Safety and efficacy of aripiprazole for the treatment of pediatric Tourette syndrome and other chronic tic disorders

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Abstract: Tourette syndrome is a childhood-onset chronic tic disorder characterized by multiple motor and vocal tics and often accompanied by specific behavioral symptoms ranging from obsessionality to impulsivity. A considerable proportion of patients report significant impairment in health-related quality of life caused by the severity of their tics and behavioral symptoms and require medical intervention. The most commonly used medications are antidopaminergic agents, which have been consistently shown to be effective for tic control, but are also associated with poor tolerability because of their adverse effects. The newer antipsychotic medication aripiprazole is characterized by a unique mechanism of action (D2 partial agonism), and over the last decade has increasingly been used for the treatment of tics. We conducted a systematic literature review to assess the available evidence on the efficacy and safety of aripiprazole in pediatric patients with Tourette syndrome and other chronic tic disorders (age range: 4–18 years). Our search identified two randomized controlled trials (involving 60 and 61 participants) and ten open-label studies (involving between six and 81 participants). The majority of these studies used two validated clinician-rated instruments (Yale Global Tic Severity Scale and Clinical Global Impression scale) as primary outcome measures. The combined results from randomized controlled trials and open-label studies showed that aripiprazole is an effective, safe, and well-tolerated medication for the treatment of tics. Aripiprazole-related adverse effects (nausea, sedation, and weight gain) were less frequent compared to other antidopaminergic medications used for tic management and, when present, were mostly transient and mild. The reviewed studies were conducted on small samples and had relatively short follow-up periods, thus highlighting a need for further trials to assess the long-term use of aripiprazole in pediatric patients with Tourette syndrome and other chronic tic disorders with measurement of its efficacy using both clinician-rated and self-report scales.

Keywords: Tourette syndrome, tics, aripiprazole, efficacy, tolerability

Background

Tourette syndrome (TS) is a chronic tic disorder characterized by the presence of both motor and vocal tics: repetitive movements and noises expressed as a result of specific sensory experiences or premonitory urges.[1] The prevalence of TS worldwide is estimated to be up to 1% in school-age children and a male:female prevalence ratio of 3–4:1 has been consistently documented.[2] The average age of tic onset is reported to be 6–7 years and peak severity is usually reached by early teenage years.[3–5] The other chronic tic disorders (chronic motor or vocal tic disorder) follow a similar neurodevelopmental trajectory, often with less severe symptoms than TS. In a significant

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proportion of patients, tics improve and, in some cases, disappear by adulthood,[6,7] although the characteristic urges are reported by the vast majority of adult patients with persisting symptoms.[8,9] TS is associated with neuropsychiatric comorbidities in ~90% of patients.[2,3,10] The most common comorbid conditions are obsessive–compulsive disorder[11] and attention-deficit and hyperactivity disorder,[12] which have been shown to significantly affect health-related quality of life,[13] as well as impulse control disorders.[14,15]

Although the exact neurobiological mechanisms underlying TS and other chronic tic disorders remain unclear, there is converging evidence on the role of disruption to neurotransmission within the cortico-striato-thalamo-cortical pathways.[6,16] The pathophysiological processes are thought to involve dysregulation of dopaminergic neurotransmission; however, both histaminergic[17,18] and noradrenergic[19,20] pathways have also been proposed to be involved. These neurochemical changes have consistently been associated with genetic susceptibility, although no single causative gene defect has been identified.[21,22] It is possible that the genetic heterogeneity which characterizes TS reflects the heterogeneity of the clinical phenotypes.

Treatment approaches to TS and other chronic tic disorders show a considerable variability, depending on the severity and complexity of the clinical picture. In some cases, simple reassurance and psychoeducation are the only required interventions.[23] In more severe cases, pharmacological therapy or behavioral interventions, such as habit reversal therapy, are often indicated.[24,25] Furthermore, over the last 15 years, there have been several reports of patients with severe and treatment-refractory TS who underwent the neurosurgical procedure of deep brain stimulation in order to control their symptoms.[26]

The pharmacological treatment of TS and other chronic tic disorders encompasses different drug classes and recommendations are often based on the findings of open-label studies.[27] The most commonly used medications are antidopaminergic agents (neuroleptics or atypical antipsychotics),[28,29] which are associated with known adverse effects.[30] Other medications used include alpha-2 adrenoreceptor agonists, such as clonidine and guanfacine.[31] Serotonergic medications are helpful for obsessive–compulsive disorder symptoms, whereas central nervous system stimulants, such as methylphenidate, can be used for the treatment of comorbid attention-deficit and hyperactivity disorder.

Over the last decade, aripiprazole has increasingly been used for the treatment of children and adolescents with TS and other chronic tic disorders. Aripiprazole is an atypi-

cal antipsychotic agent licensed for use in the treatment of schizophrenia and mania in bipolar affective disorder.[32,33] The mechanism of action of aripiprazole appears to be pharmacologically distinct from that of other atypical antipsychotics. This medication was initially reported to be a high-affinity D2 dopamine receptor partial agonist,[34,35] although more recent pharmacological profiling studies have indicated a more complex mechanism of action.[36] Aripiprazole appears to display functionally significant interactions at a large number of amine G-protein coupled receptors, including D2, D3, and D4 dopamine receptors, as well as at least six subtypes of serotonin receptors. The mode of action of aripiprazole at the level of the different receptors appears to be variable, with studies showing evidence for action as a full agonist, partial agonist, inverse agonist, and antagonist, depending on the receptor involved. The most frequently demonstrated mechanism is partial agonism at the level of dopaminergic and serotonergic receptors. In consideration of the rapidly expanding literature on the usefulness of aripiprazole in children and adolescents with TS, we set out to conduct a systematic review focusing on both safety and efficacy and encompassing randomized controlled trials and open-label studies in pediatric patients with TS and other chronic tic disorders.

Methods

This article reviews the available evidence on the efficacy and safety of aripiprazole in pediatric patients with TS and other chronic tic disorders. We conducted a systematic literature review on the PubMed database according to the methodological standards set out in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[37] Exclusion criteria covered studies published in languages other than English, studies involving adult populations only, studies assessing the use of aripiprazole in conditions other than chronic tic disorders, and any molecular or animal studies. Case reports were individually assessed for relevance to our review. Studies in which the full data were not available (eg, conference abstracts) and other types of publications (eg, editorials, commentaries, letters to the editor) were excluded. Finally, reference lists from both retrieved studies and recent review articles were manually scanned to ensure that any additional relevant studies were not missed.

Our search identified two randomized controlled trials and ten open-label studies. The majority of these studies used Yale Global Tic Severity Scale (YGTSS) scores as their primary outcome measure for drug efficacy on tic control. The YGTSS is a clinician-rated scale of tic severity, which includes a number of different subscores.[38,39] Patients are

scored on the severity of their motor and phonic tics separately, and these scores can be combined to produce a total tic severity score out of 50. A higher score denotes a higher severity of tics. The total tic severity score, which takes into account the number, frequency, intensity, complexity, and interference of tics, is subsequently combined with a 0–50 impairment score, measuring the effect of tics on a person's overall daily functioning. The sum of the tic severity and impairment scores yields the global YGTSS score, with a maximum of 100 points. A few relevant studies also used the Clinical Global Impression (CGI) scale, a clinician-rated measure which assesses change in global daily functioning on a 7-point Likert-type scale.[40] The CGI scale is not uniquely used in patients with tic disorders as it is frequently used across different neuropsychiatric and psychiatric conditions.[41] This instrument includes two subscores assessing the severity of symptoms and clinical improvement, respectively.

Randomized controlled trials

To date, two randomized controlled trials assessing the use of aripiprazole in young patients with TS and other chronic tic disorders have been published. The first trial was carried out between 2008 and 2010 by a research group based in the South Korea.[42] Their study involved 61 patients (age range: 6–18 years) recruited across six centers. The authors assessed the efficacy of aripiprazole by measuring change in the total YGTSS scores and CGI-Improvement scores from baseline in 32 patients treated with aripiprazole compared to 29 patients who received placebo. The study took place over a 10-week period with YGTSS scores, CGI scores, and tolerability being assessed on a fortnightly basis. Aripiprazole was started at a dose of 2 mg/day with the possibility of gradually increasing it to 5, 10, 15, or 20 mg/day, according to tolerability and tic severity. The mean dose of aripiprazole across the study sample was 11 mg/day. At the end of the study period, mean YGTSS scores were decreased by 15.0 points in the aripiprazole group and 9.6 points in the placebo group. This difference was statistically significant. Interestingly, the mean decrease in phonic tic severity was significantly larger in the aripiprazole group when compared to placebo. No difference was found in motor tic severity. Furthermore, the magnitude of the TS CGI severity score was significantly lower in the aripiprazole group compared to the placebo group. No patients in this study discontinued their treatment due to adverse effects; however, 75% of patients in the aripiprazole group reported adverse effects. Notably, over 71% of patients in the placebo group also reported adverse effects. The most frequently reported effects included nausea,

headache, sedation, somnolence, and nasopharyngitis. Both body weight and body mass index were significantly increased following aripiprazole treatment; however, no clinically significant changes were found on glucose and cholesterol measurement. The authors concluded that aripiprazole is an efficacious treatment for the management of TS in children and adolescents that is generally well tolerated and safe in the short term.

In the second randomized controlled trial, which was published in 2013, aripiprazole was compared to risperidone in the treatment of children and adolescents with tic disorders.[43] The study involved 60 patients between the ages of 6 and 18 years recruited from child psychiatry clinics affiliated with the Shiraz University of Medical Sciences in Iran. The study participants were randomly allocated to receiving either aripiprazole (n=31) or risperidone (n=29), and their YGTSS scores were assessed at baseline, week 4, and week 8. The initial dose of aripiprazole was 1.25 mg/day to be gradually increased up to 10 or 15 mg/day, depending on the child's weight. The mean dose of aripiprazole used was 3.22 and 4.0 mg/day in the first and second month of the trial, respectively. At baseline, the mean tic severity scores did not differ between the two groups. At the end of the study, both aripiprazole and risperidone were found to significantly decrease the YGTSS total tic severity score, as well as the motor and phonic tic subscores. The authors found no significant differences in the decrease in scores between the aripiprazole and the risperidone groups. The most common adverse effects reported in the aripiprazole group were drowsiness (26%), increased appetite (26%), and decreased appetite (13%). One patient dropped out of the study due to severe sedation. The authors concluded that risperidone and aripiprazole are both effective in managing tics in children and adolescents with TS. They suggested that further studies assessing tolerability and efficacy of long-term use of these medications should be undertaken.

Open-label studies

Our literature search identified ten open-label trials of aripiprazole in young patients with chronic tic disorders, which are summarized in Table 1.

The first pilot study assessing the efficacy of aripiprazole in a pediatric population was published by a Korean group in 2006.[44] The authors treated six patients aged between 7 and 17 years with aripiprazole at a mean dose of 10.9 mg and compared their YGTSS total severity scores at baseline with those after 8 weeks of treatment. In this study population, there was a 40.1% decrease in YGTSS scores at 8 weeks

Table 1 Summary of open-label studies on the use of aripiprazole in children and adolescents with tic disorders

Study	Location	Patients, n	Protocol length, mean dose	YGTSS (decrease in total tic score), %	CGI	Adverse effects	Dropout due to adverse effects, %
Yoo et al[44]	South Korea	6	8 weeks, 10.9 mg/day	40.1	–	Vomiting, sedation, weight gain	16.7
Yoo et al[45]	South Korea	24	8 weeks, 9.8 mg/day	52.8	79.2% much/very much improved	Sedation, nausea, headache	25.0
Seo et al[48]	South Korea	15	12 weeks, 8.2 mg/day	55.7	–	Nausea, sedation	6.7
Budman et al[49]	USA	37	12 weeks, 11.7 mg/day	–	38.6% decrease in CGI severity score	Headaches, dizziness, nausea	22.0
Lyon et al[50]	USA	11	10 weeks, 4.5 mg/day	40.8	91.0% much/very much improved, 28.5% decrease in CGI severity score	Increased appetite, extrapyramidal, akathisia	9.1
Murphy et al[51]	USA	16	6 weeks, 3.3 mg/day	54.1	–	Restlessness, irritability, nausea	0.0
Cui et al[52]	People's Republic of China	72	8 weeks, 8.2 mg/day	50.3	53.9% decrease in CGI severity score	Nausea, sedation	2.8
Yoo et al[46]	South Korea	48	8 weeks, 10.6 mg/day	54.3	71.0% much/very much improved	Sedation, nausea, extrapyramidal	16.1
Masi et al[53]	Italy	28	12 weeks, 10.0 mg/day	44.7	–	Sedation, agitation, nausea	0.0
Ho et al[47]	Taiwan	81	14 weeks, 2.8 mg/day	7.0*	–	Sedation, increased appetite, decreased appetite	11.1

Note: *Total YGTSS scores (including overall impairment). "–" indicates the data is not available.
Abbreviations: CGI, Clinical Global Impression; YGTSS, Yale Global Tic Severity Scale.

compared to baseline, with a decrease in the mean scores from 27.6 to 16.6. One patient withdrew from the study due to vomiting, but aripiprazole was otherwise well tolerated.

This research group subsequently published two further studies on the use of aripiprazole in children and adolescents with tic disorders. The first of these two studies was a larger open-label trial involving 24 patients with tic disorders aged 7–18 years.[45] The mean dose of aripiprazole administered to participants was 9.8 mg. There was an overall 52.8% reduction in YGTSS scores at 8 weeks, and 79.2% of the cohort was rated as having tic symptoms either much improved or very much improved on the CGI scale. In this study, six patients (25%) prematurely discontinued aripiprazole due to adverse effects. The second study compared aripiprazole to haloperidol in the treatment of TS over an 8-week period.[46] This study involved 48 patients aged 6–15 years, 31 of whom were prescribed aripiprazole at a mean dose of 10.6 mg. At 8 weeks, there was a higher percentage decrease in total YGTSS scores in the haloperidol group compared to the aripiprazole group (63.4% vs 54.3%); however, the dropout rate due to adverse effects was higher in the haloperidol group. Interestingly, the proportion of patients deemed to be much improved or very much improved on the CGI scale

was higher in the aripiprazole group (71.0%) compared to the haloperidol group (58.8%).

The largest open-label study to date was published in 2013 by a research group based in Taiwan.[47] These authors treated 81 patients with TS aged between 4 and 18 years with aripiprazole at a mean dose of 2.84 mg/day and recorded their YGTSS following 14 weeks of therapy. Nine patients withdrew due to adverse effects, 15 withdrew due to being symptom free for 2 weeks, and two withdrew as they experienced no significant beneficial effect. There was a mean reduction of 51% in motor tic scores, 67.1% in phonic tic scores, and 70% in total YGTSS scores. The authors concluded that aripiprazole is a safe and generally well tolerated, effective medication for the treatment of tics in children. One of the main limitations of this study was the large percentage (65.4%) of patients with a diagnosis of transient tic disorder. This reduces the generalizability of the results to the wider patient with TS population, as the positive results may have been biased by the large number of patients who had transient and mild symptoms.

The combined results of the remaining six open-label studies[48–53] confirmed the efficacy of aripiprazole in reducing both motor and vocal tic severity (Table 1). These studies

were conducted on clinical cohorts of between eleven[50] and 72[52] children and adolescents with tic disorders. Over study periods of 6–14 weeks, aripiprazole resulted in an overall reduction in tic severity in all cohorts for which data have been published. The mean dose of aripiprazole used in these open-label studies varied considerably from 2.8 mg/day in the study by Ho et al[47] to 11.7 mg/day in the study by Budman et al,[49] possibly accounting for some of the variability in effect size across studies. A few studies reported evidence for a larger improvement in vocal tics following administration of aripiprazole.[47,51,53] Interestingly, this observation is in line with the findings of the randomized controlled trial by Yoo et al.[42] Moreover, one study assessed aripiprazole in the setting of patients with comorbid TS and attention-deficit and hyperactivity disorder, and presented encouraging results for the role of this medication in managing comorbidities in addition to improving tics.[53]

The full picture emerging from the combined analysis of all the reviewed open-label studies (ten studies; 338 patients) indicates a decrease in YGTSS total tic severity scores of 49.1% (combined data from eight studies) and a dropout due to adverse effects of 11.0% (combined data from ten studies).

Safety and tolerability issues

Aripiprazole appears to be a safe and generally well tolerated pharmacological option for young patients with TS and other chronic tic disorders. In the published randomized controlled trials and open-label studies, withdrawal rates varied between 0% and 25%. The most frequently cited adverse effects included nausea, vomiting, fatigue, sedation, and weight gain, similar to what has been reported in the wider scientific literature on its use in child and adolescent psychiatry.[54] The majority of adverse effects appear to be transient and settle within the first few weeks of treatment, although in a few cases increased appetite and weight gain can cause long-term problems. Not all the reviewed studies quantified weight gain in their patient cohorts, and there is wide variability in the reported findings. Some studies reported prevalence figures of significant weight gain as high as 87%,[49] whereas other studies found no significant difference in body mass index after comparing pre- and post-aripiprazole body weight.[48] Moreover, although weight gain was frequently reported as a possible adverse effect of aripiprazole, it was not clinically significant in the majority of studies. Of note, the longest observational period for the reviewed studies was 14 weeks, thus suggesting that more long-term studies are required to assess the true impact of aripiprazole on body weight. Another adverse effect associated with atypical antipsychot-

ics is QTc prolongation on electrocardiogram. This is often an asymptomatic complication of drug treatment but can predispose to dangerous cardiac arrhythmias. The available evidence, including findings from studies conducted in young patients with TS,[30] indicates that aripiprazole is characterized by an overall safer cardiological profile than other antidopaminergic agents.[55,56] In the study by Cui et al[52] on 72 Chinese children with tic disorders, 13 were found to have a longer QTc on electrocardiogram after aripiprazole treatment when compared to baseline; however, the QTc alteration did not meet age- and sex-related criteria to be defined as prolonged.

Patient-focused perspectives

Patient-focused perspectives are important components of the clinical assessment and outcome of patients with conditions characterized by both physical and psychological symptoms. TS is a neuropsychiatric disorder with motor and behavioral aspects, which can have significant effects on patients' health-related quality of life[57] from an early age.[58] It is therefore important to consider the effects of pharmacological treatments on subjective aspects quality of life, in addition to tic frequency and severity. Both the YGTSS and CGI scales used in the reviewed studies of aripiprazole in young patients with tic disorder are clinician-rated instruments. Although use of these instruments may provide more consistency among assessments, there is the possibility that opinions and feelings of the patients and their caregivers are overlooked. Medications, particularly antipsychotics, are associated with a range of adverse effects of different severity, which can have a negative impact on overall quality of life. In a recent qualitative study, young patients with TS and their parents were surveyed and interviewed to explore their perceptions of treatment.[59] There was a strong perception among participants that health professionals had limited knowledge of the multifaceted clinical picture of TS and the available treatment options. The general consensus was that pharmacological treatment was beneficial in the management of TS; however, adverse effects were common. Interestingly, this study found that aripiprazole was viewed the most positively, with almost 70% of participants reporting it as being somewhat or very helpful, and only 25% reporting moderate or severe adverse effects. These figures were significantly better than those reported for the other seven frequently used medications for tic symptoms.

Conclusion

Taken together, the available evidence from both randomized controlled trials and open-label studies suggests that

aripiprazole is an effective, safe, and well-tolerated medication for the treatment of TS and other tic disorders in pediatric populations. These findings are in line with the results of three recently published meta-analyses, which suggested that aripiprazole appears to be a safe and promising therapy for children tic disorders,[60,61] with similar efficacy to established treatment options, such as the neuroleptics haloperidol and tiapride, and fewer extrapyramidal adverse effects than haloperidol.[62] Large case series of adult patients with TS provide further support to these observations in terms of both safety[63] and efficacy.[64,65] Specifically, pharmacotherapy with aripiprazole has been consistently shown to result in significant reductions in tic severity as measured by the YGTSS. Likewise, the studies that used the CGI scale as an outcome measure found significant improvements in a large proportion of patients. Variable proportions of patients reported adverse effects from aripiprazole, most commonly nausea, sedation, and weight gain. These adverse effects appeared to be primarily transient and mild, and withdrawal rates from trials were low. Adverse effects also appeared to be fewer in frequency and milder in severity when compared to other medications used in the pharmacological treatment of tic symptoms.

In conclusion, the vast majority of studies considered in this review were of relatively low power due to small sample sizes. Of note, only two studies were deemed eligible to be included in a recent meta-analysis on the efficacy and safety of aripiprazole for patients of all ages with a diagnosis of TS,[62] suggesting that further randomized controlled trials should be undertaken on larger patient cohorts. A multicenter randomized controlled trial on the efficacy and safety of once-weekly oral aripiprazole in children adolescents with TS was registered in 2011 (ClinicalTrials.gov identifier: NCT01418339). Moreover, the patients recruited in the reviewed studies were followed-up for a relatively short period of time (up to 3–4 months) and the fact that most of the studies were performed in Asian countries might have possibly introduced a bias in their results. Further studies are needed to establish whether the beneficial effects and tolerability of aripiprazole persist with time and whether they can lead to symptom freedom. Future research should therefore be targeted at longer-term use of aripiprazole in pediatric patients with TS and other chronic tic disorders with measurement of its efficacy using both clinician-rated and self-report scales. This will help defining the role of aripiprazole in evidence-based practice guidelines on the treatment of children and adolescents with tic disorders.[66]

Disclosure

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