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Aripiprazole in patients with autistic spectrum disorders: a review and case reports

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Abstract

Background: Although a significant amount of literature regarding use of aripiprazole (APZ) in autistic spectrum disorders (ASDs) has benne published, APZ is not approved for use in autism or ASDs in countries other than the United States. Even in the United States, approved use of APZ is limited to the patients with autism in children and adolescents. This review and case reports focus on the available evidence and clinical experience regarding the use of APZ in patients with ASDs including adults

Methods: A literature review was conducted, using the PubMed search term 'aripiprazole'and('autistic spectrum disorder', 'pervasive developmental disorders' or 'Asperger's disorder').

Results: In previous reports, APZ can target symptoms such as anxiety, depression, aggression, and irritability. Compared with other antipsychotics, APZ also causes fewer adverse events that can lead to drug discontinuation. The case reports supported the literature review: APZ has moderate sedative, antidepressant, and antianxiety effects, when used to treat ASDs. None of the patients experienced adverse reactions (e.g., extrapyramidal symptoms, weight gain, and sedation).

Conclusion: APZ reduces aggression in ASDs and improves qualitative deficits in interpersonal interactions and motivation. APZ also causes fewer adverse events. APZ may be associated with favorable treatment compliance, and may improve treatment of ASDs.

Keywords: Aripiprazole; Autistic spectrum disorder; Pervasive developmental disorders; Asperger's disorder

Introduction

Treatment for autistic spectrum disorders (ASDs) or pervasive developmental disorders (PDDs), a wide spectrum of disorders including autism and Asperger's disorder, includes therapeutic education regarding each symptom, arranging the home and classroom environment, and pharmacotherapy. Pharmacotherapy is not curative, but rather serves as treatment for secondary symptoms such as panic, excitation, hyperactivity, compulsion, and anxiety. Social impairment is best treated with behavioral therapy and social skills training [1]. Stachnik, et al. [2] reviewed clinical trials, case reports, and retrospective studies regarding the efficacy and safety of atypical antipsychotics for autistic and other PDDs, and extracted data regarding atypical antipsychotics selected for the treatment of autistic disorder in children, adolescents, and adults. They reported that autistic disorder was a chronic neurodevelopmental disorder, and that among limited treatment options, non-pharmacologic approaches may be most beneficial, but that for some cases with behavioral abnormalities, pharmacotherapy may be needed. Atypical antipsychotics were found to improve symptoms of autism, such as aggressiveness, hyperactivity, and self-injurious behavior. Aripiprazole (APZ) is an antipsychotic drug, approved by the Food and Drug Administration (FDA) in the United States, for the treatment of schizophrenia in 2002. Since then, it has been approved worldwide for the treatment of schizophrenia. The efficacy and tolerability of APZ, a dopamine D2 partial agonist [3] that is distinctive from conventional antipsychotics, have been demonstrated in various psychiatric diseases. APZ is indicated in the United States for the treatment of schizophrenia and bipolar I disorder, and has been recently approved to treat irritability associated with autistic disorder, in children and adolescents (5-16 years of age). Although, antipsychotics have not yet been approved for the treatment of ASDs by many countries, they are often used to reduce symptoms of excitation and panic. However, among antipsychotics, the FDA has approved only risperidone (RIS) and APZ, to treat irritability in autism [1,4].

This paper provides a literature review regarding the efficacy and tolerability of APZ, as well as case reports of three patients with ASDs. Although, a significant amount of literature regarding use of APZ in ASDs has benne published, there are some disagreements among the previous reports concerning the efficacy and safety of APZ, in the use for the treatment of ASDs. Furthermore, approved use of APZ is limited to the patients with autism in children and adolescents in the United States. This review and case reports focus on the available evidence and clinical experience, regarding the use of APZ in patients with ASDs, including adults. The previous reports evaluated mainly efficacy in positive symptoms, such as aggressive behavior, irritability, self-injurious behavior, stereotypic behavior, obsessive behavior, hyperactivity, and mood fluctuation. The case reports complement the literature review, regarding the efficacy in motivation and cognitive function, communications skills, and social adjustment.

Mechanism of Action for Effectiveness

The mechanism of action underlying the effectiveness of APZ in the treatment of ASDs is unclear. A partial agonist effect on dopamine D2 [5-7] and serotonin 5-HT1A [8,9] receptors, and an antagonistic effect on serotonin 5-HT2A [10] receptors, are proposed pharmacological

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activities that may be involved. Chavez et al. [11] reviewed the literature and suggested that PDD is likely a heterogeneous disorder, with a multifactorial etiology. They discussed the possible relationship between serotonin, dopamine, and norepinephrine and the observed clinical response to atypical antipsychotic treatment for autism, and argued that the observed efficacy of atypical antipsychotics may be related to their ability to affect more than one neurotransmitter system.

The finding of hyperserotonemia [12-14] in a significant percentage of individuals with autism, suggests that serotonin may be a potential target for pharmacotherapy. Dopamine neurotransmitter deregulation may also occur in autism. Dopamine is associated with certain functions including attention, motivation, and planning. If these areas of cognition are impaired and certain behaviors occur, such as aggression or irritability, then treatment with antipsychotic agents may result in modest improvements [15]. Therefore, the pharmacological action of APZ as a dopamine D2 partial-antagonist or dopamine system stabilizer may effectively reduce behavioral abnormalities in ASDs.

Bruins et al. [16] demonstrated that APZ improves deficits in social interaction induced by phencyclidine (an NMDA antagonist) in rats, and hypothesized that this improvement was mediated through D2 antagonist and 5-HT1A agonist effects. The therapeutic effect of APZ in depression and anxiety may be mediated by a potent partial agonistic effect, at the 5-HT1A receptor [17-19].

Literature Review

A literature review was conducted using the PubMed search term 'aripiprazole' and ('autistic spectrum disorder', 'pervasive developmental disorders', or 'Asperger's disorder') with limits 'human trials', 'English language', and ('open study', 'retrospective study', 'controlled study', 'randomized study', or 'blind study'). Additional articles were identified from reference information.

Open studies

Stigler et al. [20] conducted a 14-week prospective, open-label trial of APZ (N=25) in patients, including four with Asperger's disorder and 21 with PDD, not otherwise specified (PDD-NOS). Of the 25 patients, 22 experienced improvement in symptoms of irritability, including aggression, self-injurious behavior, and tantrums. Clinical Global Impression-Improvement (CGI-I) was 1 or 2 (very much or much improved), and the Aberrant Behavior Checklist Irritability (ABC-I) improved ≥ 25%. All four patients with Asperger's disorder showed improvement. Adverse events included mild EPS in nine patients, although treatment was not discontinued, owing to adverse events in any patient. Prolactin levels decreased significantly. These results suggested that APZ was effective and well tolerated for severe irritability in PDD-NOS and Asperger's disorder.

Retrospective studies

Kim et al. [21] retrospectively evaluated the effectiveness and tolerability of adjunctive use of APZ, in children and adolescents (N=14) with PDD who had been resistant to various treatment regimens, including five with Asperger's disorder. APZ had been preceded by other antipsychotics, prescribed to 11 patients. The Clinical Global Impression-Severity (CGI-S) improved in 11 patients, and the mean CGI-S score also improved significantly. With adjunctive APZ, the positive psychotic symptoms effectively improved in association with decreases in aggressive behavior, self-injurious behavior, stereotypic behavior, tics, irritability, obsessive behavior, hyperactivity, and mood fluctuation. Six patients discontinued treatment: five because of adverse events (akathisia, insomnia, withdrawal symptoms), and one because of improved symptoms (hyperactivity and tic). The results of this study suggest that APZ augmentation may be used safely to treat maladaptive behaviors, in some populations of PDD.

A retrospective study of Masi et al. [22] described clinical outcomes and adverse effects, during naturalistic treatment with APZ monotherapy, in patients (N=34) diagnosed with PDD who had exhibited aggression against themselves or others, hostility, and severe impulsiveness. At the endpoint, 11 patients (32.4%) were very much improved or much improved (CGI-I 1 or 2), 12 (35.3%) were minimally improved (CGI-I 3), and 10 were unchanged or worse (CGI-I 4 or 5). The Children-Global Assessment Scale (C-GAS) and Childhood Autism Rating Scale (CARS) scores were significantly improved. Nine patients experienced moderate to severe agitation (which was associated with self-injurious behaviors in five of these patients), and five patients presented with sleep disorders. Twelve patients discontinued medication during follow-up, because of lack of efficacy or adverse effects. The report concluded that APZ monotherapy was associated with a significant improvement in maladaptive behaviors, among one-third of patients with PDD who were severely impaired.

Controlled, randomized, or blind studies

Owen et al. [26] conducted an 8-week, placebo-controlled, randomized, double-blind trial (N=98), to evaluate the efficacy of APZ for treating irritability in patients with autistic disorder, who had tantrums, aggression, self-injurious behavior, or a combination of these symptoms. Ninety-eight patients were randomly assigned (1:1) to flexibly dosed APZ (target dosage: 5, 10, or 15 mg/day) or placebo. Efficacy outcome measures included the ABC-I subscale and CGI-I; safety and tolerability were also assessed. The mean improvement in the ABC-I subscale score from week 1 through week 8 was significantly greater in the APZ group, than in the placebo group. Although, the CGI-I score was also significantly improved, clinically significant residual symptoms may still persist for some patients. Discontinuation rates as a result of adverse events were 10.6% for APZ and 5.9% for placebo. The EPS-related adverse event rate was 14.9% for APZ and 8.0% for placebo; however, no serious adverse events were reported. These results suggested that APZ was an effective treatment for irritability associated with autistic disorder, and was generally safe and well tolerated.

Marcus et al. [25] conducted an 8-week, double-blind, randomized, placebo-controlled trial (N=218) in children and adolescents with autistic disorder and behaviors such as tantrums, aggression, and self-injury. Patients were randomly assigned to four groups (APZ 5, 10, or 15 mg/day, and placebo). Efficacy was assessed, using the caregiver-rated ABC-I and the clinician-rated CGI-I. After 8 weeks, all APZ dose groups exhibited significantly greater improvements in the ABC-I score, than the placebo group. The CGI-I score was also significantly improved. The discontinuation rates due to adverse events were placebo, 7.7%; 5 mg, 9.4%; 10 mg, 13.6%; and 15 mg, 7.4%. The most common adverse event leading to discontinuation was sedation (23.6%). Two serious adverse reactions occurred: presyncope (5 mg/day) and aggression (10 mg/day). APZ was highly effective and well tolerated in children and adolescents with autistic disorder, associated with irritability.

The reported clinical and safety outcomes of APZ in children and adolescents referenced above are summarized in Table 1.

Reference	Study design	Subjects (N)	Age (years)	Duration	Dosage of APZ	Clinical outcomes	Tolerability
Stigler *et al.* (2009)	Prospective, open-label trial	Asperger's disorder (4) & PDD-NOS (21)	5-17	14 weeks	2.5-15 mg/ day. Mezn final dose:7.8 mg/day	Improvement in symptoms of irritability, including aggression, self-injurious behavior, and tantrums (88%). Much improved or very much improved in CGI-I. ABC-I improved ≥ 25%.	Mild EPS (36%). BMI increased (from 20.3 to 21.1 kg/ cm2). Prolactin levels significantly decreased (from 9.3 to 2.9 ng/mL).
Erickson *et al.* (2009)	Prospective open-label study	Fragile X syndrome (12)	6-35	12 weeks	Initial dose: 2.5 mg/day (increased to a maximum of 20 mg/day for 8	Much improved or very much improved in CGI-I. ABC-I improved ≥25%.	No tardive dyskinesia or EPS. Well tolerated. Weight decreased by a mean of 2.18 kg.
Kim *et al.* (2010)	Retrospective study	PDD (14) including Asperger's disorder (5), who had been resistant to various treatment regimens	7-17	Mean: 183.4 days.	Mean initial dose: 6.1 mg/day. Mean final dose: 7.7 mg/day.	CGI-S mean score significantly improved. Decreases in positive psychotic symptoms, aggressive behavior, self-injurious behavior, stereotypic behavior, tics, irritability, obsessive behavior, hyperactivity, and mood fluctuation.	Adverse events (35%): akathisia, insomnia, withdrawal symptoms.
Masi *et al* .(2009)	Retrospective naturalistic study	PDD who had aggression against self or others, hostility, and severe impulsiveness (34)	4-15	4-12 months	Mean final dose :8.1 ± 4.9 mg	Much improved or very much improved (32.4%), minimally improved (35.3%), unchanged or worse (29.4%) in CGI-I. C-GAS and CARS were significantly improved.	Moderate to severe agitation (26.5%), sleep disorders (14.7%). Discontinuation due to lack of efficacy or adverse effects (35.3%).
Owen *et al.* (2009)	Placebo-controlled, randomized, double-blind trial	Autistic disorder who had tantrums, aggression, or self-injury (98)	6-17	8-weeks	5, 10, 15 mg/day and placebo	ABC-I subscale score and CGI-I score were significantly greater in the APZ group compared with the placebo group. Clinically significant residual symptoms may still persist for some patients.	No serious adverse events. Discontinuation due to adverse events: APZ; 10.6%, placebo; 5.9%. EPS: APZ; 14.9%, placebo; 8.0%. Mean weight gain:APZ; 2.0 kg, placebo; 0.8 kg.
Marcus *et al.* (2009)	Randomized, placebo-controlled, parallel-group study	Autistic disorder who had tantrums, aggression, or self-injury (218)	6-17	8-weeks	5, 10, or 15 mg/ day and placebo	Adverse event leading to discontinuation: sedation (23.6%). Serious adverse events: presyncope (0.46%), aggression (0.46%).	Adverse event leading to discontinuation: sedation (23.6%). Serious adverse events: presyncope (0.46%), aggression (0.46%).

Table 1: Summary of reported clinical and safety outcomes of APZ in ASDs.

Tolerability

EPS

In randomized, double-blind, placebo-controlled trials involving schizophrenia [23], bipolar type I disorder [24], and autism [25,26] in childhood and adolescence, the occurrence of EPS was more frequent in the APZ group than in the placebo group, and salivation, tremor, and dystonia were observed. However, the degree of EPS was considered mild to moderate.

Akathisia

Findling et al. reported that akathisia was more frequently observed in the high-dose APZ group (30 mg/day) of adolescents with schizophrenia. However, it was comparably observed between the group receiving APZ at 10 mg/day, and the placebo group [23]. Meanwhile, akathisia occurred at a higher rate among pediatric patients with bipolar I disorder, receiving APZ 10 mg/day or greater than among the control group [24]. Moreover, there was another report that the occurrence rate was comparable between the APZ and placebo groups of autistic disorders [25,26]. Therefore, no consensus has been reached regarding the occurrence rate of akathisia in patients taking APZ. However, it is possible that akathisia occurs at a higher rate in patients receiving a higher dose of APZ.

Serum prolactin

Serum prolactin was significantly reduced after APZ administration compared with baseline, and was also significantly lower in the APZ group than in the placebo group in randomized, double-blind, placebo-controlled trials for schizophrenia [23], bipolar I disorder [24], and autism [25,26].

Weight gain, metabolic consequences, and QT prolongation

Among atypical antipsychotics, OLZ [27-30] and QTP [31-33] are limited in their use for ASDs in children and adolescents, because of high incidences of weight gain and sedation. In comparison, APZ [34,35] and ziprasidone (ZPD) [36,37] cause less weight gain and sedation. Regarding side effects, APZ and ZPD are considered promising drugs [11,38]. However, because QT prolongation associated with ZPD has been reported in studies in adults [39, 40], possible cardiovascular risk must be considered and the use of ZPD should be limited in children and adolescents. However, no changes were evident in blood pressure, heart rates, ECG, or QT interval, in any of the double-blind, placebo-controlled trials for APZ [23,25,26].

APZ causes less weight gain because it has a low affinity for histamine H1 receptors, and is a partial agonist of serotonin 5-HT2C receptors, which are associated with weight gain and obesity [8,9,41]. Additionally, because of the low affinity for histamine H1 receptors, the incidence of oversedation is low [41]. Furthermore, APZ has almost

no affinity for muscarinic M1 receptors, so it has few anticholinergic effects, such as constipation, dry mouth, urinary retention, or effects on cognitive function [42]. In the nonrandomized Second-Generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth (SATIETY) cohort study, Correll et al. [42] evaluated the effects of OLZ, QTP, RIS, and APZ on body composition and metabolic parameters in 338 pediatric and adolescent patients, treated for 12 weeks without prior antipsychotic medication exposure. Weight increased significantly in the antipsychotic treatment groups; APZ caused the least weight gain. Furthermore, serum total cholesterol, triglycerides, and non-high-density lipoprotein cholesterol (total cholesterol minus HDL cholesterol) increased significantly with OLZ, QTP, and RIS, but not APZ.

Case Reports

Case #1: 32-year-old male

In early childhood, this patient had mild stuttering and mild intellectual delay; however, he had no particular problems in regular classes after entering school. However, when his mother spoke to him, he would often ignore her and not reply. Moreover, he exhibited obsessive behaviors, such as endless rechecking, fear of contamination, and compulsive hand washing.

The patient worked in janitorial and cleaning jobs, after graduating. With time, his obsessive behaviors became more pronounced. Eventually, the patient quit his job and remained in his own bedroom. In his bedroom, he continually read his favorite bike, car, and audio magazines. He only left his bedroom to go to the bathroom; he even stopped bathing and washing his face. The patient's room started to smell, but he would not allow his family to enter or clean the room. This lifestyle, in which he remained continually in his bedroom, lasted for several years. At the request of his worried mother, a public health nurse from an agency would occasionally visit. The patient let his hair and beard continue to grow, and his underwear and bedding were not changed for years.

In March X, the patient developed cellulitis and osteomyelitis of his right foot, due to unsanitary conditions. He was admitted to our hospital by an orthopedist. During the previous 2 years, he had never stepped outside his room. Hoping for an improvement in his mental condition, his mother requested a consultation at our psychiatric clinic, and the patient was initially evaluated. The patient had social impairment, qualitative communication impairment, a limited range of interests, and obsessive behaviors, but lacked any severe intellectual disability. He was diagnosed with high-functioning autism, and an oral solution of APZ (6 mg) was prescribed. Subsequently, the patient no longer disliked conversing with his family, and began to eat meals with them. Sometimes, he even helped his mother with cooking. When his mother spoke to him, he listened and responded. In addition, he no longer refused to attend regular orthopedic outpatient visits for rehabilitation.

Case #2: 27-year-old male

From early childhood, this patient's parents noticed that their son was a perfectionist, very inflexible, and had an obsessive personality. Just after entering high school in X-12, the patient began to complain about "not being able to mix with groups of people," "difficulty meeting people," "not wanting to go out." He had suicidal ideation; because he tried to hang himself, he was admitted to the emergency department of our hospital in March X-11. After admission, prodromal symptoms of schizophrenia were suspected, but there was no definitive diagnosis. With chlorpromazine (CPZ), his depressed mood, suicidal ideation, and motivation improved; and in April he was discharged.

After discharge, the patient sometimes experienced increased restlessness, so OLZ and QTP were added to the CPZ regimen; however, his motivation and ability to communicate did not improve. Subsequently, he continued outpatient visits; however, he still experienced interpersonal tension and depressed mood, and was unable to communicate with classmates. He barely managed to graduate from high school and did enter university, where he felt isolated and tended to be absent.

In July X-5, there had been no active progression of symptoms to suggest schizophrenia, and the core symptom appeared to be a lack of communication skills. The patient was diagnosed with Asperger's disorder, and treatment was switched to APZ 6 mg/day. After switching to APZ, the patient became more motivated, attended lectures, and was enthusiastic about his graduation thesis and obtaining a teaching credential. After APZ was increased from 6 to 12 mg/day, the patient was able to communicate with classmates at lectures, his facial expression became more lively, and even his family noticed the improvements. He was able to get up early and no longer felt tired in the morning. The patient stated that he was no longer depressed. After university graduation, he opened a cram school in the area and taught children.

Case #3: 38-year-old male

From early childhood, this patient did not make eye contact with other people. He did poorly in group activities, and would try to walk behind the other children. After entering school, he had almost no friends. In high school, the patient himself realized that he was unable to understand other people's feelings, and he barely spoke to his family.

He graduated from a local university, and also completed graduate school. He subsequently found a job in a company, but was unable to establish relationships with others and appeared depressed. He had difficulty understanding the subtle nuances of what his boss and colleagues were saying, which often led to conflicts. He tended to be absent from work, would become very anxious before going to work in the morning, and would sometimes become panicked.

In September X-1, the patient consulted a local mental health clinic, was diagnosed with depression, and was prescribed antidepressants. However, the antidepressants were ineffective.

He was initially evaluated at our hospital in November X, to seek a second opinion. Based on his impaired communication, impaired imagination, and a time-slip phenomenon, the patient was diagnosed with Asperger's syndrome. Treatment was started with APZ 6 mg/day, in combination with social skills training, designed by the psychologist of our clinic. Subsequently, his morning anxiety and panic improved, and he was absent less from work.

In February X+1, APZ was increased to 12 mg/day. Although, communication with his boss and colleagues remained sparse, the patient experienced less difficulty, understanding what others meant and their facial expressions, and he was able to concentrate on his work.

Comments about the presented cases

The antianxiety and cognitive function improvement effects of APZ as a 5-HT1A agonist, and the motivation-improving effects of APZ as a D2 partial agonist, were safely achieved. Moreover, as a result of improved motivation and cognitive function, communications skills and social adjustment were secondarily improved. When administered

as an oral solution to children and adolescents, the APZ dosage can be adjusted by parents for easy titration. Based on the above case review, APZ has moderate sedative, antidepressant, and antianxiety effects when used to treat ASDs. APZ can target symptoms such as anxiety, depression, and irritability. In addition, it can improve motivation, emotional stability, and communication ability, thus contributing to patients' increased quality of life. Furthermore, because of high tolerability, APZ can safely be administered to children. The risk of exacerbation, including disinhibition and acting out, is low in children and adolescents, in cases without a definitive diagnosis and across a multiple spectrum of disorders. Because the safety of antidepressants has not been established in children and adolescents, the antidepressant effects of APZ are highly needed in this group.

Limitation

This study has some limitations. First, randomized or blind studies are still limited; the majority of reports referenced here are open-label studies and case-reports. Conclusions drawn from such studies must be evaluated with caution, and further accumulation of controlled studies is needed. Second, studies evaluating long-term consequences of treatment with APZ, or effects of APZ on cognitive function and communications skills are limited. Further investigations will provide the answers to these problems, which are fundamental for clinicians. Third, the case reports included patients with various ages and diagnose among ASDs, and APZ regimen and non-pharmacologic approaches such as social skills training were not controlled. Furthermore, long-term prognoses of the cases were not evaluated. In this regard, case series with unified diagnosis, controlled APZ regime and non-pharmacologic approaches, and long-term observation are needed.

Conclusion

This paper reviewed the pharmacological profile and the outcomes of previous clinical studies of APZ in ASDs, and provided three cases of ASD patients treated with APZ. APZ reduces aggression observed in ASDs, and also improves qualitative disorders in interpersonal interactions, including communication skills, and motivation. In addition, compared with other antipsychotics, APZ causes fewer adverse events that can lead to drug discontinuation (e.g., EPS, weight gain, and sedation). Therefore, APZ is associated with excellent treatment compliance and is a promising drug to improve treatment outcomes in ASDs.

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