A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Aripiprazole in Children and Adolescents With Tourette’s Disorder

Hanik K. Yoo, MD, PhD; Yoo Sook Joung, MD, PhD; Jeong-Seop Lee, MD, PhD; Dong Ho Song, MD, PhD; Young Sik Lee, MD, PhD; Jae-Won Kim, MD, PhD; Bung-Nyun Kim, MD, PhD; and Soo Churl Cho, MD, PhD

ABSTRACT
Objective: To examine the short-term efficacy and tolerability of aripiprazole for children and adolescents with Tourette’s disorder.
Method: This 10-week multicenter, double-blind, randomized, placebo-controlled trial was conducted from August 2008 to April 2010. Children and adolescents (aged 6–18 years) with a DSM-IV diagnosis of Tourette’s disorder and a Yale Global Tic Severity Scale total tic score of 22 or more were randomly assigned (1:1 ratio) to placebo or aripiprazole. The primary outcome measure was mean change from baseline in the total tic score on the Yale Global Tic Severity Scale (last observation carried forward). Assessments of safety and tolerability included spontaneously reported adverse events, extrapyramidal symptoms, serum prolactin level, metabolic variables, and other laboratory evaluations.
Results: Of 61 subjects, 89% completed the study. Patients who received aripiprazole demonstrated a significant reduction from baseline to end of study on the mean (SD) total tic score of the Yale Global Tic Severity Scale compared to those who received placebo (−15.0 [8.4] and −9.6 [8.8], respectively, \(P = 0.0196\)). Response rate on the Tourette’s Syndrome Clinical Global Impression-Improvement was 66% and 45% in the aripiprazole and placebo groups, respectively. Mean decrease in the Tourette’s Syndrome Clinical Global Impression-Severity of Illness score was significantly different between the groups (\(P = 0.0321\)). In general, aripiprazole was well tolerated and there were no early discontinuations due to adverse events. The incidence of treatment-emergent adverse events between the groups was not significantly different (\(P = 0.7550\)). While aripiprazole decreased serum prolactin concentration (\(P < 0.001\)), it increased mean body weight, body mass index, and waist circumference significantly (\(P = 0.0055\), \(P = 0.0142\), and \(P = 0.0270\), respectively).
Conclusions: In comparison with placebo, aripiprazole was efficacious, generally tolerated and safe in the short-term treatment of children and adolescents with Tourette’s disorder.

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Aproximately 1% of children meet diagnostic criteria for Tourette’s disorder, which is defined by the presence of both multiple motor tics and 1 or more phonic tics during a period of more than 1 year, without more than 3 consecutive tic-free months.1

Along with currently approved drugs for Tourette’s disorder, such as haloperidol, atypical antipsychotics are broadly used because of their overall favorable tolerability profile despite absence of registrational approval.1,2 Atypical antipsychotics, however, have failed to demonstrate superior efficacy compared to typical agents.3,4 In addition, risperidone,3 quetiapine,5 and olanzapine6 are associated with metabolic side effects, which can affect patients’ quality of life, psychosocial development, and long-term physical health outcomes. Significant unmet needs remain for the safe and effective treatment of these vulnerable youths.

Aripiprazole, an atypical antipsychotic with a unique mechanism of action and a relatively favorable adverse event profile, has been approved for use in various adult and pediatric indications. Previously published small-scale studies have revealed the potential of aripiprazole as a promising candidate for treatment of Tourette’s disorder.4,7–10 Experts have speculated that the rationale for aripiprazole’s apparent anti-tic potency may be related to its unique pharmacology, dopamine partial agonism.11 Since the pathophysiology of tic disorders is postulated to be associated with tonic dysregulation of dopamine signaling, it is reasonable to propose that a dopamine partial agonist (with proposed regionally specific properties of agonism and antagonism) may promote “normalized” dopaminergic transmission.1

To our knowledge, no randomized, double-blind, placebo-controlled studies of aripiprazole for the acute treatment of Tourette’s disorder have been conducted. Our a priori hypothesis was that aripiprazole would demonstrate superior efficacy as well as a satisfactory tolerability profile compared to placebo in the reduction of tic behavior in children and adolescents with Tourette’s disorder.

METHOD

Study Design
This was a randomized, double-blind, placebo-controlled, 2-arm, parallel-group, phase 3 clinical trial. This study was conducted at 6 centers located in the Republic of Korea from August 2008 to April 2010.
Current evidence supports that aripiprazole can reduce tic symptoms in youth effectively.

In general, aripiprazole is tolerated and safe in children and adolescents with Tourette's disorder.

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### Table 1. Descriptive Data and Medication Information for 61 Children and Adolescents With Tourette's Disorder (intention-to-treat population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aripiprazole (n = 32)</th>
<th>Placebo (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, n (%)</td>
<td>30 (93.8)</td>
<td>23 (79.3)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>11.0 (2.5)</td>
<td>10.9 (3.0)</td>
</tr>
<tr>
<td>Tourette's disorder</td>
<td>32 (100.0)</td>
<td>29 (100.0)</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention-deficit/hyperactivity disorder</td>
<td>5 (15.6)</td>
<td>1 (3.5)</td>
</tr>
<tr>
<td>Oppositional defiant disorder</td>
<td>3 (9.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>0 (0.0)</td>
<td>1 (3.5)</td>
</tr>
<tr>
<td>Body weight, mean (SD), kg</td>
<td>46.2 (17.0)</td>
<td>41.5 (14.7)</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>149.4 (15.1)</td>
<td>144.3 (15.2)</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean (SD)</td>
<td>20.2 (4.4)</td>
<td>19.2 (3.4)</td>
</tr>
<tr>
<td>Waist circumference, mean (SD), cm</td>
<td>69.7 (11.6)</td>
<td>67.8 (9.7)</td>
</tr>
<tr>
<td>Previous antipsychotics with discontinuation just 1 week before aripiprazole commencement, n (%)</td>
<td>7 (21.9)</td>
<td>...</td>
</tr>
<tr>
<td>Medication information (safety population)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final dose, mean (SD), mg/d</td>
<td>11.0 (6.1)</td>
<td>...</td>
</tr>
<tr>
<td>Duration of study medication, mean (SD), d</td>
<td>68.6 (10.0)</td>
<td>63.8 (19.1)</td>
</tr>
</tbody>
</table>

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Eligibility criteria were assessed after obtaining written informed consent and assent from both the study subjects and primary caregivers, respectively. Local institutional review boards or ethics committee of each participating center approved the study protocol. Prior trial registration was also completed (ClinicalTrials.gov identifier: NCT00706589).

Baseline assessments included routine laboratory tests, pregnancy test for female subjects, 12-lead electrocardiogram (ECG), resting pulse and blood pressure while sitting, height and weight measurement, medical history, and physical examination. We used the block randomization method stratified by the clinical trial site and age group (children: 6–11 years; adolescents: 12–18 years) to achieve a balanced distribution of the study subjects between the study drug group and comparator group. After subjects were randomly assigned, investigators initiated treatment with either aripiprazole or placebo at 2 mg/d and then were permitted to increase the dose to 5 mg/d, 10 mg/d, 15 mg/d, and 20 mg/d according to the assessment criteria below, which were evaluated every 2 weeks. The dose escalation was based on assessment every 2 weeks of tic-related global state and overall tolerability. An investigator’s decision to keep the dose at the same level was prompted by a score of 1 or 2 on the Tourette's Syndrome Clinical Global Impression (CGI)-Improvement and bearable tolerability (as assessed by spontaneously reported adverse events). Investigators were permitted to titrate to the next dose level when a score of ≥ 3 on the Tourette's Syndrome CGI-Improvement scale and a favorable tolerability assessment were achieved. In the instance of subjects lacking tolerability, dose reduction to the prior dose level was permitted, or the subject could be discontinued. No intermediary doses were allowed. Treatment of comorbid psychiatric symptoms and use of other psychotropic medications except for study drugs were not permitted during the study period. The final assessment was performed 10 weeks after randomization.

Drug compliance was defined as a ratio of the quantity actually administered to the quantity planned to be administered and determined by pill counts at every visit.

### Subjects

Subjects deemed appropriate candidates by pediatric psychiatrists from outpatient clinics in university hospitals were randomized in a 1:1 ratio to receive aripiprazole or placebo. The candidates were 6 to 18 years of age, with a DSM-IV diagnosis of Tourette's disorder or chronic motor or vocal tic disorder, as assessed by trained psychiatrists using the Korean version of the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version. Subjects were eligible for participation if their baseline total tic score was ≥ 22 on the Korean version of the Yale Global Tic Severity Scale, which corresponds to moderate tic severity.

Exclusion criteria included current mood disorders, schizophrenia and other psychotic disorders, or other psychiatric comorbidity requiring medication during the study period and a history of psychotropic substance or alcohol use disorders during the 3 months preceding screening. Subjects with an IQ of 70 or less, as assessed by the Korean version of the Wechsler Intelligence Scale-Revised for Children, were also excluded. Patients with seizure disorders, a history of neuroleptic malignant syndrome, serious brain injury, stroke, or other neurologic disorders were also excluded. Children and adolescents with secondary tic symptoms accompanied by tardive tics, Huntington disease, neuroacanthocytosis, or autism were also excluded. Subjects who had used antipsychotic or antiparkinson drugs had to be free from the drugs for at least 1 week and from fluoxetine for at least 4 weeks prior to randomization. In addition, participants were also required to be devoid of any significant medical problems. Subjects with clinically significant abnormalities in clinical laboratory tests, vital signs, 12-lead ECG or physical examination...
or ≤ 16 kg of body weight at randomization were not able to participate. Subjects with a history of allergy or hypersensitivity reactions to aripiprazole, nonresponsiveness to treatment with antipsychotics, participation in another clinical study within 1 month prior to screening, or previous use of aripiprazole for either treatment or study purposes were not included. Pregnant or lactating female adolescents with child-bearing potential who did not consent to contraception during the study period and up to 8 weeks after study completion were not eligible for inclusion. Subjects requiring cognitive-behavioral therapy during the study period were excluded.

**Efficacy Assessments**

The primary efficacy outcome measure was the mean change from baseline in the total tic score on the Yale Global Tic Severity Scale (with the last observation carried forward). The scale is a semistructured clinical interview designed to assess current tic severity, which yields 3 summary scores: total motor (0–25), total phonic (0–25), and total tic (sum of motor and phonic). This scale also contains an impairment scale (0–50), which evaluates the global level of functional impairment arising from tics.14 The scale was administered at each visit. Using video-recorded cases, all 21 raters, who were psychiatrists, were trained 3 times, and interrater reliability on the total tic score was established. The intraclass correlation coefficient was 0.947 (95% CI, 0.750–0.999).

Secondary efficacy outcome measures included the percent change of total tic score on the Yale Global Tic Severity Scale and mean change in score on the Tourette's Syndrome CGI-Severity of Illness scale12 from randomization to the final visit. In addition, response rate (the percentage of subjects with scores of 1 or 2 on the Tourette's Syndrome CGI-Improvement scale at the last visit) and partial response rate (the percentage of subjects with a score of 3 on the Tourette's Syndrome CGI-Improvement scale at the last visit) were also assessed as secondary efficacy outcome measures. These assessments were administered every 2 weeks.

**Safety and Tolerability Assessments**

To assess emergence of adverse events, investigators asked open questions that covered general feelings and overall condition since the study drug commencement and recorded all spontaneously reported adverse events every 2 weeks.
Extrapyramidal symptoms were assessed by using the Simpson-Angus Rating Scale,16 Barnes Akathisia Rating Scale,17 and Abnormal Involuntary Movements Scale18 at each visit. We measured body mass index, waist circumference, vital signs, clinical laboratory tests, and serum prolactin concentration and performed a 12-lead ECG and physical examination both at randomization and at the study end point. These safety and tolerability data were examined 3 times by a safety monitoring board.

**Statistical Analyses**

Prespecified primary analyses were performed on the last-observation-carried-forward data set from all randomized subjects. Descriptive statistics for total tic score were presented for baseline, end point, and the change from baseline to study end point by treatment group. A 2-tailed t test was used to evaluate differences in both changes in total tic score and percent change from baseline to the last visit between treatment groups. Response rates and partial response rates in the Tourette’s Syndrome CGI-Improvement and the Simpson-Angus Rating Scale,16 Barnes Akathisia Rating Scale,17 and Abnormal Involuntary Movements Scale18 were in the model though they were both not significant.)

### RESULTS

**Subject Characteristics and Disposition**

Sixty-one children and adolescents with Tourette’s disorder (mean [SD] age = 11.0 [2.7] years; range, 6–18; 53 males and 8 females) were randomized among 83 screened subjects. Demographic and other baseline characteristics are summarized for the intention-to-treat population in Table 1. Of 61 enrolled subjects, 32 were randomized to receive aripiprazole and 29 subjects were randomized to receive placebo according to the pregenerated randomization scheme. All randomized subjects, except for 1 in the aripiprazole group who was withdrawn from the study due to a protocol deviation, were treated with the investigational product. Fifty-four subjects (88.5%) completed the study (29 subjects in the aripiprazole group and 25 in the placebo group) (Figure 1).

Seven participants (11.5%) discontinued from the study, seven participants (11.5%) discontinued from the study, and the disposition of study completion status did not differ between the groups. Three subjects (4.9%) discontinued due to withdrawal by investigators, 3 subjects (4.9%) withdrew themselves from the study on their own volition, and 1 subject (1.6%) was discontinued due to protocol deviation (Figure 1). Ten subjects (16.4%) had other current psychiatric diagnoses. There were no differences in demographic and

### Table 2. Efficacy of Study Drugs Between Baseline and End Point (intention-to-treat population, last observation carried forward)

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Aripiprazole (n = 32)</th>
<th>Placebo (n = 29)</th>
<th>P Value</th>
<th>Mean Difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yale Global Tic Severity Scale, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor tic score</td>
<td>15.9 (4.0)</td>
<td>8.6 (6.1)</td>
<td>.1839</td>
<td>.1318</td>
<td>1.9388</td>
</tr>
<tr>
<td>Phonic tic score</td>
<td>12.4 (3.7)</td>
<td>5.0 (4.6)</td>
<td>.0043</td>
<td>.0081</td>
<td>3.4082</td>
</tr>
<tr>
<td>Total tic score</td>
<td>28.3 (5.5)</td>
<td>13.6 (9.1)</td>
<td>.0196</td>
<td>.0269</td>
<td>5.3471</td>
</tr>
</tbody>
</table>
| Tourette's Syndrome CGI-Severity of Illness scores between treatment groups. A χ² test was used to compare the incidence of adverse events between treatment groups. Statistical significance for all analyses was set at a 2-tailed a level of .05.

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clinical characteristics at baseline between the 2 groups (Table 1). The mean compliance rate was 96.4% for the aripiprazole group and 96.2% for the placebo group, which was not different between the groups.

Efficacy

Subjects who received aripiprazole demonstrated a significant reduction from baseline to end point in the mean (SD) total tic score compared to those who received placebo (−15.0 [8.4] and −9.6 [8.8], respectively, \( P = .0196 \)) (Table 2). Mean decreases in the phonic tic score and the Tourette's Syndrome CGI-Severity of Illness score in the aripiprazole group were larger than those in the placebo group. Mean change in the motor tic score, however, was not different between the groups (Table 2). There were no statistically significant outcomes affected by adjustment for age, study site, and baseline scores as covariates (Table 2). The pattern of the changes in the total tic score from baseline appeared to be linear over time (Figure 2). Differences between the 2 groups were significant at weeks 2, 6, and 10 (\( P = .0283, \ P = .0403, \) and \( P = .0196, \) respectively).

Mean (SD) percent change in the total tic score from randomization to the final visit was significantly different for the aripiprazole group (−52.9% [27.8%]) and the placebo group (−32.6% [27.8%]) (\( P = .0077 \)). Response rate on the Tourette's Syndrome CGI-Improvement at the final visit was 65.6% (21 subjects) and 44.8% (13 subjects) in aripiprazole and placebo group, respectively. Partial response at the final visit was shown in 6 subjects (18.8%) and 4 subjects (13.8%) in the aripiprazole and placebo groups, respectively. Mean (SD) decrease in the Tourette's Syndrome CGI-Severity of Illness score was −1.7 (1.3) and −1.1 (1.1) for the aripiprazole and placebo groups, respectively, indicating a significant difference (\( P = .0321 \) by Wilcoxon rank sum test) (Table 2).

Safety and Tolerability

Adverse events and dropout rate. One subject who had not taken the study drug after randomization to the aripiprazole group was excluded for the safety analysis. One subject who had been randomized to the placebo group originally and had taken aripiprazole by mistake was included in the aripiprazole group as per the actual administration for the safety analysis. Thirty-two subjects in the aripiprazole group and 28 subjects in the placebo group were included for safety evaluation (Table 3).

Aripiprazole was generally well tolerated, and no subjects discontinued medication because of intolerability. Twenty-four subjects (75.0%) in the aripiprazole group and 20 (71.4%) in the placebo group experienced treatment-emergent adverse events, all of which were graded as mild to moderate in severity. The incidence of treatment-emergent adverse events was not different between the groups (\( P = .7550 \)). The most common treatment-emergent adverse events included nausea (6 subjects [18.8%]), headache (5 subjects [15.6%]), sedation (4 subjects [12.5%]), somnolence (4 subjects [12.5%]), and nasopharyngitis (4 subjects [12.5%]) in the aripiprazole group. In the placebo group, akathisia (4 subjects [14.3%]) and dizziness (4 subjects [14.3%]) were reported most frequently (Table 3).

Extrapyramidal symptoms. There were no significant differences between the groups in change from baseline scores on the Simpson-Angus Rating Scale, Abnormal Involuntary Movements Scale, and Barnes Akathisia Rating Scale assessments (Table 3).

Metabolic variables. Analysis of quantitative metabolic parameters is summarized in Table 3. Body weight increased by a mean (SD) of 1.6 (2.0) kg and 0.2 (1.7) kg in the aripiprazole and placebo groups, respectively (\( P = .0001 \) and \( P = .5596 \)). This change was significantly different between

![Figure 2. Change From Baseline to End Point](https://example.com/figure2)

**Figure 2. Change From Baseline to End Point**

A. Change From Baseline for Total Tic Score in the Yale Global Tic Severity Scale

B. Changes From Baseline in the Tourette's Syndrome Clinical Global Impression-Improvement in the Aripiprazole Group

*Statistically significant, \( P < .05 \).
the 2 groups ($P = .0055$). Although mean body mass index (kg/m²) increased by 0.5 (0.8) in the aripiprazole group ($P = .0050$), it was reduced by 0.1 (0.8) in the placebo group. This change was significantly different ($P = .0055$). For waist circumference, a significant mean change was also shown by 1.7 (3.7) cm in the aripiprazole group ($P = .0062$), which was significantly different ($P < .0001$) from that in the placebo group ($P = .0236$); however, the group difference was not significant. Mean change in serum prolactin level was −6.0 (4.8) in the aripiprazole group ($P < .0001$), which was significantly different ($P < .0001$) from that in the placebo group (−0.4 [3.4]).

**Other laboratory evaluations.** Changes from baseline and study end point in total creatine phosphatase, lactate dehydrogenase, and neutrophil count were observed in the aripiprazole group ($P = .0482$, $P = .0375$, and $P = .0439$). There were no significant differences between the groups. Monocyte levels decreased in the aripiprazole group ($P = .0011$), indicating a significantly different change ($P = .0140$) from that in the placebo group. These changes were not considered clinically relevant.

**Vital signs, ECG, and physical examination.** There were no significant changes in blood pressure, heart rate, ECG, or other parameters of physical examination with clinical significance over the course of the study.
To our knowledge, this study is the first report of a double-blind, placebo-controlled investigation for the efficacy and tolerability of aripiprazole in children and adolescents with Tourette’s disorder. Aripiprazole was superior to placebo in reduction of tic symptoms and generally tolerated and safe in children and adolescents with Tourette’s disorder. These findings are consistent with those from previous small-scale studies.

Previously reported estimates of mean daily dose of aripiprazole for the treatment of tic symptoms of children and adolescents with tic disorders ranged from 3.3 to 14.3 mg/d. The mean dose of aripiprazole in this study was 11.0 mg/d, which is consistent with dosing regimens of aripiprazole in children and adolescents with other psychiatric conditions.

While tic behaviors in the majority of patients were effectively managed with approximately 10 mg/d of aripiprazole, individualized and tailored titration strategies were required for optimization of tolerability and efficacy response in some patients. Consistent with labeled dosing in children and adolescent cohorts, a recommended starting dose of 2–2.5 mg/d titrated every week or every 2 weeks in steps of 2.5–5 mg/step appeared to improve tolerability.

The effect size and mean percent change, in terms of tic reduction in the aripiprazole group, were 0.62 and –52.9% in this study; this percent change is greater than those in previous placebo-controlled studies with other medications, including haloperidol, pimozide, risperidone, ziprasidone, clonidine, and guanfacine, which ranged from –25.8% to –39.0%.

Although atypical antipsychotics, including clozapine (which has not been shown to sufficiently abate tic symptoms), quetiapine, and olanzapine, have also been investigated in other open trials as anti-tic drugs, their efficacy was relatively weak, and adverse events, particularly weight gain and sedation, were treatment limiting.

With respect to aripiprazole, even though tic severity was apparently reduced linearly (Figure 1), the observed improvement after 2, 4, and 6 weeks of treatment accounted for 41.5%, 65.3%, and 78.9% of the total reduction in the total tic score, respectively. Thus, these data suggest that aripiprazole at 5 mg/d or less may diminish tic symptoms up to 65% of total improvement within the initial 4 weeks of administration, as previous studies have reported.

Within 6 weeks of aripiprazole initiation, we demonstrated effective management of tic behavior, nearly 80% of the full efficacy response, with doses of 10 mg/d or less. Risperidone, in contrast, has historically shown a less rapid onset of efficacy.

In this study, aripiprazole was not superior to placebo in decreasing motor tics, possibly because of the relatively large placebo effect, a 31.5% reduction of motor tics, as well as the small study population, which was not sufficient to compare subscale outcome. To our knowledge, no placebo-controlled study of atypical antipsychotics that has examined motor tic reduction has been published. Instead, 1 placebo-controlled study, which investigated the changes of motor tics by counting tic frequencies using videotapes, revealed that haloperidol and pimozide were not superior to placebo in reducing motor tics. Further placebo-controlled studies with appropriate sample size would be necessary.

Although 75.0% of subjects experienced adverse events in the aripiprazole group, this rate was similar to the placebo group; and no subjects discontinued due to adverse events. All extrapyramidal symptom assessments were unremarkable in the aripiprazole treatment group, a finding that is clinically meaningful in contrast to haloperidol. The reduced propensity for extrapyramidal symptoms emergence with aripiprazole, in comparison to conventional agents, is thought to be related to the partial agonist activity of aripiprazole at striatal dopamine 2 (D2) receptors.

Decreases in prolactin levels in the aripiprazole group may have been related to the dopamine partial agonist activity of aripiprazole that can inhibit dopamine action in the pituitary gland. This phenomenon is in line with that in a clinical trial of aripiprazole in adolescents with schizophrenia.

Metabolic assessments in this study are consistent with previously reported findings that suggest that aripiprazole treatment results in increased body weight, body mass index, and waist circumference. However, no significant changes in cholesterol and glucose levels were observed during the course of aripiprazole treatment. While aripiprazole is generally considered to be relatively neutral with regard to metabolic side effects in comparison to first-generation atypical antipsychotics, such as olanzapine, risperidone, and quetiapine, weight gain has been observed with its use in the treatment of tic disorders, even with doses lower than 5 mg.

Interestingly, in this study, children were more vulnerable to weight gain with aripiprazole than adolescents (1.4 [4.7] kg vs −0.5 [2.1] kg, P = .012). Although it might be associated with neurodevelopmental differences between preadolescence and postadolescence, it is hard to determine whether age factor may be related to the vulnerability of metabolic adverse events of aripiprazole because other metabolic variables were not changed during medication. Because of the lack of longer term safety data in this population, further identification to determine the influences of aripiprazole on metabolic outcomes in Asian children and adolescents is warranted. Physicians and caregivers are encouraged to monitor metabolic outcomes in all children and adolescents receiving aripiprazole because most young patients with Tourette’s disorder will need longer term medication.

As Tourette’s disorder has more recently been attributed to an “imbalance” in tonic dopamine neurotransmission, we suggest that the robust anti-tic profile of aripiprazole is due to its unique pharmacodynamic profile at dopamine D2 and D3 receptors. As a dopamine partial agonist, aripiprazole possesses both antagonistic and agonistic dopamine neuropharmacological properties, perhaps depending on the local dopamine system tone. The stabilizing action of a partial agonist may modulate aberrant dopamine signaling.
This pharmacology has been discussed in relation to efficacy and safety outcomes in previous studies.\textsuperscript{5,7–10,19–21}

The serotonin 2A receptor may be associated with tics, as indicated in human study.\textsuperscript{37}

In addition, the partial agonistic actions of aripiprazole at the serotonin 1A receptor might decrease tic symptoms through reduction in anxiety,\textsuperscript{11} a common comorbidity in patients with tic disorders thought to exacerbate tic behavior.\textsuperscript{1} Further, the partial agonistic activities of aripiprazole on the dopamine D3 and D4 receptors may be associated with tic reduction, as clinical and genetic studies have suggested.\textsuperscript{36,39}

In this study, the mean percent change in terms of tic reduction with placebo was –32.6%, which is a smaller change than that in a previous study of clonidine.\textsuperscript{33} However, it is larger than in other placebo-controlled studies,\textsuperscript{25–31,34} which ranged from 0.0% to –29.3%. Although we have no data on placebo effect in Asian children and adolescents with Tourette's disorder, it might be related to cultural or ethnic factors, because, in general, such effect could be more affected by cultural factors.\textsuperscript{80} It might be more prominent in the child and adolescent patient populations, who are more vulnerable than adults.\textsuperscript{23} At the same time, we acknowledge that placebo-controlled studies are indispensable in the determination of tic treatment effect.

The findings in this study should be considered in light of several limitations, including the relatively small sample size, lack of comorbidity, short-term use of medication, and lack of independent raters. The limitations, such as the exclusion of potential subjects who required medication for comorbidity disorders, prevent manifest conclusions regarding the generalizability to other clinical situations. A study longer in duration is necessary to identify the long-term efficacy and safety of aripiprazole for treatment in a larger sample size of children and adolescents with Tourette's disorder and other comorbidity conditions. In addition, randomized, head-to-head trials with existing treatment options may also be useful to confirm the efficacy of aripiprazole.

To conclude, our findings suggest that aripiprazole is efficacious and tolerated in children and adolescents with Tourette's disorder.

\textbf{Drug names:} aripiprazole (Abilify), clonidine (Catapres, Duracolon, and others), clozapine (Clozaril, FazaClO, and others), fluoxetine (Prozac and others), guanfacine (Intuniv, Tenex, and others), haloperidol (Haldol and others), olanzapine (Zyprexa and others), pimozide (Orap), quetiapine (Seroquel and others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

\textbf{Author affiliations:} Seoul Brain Research Institute (Dr Yoo); Department of Psychiatry, Samsung Medical Center School of Medicine, Sungkyunkwan University (Dr Joung); Department of Psychiatry, Yonsei University College of Medicine (Dr Song); Department of Neuropsychiatry, Chung-Ang University College of Medicine (Dr TS Lee); Department of Psychiatry, Division of Child and Adolescent Psychiatry, Seoul National University, Seoul National University Hospital (Drs JW Kim, BN Kim, and Cho), Seoul; and Department of Psychiatry, College of Medicine, Inha University, Incheon (Dr JS Lee); Republic of Korea.

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\textbf{REFERENCES}


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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 Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.