsynaptic D_2 receptors and presynaptic autoreceptors. In addition, aripiprazole has a high receptor affinity for D_3 and 5-HT_{1A} receptors and a moderate affinity for D_4 receptors.[23] Partial agonism at the postsynaptic D_2 receptors results in a reduced tendency for receptor upregulation and EPS development. Partial agonism at the dopamine autoreceptor diminishes dopamine synthesis and release. These antagonistic and agonistic activities

Figure 1. Yale Global Tic Severity Scale Total Tic Score During Aripiprazole Treatment[a]



[a]Scores shown as mean (95% CI); observed cases only.

Table 3. Adverse Events (total N = 24)

Adverse Event	N (%)
Hypersomnia	9 (37.5)
Nausea	5 (20.8)
Headache	4 (16.7)
Extrapyramidal symptoms	2 (8.3)
Akathisia	2 (8.3)
Decreased volition	2 (8.3)
Dizziness	1 (4.2)
Myalgia	1 (4.2)
Dry mouth	1 (4.2)
Fatigue	1 (4.2)
Dyspepsia	1 (4.2)
Vomiting	1 (4.2)
Blurred vision	1 (4.2)
Insomnia	1 (4.2)
Hand tremor	1 (4.2)
Increased appetite	1 (4.2)
Loss of appetite	1 (4.2)
Polydipsia	1 (4.2)
Fear attack	1 (4.2)

of aripiprazole have been confirmed as depending on the presence of a hyperdopaminergic or hypodopaminergic environment, respectively.[23,42] Although presynaptic abnormality or dopamine receptor supersensitivity is assumed to underlie tic disorders,[43] the evidence is conflicting. Many studies supporting hyperdopaminergic abnormalities in Tourette's disorder have been conducted without consideration of the effects of dopamine antagonists.[44–46] Studies contemplating the drug effects on dopamine activity in patients with tic disorders have revealed somewhat inconsistent results,[47–49] with even the dopamine agonist pergolide found efficacious for tic reduction.[50,51] Therefore, dual actions of aripiprazole toward dopaminergic imbalance may be ideal for stabilizing both the decreased and increased activity at the postsynaptic and presynaptic dopamine sites.

The dopamine coordinating actions can also be related to and facilitated by the antagonistic action of aripiprazole at the 5-HT_{2A} receptor, which minimizes excessive dopaminergic blockade by increasing dopaminergic release.[52] Previous studies have suggested a relationship between the 5-HT_{2A} receptor and tic disorders.[53,54] Additionally, partial agonism at the 5-HT_{1A} receptor by aripiprazole is associated with reducing anxiety,[55] which is one of the most frequent comorbid conditions in patients with tic disorders.[1] Moreover, we can propose that this effect of aripiprazole partly stems from its partial agonistic action on the D_3 and D_4 receptors. Pergolide, one of the D_3 receptor agonists, was efficacious against tic symptoms.[50,51] A number of studies have been conducted examining a genetic association between D_4 receptors and tic disorders.[56–58]

Limitations of the current study are a small sample size, a short-term study, and an open-label design, which is not able to control the rater bias. This study was conducted without a placebo-controlled group, hence we could not completely identify whether the symptom changes resulted from medication or the waxing and waning nature of tic disorders. In order to confirm our results, therefore, randomized, double-blind, placebo-controlled studies should be conducted. However, the result of this pilot study suggests that aripiprazole can be considered as an efficacious and safe drug for children and adolescents with tic disorders. In particular, low doses of aripiprazole may result in a rapid and significant symptom reduction.

Drug names: aripiprazole (Abilify), clonidine (Catapres and others), clozapine (FazaClo and others), guanfacine (Tenex and others), haloperidol (Haldol and others), olanzapine (Zyprexa), pergolide (Permax and others), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Melissa P. DelBello, M.D., at delbelmp@email.uc.edu.

