

Aripiprazole Improves Social Interaction in Taiwanese Children with Pervasive Developmental Disorder

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Aripiprazole, an atypical antipsychotic, is effective in children with psychosis and few adverse effects have been reported. However, little is known about the efficacy and safety of aripiprazole in the treatment of autistic or other pervasive developmental disorders. We report three children with pervasive developmental disorders who were treated with aripiprazole for associated behavioral syndromes. Aripiprazole significantly improved the social interaction of all three children. Furthermore, two patients also showed significant improvement in depression/anxiety syndromes. The outcomes achieved with aripiprazole in these cases suggest that it is a potential therapeutic agent for children with pervasive developmental disorders. (*Chang Gung Med J* 2010;33:211-5)

Key words: aripiprazole, pervasive developmental disorders, social interaction, attention

Aripiprazole is a quinolinone derivative that has a unique mechanism of action as a dopamine D2 partial agonist and is the most recent addition to the new class of atypical antipsychotic medications. Like other atypical antipsychotics, it displays potent 5HT2A antagonism and is similar to ziprasidone in having 5HT1A agonism.^(1,2) Aripiprazole has been reported to be an effective and well-tolerated treatment for children and adolescents with bipolar disorders and Tourette syndrome.^(3,4) However, little is known about the clinical efficacy and side effects of aripiprazole in children with pervasive developmental disorders. Here, we report three children with pervasive developmental disorders who were treated with aripiprazole for associated behavioral syndromes.

CASE REPORT

Case 1

This 9 year-old child was diagnosed with perva-

sive developmental disorder (PDD) that was not otherwise specified at the age of 5 years. He displayed marked impairment in social interaction, a lack of varied play associated with his age, a preoccupation with certain cloth materials and dinosaur toys and inadequate language skills. He also displayed severe inattentive symptoms in kindergarten and had trouble keeping up academically with his classmates. For these reasons he was started on methylphenidate 5 mg per day. The Wechsler Preschool and Primary Scale of Intelligence test showed his verbal intelligence quotient was 70, performance intelligence quotient 91 and full intelligence quotient 78. He made some progress in his academic performance with methylphenidate treatment but the dose was increased to 10 mg per day five months later in order to maintain this therapeutic effect. This dose was continued until he reached the age of seven years, when it was increased to 12.5 mg per day to maintain its effect. At the age of 8 years, his medication was changed to an osmotic controlled-release (OROS)

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formulation of methylphenidate, 36 mg per day. No side effects were noted, and his symptoms improved. One year later, he began to display hyperactive and impulsive behaviors with this treatment although he was able to concentrate on his school work. Methylphenidate treatment was discontinued and aripiprazole 5 mg per day was commenced. Approximately one week later, he was found to be less hyperactive; his academic performance improved and he was more active in his school activities. He was also more communicable and more compliant. To the surprise of his mother, he became eager to help others. Aripiprazole was discontinued in a trial off medication and he began to resume the original symptoms about two weeks later. Aripiprazole was therefore restarted and marked improvement was again noted two weeks later. All subscale scores in the Child Behavior Checklist (CBCL) improved with aripiprazole treatment (Table 1). Improvements in behavior and social interaction were maintained at the 9-month follow-up. No adverse effects were noted.

Case 2

A 7-year-old boy with an autistic disorder had a history of delayed speech, poor peer interaction and special interests in pyramids, tombs and coffins. Methylphenidate was prescribed when he was six years old because of poor concentration. The initial dose was 5 mg in the morning but he developed psychomotor retardation and lost his appetite when the dose was increased to 10 mg. A dose of 7.5 mg was

found to improve his concentration with few adverse effects. Despite this treatment, he had little interest in peer interaction. All these symptoms improved approximately one week after aripiprazole 5 mg was added each night. Increased sleepiness resolved after the first few days of aripiprazole treatment and no other adverse effects were noted. All subscale scores from the CBCL improved at follow-up three months after aripiprazole treatment was begun (Table 1). He remained preoccupied with his restricted interests so methylphenidate 7.5 mg per day was continued to treat his learning disability.

Case 3

An 11 year old boy with PDD that was not otherwise specified was treated with methylphenidate 10 mg twice a day to help his learning disability. His attention span improved only modestly after one week, so the dose was increased to 20 mg twice a day and it was noted that he could then concentrate in class. This dose was converted to OROS formulation methylphenidate 54 mg as he usually forgot to take his lunchtime dose. He remained slow and forgetful and his school performance improved only slightly. Six weeks later he showed some loss of interest, loss of pleasure, easy fatigability and poor appetite. Fluoxetine 20 mg per day was added. These symptoms improved two weeks after fluoxetine treatment was commenced and the OROS methylphenidate was discontinued during the winter vacation. During the following 8 months he took methylphenidate 20 mg three times per day on

Table 1. Child Behavior Checklist Subscale Scores in Cases 1 and 2 before and after Aripiprazole Treatment

	Anxious depressed	Withdrawn depressed	Somatic complaints	Social problems	Thought problems	Attention problems	Rule breaking behavior	Aggressive behavior	Internalizing	Externalizing	Total
Case 1											
Before	11	2	0	11	6	11	6	15	13	21	62
After	3	1	0	2	3	9	1	4	4	5	23
Case 2											
Before	20	12	4	19	20	19	27	31	36	58	152
After	6	7	3	12	14	11	14	26	16	40	93

A high number indicates a worse status.

school days but the therapeutic effect is thought to last only 1.5 hours. Bupropion 150 mg per day was substituted for methylphenidate but one month into treatment his appetite became worse and he began to exhibit disruptive behaviors. Bupropion was then changed to aripiprazole 5 mg per day and one week later his mother reported a marked improvement in his motor coordination and involvement in daily routines. He also became less stubborn, more able to express his thoughts, more skillful in solving problems and better mannered. Interaction with his peers also improved. His social function improved again one week after the dose of aripiprazole was increased to 20 mg per day. However, he still did poorly at school and this was attributed to poor memory function. Three weeks later, atomoxetine 25 mg per day was added to the regimen and this was titrated to 65 mg per day over four weeks. His concentration and memory both improved, and his school teacher reported that he was "gentler". The dose of aripiprazole was tapered to 5 mg per day to assess whether atomoxetine alone could help but he became irritable, self-centered and his memory and concentration deteriorated. Therefore, he restarted aripiprazole 20 mg per day and his symptoms began to improve again about 2-3 days later.

DISCUSSION

Currently, there are no pharmacological interventions that specifically target the core symptoms of PDD. However, studies have demonstrated that atypical antipsychotics and selective serotonin reuptake inhibitors may be beneficial for behavioral problems associated with PDD.⁽⁶⁾ To our knowledge, only two reports have been published about the use of aripiprazole in children with PDD. In both studies, treatment with aripiprazole led to significant improvements in aggressive, self-injurious and disruptive behavior.^(6,7) Similar to their findings, the aggressive behavior score was greatly reduced in Case 1 after treated with aripiprazole (from 15 to 4; Table 1). However, in Case 2, treatment with aripiprazole did not improve the aggressive behavior score much (31 to 26), suggesting aripiprazole could be of help for some aggressive behaviors but not all. In this report, aripiprazole significantly improved the social interaction of all three children with PDD. In the first case study, the medication not only improved the

patient's hyperactive symptoms but also some core PDD symptoms. The patient became more interested in school activities, more communicable and even became eager to help others. It should be noted that this effect was lost and then re-established with the discontinuation and re-introduction of this treatment, respectively. Similar improvements in social interaction were also observed in the second case study. The mechanism through which aripiprazole improves some core symptoms of PDD is not clear. Improved sociability has also been reported in patients with treatment-resistant schizophrenia when aripiprazole was added to augment the effect of clozapine.⁽⁸⁾ Bruins and colleagues demonstrated that aripiprazole improves deficits in phencyclidine-induced social interaction (an NMDA antagonist) in rats and hypothesized that this improvement was mediated through a D2 antagonist/5HT1A agonist effect.⁽⁹⁾ Further prospective large-scale studies are needed to better understand the therapeutic effects of aripiprazole in improving social and communication impairment in patients with PDD. In addition to improvements in social interaction, Cases 1 and 2 also showed significant improvement in depression and anxiety syndromes according to their CBCL scores. Aripiprazole has also been reported to improve depression and anxiety in patients with major depression as well as schizophrenia.^(10,11) It is thought that the therapeutic effect of aripiprazole in depression and anxiety is mediated by a potent partial agonistic effect at the 5HT1A receptor.^(10,11)

Many children with PDD have motor clumsiness in addition to social deficits. In the third case study, motor coordination improved with social interaction after taking aripiprazole. Dopaminergic dysfunction has been reported to be associated with decreased motor coordination and given that aripiprazole can be thought of as a dopamine system stabilizer, this may represent the mechanism of therapeutic action.^(12,13)

The encouraging outcomes achieved with aripiprazole in the three case studies described above offer new hope in the treatment of behavioral and core symptoms in children with PDD.

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Aripiprazole 改善台灣兒童廣泛性發展障礙之社交功能

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Aripiprazole 是一種非典型抗精神病藥物，過去研究顯示它對兒童精神病有療效並少有副作用，不過 Aripiprazole 對於兒童自閉症或廣泛性發展障礙的療效所知甚少。本研究我們報告 Aripiprazole 對三個兒童廣泛性發展障礙合併相關行為症狀的治療結果。Aripiprazole 對此三個個案之社交功能有顯著改善，其中兩名患者在抑鬱 / 焦慮症狀也有顯著改善。這些結果顯示 Aripiprazole 對兒童廣泛性發展障礙之社交功能可能有潛在的療效。(長庚醫誌 2010;33:211-5)

關鍵詞：Aripiprazole，兒童廣泛性發展障礙，社交功能，注意力