

Atypical Antipsychotics in Children and Adolescents With Autistic and Other Pervasive Developmental Disorders

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Atypical antipsychotics are emerging as the first-line pharmacologic treatment for irritability (i.e., aggression, self-injurious behavior, and severe tantrums) in children and adolescents with autistic and other pervasive developmental disorders. Results from placebo-controlled and open-label studies of clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole in this subject population are reviewed. Additional placebo-controlled trials and studies of longer-term safety and tolerability are needed.
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Autistic disorder (autism) and other pervasive developmental disorders (PDDs) are early onset brain-based syndromes characterized by impaired development in social interaction and communication and a restricted repertoire of activity and interests.¹ In addition to these core features, associated target symptoms of treatment often include hyperactivity and inattention, interfering stereotypical and repetitive behavior, and irritability (aggression, self-injurious behavior, and severe tantrums), among others.² The irritability can present as aggression, which is

often impulsive in nature and can result in substantial physical injury toward others or destruction of property. The self-injurious behavior may have a repetitive or compulsive quality and may be related to some element of sensory stimulation. At times, the self-injurious behavior can result in severe damage, including retinal detachment and subdural hematoma. These aggressive and self-injurious acts may be related to the individual experiencing frustration with his or her inability to communicate effectively or due to sensory sensitivities to visual, auditory, or tactile input. Clearly, aggression, self-injurious behavior, and severe tantrums can interfere with the educational or vocational environment for the individual and on-site staff, and require effective and often intensive intervention.³

This review will focus on the effectiveness of atypical antipsychotics for the treatment of irritability in children and adolescents with autism and other PDDs (Table 1). Adverse events associated with this class of drugs will be mentioned but are described in more detail in another article focused on that topic within this supplement.⁴

CLOZAPINE

Clozapine was the first atypical antipsychotic to be introduced in the United States. To our knowledge, there have been only 3 reports describing the use of clozapine in persons with autism.^{5–7} Zuddas et al.⁵ treated 3 children who displayed marked hyperactivity, fidgetiness, or aggression for up to 8 months with doses ranging from 200 to 450 mg/day. Two of the 3 children showed sustained improvement although the third had a return of symptoms to baseline levels after an initial response. Chen et al.⁶ reported the case of a 17-year-old male with autism and severe mental retardation who showed a marked reduction in signs of “overt tension,” hyperactivity, and repetitive motions in response to 275 mg/day of clozapine during a 15-day hospitalization. In the third report, a 32-year-old

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Table 1. Atypical Antipsychotics for Irritability in Children and Adolescents With Autistic and Other Pervasive Developmental Disorders

Drug	Studies	Symptoms Improved	Notable Side Effects
Clozapine	No placebo-controlled studies. Letters to the editor ⁵⁻⁷ have reported symptomatic improvement	Hyperactivity, aggression, repetitive behavior, social withdrawal	Constipation (mild), enuresis, sedation, sialorrhea
Risperidone	Risperidone (1.8 mg/d) > placebo in 101 children with autistic disorder ⁸	Aggression, hyperactivity, irritability, repetitive behavior	Hypersalivation, sedation, weight gain
	Risperidone (1.2 mg/d) > placebo in 79 children with pervasive developmental disorders ¹⁵	Aggression, hyperactivity, irritability, repetitive language and behavior, social withdrawal	Sedation, weight gain
	Risperidone (1 mg/d) > placebo in 40 young children with pervasive developmental disorders ¹⁷	Aggression, hyperactivity, nonverbal communication, social responsiveness	Sedation, weight gain
	Risperidone (1.1 mg/d) > placebo in 24 preschool children with pervasive developmental disorders ¹⁸	Mild improvement in autism severity	Hypersalivation, weight gain
Olanzapine	Olanzapine (10 mg/d) > placebo in 11 children with autistic disorder ²²	Global improvement	Sedation, weight gain
Quetiapine	No placebo-controlled studies. Four open-label investigations ²³⁻²⁶ have reported 22%–60% response rate (N = 6, 9, 20, and 10, respectively)	Aggression, hyperactivity, inattention	Agitation, sedation, weight gain
Ziprasidone	No placebo-controlled studies. One open-label investigation ²⁷ reported 50% response rate (N = 12)	Aggression, irritability	Sedation
Aripiprazole	No placebo-controlled studies. Three open-label investigations ²⁸⁻³⁰ have reported 37%–100% response rate (N = 5, 24, and 25, respectively)	Aggression, irritability	Extrapyramidal symptoms (mild), sedation, weight gain (mild)

man with autism and profound mental retardation showed markedly improved aggressiveness and social interaction after 2 months of treatment with 300 mg/day of clozapine.⁷ The patient had been refractory to numerous prior medication trials and had been admitted to the hospital frequently for self-inflicted injuries and to various institutions for harming his parents and destroying household items. The patient showed progressive improvement over a 5-year period.

Clozapine is rarely used clinically because it has the potential to cause life-threatening agranulocytosis and requires weekly to biweekly venipuncture to monitor white blood cell counts. Cognitively impaired children with high degrees of irritability often do not tolerate blood draws well. In addition, clozapine can lower the seizure threshold, probably to a degree greater than the other atypical antipsychotics.

RISPERIDONE

Multiple open-label reports and case series, as well as double-blind, placebo-controlled trials, have described the beneficial effects of risperidone for irritability in children and adolescents with autism and other PDDs.

The first double-blind, placebo-controlled study of risperidone in children and adolescents with autism was completed by the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network.⁸ A total of 101 children (mean age = 8.8 years) were randomly assigned to receive 8 weeks of risperidone or placebo. At baseline, all subjects had significant irritability, aggression, or self-injurious behavior as rated by an Aberrant Behavior Checklist (ABC)⁹ Irritability subscale score of 18 or

greater. Treatment with risperidone for 8 weeks (mean dose = 1.8 mg/day) resulted in a 57% reduction in the ABC Irritability subscale score compared with a 14% decrease in the placebo group. Of the risperidone-treated subjects, 69% were categorized as treatment responders, compared with 12% of those who received placebo. Risperidone was associated with an average weight gain of 5.9 lb, as compared with 1.8 lb with placebo. Drooling was more commonly reported with risperidone than placebo, but clinician-administered standardized measures of acute extrapyramidal symptoms (EPS) and tardive dyskinesia were not significantly different between groups.⁸

The RUPP Autism Network study also examined the other 4 subscales of the ABC, which include social withdrawal, stereotypy, hyperactivity, and inappropriate speech.⁸ Risperidone was associated with a greater improvement on these scales, but the reductions in social withdrawal and inappropriate speech were not statistically significant following Bonferroni correction for multiple comparisons. To further analyze the efficacy of risperidone for the core symptoms of autism in this group of subjects, McDougle et al.¹⁰ examined secondary outcome measures that included a modified Ritvo-Freeman Real Life Rating Scale (R-F RLRS)¹¹ and modified Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS).¹² On the R-F RLRS, significant improvement was seen on the following subscales: sensory motor behaviors ($p = .002$), affectual reactions ($p < .001$), and sensory responses ($p = .004$). However, there was no significant change on the social relationship to people or language subscales. Risperidone was more efficacious than placebo for reducing interfering repetitive behavior as measured with the CY-BOCS.¹⁰

A companion study to the initial 8-week acute risperidone trial by the RUPP Autism Network has also been published.¹³ In this study, 63 subjects who responded to 8 weeks of acute treatment continued on open-label risperidone for an additional 16 weeks. During this open-label continuation phase, the mean risperidone dose remained stable and there was no clinically significant worsening of target symptoms. Only 5 subjects discontinued the drug due to loss of effectiveness; 1 discontinued due to an adverse event. Subjects gained an average of 11.2 lb of body weight during the entire 6-month course of risperidone treatment. Thirty-two subjects who continued to be classified as responders after the 16-week continuation phase were then randomly assigned to continued risperidone treatment versus gradual placebo substitution over the course of 3 weeks. In subjects randomly assigned to placebo, 10 (62.5%) of 16 showed significant worsening of symptoms, compared with 2 (12.5%) of 16 subjects who continued on risperidone, suggesting that treatment with risperidone beyond 6 months is necessary to prevent relapse.¹³ This relapse with drug withdrawal has also been confirmed in another placebo-controlled discontinuation study of risperidone in PDDs.¹⁴

A second multicenter, placebo-controlled study of risperidone in children with PDDs was conducted in Canada.¹⁵ A total of 79 children (mean age = 7.5 years) were randomly assigned to either risperidone (mean dose = 1.2 mg/day) or placebo for 8 weeks. No specific entry criteria were reported other than a diagnosis of a PDD and a Childhood Autism Rating Scale (CARS)¹⁶ score greater than 30. The mean baseline ABC Irritability subscale score of 20, however, suggests that the subjects were highly symptomatic upon study entry. Risperidone was associated with a 64% reduction in ABC Irritability subscale scores versus 31% with placebo. Fifty-three percent of the risperidone-treated subjects were considered responders versus 18% of those given placebo. Significant improvement ($p \leq .05$) was seen on all 5 subscales of the ABC, but the greatest magnitude of improvement was observed for irritability and hyperactivity. Social withdrawal decreased by 63% in the risperidone group compared with 40% in the placebo group. Subjects treated with risperidone gained an average of 5.9 lb, whereas those who received placebo gained an average of 2.2 lb. There was no statistically significant difference between groups in measures of EPS.¹⁵

The results of these 2 randomized controlled trials of risperidone led to U.S. Food and Drug Administration (FDA) approval of risperidone for the treatment of irritability in children and adolescents with autism aged 5 to 16 years. At this time, risperidone is the only drug approved by the FDA for the treatment of symptoms in children and adolescents with autism or any other PDD.

Other investigators have studied risperidone in samples that included even younger children. Nagaraj et al.¹⁷ pub-

lished a study that included children with autism as young as 2 years using a 1 mg/day dose of risperidone. In this placebo-controlled trial involving 40 children (age range, 2 to 9 years), risperidone was highly efficacious as measured by ratings on the CARS and Children's Global Assessment Scale. In another recent study, Luby et al.¹⁸ also found some evidence for efficacy in a placebo-controlled trial of 24 children less than 6 years of age with PDDs. However, these investigators found risperidone (dose range, 0.5 to 1.5 mg/day) only minimally efficacious compared with placebo at 6 months, possibly owing to group differences at baseline or sample size. In the latter study, high degrees of irritability were not required for study entry. This too may have contributed to the limited observed improvement.

OLANZAPINE

Case reports, 2 open-label case series, a prospective open-label comparison trial with haloperidol, and a small placebo-controlled study have described positive responses to olanzapine in subjects with autism and other PDDs.

In a case series evaluating olanzapine (mean dose = 7.8 mg/day) monotherapy in children, adolescents, and adults with autism and other PDDs (age range, 5 to 42 years), Potenza et al.¹⁹ reported that 6 of 7 subjects who completed a 12-week open-label trial were responders. Significant improvement ($p < .05$) in overall symptoms of autism, motor restlessness or hyperactivity, social relatedness, affectual reactions, sensory responses, language usage, self-injurious behavior, aggression, irritability or anger, anxiety, and depressive symptoms was recorded. Changes in repetitive behavior did not occur for the group. The most prominent adverse events were increased appetite and weight gain in 6 subjects and sedation in 3 subjects. Significant EPS were not observed. The mean weight for the group of subjects increased from 137.5 lb at baseline to 155.9 lb after 12 weeks of treatment.

In a study employing a parallel groups design, 12 children with autism (mean age, 7.8 years) were randomly assigned to receive 6 weeks of open-label treatment with olanzapine (7.9 mg/day) or haloperidol (1.4 mg/day).²⁰ Five of 6 subjects in the olanzapine group and 3 of 6 in the haloperidol group were rated as responders. Weight gain from baseline to endpoint was significantly higher ($p = .04$) in the olanzapine group (mean weight change = 9 lb; range, 5.9 to 15.8 lb) compared with the haloperidol group (mean weight change = 3.2 lb; range, -5.5 to 8.8 lb).

In another open-label trial of olanzapine, 25 children (mean age = 11.2 years) with a PDD were treated with the drug (mean dose = 10.7 mg/day) for 3 months.²¹ In contrast to the 2 studies described above, olanzapine was effective in only 3 subjects (12%). The reason for the low response rate is unclear, but may have been related to the

relatively low level of disruptive behavior at study entry. In this study, the mean baseline ABC Irritability subscale score was 11, which is substantially less than that of the 2 large placebo-controlled studies of risperidone in children and adolescents with autism and other PDDs described earlier (26 and 20, respectively).^{8,15} The other 2 olanzapine trials discussed above had specific entry criteria based on degree of disruptive and irritable behavior.

One small placebo-controlled study of olanzapine has been published.²² In this study, 11 subjects (age range, 6 to 14 years) with a PDD were randomly assigned to receive either olanzapine (mean dose = 10 mg/day) or placebo for 8 weeks. Three of 6 subjects receiving olanzapine compared with 1 of 5 given placebo were judged treatment responders. The mean weight gain associated with the drug was 7.5 lb versus 1.5 lb with placebo.

QUETIAPINE

There are 4 published reports of quetiapine in the treatment of individuals with PDDs. In the first, Martin and colleagues²³ conducted a 16-week open-label study of quetiapine (mean dose = 225 mg/day) in 6 children and adolescents (age range, 6 to 15 years) with autism. Two of 6 subjects were judged responders, whereas the 4 other subjects discontinued treatment prematurely. Three subjects withdrew because of sedation or lack of response, and 1 subject dropped out after a possible seizure. Increased appetite and weight gain (range, 2 to 18 lb) were also reported. The investigators concluded that quetiapine was poorly tolerated and generally ineffective in this diagnostic group.

The second study involved a 12-week open-label trial of quetiapine (mean dose = 292 mg/day; range, 100 to 450 mg/day) in 9 adolescent males (mean age = 14.6 years; range, 12 to 17 years) with autism.²⁴ Six of 9 subjects completed the trial and 2 of 9 were judged responders. One subject discontinued quetiapine due to sedation and another discontinued due to agitation/aggression. Overall, adverse events reported for the group included sedation (N = 7), weight gain (N = 5), agitation (N = 4), and aggression (N = 2).

In a retrospective case series, 20 subjects with a PDD (mean age = 12.1 years; range, 5 to 28 years) who had been receiving quetiapine (mean dose = 249 mg/day; range, 25 to 600 mg/day) for at least 4 weeks (mean duration = 59.8 weeks; range, 4 to 180 weeks) were evaluated.²⁵ None of the subjects was being treated concurrently with another antipsychotic or mood-stabilizing agent. Eight of 20 subjects were judged responders to quetiapine. Adverse events occurred in 50% of subjects and led to drug discontinuation in 15% of cases.

In another retrospective case series, quetiapine (mean dose = 477 mg/day) was administered to 10 youths (age range, 5 to 19 years) with diagnoses of both a PDD and mental retardation.²⁶ Subjects receiving concomitant medi-

cations were included in the study if the dosages of those drugs were held constant during the trial. Clinically significant improvement was observed in symptoms of hyperactivity and inattention, and 6 of 10 subjects were judged responders to treatment. Adverse events were mild and included sedation, sialorrhea, and weight gain.

ZIPRASIDONE

A preliminary report on the effectiveness and safety of ziprasidone in children, adolescents, and young adults with autism has been published.²⁷ Twelve subjects (mean age = 11.6 years; range, 8 to 20 years), 9 with autism and 3 with PDD not otherwise specified (NOS), received open-label treatment with ziprasidone (mean dose = 59.2 mg/day; range, 20 to 120 mg/day) for at least 6 weeks (mean duration = 14.2 weeks; range, 6 to 30 weeks). Six of the 12 subjects were judged treatment responders with improvement noted in symptoms of aggression, agitation, and irritability. Transient sedation was the most common adverse event. No cardiovascular side effects, including chest pain, tachycardia, palpitations, dizziness, or syncope were observed or reported. The mean change in weight for the group was -5.8 lb (range, -35 to 6 lb). The weight loss was likely the result of a number of subjects being switched from other drugs that had caused substantial weight gain. Five subjects lost weight, 5 had no change, 1 gained weight, and 1 had no follow-up weight beyond the baseline measure. The FDA has raised some concerns about the potential for QTc interval prolongation with ziprasidone on the electrocardiogram. If ziprasidone is given to individuals with known cardiac disease or who are taking other drugs that can prolong the QTc interval, they should be monitored carefully.

ARIPIPRAZOLE

Results from preliminary studies of aripiprazole in children and adolescents with autism and other PDDs have been published. Stigler and colleagues²⁸ described their findings from a prospective, open-label case series involving 5 subjects (mean age = 12.2 years; range, 5 to 18 years) with autism treated with aripiprazole (mean dose = 12 mg/day; range, 10 to 15 mg/day) for an average of 12.8 weeks (range, 8 to 16 weeks). All 5 subjects were determined to be responders with clinically significant improvement noted in aggression, self-injurious behavior, and irritability. No acute EPS or clinically significant changes in heart rate or blood pressure occurred. Two subjects experienced mild transient somnolence. Two subjects lost weight, 2 had no change in weight, and 1 subject gained 1 lb (mean change in weight = -8.2 lb; range, -30 to 1 lb). The weight loss was likely secondary to discontinuation of prior treatment with other atypical antipsychotics that had led to substantial weight gain.

Valicenti-McDermott and Demb²⁹ subsequently reported results of a retrospective chart review of the first 32 children and adolescents they treated with aripiprazole (mean dose = 10.6 mg/day; range, 1.25 to 30 mg/day) for 6 to 15 months in a clinic for patients with developmental disabilities. The subjects ranged in age from 5 to 19 years (mean age = 10.9 years); 24 subjects had a PDD and 18 had mental retardation. Aripiprazole was found to be effective in 18 subjects (56%), including 9 (37%) of the 24 youth with a PDD. Side effects were reported in 50% of the subjects and led to drug discontinuation in 7 children. The mean body mass index at the beginning of treatment (N = 27) was 22.5 and at the end of treatment (N = 23) was 24.1. Weight gain was observed to be greater in subjects less than 12 years of age compared with the adolescents.

Most recently, Stigler et al.³⁰ presented results of a 14-week prospective open-label study of aripiprazole (mean dose = 7.8 mg/day; range, 2.5 to 15 mg/day) in 25 children and adolescents (mean age = 8.6 years; range, 5 to 17 years) with PDD NOS or Asperger's disorder. Twenty-two of 25 subjects were considered responders, with target symptoms of aggression, self-injurious behavior, and severe tantrums. The ABC Irritability subscale score decreased from a mean score of 29 at baseline to a mean score of 6.6 at study endpoint. Sixteen subjects experienced mild tiredness and 1 subject had moderate tiredness. Mild EPS were recorded in 6 subjects. Nineteen subjects gained weight during the study (mean = 2.3 lb; range, -3.3 to 7.7 lb).

CONCLUSION

Atypical antipsychotics are emerging as the first-line pharmacologic treatment for irritability (i.e., aggression, self-injurious behavior, and severe tantrums) in children and adolescents with autism and other PDDs. To date, results from double-blind, placebo-controlled trials support the use of risperidone for this purpose, as evidenced by the FDA's recent approval of risperidone for the treatment of irritability in children and adolescents with autism aged 5 to 16 years. Large-scale placebo-controlled investigations of olanzapine and aripiprazole in youth with autism are currently underway. Considering that autism and other PDDs are lifelong disorders, and many adults have persistent irritability, it will be important to study this class of drugs in this population as well. Results from a published placebo-controlled study of risperidone in adults with autism and PDD NOS indicated that irritability responds in a manner similar to that which has been reported in youth with autism.³¹ It is important to always balance the efficacy of any treatment with the potential short- and long-term adverse events associated with the drug. For this reason, additional longitudinal studies of potential adverse events associated with atypical antipsychotic use in chil-

dren and adolescents with autism are required. As newer atypical antipsychotics such as paliperidone³² and others with unique mechanisms of action are released, controlled studies in individuals with autism and other PDDs across the age range will be needed.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, aripiprazole, clozapine, haloperidol, olanzapine, paliperidone, quetiapine, and ziprasidone are not approved by the U.S. Food and Drug Administration for treating symptoms associated with autism. Risperidone is approved to treat the irritability associated with autistic disorder.

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