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Aripiprazole for irritability associated with autistic disorder in children and adolescents aged 6–17 years

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Abstract

Aripiprazole was recently US FDA-approved to treat irritability in children and adolescents with autistic disorder aged 6–17 years. There are currently only two psychotropics approved by the FDA to treat irritability in the autistic population. This drug profile will discuss available studies of aripiprazole in individuals with pervasive developmental disorders, two of which led to its recent FDA approval. We will discuss the efficacy, as well as the safety and tolerability of the drug documented in these studies. In addition, the chemistry, pharmacokinetics, metabolism and mechanism of action of aripiprazole will be reviewed.

Keywords

aripiprazole; Asperger's disorder; autistic disorder; dehydro-aripiprazole; pervasive developmental disorder; pervasive developmental disorder not otherwise specified; quinolinone antipsychotic

Autistic disorder (autism) is a neuropsychiatric syndrome characterized by deficits in social interaction, qualitative impairments in communication and restricted repetitive and stereotyped patterns of behavior, interests or activities. It is classified as a type of pervasive developmental disorder (PDD). PDD not otherwise specified, Asperger's disorder, Rett's disorder and childhood disintegrative disorder represent the other diagnostic types of PDDs [1]. All types of PDDs have a qualitative impairment in social relatedness. However, many individuals with PDDs also have other interfering symptoms, including irritability (aggression, self-injurious behavior and severe tantrums). Behavioral therapy is often helpful in decreasing these behaviors; however, sometimes medications are needed adjunctively owing to the intensity and severity of the irritability [2].

The typical antipsychotics were one of the initial classes of medication to be studied for the treatment of irritability in autism [2,3]. However, concerns regarding their propensity to cause extrapyramidal symptoms (EPS) limited their use [2,4-7]. Atypical antipsychotics have largely replaced the use of typical antipsychotics to treat irritability in autism [3]. Atypical antipsychotics are thought to result in less tardive dyskinesia (TD) and EPS compared with typical antipsychotics owing to differences in D₂-receptor affinity.

Until recently, risperidone was the most studied and the only psychotropic approved by the US FDA to treat irritability related to autism. Aripiprazole has recently undergone several placebo-controlled studies validating its use in individuals with irritability associated with autistic disorder, leading to its recent US FDA approval.

Overview of the market

Social awareness and interest in autism has increased rapidly. The most recent data suggest that one in 110 children have an autism spectrum disorder (ASD) [101]. Owing to an increase in the diagnosis of these disorders and an increase in public awareness, research surrounding the treatment of target symptoms of PDDs has also increased. The American Academy of Child and Adolescent Psychiatry (AACAP) has developed general guidelines for treating individuals with PDDs [8]. However, there are only two medications that have received FDA approval for use in this population. This is challenging, as pharmacotherapy is often the rule and not the exception in this population. As described previously, atypical antipsychotics are commonly used in this population to treat irritability. Currently, the only two FDA-approved medications to treat irritability in autistic individuals are risperidone and aripiprazole.

Introduction to aripiprazole

Aripiprazole is a second-generation antipsychotic. Second-generation antipsychotics, often called atypical antipsychotics, have a lower propensity to cause TD and EPS [9]. Aripiprazole is approved to treat schizophrenia, mixed and manic states of bipolar I disorder (as monotherapy or as an adjunct to either lithium or valproate) and as adjunctive treatment for major depressive disorder (MDD) in adults. It is also FDA-approved to treat adolescents (aged 13–17 years) with schizophrenia and manic and mixed states of bipolar I disorder in children and adolescents (aged 10–17 years) [102]. The intramuscular formulation of aripiprazole is also indicated for the acute treatment of agitation associated with schizophrenia or manic and mixed states of bipolar I disorder in adults.

Chemistry

Aripiprazole is a quinolinone antipsychotic. The empirical formula is $C_{23}H_{27}Cl_2N_3O_2$. It has a molecular weight of 448.38 [10,103].

Pharmacodynamics

Aripiprazole is a partial agonist at the D_2 (dopamine), D_3 and $5-HT_{1A}$ (serotonin) receptors. It also functions as an antagonist at the $5-HT_{2A}$ receptor. It exhibits high affinity for D_2 , D_3 , $5-HT_{1A}$ and $5-HT_{2A}$ receptors. Aripiprazole possesses moderate affinity for D_4 , $5-HT_{2C}$, $5-HT_7$, α_1 adrenergic and H_1 histaminic receptors. Aripiprazole does not have significant affinity for muscarinic receptors [10,103].

Pharmacokinetics & metabolism

Although initial studies of the pharmacokinetics of aripiprazole were performed in adults, pediatric studies have revealed similar pharmacokinetic properties [9]. Aripiprazole and its active metabolite dehydro-aripiprazole have average elimination half-lives of 75 and 94 h, respectively. It has a bioavailability of 87%. Peak plasma concentrations are reported 3–5 h after ingestion. It is 99% protein bound [104]. The onset of action is 1–3 weeks [103].

Aripiprazole is metabolized through two primary cytochromes. It is dehydrogenated and hydroxylated by cytochrome P450 3A4 and 2D6. It is *N*-dealkylated by cytochrome P450 3A4 [104].

Aripiprazole is mainly excreted in the feces with a smaller amount excreted in the urine [103].

Clinical efficacy

Aripiprazole has been evaluated in several openlabel studies and two large placebo-controlled trials in children with autistic disorder. In these studies, aripiprazole has been found to be effective in the treatment of children and adolescents with irritability associated with autism.

Clinical trials

Double-blind studies

Two large controlled studies of aripiprazole have been performed in children and adolescents with autistic disorder. They were both conducted to determine the short-term efficacy and safety of aripiprazole in treating irritability in children and adolescents with autistic disorder.

The first of the double-blind, randomized, placebo-controlled, parallel-group studies included 218 autistic children and adolescents (aged 6–17 years). The subjects in this study were randomized to receive aripiprazole 5, 10 or 15 mg per day or placebo for 8 weeks. All groups receiving aripiprazole demonstrated significantly greater improvement compared with placebo at week 8 as judged by the Aberrant Behavior Checklist Irritability subscale (ABC-I; primary end point) [11] and the Clinical Global Impressions-Improvement scale (CGI-I) [12]. There was no statistically significant difference in efficacy between the aripiprazole 5, 10 and 15 mg groups. Discontinuation rates owing to adverse events were 9.4, 13.6 and 7.4% for the 5-, 10- and 15-mg groups, respectively, and 7.7% for placebo. The three most common adverse events leading to discontinuation were sedation (n = 7), drooling (n = 4) and tremor (n = 4) [13].

The second study was an 8-week, randomized, double-blind, placebo-controlled, parallel-group study with 98 children and adolescents (aged 6–17 years) diagnosed with autistic disorder. Subjects were randomly assigned to receive flexibly-dosed aripiprazole or placebo. At the end of the study, two individuals were receiving 2 mg/day, 13 were receiving 5 mg/day, 16 were receiving 10 mg/day and eight were receiving 15 mg/day of aripiprazole. The mean dose at the end of the study was 8.6 mg/day. Aripiprazole was found to be significantly more efficacious than placebo from week 1 through week 8 as judged by the CGI-I and mean improvement on the ABC-I (primary study end point). Discontinuation rates of 10.6% were noted in the aripiprazole group and 5.9% in the placebo group [14].

Open-label trials & retrospective chart reviews

There have been several open-label studies and retrospective chart reviews investigating aripiprazole in individuals with PDDs (Table 1). A naturalistic, open-label study of aripiprazole in five male youths with PDDs aged 5–18 years was performed for a mean duration of 12 weeks (range 8–16 weeks). The dose ranged from 10–15 mg/day. All five subjects were judged to be responders as indicated by a rating of ‘much improved’ or ‘very much improved’ on the CGI-I. Aripiprazole was generally well tolerated in this study [15]. A second open-label study with aripiprazole in 25 children and adolescents (aged 5–17 years) diagnosed with Asperger’s disorder or PDD not otherwise specified was performed for a duration of 14 weeks. The average dose of medication used in this study was 7.8 mg/day. A total of 22 (88%) of the subjects were deemed to be responders as judged by a score of ‘much improved’ or ‘very much improved’ on the CGI-I and a decrease in score of 25% or greater on the ABC-I. Aripiprazole was generally well tolerated in this study [16].

Two retrospective studies have been performed with aripiprazole in children and adolescents with developmental disabilities. The first included 32 children aged 5–19 years with developmental disabilities that had been prescribed aripiprazole [17]. A total of 24 of the subjects were diagnosed with a PDD and 18 with mental retardation. Target symptoms included aggression, hyperactivity, impulsivity and self-injurious behavior. The mean dose was 10.55 mg/day. The duration of treatment ranged from 6 to 15 months. A total of 18 of the 32 (56%) individuals were judged to be responders by the CGI-I. However, only 9 of the 24 (37%) children with PDDs were noted to improve and only five of the 13 (38%) children with both PDD and mental retardation responded. Side effects caused seven children to stop the study. The second naturalistic retrospective study was performed in 34 subjects (aged 4.5–15 years) diagnosed with a PDD. These children were followed for a mean duration of 7 months. The average CGI severity score prior to starting the study was 5.7. A score of 5 is considered 'markedly ill' and 6 is considered 'severely ill'. The mean CGI severity score at the end of the study was 3.1. A CGI severity score of 3 is considered 'mildly ill' and 4 is considered 'moderately ill'. Aripiprazole was given as monotherapy with a mean final dose of 8.1 mg/day. As many as 11 of the patients (32.4%) were judged to be 'much improved' or 'very much improved' by the CGI-I. A total of 12 of the subjects (35.3%) were determined to be 'minimally improved' and 12 of the children (35.3%) stopped the medication owing to side effects or lack of efficacy [18].

Safety & tolerability

Although aripiprazole has been noted to be safe and generally well tolerated in most of the studies in PDDs, some concern remains over its propensity to cause weight gain, EPS and sedation (Table 1). The increased incidence of weight gain and sedation are in contrast to the limited incidence of these found in adult aripiprazole studies in schizophrenia and bipolar disorder [19,20].

Weight gain, fasting glucose & hyperlipidemia

Weight gain is a noted side effect of atypical antipsychotics particularly when prescribed for children and adolescents [21]. Available research suggests that of the atypical antipsychotics, aripiprazole has a lower propensity to cause weight gain than the majority of others in the same class [3]. Of note is its lower propensity to cause weight gain compared with risperidone, the only other FDA-approved medication to treat irritability related to autistic disorder. However, this conclusion is based on average weight gain. Some children can gain a large amount of weight on atypical antipsychotics that are considered to be 'weight-neutral'. Weight gain and its associated comorbid medical conditions are of significant concern in children and adolescents. Weight gain in this population can be associated with diabetes, hyperlipidemia and cardiovascular disease [2]. Among each of the trials discussed above, with the exception of the Stigler *et al.* 2004 open-label study, weight gain was described as a side effect of the medication.

In the open-label naturalistic study by Stigler *et al.*, one of the five subjects (20%) gained weight (1 lb). Two of the subjects lost weight; however, this was hypothesized to be secondary to the discontinuation of a different atypical antipsychotic that had originally caused significant weight gain [15].

In the second open-label study performed by Stigler *et al.*, 19 of the 25 participants gained weight [16]. The average BMI of participants increased from 20.3 to 21.1 with an average weight gain of 2.7 kg over the 14 weeks of the study. Although the majority of the subjects did gain weight, it was within what would be expected for normal growing youths. Fasting blood glucose did not increase above the normal range in any subjects during this study.

However, the average value for blood glucose did increase over the 14 weeks of the study. Three subjects had a clinically significant increase in lipid values during the study.

In the retrospective study performed by Valicenti-McDermott and Demb, the mean BMI increased from 23.3 to 24 [17]. The change was clinically significant for those under 12 years of age who experienced an increase in mean BMI from 21.3 to 23. In adolescents, the mean increase was not clinically significant (26.7 to 27).

In the fixed dose placebo-controlled study by Marcus *et al.*, mean changes in weight were +0.3, +1.3, +1.3 and +1.5 kg for placebo, and aripiprazole 5, 10 and 15 mg/day, respectively [13]. Aripiprazole and 15 mg/day was associated with clinically significant weight gain when compared with placebo. One individual treated with aripiprazole 15 mg/day and one receiving 10 mg/day had an increase in fasting blood glucose to 115 mg/dl or greater. At the end of the study, the incidence of individuals with fasting triglycerides of 120 mg/dl or more (female subjects) and 160 mg/dl or more (male subjects) was 11.5, 3.1 and 10% for aripiprazole 5, 10 and 15 mg/day, respectively, and 3.6% for placebo.

In the flexibly dosed, placebo-controlled study by Owen *et al.*, mean changes in weight were significantly greater for aripiprazole (2 kg) than for placebo (0.8 kg). A greater increase in BMI was noted in the aripiprazole group (0.7 kg/m²) compared with the placebo group (0.1 kg/m²) in the observed case analysis. One individual receiving aripiprazole discontinued the study owing to weight gain. In this study there was no statistically significant change in fasting triglycerides, total cholesterol, low-density lipoprotein, high-density lipoprotein or serum glucose levels [14].

Change in prolactin

Prolactin elevation has been reported frequently in studies involving antipsychotics. In three of the studies discussed above, the prolactin levels were recorded at baseline and at the end of the study [13,14,16]. Stigler *et al.* reported a decrease from a mean value of 9.3 ng/ml at the beginning to 2.9 ng/ml serum prolactin at the end of the 14-week study [16]. Owen *et al.* noted a decrease from a mean value of 9.8 ng/ml at the onset of the study to 3.5 ng/ml at the end of the 8-week study [14]. Marcus *et al.* reported a decrease in mean serum prolactin levels of 5.4 ng/ml in the aripiprazole 5-mg/day group, 5.2 ng/ml in the aripiprazole 10-mg/day group and 5.8 ng/ml in the aripiprazole 15-mg/day group [13]. At study end point, the aripiprazole groups in each of the controlled studies noted a significant decrease in serum prolactin levels when compared with the placebo group.

Sedation

Sedation is exhibited in a dose-response relationship in those prescribed aripiprazole [15]. In the studies discussed above, two of the five patients in the Stigler *et al.* study experienced mild somnolence [15]. In the Valicenti-McDermott and Demb study, six of the 32 patients reported sedation [17]. In this study, the sedation caused four of the children to discontinue treatment. In the Stigler *et al.* open-label study, 14 of the 25 participants acknowledged mild tiredness and one acknowledged moderate tiredness owing to aripiprazole; however, none of the 14 individuals discontinued the study owing to tiredness [16]. Owen *et al.* reported sedation and/or somnolence as the most common side effect. A total of five of the 47 aripiprazole-treated individuals reported sedation while only one out of 50 individuals in the placebo group complained of sedation. Eight individuals in the aripiprazole group and two in the placebo group reported somnolence. One individual receiving aripiprazole discontinued the study owing to fatigue [14]. Marcus *et al.* reported seven individuals discontinuing the study owing to sedation. One child was receiving aripiprazole 5 mg/day, four were receiving 10 mg/day and two were receiving 15 mg/day. Over the entire study,

three of the 51 participants in the placebo group reported sedation, while nine of the 52 in the aripiprazole 5 mg/day, 17 of the 59 in the 10 mg/day and 13 of the 54 in the 15-mg/day group complained of sedation [13].

Abnormal movements

Abnormal movements in individuals with autism have been reported when pharmacotherapy with aripiprazole has been initiated. Stigler *et al.* noted that mild EPS was reported in nine of the 25 participants in their study. Clinician assessment revealed no EPS during the study; however, mild sialorrhea was reported by four participants, mild tremor in two, mild sialorrhea and mild tremor in one, mild sialorrhea and muscle stiffness in one and moderate neck stiffness and mild tremor in one [16]. Owen *et al.* reported an EPS event in seven of the 47 (a total of eight EPS events) participants receiving aripiprazole and four of the 50 participants receiving placebo [14]. In the aripiprazole group, of the eight EPS events reported, three were considered possibly related to the study, four were recorded as probably related to the study and one was recorded as certainly related to the study medication. One of the individuals received treatment with benztropine. Marcus *et al.* reported that six of the 51 individuals in the placebo group, 12 of 52 (23%) in the aripiprazole 5-mg/day group, 13 of 59 (22%) in the 10-mg/day group and 12 of 54 (22.2%) in the 15-mg/day group complained of EPS [13]. A total of eleven individuals, one in the placebo group and ten in one of the active treatment groups, received medication for treatment of possible EPS.

Other adverse effects

Other atypical antipsychotics have been associated with increased blood pressure and pulse rate [2]. In the three systematic aripiprazole studies mentioned above, none reported a clinically significant change in heart rate or blood pressure.

Regulatory affairs

Aripiprazole was recently approved by the FDA for use in children and adolescents aged 6–17 years for treatment of irritability associated with autistic disorder. The FDA has approved the use of aripiprazole up to 15 mg/day (initial dose 2 mg/day; recommended dose 10 mg/day) in autistic children and adolescents [104]. Previously, the FDA placed a black box warning on all atypical antipsychotics, including aripiprazole, for use in treatment of dementia-related psychosis. Elderly individuals treated with atypical antipsychotics for dementia-related psychosis are at an increased risk of death compared to those treated with placebo [2]. The FDA has also placed a black box warning on all products with an indication for MDD, including aripiprazole. Children, adolescents and young adults taking antidepressants for MDD and other psychiatric disorders are at increased risk of suicidal thinking and behavior when compared to placebo.

Conclusion

Autistic disorder and other PDDs are lifelong illnesses that can cause multiple symptoms that may interfere with many facets of functioning. Among other symptoms, individuals with PDDs may exhibit irritability that can take the form of aggression, self-injurious behavior or severe tantrums. Left untreated, these can become dangerous for the individuals and their caregivers [2]. Until recently, risperidone was the only FDA-approved medication to treat these symptoms. Aripiprazole has recently received approval to treat these behaviors in individuals with autistic disorder aged 6–17 years. In clinical practice, aripiprazole has been effective in decreasing irritability and aggression in those older than 17 years. However, dosing guidelines for those older than 17 years have not been approved by the FDA.

Studies of aripiprazole have provided information regarding the side-effect profile, clinical efficacy and safety in the PDD population. The studies that have been performed demonstrate aripiprazole's efficacy in treating irritability associated with PDDs. Owing to the potential side effects, the American Psychiatric Association and the American Diabetes Association recommended that those prescribing aripiprazole (and all atypical antipsychotics) monitor vital signs, fasting lipids and fasting glucose at baseline, 3 months after treatment onset and then annually. Weight should be assessed prior to treatment, at 4, 8 and 12 weeks and then quarterly [22]. As in any individual receiving an antipsychotic, monitoring for abnormal movements is also recommended [104]. Results pertaining to longer-term safety and tolerability studies of aripiprazole in children and adolescents with autism will be important to consider once they are published.

For optimal results when treating an individual with PDD, behavioral therapy interventions should be considered.

Future perspective

It is likely that in the future, atypical antipsychotics will continue to be used to treat irritability in PDDs. Results from studies of aripiprazole reveal the possibility of significant weight gain in children, especially those younger than 12 years. Thus, there will likely be continued research of atypical antipsychotics to identify those with efficacy similar to risperidone and aripiprazole, but without severe side effects.

Long-term studies have not been published documenting aripiprazole's safety and efficacy for the treatment of irritability in the PDD population. These studies would help to provide evidence-based monitoring guidelines. This will likely be another focus of future research.

As there are currently only two FDA-approved medications for treatment of PDDs, aripiprazole remains a viable option to treat irritability in this population.

Information resources

- Autism and Pervasive Developmental Disorders. (2nd Edition). Volkmar FR (Ed.). Cambridge University Press, NY, USA (2007).
- US FDA www.fda.gov
- Aripiprazole Prescribing Information: www.abilify.com/utilities/fullproductinfo.aspx

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Prospective, systematic trials of aripiprazole in individuals with pervasive developmental disorder

Table 1

Study type	Sample, n (age in years)	Mean dose (mg/day)	Duration (weeks)	Results	Side effects	Ref.
Open-label	n = 5 (5–18)	10–15	12	5/5 (100%) responded	2/5 reported somnolence, 1/5 gained weight	[15]
Open-label	n = 25 (5–17)	7.8	14	22/25 (88%) responded	19/25 experienced an increase in BMI, 9/25 reported EPS	[16]
Double-blind	n = 218 (6–17)	5, 10 and 15 fixed dosing	8	17/49 (35%), 29/52 (56%), 29/59 (49%) and 28/53 (53%) responded to placebo, aripiprazole 5, 10 and 15 mg, respectively; all doses demonstrated significantly greater improvement than placebo on ABC-I and CGI-I	For the placebo, 5, 10 and 15 mg groups, respectively, an increase in BMI was experienced by 1/49, 4/52, 1/59 and 2/53; EPS was reported by 1/49, 2/52, 4/59 and 6/53; and sedation was reported by 3/49, 9/52, 17/59 and 13/53	[13]
Double-blind	n = 98 (6–17)	8.6	8	Aripiprazole demonstrated significantly greater improvement compared with placebo on the ABC-I and CGI-I (67% were rated as improved or much improved)	For the aripiprazole and placebo groups, respectively, there was an increase in weight (2.0 and 0.8 kg); EPS (7/47 and 4/50); and sedation (5/47 and 1/50)	[14]

ABC-I: Aberrant Behavior Checklist Irritability subscale; CGI-I: Clinical Global Impressions-Improvement scale; EPS: Extrapyramidal symptoms.