

Systemic review of aripiprazole for the treatment of children and adolescents with tic disorders

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ABSTRACT

تهدف هذه الدراسة إلى مراجعة الدراسات والبيانات المتعلقة بعلاج الحركات اللاإرادية للجسم (العرات الحركية) وذلك عن طريق استخدام عقار أريببيازول وهو من الأدوية المضادة للذهان. لقد قمنا بالبحث في قاعدة بيانات باب ميد/ ميد لاين وغوغل باستخدام كلمات البحث التالية: أريببيازول، والعرات الحركية، واضطراب توريت، وهكذا قمنا باسترجاع العناوين المتعلقة بنفس الموضوع. وقد شمل البحث 35 مقالا، وكانت أكثر المقالات مقالات حالات مرضية فيما كان مقالين فقط من التجارب التي تضمنت مجموعة شاهد. ولم يتضمن البحث أي من الدراسات المغشاة العشوائية المزدوجة التعمية المضبوطة ولذلك فإننا لم نجد دليلاً قوياً واحداً يعتمد على دراسات سريرية من مثل هذا النوع من الدراسات. وأشارت الأدلة الحالية إلى فعالية عقار أريببيازول في علاج العرات الحركية واضطراب توريت لكلي الأطفال والبالغين. كما يبدو من أن آثار هذا العقار الجانبية أكثر أمناً من عقار بيموزايد والأدوية الأخرى المضادة للذهان. ولهذا فإننا بحاجة إلى عمل دراسات مغشاة مزدوجة التعمية مضبوطة بالغفل حتى تقدم دليلاً قوياً يثبت فعالية عقار أريببيازول.

This study aimed to systematically review the data related to the treatment of tic disorders through aripiprazole administration, an atypical antipsychotic. The databases of MEDLINE/PubMed and Google Scholar were searched using the key words: "aripiprazole," "tic," and "Tourette," and the relevant titles retrieved. Thirty-five articles met the inclusion criteria and were further scrutinized. Most of the articles were case reports, and only 2 published trials included control groups. The number of randomized double-blind controlled clinical trials was zero, therefore, no strong evidence, provided by one, or more well-designed randomized controlled clinical trials, was found. Current evidence suggests that aripiprazole is effective for treating tic and Tourette disorders in both children and adolescents. Moreover, it seems that its adverse effect profile is safer than pimozide and some other antipsychotics. Therefore, double-blind randomized placebo-controlled studies are needed to provide strong evidence on the issue.

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Tic disorders and their management. The intermittent and unpredictable brief non-rhythmic movements or sounds that happen out of a background of normal motor activity are called tics. There are 2 types of tics; motor tics and vocal tics. Tic neurobiology is not clearly known, but involves both genetic and environmental factors. When both motor and vocal tics appear in a person younger than 18, it is called Tourette's disorder. Tics can be simple or complex. Blinking (54.3%), mouth movement (31.4%), and shoulder motor tics (31.4%) are the most frequent tics.¹ There is no diagnostic test for tic disorders and, consequently, it is diagnosed clinically.² At least in clinical samples, it is usually co-morbid with other psychiatric disorders; most likely attention deficit hyperactivity disorder (ADHD) (68.6%).¹ A study reported that only one out of 35 patients with Tourette's disorder did not suffer from any types of co-morbid psychiatric disorders.¹

Non-pharmacological interventions, such as educational interventions, supportive psychotherapy, and improving the knowledge of families, educators, and peers regarding tics, are recommended. Since stress may exacerbate tics, lifestyle and stress management might affect them. However, no specific diet is effective.² Behavioral therapy is also applied. Different pharmacological interventions are used and considered

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effective for treating tics. These pharmacological interventions include non-antipsychotics, alpha-adrenergic drugs, such as asclonidine³ and guanfacine,⁴ an ergoline-based dopamine receptor agonists, such as pergolide,⁵ and botulinum toxin A. From antipsychotics, both typical and atypical antipsychotics are effective. Haloperidol efficacy has been well studied in double-blind trials.⁶ Other antipsychotics, such as risperidone⁷ and pimozide,⁸ are also proven effective. However, there are many adverse effects related to current antipsychotics, such as extrapyramidal adverse effects, weight gain, sedation, hypersomnia, dry mouth, galactorrhea, gynecomastia, urinary retention, metabolic syndrome, and electrocardiographic changes, including tachycardia and tardive dyskinesia.^{2,9,10}

Aripiprazole. Aripiprazole is an atypical antipsychotic. It is a partial dopamine agonist and serotonin 2A antagonist, which stabilizes the dopamine system by increasing the dopamine release.¹¹ Agonist activity on dopamine 3 and 4 receptors can reduce tic severity.⁵ Aripiprazole is the first atypical antipsychotic with a dopamine partial agonist.¹² This effect leads to a reduction, and an increase in dopaminergic-mediated neurotransmission in areas of hyper- and hypodopaminergic activity.¹³ Aripiprazole also has high affinity for 5-HT_{1A} and 5-HT_{2A} receptors on serotonin neurons causing partial agonism and antagonism.¹²

Aripiprazole is a US Food and Drug Administration approved medication for treating bipolar disorders and schizophrenia. The safety and tolerability profile of aripiprazole is favorable and the rate of marked side effects, such as extrapyramidal adverse effects, weight gain, cardiovascular abnormalities, hyperprolactinemia, and hypercholesterolemia, is very low.¹² In addition, it does not increase QTc interval, prolactin level, serum lipid, and plasma glucose concentrations in the short term.¹⁴ However, more studies need to be conducted on the issue.¹⁵

The present systematic review aims to evaluate the current evidence for therapeutic interventions testing aripiprazole for tic and Tourette's disorder in both children and adolescents.

Literature search. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol was used to conduct this systematic review.¹⁶ A systematic literature search was conducted using the PubMed/MEDLINE and Google Scholar databases to find all clinical trials using aripiprazole for treating children and adolescents with tics or Tourette's disorder. The findings of these trials were published in peer-reviewed journals up to August 2011. The keywords used for the search were [aripiprazole*tic] and

[aripiprazole*Tourette]. The search was not limited to any language, time, the measurement or values cited, or publication type. The recovered articles were scrutinized to find more possible relevant references. Moreover, an extraction data sheet was designed to extract study design, sampling, intervention, and adverse effects. Tic and Tourette disorders are usually measured using the Yale Global Tic Severity Scale (YGTSS), which is a widely used clinical rating instrument. It rates number, frequency, intensity, complexity, interference, and impairment of both phonic and motor tics.¹⁷

Literature review. Among the 35 identified titles, 2 were irrelevant, the first of which was on the role of aripiprazole for treating impulse regulation disorder,¹⁸ and the other on acute dystonia with aripiprazole.¹⁹ The abstracts of the remaining 33 titles were studied. The main points of design of these studies were controlled non-randomized clinical trials,²⁰ case reports,²¹⁻³⁶ open-label studies without a control group,³⁷⁻⁴² randomized open-labeled controlled trial,⁴³ non-clinical trials,⁴⁴⁻⁴⁹ retrospective, observational studies,^{6,50} and commentary.⁵¹ However, no double-blind randomized controlled clinical trial was found (Figure 1).

An 8-week, open-label trial with a flexible dosing strategy of aripiprazole in 72 children and adolescents aged 6-18 years suffering from Tourette's disorder showed that aripiprazole significantly diminished total tic severity. The common adverse effects were nausea (29.2%) and sedation (26.4%). Nevertheless, no change was observed in the body mass index and cardiac conduction assessed by electrocardiogram.³⁷ The abstract of a Chinese language published 12-week treatment study reported that the authors compared the

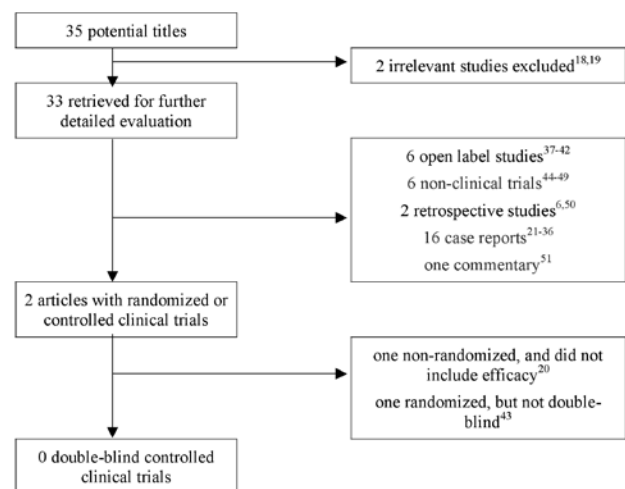


Figure 1 - Flowchart of trial selection process.

Table 1 - Characteristics of studies on the efficacy of aripiprazole for treating tic disorders.

Study	Type of study	Controlled	Randomized	Effect	Adverse effects
Yoo et al ⁵²	Open-labeled	Yes	No	Yes, no significant difference between aripiprazole and haloperidol	Total extrapyramidal adverse effects were lower than that of haloperidol The most common side effects were hypersomnia (58.1%), nausea/vomiting (29.0%), EPS (19.4%), and headache (16.1%)
Liu et al ⁴³	Open-labeled	Yes	Yes	Yes, more than tiapride treatment	No severe adverse effects
Gulisano et al ²⁰	Open-labeled	Yes	No	This study did not aim to investigate the efficacy of aripiprazole on tic disorders	No effect on heart rate Increased both systolic and diastolic blood pressure No significant increase of QT and QTc
Budman et al ⁵⁰	Retrospective	No	No	Yes	Weight gain, akathisia, sedation
Lyon et al ³⁹	Case series	No	No	Yes	Common adverse effects (N=11): appetite increase and weight gain (n=5), mild extrapyramidal effects (n=7), headaches and tiredness/fatigue (n=7), akathisia and muscle cramps (n=1)
Cui et al ³⁷	Case series	No	No	Yes	Well tolerated, nausea (29.2%), sedation (26.4%) No significant changes in laboratory results No significant impact on cardiac conduction

EPS - extrapyramidal symptoms

effect of aripiprazole and tiapride in the treatment of 65 children between 6-14 years old with tic disorders. They indicated that aripiprazole (2.5-10 mg/d) significantly reduced tic symptoms in comparison to tiapride (25-400 mg/d). They did not report any severe adverse events (Table 1).⁴³

An open-label 8 week long study compared the efficacy and tolerability of aripiprazole (initial dose, 5.0 mg/d; maximum dose 20 mg/d) and haloperidol in a clinical sample of 40 children and adolescents between 6-15 years with tic disorders. Both aripiprazole and haloperidol reduced tic severity; however, no significant difference was observed between the 2 groups regarding efficacy. Of course, the rate of extrapyramidal symptoms in the aripiprazole group was less than the haloperidol group. Only 16.1% of the patients in the aripiprazole group discontinued medication due to side effects, which was lower than the haloperidol group (35.3%). The side effects leading to discontinuation in the aripiprazole group were nausea (2 patients), headache (2 patients), and sedation (one patient). Other frequently reported adverse effects were hypersomnia (58.1%), nausea and vomiting (29%), extrapyramidal symptoms (19.4%), headache (16.1%), gastrointestinal disturbances (2.5%), and dry mouth (2.5%). The 2 groups were the same regarding weight gain. Overall, over 80% of the patients taking aripiprazole experienced one or more adverse

effect, which might have occurred due to starting with a dosage of 5 mg/day.⁵²

Gulisano et al²⁰ studied the cardiovascular safety of aripiprazole in a clinical sample of 50 children and adolescents between 6-18 years who suffered from Tourette's disorder. They used the YGTSS to evaluate the tic symptoms. In that study, 25 patients took aripiprazole, while the other 25 patients took pimozide for a period of 24 months. The mean dosages used were 5.3 mg/day for aripiprazole, and 4.4mg/day for pimozide.²⁰ Aripiprazole neither significantly changed the heart rate nor did it induce echocardiographic modification, and it did not cause orthostatic hypotension or syncope. Aripiprazole significantly increased the diastolic and the systolic blood pressure, while pimozide decreased both systolic and diastolic blood pressure. Aripiprazole, similar to pimozide, did not significantly change heart rate. In addition, aripiprazole, mildly but not significantly, increased the QT and QTc interval, while pimozide significantly prolonged both QT and QTc.²⁰ The authors concluded that aripiprazole is safer than pimozide for treating children and adolescents with Tourette's disorder.²⁰

Expected advantages of aripiprazole. Aripiprazole does not significantly increase weight in pediatrics,⁵³ and some pediatric cases may lose weight after taking aripiprazole.⁵⁴ In comparison to olanzapine or

risperidone, aripiprazole caused a significantly lower incidence of metabolic syndrome in patients with schizophrenia.⁵⁵ Moreover, a switch to aripiprazole from atypical antipsychotics significantly decreased body weight, total cholesterol, triglycerides, serum prolactin level, and corrected QT (QTc) intervals in patients with schizophrenia.⁵⁶ Furthermore, the risk of hyperprolactinemia after taking aripiprazole is very low.⁵⁷ Another study reported that there is no risk of hyperprolactinemia after taking aripiprazole.⁵⁸ Although these promising reports support the relative safety of aripiprazole, it does not guarantee the administration of aripiprazole as the first line of medication for treating tic disorders in both children and adolescents.

In conclusion, current non-well controlled evidence indicates that aripiprazole may be effective for the treatment of tics and Tourette's disorder in children and adolescents. Current published studies have several limitations, including small sample sizes, an open-label approach, being case reports or case series, and the short-term nature of the studies. Therefore, its long-term efficacy and safety cannot be guaranteed. We need further double-blind randomized placebo-controlled studies to determine the efficacy, tolerability, and safety of aripiprazole in children and adolescents suffering from tic disorders. These further clinical studies should use starting dosages less than 5 mg/day to determine whether the very high rate of adverse effects can be reduced.⁵² In addition, the co-morbidity of tic disorders and ADHD should be considered.^{59,60} A recent open-label uncontrolled study reported lower aripiprazole related tic improvement in patients with co-morbid ADHD symptoms compared to patients without co-morbid ADHD symptoms.⁶¹

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