REVIEW ARTICLE

Pediatr Drugs 2007; 9 (4): 249-266
1174-5878/07/0004-0249/$44.95/0

Atypical Antipsychotics in Children with Pervasive Developmental Disorders

Benjamin Chavez,[1,2] *Mapy Chavez-Brown*,[3] *Michael A. Sopko Jr*[1] and *Jose A. Rey*[4]

1 Rutgers, State University of New Jersey, Piscataway, New Jersey, USA
2 Monmouth Medical Center, Long Branch, New Jersey, USA
3 Wagner College, Staten Island, New York, USA
4 Nova Southeastern University, Fort Lauderdale, Florida, USA

Contents

Abstract

The treatment of pervasive developmental disorders (PDDs) is a challenging task, which should include behavioral therapy modifications as well as pharmacologic therapy. There has been a lack of data on using medications in children with PDDs until recent years. Within the last 10 years, an increase in clinical research has attempted to provide efficacy and safety data to support the use of medications in children with PDDs. Double-blinded and open-label research of atypical antipsychotics has been of particular focus.

Evidence shows that atypical antipsychotics (AAs) may be useful in treating certain symptoms associated with PDDs, such as aggression, irritability, and self-injurious behavior. This article reviews the literature regarding the use of AAs in children with PDDs. Of the AAs, risperidone has the largest amount of evidence with five published double-blinded, placebo-controlled trials and nine open-label trials. These risperidone trials have consistently shown improvements in aggression, irritability, self-injurious behavior, temper tantrums, and quickly changing moods associated with autistic disorder and other PDDs. Data for the other AAs are limited, but ziprasidone and aripiprazole appear to be promising treatment options. Based on clinical trials, olanzapine and quetiapine have shown minimal clinical benefit and a high incidence of weight gain and sedation. It should

be noted that all AAs do have a risk of metabolic syndrome, and patients should be monitored appropriately while receiving these medications.

Overall, AAs can be beneficial in alleviating behavioral symptoms, and should be considered an appropriate therapeutic option, as part of a comprehensive treatment strategy, for children with PDD.

Pervasive developmental disorders (PDDs) are some of the most intriguing, fascinating, and puzzling childhood disorders. The five disorders encompassed under PDDs are: (i) autistic disorder; (ii) Asperger's disorder; (iii) childhood disintegrative disorder; (iv) Rett's disorder; and (v) PDD – not otherwise specified (PDD-NOS).[1] PDDs are neurobehavioral syndromes marked by qualitative impairments of social interaction and communication, and restricted, repetitive, and stereotypic patterns of behavior.[2] PDDs are spectrum disorders. Each disorder is defined by a specific set of behaviors in the areas of social skills, communication deficits, and stereotypic behavior; however, individuals within the spectrum can exhibit any combination of these behaviors in various degrees of severity.[1,3] A more detailed description of the behavior exhibited by individuals with each of these disorders is presented in table I.

The defining characteristics of autistic disorder that differentiate it from other disorders in the spectrum are substantial qualitative impairment of social interaction, greater qualitative impairment of communication, and restricted, repetitive, and stereotypic patterns of behavior, interests, and activities. These three defining features are present before the age of 3 years.[1,3,4]

The key essential characteristics of Asperger's disorder are severe and sustained deficits in social interaction as well as restricted repetitive patterns of behavior, interests, and activity. Unlike autistic disorder, individuals with Asperger's disorder do not present with significant delays in language, cognitive, or self-help skills.[1,3]

In terms of language development differences, the main difference between individuals with autistic disorder and those with Asperger's disorder is that the latter usually present with good language skills, but have trouble understanding the subtleties of language, such as irony and humor.[1] Both populations present with deficits in their perspective taking and empathy skills. Just like children with autistic disorder, children with Asperger's disorder are unable to comprehend what it means to interact with other people in an acceptable and appropriate manner.[5,6] Other behaviors emitted by individuals with Asperger's disorder are clumsiness, difficulty with fine-gross motor skills, preoccupation with one's own interests, difficulty judging one's own space, difficulty understanding other people's feelings, and repetitive and stereotypic behaviors.[3]

This article reviews the data available on the use of atypical antipsychotics (AAs) in children and adolescents with PDD, and discusses the possible relationship between AA pharmacology and the neurochemical aspects of PDDs; the epidemiology, etiology and comorbidity associated with PDDs are also discussed. A MEDLINE search (1988–January 2007) was conducted to find published reports regarding the use of AAs in PDDs. Keywords used were 'autism,' 'PDD,' 'risperidone,' 'olanzapine,' 'quetiapine,' 'ziprasidone,' 'aripiprazole,' 'clozapine,' and 'Asperger's.' Also, the references of the articles found were reviewed for other reports. All published, open-label, and double-blind studies in patients with PDDs aged ≤18 years were included. The PDDs included autistic disorder, Asperger's disorder, childhood disintegrative disorder, and PDD-NOS. Retrospective chart reviews and case reports were excluded, except those for clozapine (there were only two published case reports in the literature).

1. Epidemiology, Comorbidity and Etiology

1.1 Prevalence

The incidence of individuals diagnosed under the umbrella of PDDs in the US population continues to increase. Recent data from the Centers for Disease Control Prevention show that up to 1 in 166 individuals in the US will be diagnosed with one of the PDDs.[7] PDD-NOS is more common with a prevalence rate of 1 per several 100 children.[8] This higher incidence of PDD-NOS is partly due to the wide scope of its diagnostic criteria.[1] Rett's disorder and childhood disintegrative disorder are much rarer. The exact prevalence of Asperger's disorder is unknown, although it is commonly seen in clinical practice. The PDDs are four times more prevalent in males than in females, with the exception of Rett's disorder, which seems to occur exclusively in females.

1.2 Co-Existing Disorders

Individuals with PDDs have a higher risk of certain co-existing disorders, including attention-deficit disorder, congenital rubella syndrome, epileptic seizure, fragile X syndrome, learning disabilities, Tourette's disorder, and tuberous sclerosis.[3,9] Additionally, about 20–30% of individuals with autism will develop epilepsy by the time they reach adulthood.[9]

Table I. Characteristics of the different pervasive developmental disorders[1,2]

Disorder	Essential features	Course/prognosis	Other possible symptoms
Autistic disorder	Markedly abnormal or impaired development in social interaction and communication; restricted, repetitive, stereotypic patterns of behavior, interests, and activities	Onset before age 3 years; continuous course; only a small percentage go on to live and work independently. Language and intellect are strong factors for prognosis	Gaze aversion, no interest in making friends, preference for solitary activities, lack of awareness of others' feelings, repetition of words or phrases, lack of language skills, monotonous tone, preoccupation with one narrow subject, insisting on sameness, walking on tiptoe, rocking
Asperger's disorder	Impairments in all social skills areas, especially in the ability to interact socially with others; restricted, repetitive, and stereotypic patterns of behavior, interests, and activities. No delays in language skills. No impairment in cognitive development	Later onset than autistic disorder and symptoms are milder; social interaction difficulties become more noticeable at school; lifelong disorder but more functional than autistic disorder	Motor milestones may be delayed, motor clumsiness, nonspecific neurologic symptoms; shares some symptoms with autistic disorder
Childhood disintegrative disorder	Same deficits as those seen in autistic disorder	Marked regression in multiple areas of functioning after at least 2 years of normal development; occurs between 2 and 10 years of age; loss of skills usually plateau but can progress in more severe cases	Severe mental retardation, seizures or EEG abnormalities, neurologic or medical comorbidities
Rett's disorder	Deceleration of head growth between 5 and 48 months of age; poorly coordinated gait or trunk movements; stereotypic hand movements (hand-wringing); severe impairments in language skills	Normal development for first 5 months; loss of skills is persistent and progressive; recovery is limited. Reported only in females	Seizures or EEG abnormalities, severe or profound mental retardation, diminished social interaction
Pervasive development disorder – not otherwise specified	Presents with some of the deficits of the other disorders, but not enough to warrant a diagnosis under the other categories	Boundaries for this disorder are not clear; symptoms may not develop until a later age	Might have atypical symptoms or subthreshold symptoms

1.3 Proposed Etiology

Although the specific cause of each PDD is still unknown, there is agreement that a PDD is the result of a neurologic disorder that affects the normal functioning of an individual's brain, impacting upon their development in the social and communication skills areas.[5,6,10] Deficits in social cognition, central coherence, and executive function have been found in individuals diagnosed within the PDD spectrum.[5,6,10] It is clear that there is a correlation between PDDs and deficits in executive functions; however, it is not clear if these deficits cause the disorders, or if the disorders cause these deficits.[10]

It is important to note that individuals with injuries to the frontal lobes of the brain as well as those with other development disabilities have also shown deficits in social cognition as well as executive function.[10] Finally, recent research seems to suggest that the inability to imitate gestures, a common deficit in individuals with PDDs, might be associated with dyspraxia, which would indicate abnormalities in frontal/parietal-subcortical circuits, which are associated with the acquisition of the sensory representations of movement.[11]

Past research has shown that brain scans show differences in the shape and structure of the brain of individuals with autism and those without autism.[12] Current research continues to look at the role of heredity, genetics, and medical problems, as patterns of PDDs or related disabilities in many families seem to support a genetic basis to these disorders. More importantly, researchers are beginning to recognize that there might not be a single explanation for these disorders.[13] Results of a recent study by Williams et al.[14] suggest that autism might affect how the brain processes information, making it more of a global disorder than a social interaction disorder. Furthermore, ongoing research is looking at

the role of irregular segments of genetic code or other factors that might result in higher susceptibility to a diagnosis of PDD.[15] In addition, research continues to investigate the possibility that under certain conditions a cluster of unstable genes may interfere with brain development resulting in one of the disorders in the PDD spectrum.[16]

Additionally, other researchers are investigating other factors that might play a role in the onset of PDDs, such as problems during pregnancy or delivery and environment factors (i.e. viral infections, metabolic imbalances, exposure to environmental chemicals). Exposure to certain chemicals during pregnancy has been suspected to cause an increased incidence of PDD; however, initial research has not shown a definite link.[17]

Although initial research seemed to point to a link between vaccines and autism,[18] an investigation by a committee of the Institute of Medicine (Washington, DC, USA) in 2004 concluded that the available data showed no clear relationship between the measles-mumps-rubella vaccine and autism.[19] Furthermore, there are data from different countries showing no relationship between vaccines and autism.[20-22]

2. Pharmacotherapy and Educational/ Behavioral Interventions

Researchers and practitioners in the medical and education fields agree that there is no cure for PDDs, and all pharmacotherapies and other interventions are intended to address specific symptoms of the disorders. The majority of the professionals agree that early intervention is key.[23] Since PDDs are spectrum disorders, treatment should be tailored to each individual's specific deficits and assets.

As outlined by the National Institutes of Health (Bethesda, MD, USA), evidence-based treatment strategies include the use of medications and education/behavior intervention.[9] The use of highly structured and intensive skill-oriented education practices based on the principles of applied behavior analysis has been shown to help individuals with PDDs develop social and language skills.[3,24-26] A full review of behavior interventions is beyond the scope of this article; the reader is referred elsewhere for such an overview.[26,27]

Antidepressant medications are often prescribed to treat anxiety, depression, and or obsessive-compulsive symptoms in patients with PDDs. Antipsychotic medications are prescribed for those individuals with several behavior problems, such as aggression and irritability. Anticonvulsant medications are used to treat those individuals who present with seizures or mood disorders. Individuals who present with attention-deficit disorder characteristics are often treated with stimulant medications.

Historically, conventional antipsychotics, such as haloperidol, have been used to treat children with PDDs. They have targeted symptoms such as irritability, aggression, hyperactivity, stereotypic behavior, impulsivity, and social adaptation.[28,29] However, their use in this population has been limited because of the high incidence of movement disorders. With the introduction of atypical antipsychotics (AAs), which include risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and clozapine, a new treatment option for PDDs has emerged. However, this class of drugs does not come without their own risks, mainly weight gain and an increased risk of metabolic syndrome.[30]

Risperidone was the first AA to be rigorously studied in PDDs and has shown consistent efficacy. There is published trial data for the other AAs, but the evidence is not as extensive as with risperidone.

2.1 Efficacy of Atypical Antipsychotics

2.1.1 Risperidone

Double-Blind Studies

Data from the double-blind, placebo-controlled trials of risperidone in PDDs are summarized in table II and discussed in this section. For a more in-depth look at the risperidone studies reviewed here the reader is referred to a recently written article.[31]

The RUPPAN (Research Units on Pediatric Psychopharmacology Autism Network)[32] conducted an 8-week study evaluating the safety and efficacy of risperidone in autistic children with serious behavioral disturbances. Inclusion criteria were a diagnosis of autistic disorder as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), as well as a score of at least 18 on the irritability subscale on the Aberrant Behavior Checklist (ABC). The children must have also exhibited tantrums, aggression, self-injurious behaviors, or a combination of these problems. A total of 101 patients were enrolled in this study; 49 were assigned to risperidone (at 0.5 mg/day; final dose 1.8 ± 0.7 mg/day) and 52 were given placebo. Mental development was stated for only 91 patients: 5 had average or above average IQ, 12 had a borderline IQ, 43 had mild or moderate retardation, and 31 had severe retardation. To determine the children's baseline symptoms, the Clinical Global Impressions – Severity (CGI-S) scale was implemented. At baseline, 18 children had a moderate severity rating on the CGI-S, 55 had marked severity, 24 had severe impairment, and one was considered extremely impaired. Primary outcomes of this study were measured using the irritability subscale of the ABC and the Clinical Global Impressions – Improvement (CGI-I) rating.

After 8 weeks of treatment, risperidone-treated patients had a significantly greater decrease in the mean irritability score com-

Table II. Double-blind placebo-controlled trials of atypical antipsychotics in pervasive developmental disorders

Study	Study design	Active drug; mean final dosage	No. of pts (males); age range (y)	Efficacy outcomes	Symptoms improved
Research Units on Pediatric Psychopharmacology Autism Network[32,33]	Phase I: 8wk, db, pc	RIS; 1.8 ± 0.7 mg/d	101 (82); 5–17	Mean ABC irritability score: 56.9% decrease with RIS (from 26.2 ± 7.9 at baseline to 11.3 ± 7.4 at 8wk) vs 14.1% decrease with PLA (from 25.5 ± 6.6 to 21.9 ± 9.5) [p < 0.001]	Irritability, stereotypy, hyperactivity, tantrums, aggression, self-injurious behavior
	Phase II: 4mo, open	RIS; wk 0: 1.96 mg/d; wk 4: 1.80 mg/d; wk 8: 1.87 mg/d; wk 12: 2.10 mg/d; wk 16: 2.08 mg/d	63 (49)	CGI-I scale: VMI: n = 19; MI: n = 33; Min I: n = 6	
	Phase III: 8wk, PLA discontinuation protocol	NA	38 (not given)	62.5% on PLA relapsed vs 12.5% on RIS (p = 0.01)	
Shea et al.[34]	8wk, db, pc	RIS; 1.17 mg/d (0.04 mg/kg/d)	79 (61); 5–12	Mean ABC irritability score: decrease from 18.9 at baseline to 6.8 at study endpoint with RIS vs decrease from 21.2 to 14.7 with PLA (p < 0.001) CGI-I: VMI or MI: n = 21 with RIS vs n = 7 with PLA (p < 0.001)	Irritability, hyperactivity, inappropriate speech, social withdrawal, stereotypic and conduct behavior, anxiety, emotional sensitivity
Nagaraj et al.[35]	6mo, db, pc	RIS; 0.5 mg/d for first 2wk and then 1 mg/d for subsequent period	39 (34); 2–9	CARS: 12/19 RIS and 0/20 PLA pts improved by ≥20% from baseline (p < 0.001) CGAS: 17/19 RIS and 2/20 PLA pts improved by ≥20% from baseline (p = 0.035) Global Impression of Parents: with RIS 9/19 'improved to some extent;' 9/19 'considerably improved;' 1/19 worsened with PLA 6/20 'improved to some extent;' 9/20 'no change;' 4/20 worsened	Social responsiveness, non-verbal communication, hyperactivity, aggression, irritability
Troost et al.[36]	Phase I: 6mo, open	RIS; 1.81 mg/d	36 (22); 5–17	26 were considered responders	Irritability, hyperactivity, self-injurious behavior, social withdrawal
	Phase II: 8wk db discontinuation phase		24 of the 26 responders in phase I	8/12 on PLA experienced relapse vs 3/12 on RIS (p = 0.049)	
Luby et al.[37]	6mo, db, pc	RIS; 1.14 mg/d (range: 0.5–1.5 mg/d)	23 (17); 2.5–6	CARS: RIS −4.6, PLA −1.8 (p = 0.114)	No specific symptoms improved over placebo
Hollander et al.[38]	8wk, db, pc	OLZ; 10 mg/d (range: 7.5–12.5 mg/d)	11 (9); 6–14	CGI-I VMI/MI: OLZ 3/6, PLA 1/5	Global functioning; no significant improvement in any specific symptom

ABC = Aberrant Behaviour Checklist; **CARS** = Childhood Autism Rating Scale; **CGAS** = Children's Global Assessment Scale; **CGI-I** = Clinical Global Impressions-Improvement; **d** = day; **db** = double-blind; **MI** = much improved; **Min I** = minimally improved; **NA** = not applicable; **OLZ** = olanzapine; **open** = open label; **pc** = placebo-controlled; **PLA** = placebo; **pts** = patients; **RIS** = risperidone; **VMI** = very much improved.

pared with placebo recipients (from 26.2 ± 7.9 to 11.3 ± 7.4 and from 25.5 ± 6.6 to 21.9 ± 9.5; $p < 0.001$). Also, 75.5% of risperidone-treated patients had a rating of 'much improved' or 'very much improved' on the CGI-I, whereas only 11.5% of placebo patients had these ratings ($p < 0.001$). A positive response was defined as having at least a 25% improvement on the irritability subscale, as well as having a rating of 'much improved' or 'very much improved' on the CGI-I scale; 69% (34 of 49) of risperidone-treated patients had a positive response, compared with only 11.5% (6 of 52) placebo patients ($p < 0.001$). In the risperidone-treated group, the adverse effects with the highest incidence rate were weight gain, increased appetite (73%), fatigue (59%), and drowsiness (49%). The average weight gain in risperidone-treated patients was 2.7 ± 2.9kg compared with 0.8 ± 2.2kg for placebo recipients ($p < 0.001$). No extrapyramidal symptoms (EPS) were reported in either group. Three patients withdrew from the risperidone group compared with 12 from the placebo group because of a lack of efficacy. No patients withdrew from either group because of an adverse effect.

After the original 8-week study period, placebo non-responders were given the option to enter an 8-week open-label treatment period with risperidone. Patients that had a positive response during this phase, as well as those with a positive response during the initial 8-week double-blinded trial, were allowed to enter a 4-month open-label extension, with an additional 8-week double-blinded discontinuation phase.[33] Patients that entered the discontinuation phase either continued risperidone therapy or were gradually tapered off by 25% per week whilst given placebo. Sixty-three patients entered the 4-month open-label phase. The irritability subscale on the ABC and the CGI-I were again the primary outcome measures. The positive response definition in this phase was the same as in the 8-week phase. Relapse was defined as a 25% increase in the irritability subscale score, and a CGI-I rating of 'much worse' or 'very much worse' in the discontinuation phase. The maximum dosage during the 4-month open-label phase was 3.5 mg/day for patients weighing 15–45kg and 4.5 mg/day for patients weighing >45kg. Fifty-one patients completed the open-label phase, and all of these patients maintained a positive response. The most common adverse effects were increased appetite, sedation, and lethargy. Risperidone-treated patients experienced an average weight gain of 5.1 ± 3.6kg over 6 months, which was significantly higher than that in placebo recipients ($p < 0.001$). The Abnormal and Involuntary Movement Scale (AIMS) and the Simpson-Angus scale showed no evidence of EPS or other neurologic adverse effects. Of these 51 patients, 38 entered the discontinuation phase, and 32 completed it. This phase was terminated early due to a high relapse rate in the placebo group (10 of 16); 2 of 16 risperidone-treated patients also relapsed.

A separate report by Aman et al.[39] specifically focused on the acute and long-term safety and tolerability of risperidone in the RUPPAN study.[32] The short-term, double-blind study safety results, as well as the open-label extension and discontinuation phase results were included in this examination.[33] Adverse effects that were significantly more prevalent in the risperidone-treated group were as follows: tiredness during the day ($p < 0.0001$); excessive appetite ($p < 0.0001$); difficulty waking ($p < 0.05$); excessive saliva or drooling ($p = 0.04$); and dizziness or loss of balance ($p = 0.04$). However, risperidone-treated patients had fewer occurrences of anxiety ($p = 0.05$) and problems falling asleep ($p = 0.02$) than the placebo group. In the acute phase, risperidone-treated patients had an average increase in sleep time of 40 minutes, compared with only a 17-minute increase for placebo patients. There were no clinically significant changes in laboratory values; however, fasting glucose and lipid values were not mentioned. In accordance with other studies,[40] both body mass index and weight increased significantly with the use of risperidone. This increase continued throughout the study, but gradually decelerated. Also, 82% of risperidone-treated patients displayed an excessive appetite, compared with 38% of placebo patients. There were no differences between the groups in terms of heart rate, body temperature, or blood pressure throughout the entire study. In reference to the Simpson-Angus rating scale and the AIMS, data failed to suggest that risperidone caused more EPS than placebo. However, benzatropine was given to one patient for motor restlessness, and at least one patient had dose-dependent cogwheel rigidity while taking risperidone.

Prolactin-related adverse events in the RUPPAN study were examined in a separate publication.[41] Prolactin levels were two to four times higher in patients receiving risperidone versus placebo. Prolactin levels were assessed at baseline, 8 weeks, 6 months, and 22 months; the results with risperidone were 9.3 ± 7.5 ng/mL, 39.0 ± 19.2 ng/mL, 39.0 ± 19.2 ng/mL, 32.4 ± 17.8 ng/mL, and 25.3 ± 15.6 ng/mL, respectively. The placebo results were 9.3 ± 7.6 ng/mL at baseline and 10.1 ± 7.8 ng/mL ($p < 0.0001$), at 8 weeks. There were no prolactin-related adverse effects in the subset of 42 risperidone recipients reviewed in this study. These results are consistent with previously reported data showing an initial increase in prolactin levels with risperidone with a gradual decrease afterwards.[42]

McDougle et al.[43] performed an analysis of the RUPPAN database[32] but focused on the core symptoms of autism (social impairment, lack of communication skills, stereotypic movements) instead of the maladaptive behaviors. The objective of this analysis was to determine if risperidone improved the core symptoms of autism. In order to ascertain this, a modified Ritvo-Freeman Real Life Rating Scale (R-FRLRS) and the Children's

Yale-Brown Obsessive Compulsive Scale (CY-BOCS) were used. The modified R-FRLRS used the original subscales, but rephrased certain words so that parents could use the scale. The five subscales were sensory motor behaviors, social relatedness, affectual reactions, sensory responses, and language. At week 8, risperidone was more efficacious than placebo at improving the scores for the sensory motor behaviors, affectual reactions, and sensory responses subscales, as well as the overall scores. However, the changes in two of the core areas, social relationships and language, were not statistically significant. The CY-BOCS, which is normally used for obsessive-compulsive disorder, was modified to better assess autism. The modifications made were to only include the compulsion items and also to add autism-specific symptoms. At week 8, the risperidone group improved on the CY-BOCS with scores decreasing from 15.51 ± 2.73 to 11.65 ± 4.02 compared with the placebo group with scores decreasing from 15.18 ± 3.88 to only 14.21 ± 4.81 ($p = 0.005$).

Yet another sub-analysis from the RUPPAN on the same patient population showed significant improvement in communication socialization and in daily living skills for children receiving risperidone compared with placebo based on the Vineland Adaptive Behavior scale.[44]

Shea et al.[34] evaluated the safety and efficacy of risperidone in the treatment of disruptive behavioral symptoms in children with autism and other PDDs. Patients needed to have a diagnosis of a PDD as defined by the DSM-IV, and to also have a Childhood Autism Rating Scale (CARS) total score of >30, with or without mental retardation. Exclusion criteria were any concomitant medical or psychiatric disorders, and a seizure disorder that was being treated with more than one anticonvulsant. Medications to treat EPS were discontinued, but could be used throughout the trial if EPS occurred. Risperidone oral solution was used in this study, and dosing was weight based. The maximum dose was 0.06 mg/kg/day. Seventy-nine children were randomized to receive either risperidone ($n = 40$) or placebo ($n = 39$). The diagnoses were as follows: autistic disorder ($n = 55$), Asperger's disorder ($n = 12$), childhood disintegrative disorder ($n = 1$), and PDD-NOS ($n = 11$). Fourteen children had normal IQ scores, ten had borderline IQ scores, 20 had mild retardation, and 22 had severe retardation. The primary outcome was the change in the irritability subscale on the ABC.

By week 2, risperidone-treated patients had a statistically significant decrease in the irritability subscale score ($p \leq 0.001$) compared with placebo and by week 8, risperidone-treated patients improved by a mean of 12.1 points compared with 6.5 points in the placebo group ($p \leq 0.001$). The risperidone-treated group also displayed a statistically significant improvement in the other subscales of the ABC; hyperactivity/non-adherence, inappropriate speech, lethargy/social withdrawal, and stereotypic behavior. Risperidone-treated patients also showed improvement in the parent-rated Nisonger-Child Behavior Rating Form (N-CBRF) in regard to conduct problems ($p \leq 0.01$), insecurity/anxiety ($p = 0.039$), hyperactivity ($p = 0.035$), and overly sensitive ($p = 0.038$) subscales. In terms of the CGI-I, 21 risperidone-treated patients were rated as 'much improved' or 'very much improved' compared with only seven patients in the placebo group. Seventy-one percent of risperidone-treated patients reported having somnolence versus 7.7% of placebo patients. The mean weight gain increase for risperidone-treated patients was 2.7kg versus 1kg in the placebo group. Increased appetite, tachycardia, and increased systolic pressure were also reported at a significantly higher incidence with risperidone than placebo. EPS were reported in eleven risperidone-treated patients and five placebo-treated patients. For the risperidone group, tremor and hypokinesia were the most common EPS.

Nagaraj et al.[35] conducted a 6-month, randomized, double-blind, placebo-controlled study to determine if risperidone can improve the behavior, social, and emotional responsiveness, and communication skills in children with autism. The researchers also recorded the safety of risperidone throughout the trial. Participants all had a diagnosis of autism according to the DSM-IV. Patients with severe mental retardation or any significant coexisting disease or illness were excluded. Risperidone was administered at 0.5 mg/day orally for the first 2 weeks and 1 mg/day for the rest of the study. Concomitant drugs were not permitted, except antiepileptic drugs for children with epilepsy. A total of 39 children completed the study; 19 were given risperidone. Baseline characteristics were similar between the two groups. Ninety-two percent of patients had experienced irritability, and all children had some level of language impairment. Other symptoms at baseline were withdrawal, aloofness, or inattention in 50% of patients, hyperactivity in 70% of patients, and 75% of patients had restricted patterns of interests.

Twelve of 19 risperidone-treated patients displayed a response (improvement of at least 20% from baseline on the CARS) compared with no children in the placebo group. On the Children's Global Assessment Scale, 17 of 19 risperidone-treated patients had a response (increase from baseline of at least 20%), whereas only two placebo patients exhibited similar success. A 95% response rate was seen with risperidone-treated patients on the Global Impression of Parents survey, with 9 of 19 patients rated as 'improved to some extent,' and 9 of 19 of patients rated as 'considerably improved.' Only one patient was reported as having a lower level of functioning. An analysis of the items on the parent questionnaire revealed that risperidone significantly improved social responsiveness in 7 of 19 patients, non-verbal communication in 8 patients, decreased symptoms of hyperactivity in 7 patients,

and improved aggression and irritability in 5 patients. However, there was no benefit shown for risperidone with regard to restricted interests, emotional interaction, verbal communication, or speech. Adverse effects reported at a higher incidence for the risperidone-treated group were increased appetite, improved eating habits, and weight gain, although these changes were not statistically significant. All risperidone-treated patients experienced regularization of sleep habits, daily feeding, and play routines. Parents reported that the children were more easily managed while taking risperidone. Three children experienced dyskinesias, but these were mild and transient and did not require discontinuation from the trial. In the discontinuation phase, nine children experienced a relapse of disruptive behavior within 3 weeks of stopping risperidone therapy. Seven children continued to have a lack of disruptive symptoms after discontinuing risperidone therapy, and were considered to have consistent improvement. The other three children were considered to be stable after discontinuation.

Troost et al.[36] conducted a 6-month open-label trial of risperidone (mean final dose 1.8 mg/day) in patients with PDDs followed by an 8-week, double-blind, discontinuation phase. There were 36 children who entered the open-label phase. Twenty-four of these children completed the first part of this study, were considered to be responders according to the CGI-I, and entered the double-blind discontinuation phase. Irritability, hyperactivity, self-injurious behavior, and social withdrawal scores on the ABC significantly improved over the 6 months. Baseline characteristics are only given for these 24 children. Six children had a diagnosis of autism spectrum disorder, two of Asperger's disorder, and 16 of PDD-NOS. Fifteen children had an average or above average IQ, seven had a borderline IQ, and only two had mild-to-moderate mental retardation. The double-blind discontinuation phase involved one group continuing with risperidone, while the other had their dose reduced by 25% every week for 3 weeks followed by placebo for an additional 5 weeks.

Eight of the 12 children in the placebo group relapsed versus 3 of 12 children receiving risperidone. However, a set definition of relapse does not appear to have been predefined by the authors. Only the ABC irritability subscale showed a statistically significant difference at the end of the discontinuation phase (60% increase in placebo patients, 14% increase in risperidone-treated patients). No withdrawal adverse effects were reported.

Luby et al.[37] evaluated the use of risperidone in 23 preschool children (aged 2.5–6 years) with autistic spectrum disorder in a 6-month, double-blind, placebo-controlled trial. This is the youngest patient population studied in clinical trials of AAs in autism. Dosing was lower than in other trials, with a mean starting and final dose of 0.5mg and 1.14 mg, respectively. Risperidone was titrated and dosed by an unblinded child psychiatrist. It is important to note that all patients in this trial were undergoing concurrent applied behavior analysis therapy. The CARS was used as the primary outcome measure in this trial. A score of 30–37 is indicative of mild-to-moderate severity of symptoms, and a score of >37 is indicative of severe autism symptoms. Of interest in this trial is that the risperidone-treatment group had a higher baseline CARS score than the placebo recipients (37.6 ± 4 vs 33.3 ± 4.9). However, this was accounted for when performing the statistical analysis.

Risperidone-treated patients had a nonsignificantly greater improvement in the overall CARS score than placebo-treated patients (−4.6 vs −1.8) from baseline to endpoint at 6 months. The average CARS score in the risperidone group did decrease from 'severely autistic' to 'mildly to moderately autistic,' while classifications did not change in the placebo group. However, the only subscale to show any significant improvement was the CARS Emotional Response subscale. Other subscales, including symptoms such as adaptation, fear and nervousness, anxiety, and socialization did not show improvement compared with placebo. Weight gain was 2.96 ± 2.53kg in the risperidone group and 0.61 ± 1.10kg in the placebo group. Transient sedation was also a common adverse event in risperidone-treated patients. Prolactin levels increased significantly more in the risperidone-treatment group (33.38 ± 14.48 ng/mL vs 11.11 ± 18.74 ng/mL) but no prolactin-related adverse events were reported. No EPS were reported.

Open-Label Studies

There are nine open-label trials regarding the use of risperidone in autism;[45-53] data are summarized in table III. Because of the open-label design, the large number of trials, and their similar positive results, the open-label studies are summarized to a lesser extent than the double-blind trials.

The first open-label study on risperidone in children with PDDs was conducted by Fisman and Steele.[53] Thirteen of the 14 enrolled patients improved based on the Children's Global Assessment Scale. Behaviors that improved were agitation, anxiety, disruptive behaviors, and social awareness. Initial sedation was the most common adverse effect in this study. No EPS were reported in this study either.

Rausch et al.[45] approached the use of risperidone differently than in other trials. The goal of their 12-week open-label study was to determine if risperidone was effective for the 'negative symptoms' of 13 children with Asperger's disorder. They proposed that certain symptoms in Asperger's disorder are similar to negative symptoms seen in other psychiatric illnesses, such as schizophrenia. These symptoms include a lack of social interaction, lack of emotional reciprocity, depression, and a lack of speech. This study used the Scale for the Assessment of Negative Symptoms (SANS),

the Asperger's Syndrome Diagnostic Scale (ASDS), and the Montgomery-Åsberg Depression Rating Scale (MADRS) as their outcome measures. Risperidone treatment was initiated at 0.5 mg/day with a final dosage range of 0.5–1.5 mg/day. Nine children completed the 12-week study.

There was a statistically significant decrease in each of the assessment scales and their subcategories which included language dysfunction, social behavior, maladaptive behavior, cognitive dysfunction, sensorimotor dysfunction, and general dysfunction. These results seem to contradict those of McDougle et al. (see the Double-Blind Studies section),[43] who reported no improve-

Table III. Open-label trials of risperidone in pervasive developmental disorders

Study	Study duration	No. of pts (males); age range (y)	Mean final dosage (range)	Primary efficacy outcome	Symptoms improved
Rausch et al.[45]	12wk	13 (13); 6–18	No mean given (0.5–1.5 mg/day)	SANS: 41.5 at baseline; 24.3 at wk 12	Negative symptoms, social and maladaptive behavior, cognitive and general dysfunction
Malone et al.[46]	Initial 1mo; additional 6mo if responder	22 (18); 2–16	1mo: 1.2 mg/day (0.5–2.5 mg/day) 6mo: 1.8 mg/day (0.5–4 mg/day)	CGI-I 1mo: VMI: n = 4; MI: n = 13; Min I: n = 4; no change: n = 1	Hyperactivity, anger, labile affect, uncooperativeness
				CGI-I 6mo: VMI: n = 6; MI: n = 4; Min I: n = 1	
Diler et al.[47]	6mo	20 (14); 3–7	1.5 mg/day (1–2 mg/day)	CARS: 39.06 at baseline vs 32.03 at 6mo	Relating to people, imitation, adaptation to change, visual and listening response, object use
				CGI-S: improved in 13 pts	
Zuddas et al.[48]	6m; additional 6mo if responder	11 (8); 7–17	2.7 mg/day (1–6 mg/day)	CGI-I 6mo: VMI: n = 7; MI: n = 3	Hyperactivity, anger, uncooperativeness
				CGI-I: 12mo same as 6mo	
Nicolson et al.[49]	12wk	10 (10); 4–10	1.3 mg/day (1–2.5 mg/day)	CGI-I: VMI or MI: n = 8	Hyperactivity, aggression, social withdrawal, rhythmic motions, abnormal object relation
				CARS: mean decrease of 20% from baseline	
Findling et al.[50]	8wk	6 (6); 5–9	1.1 mg/day	CPRS: 32.3 at baseline vs 13.5 at wk 8	Restlessness, tantrums, irritability, fearfulness, aggression
McDougle et al.[51]	12wk	18 (15); 5–19	1.8 mg/day (1–4 mg/day)	CGI-I: VMI: n = 3; MI: n = 9;Y-BOCS: 15 at baseline vs 10.3 at 12wk	Aggression, impulsivity, repetitive behavior, sensory response
Horrigan et al.[52]	4wk	6 (6)[a]; 6–17	1 mg/day (0.5–1.5 mg/day)	CGI-I: VMI: n = 4; MI: n = 2	Aggression, self-injurious behavior, explosivity, sleep, hyperactivity
Fisman and Steele[53]	8wk, followed up to 14mo	14 (10); 9–17	No mean given (0.75–1.5 mg/day)	CGAS improvement by 1–2 levels in all pts	Agitation, anxiety, aggression, hyperactivity, temper outbursts

a Five patients in this study were aged ≥18y, and were removed from the data analysis.

CARS = Childhood Autism Rating Scale; **CGAS** = Children's Global Assessment Scale; **CGI-I** = Clinical Global Impression – Improvement (reported as no. of pts); **CGI-S** = Clinical Global Impression – Severity; **CPRS** = Children's Psychiatric Rating Scale; **MI** = much improved; **Min I** = minimally improved; **pts** = patients; **SANS** = Scale for Assessment of Negative Symptoms; **VMI** = very much improved; **Y-BOCS** = Yale-Brown Obsessive Compulsive Scale.

ment in social and communication skills. However, unlike the patients in the latter study who all had a diagnosis of autism, patients in this study had Asberger disorder. Perhaps the severity of illness may play a role in the response. Weight gain was again a common adverse effect in this study (average increase of 5.1kg). Other adverse effects included sedation and EPS (three cases); one of the latter patients withdraw from the study due to akathisia while the other two cases were not severe enough to warrant discontinuation of treatment.

Malone et al.[46] conducted a study of 22 autistic children over two phases. In the first phase, which was 1 month in duration, the children received risperidone at a mean dosage of 1.2 mg/day. Thirteen children were considered responders at the end of that month and continued on for a 6-month treatment period. At the end of the second phase, ten patients were considered responders based on the Children's Psychiatric Rating Scale (CPRS) and the CGI-I. The mean dosage at the end of the second phase was 1.8 mg/day. The most common adverse events were sedation, appetite increase, and weight gain averaging 3.3kg. None of the children experienced dyskinesias in the second phase; however, two children did develop withdrawal dyskinesias, which resolved within 2–3 weeks after discontinuation.

Diler et al.[47] investigated risperidone (mean dose 1.5 mg/day) in 20 autistic children in a 6-month open-label study. Sixteen children completed the study, and 13 were considered responders based on the CGI-I. The patients also had a significant reduction in their CARS scores at the end of 6 months. The most frequent adverse events were again sedation and weight gain; however, only two patients experienced weight gain, and both gained <10% of their weight. There was one case of akathisia in this study.

Zuddas et al.[48] conducted a study on 11 children and adolescents for 6 months. Nine children had a diagnosis of autism, and two children were diagnosed with PDD-NOS. Risperidone was started at 0.5 mg/day and titrated according to the response. Ten patients were considered responders at the end of 6 months. Along with sedation and weight gain, there were also two cases of dystonia and amenorrhea each. The higher mean dose (2.7 mg/day) used in this study than in the other open-label trials could account for the increased incidence of those adverse effects. Patients could elect to receive risperidone and to be followed for 6 additional months. Patients who elected to continue receiving risperidone were still stable at the end of 12 months. Patients who discontinued therapy before 12 months experienced a relapse in their behavioral symptoms.

Nicolson et al.[49] conducted a 12-week open-label study in ten autistic children. Patients were started on risperidone 0.5 mg/day. Based on the CGI-I and the CPRS, eight of ten children were considered responders. Sedation and weight gain (average 3.5kg) were again the most common adverse events reported.

Findling et al.[50] conducted a pilot study of risperidone in six autistic children over 8 weeks. All children completed the study, and had improvements in restlessness, tantrums, irritability, fearfulness, and aggression. There was also improvements in their CPRS scores and CGI-I ratings. Again, sedation and weight gain were the most common adverse events. There was one case of EPS in this study.

McDougle et al.[51] studied risperidone in 18 children during a 12-week open-label trial. Eleven patients had a diagnosis of autistic disorder, three had Asperger's disorder, one had childhood disintegrative disorder, and three had PDD-NOS. Risperidone was initiated at 0.5 mg/day and increased by 0.5mg increments. At the end of 12 weeks, 12 patients were considered responders based on their CGI-I, with improvements in aggression, impulsivity, and repetitive behavior. Weight gain occurred with an average increase of 7.9kg, higher than seen in other trials. Sedation was also a commonly reported adverse event. Two patients experienced a transient increase in heart rate 1–2 hours after drug intake, but no other complications were seen.

One of the earlier studies on risperidone examined 11 autistic patients.[52] Six of these patients were aged ≤17 years. Only the results for those six patients are discussed here; all had moderate-to-severe mental retardation. Five of these children finished the 4-week open-label trial with four having marked improvement based on the CGI-I, and one having moderate improvement. Conner scale scores also improved in these patients; a decrease in aggression was seen. However, this small study allowed concomitant medications, and the four patients who had marked improvement were also receiving other treatments (clonidine, valproic acid, clomipramine, cyproheptadine, and propranolol). Four patients also experienced weight gain. No EPS were reported.

2.1.2 Olanzapine

There are three trials involving the use of olanzapine in children with PDDs that match the criteria for this review; a total of 48 patients were involved and results are summarized in tables II and IV.[38,54,55] A fourth trial by Potenza et al.[56] was not reviewed because it involved both children and adults and it was not possible to single out the pediatric data.

The only double-blind, placebo-controlled trial of olanzapine in autism was conducted by Hollander et al.[38] It was a small trial with only 11 patients (six in the olanzapine arm, five in the placebo arm). Children in the active treatment arm were started on olanzapine 2.5mg every other day if <40kg in bodyweight, or 2.5mg every day if >40kg. The dosage was increased 3 days later

to 5 mg/day, and increased in 5mg increments weekly to a maximum of 20 mg/day.

The CGI-I was the primary outcome measure, with three of six children in the olanzapine-treatment group meeting the *a priori* criteria for a responder. One of the five children in the placebo group was considered a responder. However, there was no statistical improvement in any of the symptom scales, including the CY-BOCS and the Overt Aggression Scale – Modified, which evaluated aggression and irritability. Weight gain was the most common adverse event seen in this trial, with the average weight gain in the olanzapine treatment arm being 3.4 ± 2.2kg and 0.7 ± 0.7kg in the placebo group ($p = 0.028$). Four of six children treated with olanzapine gained more than 7% of their weight. Increased appetite and sedation were also common adverse events.

Malone et al.[54] conducted the only active comparator study to date regarding the use of AAs in PDDs. They compared olanzapine versus haloperidol in an open-label 6-week trial. Twelve children were enrolled and were randomly distributed into either treatment group; the two treatment groups had similar demographics. Eleven of the patients met the criteria for diagnosis of autistic disorder and one had a diagnosis of PDD-NOS. Ten of the patients had moderate-to-severe mental retardation. Patients who were being treated concomitantly with other psychotropic medications or had a history of previous response to treatment with olanzapine or haloperidol were excluded from this study. Olanzapine was initiated at 2.5mg every other day for children ≤40kg in bodyweight, and 2.5 mg/day if >40kg. Increases could be made in increments of 2.5–5 mg/week. Haloperidol was dosed starting at 0.25 mg/day for children ≤40kg, and 0.5 mg/day if >40kg. Increases could be made in increments of 0.5–1 mg/week. The final dosage ranges used in this trial were 5–10 mg/day for olanzapine, and 0.5–2.5 mg/day for haloperidol.

The primary outcome measure was the CGI-I. In the olanzapine group, one child was rated as 'very much improved,' four were rated as 'much improved,' and one as 'minimally improved.' In the haloperidol group, one child was rated as 'very much improved,' two were rated as 'much improved,' and three as 'minimally improved.' This difference between the two treatment options was not statistically significant ($p = 0.494$). Overall both treatment options were efficacious in improving overall illness symptoms. The CPRS was used as a secondary outcome measurement. Four categories were derived from different CPRS items: (i) autism factor (social withdrawal, stereotypic motions, abnormal object relations, unspontaneous relation to examiner, underproductive speech); (ii) anger/uncooperativeness factor (angry affect, labile affect, negative, uncooperative); (iii) hyperactivity factor (fidgetiness, hyperactivity); and (iv) speech deviance factor (speech deviance, low voice). Both treatment groups had similar statistically significant improvements in the CPRS autism factor; both treatment options improved all the items listed included in the autism factor with the exception of underproductive speech. The olanzapine-treatment group showed a statistically significant improvement in the CPRS anger/uncooperativeness factor and the CPRS hyperactivity factor, while the haloperidol-treatment group did not. Neither of the two treatment groups showed improvement in the CPRS speech deviance factor. Overall, both treatment options showed improvement in this patient population after 6 weeks, with olanzapine being better than haloperidol for anger/uncooperativeness and hyperactivity.

The most common adverse effect seen with olanzapine treatment was sedation upon initiation of the medication and weight gain. All six patients receiving olanzapine gained at least 2.5kg (range 2.7–7.2kg). Only two patients in the haloperidol-treatment group gained over 2.5kg, and the range was from a 2.5kg loss to a 4kg gain. As rated by the Neurologic Rating Scale (NRS) and the AIMS, one haloperidol recipient experienced an EPS; EPS were not reported in the olanzapine group. Triglycerides and blood glucose levels were not monitored in this trial.

Kemner at al.[55] conducted a 12-week open-label trial of 25 children with autism or PDD-NOS, the majority of whom were male (exact numbers not given). Only three children were identified as having mild mental retardation; the remaining children had none. Patients were started on 2.5 mg/day of olanzapine. The final dosage ranged from 2.5 to 20 mg/day, with a mean dosage of 10.7 mg/day. The CGI-I was used as the outcome measure to determine overall response. A child had to have a rating of at least 'much improved' to be considered a responder. The ABC was used to determine behavioral symptom improvement; the five behaviors measured were irritability, lethargy, stereotypy, hyperactivity, and excessive speech.

Of the 22 children who completed the study, only three were rated as 'much improved' on the CGI-I, and therefore met the *a priori* criteria of response. Ten children were rated as 'minimally improved' and nine children showed no improvement. The behaviour measures on the ABC that were statistically improved from baseline to endpoint were irritability, hyperactivity, and excessive speech; however, this improvement may not be clinically significant. Safety data were collected for all 25 children who entered the trial. There were 14 reported cases each of weight gain, general weakness, and increased appetite. The average weight gain for the 14 children who reported it as an adverse event was 5.8kg. Somnolence was reported in six of the children. Evidence of EPS, including akathisia, joint rigidity, gait abnormalities, and tremor were reported as having occurred in ten cases. It is not clear whether this was in ten different children or not. However, EPS resolved upon lowering of the dose.

In summary, when compared with the data for risperidone, olanzapine results do not appear as robust. There is much more data to support the use of risperidone; however, more controlled trials with olanzapine may show further significant improvement. However, at this time, due to its adverse effect profile, particularly its high incidence of weight gain seen in these trials, olanzapine should be reserved as a second-line treatment option for children with PDDs.

2.1.3 Quetiapine

There were two open-label trials of quetiapine that matched the criteria for review; results are summarized in table IV.[57,58] There was a total of 15 patients in both of these studies.

Martin et al.[57] conducted a pilot 16-week, prospective trial of quetiapine in six children with a diagnosis of autistic disorder; all had some degree of mental retardation. Only one of the patients had received prior treatment with an AA (risperidone); this patient underwent a 2-week washout period before the initiation of quetiapine. For all patients, quetiapine was started at 25 mg/day at bedtime and increased by as much as 100 mg/week based on the clinician's judgment. At study end the dosage range varied from 100 to 350 mg/day. Primary outcome measures in this trial included the irritability subscale of the ABC and the CGI-I. Response was defined as a score or 'much improved' or 'very much improved' on the CGI-I. Only two patients completed the 16-week trial and were the only patients to be categorized as responders. The other four patients withdrew because of a lack of symptom improvement along with inability to tolerate the medication; sedation was the reason for discontinuation in three patients and the fourth patient had a probable seizure. There was no statistical improvement seen in the irritability subscale of the ABC. The R-FRLRS and CY-BOCS were also performed at baseline and study end with no significant changes seen in either. Four patients experienced weight gain ranging from 0.9 to 8.2kg.

The second trial of quetiapine was a 12-week open-label study of nine patients with an axis I diagnosis of autistic disorder.[58] There was no mention of mental retardation status. Inclusion criteria were a CARS score of ≥30, indicating mild-to-moderate severity of symptoms, and a CGI-S score of at least moderate severity. Patients with any other significant medical, neurologic, or psychotic disorder were excluded as were patients who received an antipsychotic, anticonvulsant, or tricyclic antidepressant 1 week prior to study initiation. However, other psychotropic medications (clonidine, stimulants, fluoxetine, sertraline, and buspirone) were allowed during the study. Outcome measures included the CPRS, the ABC, and the CGI-I scale. Two target symptoms were also selected for each patient for which quetiapine was being prescribed. These symptoms varied per patient, and included, in descending order, aggression, irritability, over-activity, social withdrawal, and tantrums. An *a priori* response definition was determined to be a CGI-I of 'much improved' or 'very much improved' by the end of the 12-week trial. Quetiapine was initiated at 25mg twice daily and increased to a target dosage of 150mg twice daily. Doses could be increased after that based on the clinician's discretion. The final daily dose of quetiapine ranged from 100 to 450mg (mean of 291.7mg). Three patients did not complete the trial; one was lost to follow-up, and the other two discontinued because of increased aggression/agitation, and drowsiness, respectively.

Only two patients were responders; three were rated as 'minimally improved,' two had no change, and one was rated as 'much worse' according to the CGI-I. Only the two patients who were responders agreed to continue receiving quetiapine. The most common adverse effects reported by parents were sedation (n = 7) and weight gain (n = 5). Four parents reported increased agitation and two reported aggression. The AIMS and the NRS were also used to assess the safety of quetiapine; no differences from baseline were found at study end.

The findings from these two studies, albeit with small patient numbers, do not seem to support the use of quetiapine in children with autistic disorder. Only 4 of 15 patients were considered to have responded to treatment with quetiapine. This drug may be beneficial in a small subset of patients, but until more controlled clinical trials are performed there is little evidence to support the use of quetiapine in PDDs.

2.1.4 Ziprasidone

There is only one published, prospective, open-label trial of ziprasidone in PDDs; results are summarized in table IV. McDougle et al.[59] examined the use of ziprasidone in 12 children and adolescents with PDDs; the patients ranged from 8 to 20 years of age, with two patients being >17 years old. The data from the latter two patients have been removed for the purposes of this review. Of the remaining ten patients, seven had a diagnosis of autism disorder and three had a diagnosis of PDD-NOS. All but one of the patients had mental retardation ranging from mild to severe (mild, n = 4; moderate, n = 4; severe, n = 1; none, n = 1). Patients were not excluded if they had other axis I diagnoses. There was no set duration of treatment; the only criterion was that the patients received ziprasidone for at least 6 weeks. The mean duration of treatment was 14 weeks, with a range of 6–30 weeks. An *a priori* definition of response was set as a CGI-I score of 'much improved' or 'very much improved.' Ziprasidone was started at 20mg at bedtime and given twice daily, and was increased by 10–20 mg/week. The final mean daily dose of ziprasidone was 60mg with a range of 20–120mg.

At the end of the study, five of ten patients met the criteria for 'responder' ('much improved'). Three patients were rated as having no change, one was 'minimally improved,' and one was rated as 'much worse' based on the CGI-I. Nine patients in this study had previously been treated with another AA (risperidone, olanzapine, quetiapine, thioridazine) and had discontinued due to inadequate response or weight gain. In five patients who were still receiving another AA at baseline, it was slowly tapered over a 4-week period while ziprasidone was titrated. This did not seem to affect the outcome of the study, as only two patients who were receiving another AA at baseline were responders at endpoint. The symptoms that were reported to have responded the most were aggression, irritability, self-injurious behavior, and mood instability. Sedation was the most common adverse effect experienced. Four of the ten patients experienced no adverse effects at all. Baseline ECGs were performed on all the patients and were normal. The possible QT prolongation associated with ziprasidone[62] is usually not clinically significant unless the patient has a prolongated QT interval at baseline; therefore, no follow-up ECGs were performed. No cardiovascular adverse effects were observed during the study. Weight gain was seen in only one patient. The mean weight change was −2.7kg (range −15.9 to +2.7 kg). This is most likely due to the fact that eight patients had significant weight gain from their previous antipsychotic treatment, rather than ziprasidone having weight-reducing properties.

Data on ziprasidone in PDDs are limited due to the small sample size and nature of the only published trial; however, it does appear promising. Larger and more controlled clinical trials are warranted to determine if ziprasidone is truly efficacious for symptom control in autistic children. Also more trials would help to determine if there is a dose-response relationship, considering that the dose in the trial reviewed here was relatively low.[59] Currently, ziprasidone is an option for patients who have not responded to other AAs for which there is better evidence, or have gained significant weight from their previous treatment.

2.1.5 Aripiprazole

There is little evidence regarding the use of aripiprazole in PDDs. The only published, open-label, prospective study examined five male patients (aged 5–18 years) diagnosed with a PDD; results are summarized in table IV.[60] Four had a diagnosis of autistic disorder, and one was diagnosed with Asperger's disorder. Concomitant psychotropics were allowed, and two patients received methylphenidate and clomipramine, respectively. All patients had recently discontinued another AA (risperidone, olanzapine, or quetiapine) due to either ineffectiveness or weight gain. Response was defined as a CGI-I rating of 'much improved' or 'very much improved.' Aripiprazole was initiated at 5–10mg at bedtime based on the clinician's discretion. The mean dosage of aripiprazole at the end of the study was 12 mg/day (range of 10–15mg). All patients received aripiprazole for at least 20 weeks, and a maximum of 24 weeks.

All five patients met the *a priori* definition for being a responder. The symptoms that seemed to respond best to treatment were aggression, agitation, and self-injurious behavior. Mild sedation was the most common adverse effect. No patients experienced EPS.

There are recently presented data[61] showing improvement in 12/13 aripiprazole-treated PDD children over 14 weeks. The 12 responders, aged 5–17 years, were categorized as responders based on a CGI-I of 'much improved' or 'very much improved' and at least a 25% improvement on the ABC-Irritability subscale. The mean baseline ABC-Irritability score was 29.5 and decreased to a mean of 6.8 at week 14. The authors state that this was a significant change based on statistical tests, but no exact measures were given. Aripiprazole was initiated at 1.25 mg/day in all patients and increased to a maximum or 15 mg/day. No patients experienced EPS. An average weight gain of 1.2kg was seen (range −0.95 to +3.5kg). Enrollment for this study is ongoing.

Aripiprazole might be an option when children cannot tolerate other AAs because of weight gain or other adverse effects; however, the data are limited at this time. More rigorous and controlled trials are needed to verify the results from these small studies. Aripiprazole may prove to be unique in the treatment of PDD because of its mechanism of action as a partial dopamine agonist.

2.1.6 Clozapine

The data on the use of clozapine in PDDs are limited to two published case reports involving a total of four patients with autistic disorder.[63,64] Although these do not match the criteria for this review, it is important to mention them since they are the only data available. The patients included three boys aged 8, 8, and 17 years, and one 12-year-old girl. One of the boys had severe mental retardation; the mental condition of the other boys was not mentioned. The three boys had a positive response to clozapine with a final dose of 200–275 mg/day. Improvements in hyperactivity, blunted affect, abnormal object relation, and communication skills were reported. The girl demonstrated some initial improvement (maximum dose of 450 mg/day) but after 5 months had returned to her baseline condition. The adverse effects reported were sedation, enuresis, sialorrhea, and constipation. None of the children developed neutropenia.

Based on the limited evidence, the use of clozapine in PDD should be limited to severely refractory cases. Caution should be used when prescribing clozapine because of its risk of agranulocy-

Table IV. Open-label trials of olanzapine (OLZ), quetiapine (QTP), ziprasidone (ZIP), and aripiprazole (ARIP)

Study (duration)	No. of pts (males); age range (y)	Active drug: mean final dose (range)	CGI-I responses	Symptoms improved
Malone et al.[54] (6wk)	12 (8); 4–12	OLZ: 7.9 mg/day (5–10 mg/day)	OLZ: VMI: n = 1; MI: n = 4; Min I: n = 1	Anger, uncooperativeness, hyperactivity
		HLP: 1.4 mg/day (0.5–2.5 mg/day)	HLP: VMI: n = 1; MI: n = 2; Min I: n = 3	
Kemner et al.[55] (12wk)	25 (not given); 6–16	OLZ 10.7 mg/day (2.5–20 mg/day)	MI: n = 3; Min I: n = 10; no change: n = 9	Irritability, hyperactivity, excessive speech
Martin et al.[57] (16wk)	6 (6); 6–15	QTP 225 mg/day (100–350 mg/day)	VMI: n = 1; MI: n = 1; no change: n = 1; Min W: n = 2; MW: n = 1	No significant improvements
Findling et al.[58] (12wk)	9 (8); 12–17	QTP 291.7 mg/day (100–450 mg/day)	VMI: n = 1; MI: n = 1; Min I: n = 3; no change: n = 2; MW: n = 1; LFU: n = 1	No significant improvements
McDougle et al. (6–30 wk; average 14 wk)[59]	10 (8); 8–17[a]	ZIP 59.2 mg/day (20–120 mg/day)	MI: n = 5; Min I: n = 1; no change: n = 3; MW: n = 1	Aggression, irritability, mood instability, self-injurious behavior
Stigler et al.[60] (20–24 wk; average 22 wk)	5 (5); 5–18	ARIP 12 mg/day (10–15 mg/day)	VMI: n = 2; MI: n = 3	Aggression, agitation, self-injurious behavior
Stigler et al.[61] (14wk)	13 (10); 5–17	ARIP 7.5 mg/day (2.5–15 mg/day)	VMI or MI: n = 12 (exact numbers not given)	Irritability

a Two patients in this study were >18 years of age and were removed from this analysis.

CGI-I = Clinical Global Impressions-Improvement (reported as no. of pts); **HLP** = haloperidol; **LFU** = lost to follow-up; **MI** = much improved; **Min I** = minimally improved; **Min W** = minimally worse; **MW** = much worse; **pts** = patients; **VMI** = very much improved; **wk** = week.

tosis and its effect on the seizure threshold. The frequent monitoring and blood sampling make it inconvenient for use in children.

2.2 Pharmacokinetics of Atypical Antipsychotics in Children

Several studies have examined the pharmacokinetics of AAs in children;[65-71] however, only one deals specifically with PDD.

Casaer et al.[65] conducted the only single-dose risperidone pharmacokinetic study in children (n = 6, 3–7 years of age) with a PDD. Oral doses were 0.015 mg/kg for three of the children and 0.03 mg/kg for the other three. The peak plasma concentrations of risperidone and its main metabolite, 9-hydoxyrisperidone, were proportionally similar to those seen in adults. However, in all six children, the time to the maximum plasma concentration was shorter than that in adults (1 hour post-dose); this is similar to the characteristics of extensive metabolizers. Since the area under the plasma concentration-time curve was not affected, the clinical significance of this finding may be negligible. The half-life of the metabolite was 30–35% lower than in adults also. Because no other studies have been published confirming or refuting this data, a solid conclusion cannot be deduced.

The other literature reviewing the pharmacokinetics of AAs in children[66-71] failed to show any significant differences in pharmacokinetic parameters between children and adults, and therefore did not recommend any dosing changes in children. Of interest, in a study of aripiprazole, the starting dose had to be decreased because the first four children enrolled reported vomiting and somnolence.[70] According to this study, aripiprazole may be better tolerated in children if started at a dosage of 2.5 mg/day for at least 2 days, and then titrated over 2 weeks to the target dose.

2.3 Proposed Mechanism of Action of Atypical Antipsychotics

The pathophysiology of autism is not completely understood. It is likely a heterogeneous disorder with a multifactorial etiology. Sections 2.3.1 to 2.3.3 discuss the possible relationship between the three neurotransmitters serotonin, dopamine, and norepinephrine (noradrenaline) and the observed clinical response to AA treatment for autism. The observed efficacy of AAs may be related to their ability to affect more than one neurotransmitter system.

2.3.1 Serotonin

The finding of hyperserotoninemia in a significant percentage of individuals with autism suggests that this neurotransmitter may be a potential target for pharmacotherapy.[72-74] Increased platelet serotonin has been observed for over 40 years in patients with

autism; however, since it has not been identified in all patients with autism, its role in this disorder is yet to be fully understood.[73,75] The role for serotonin as an immunomodulator and thus affecting immunity has also been suggested.[76] The cause of the hyperserotoninemia has not been identified. Increased synthesis, dysregulation in uptake, and receptor-mediated controls of serotonin have all been implicated. Since the selective serotonin reuptake inhibitors and AAs have demonstrated a relatively consistent level of efficacy in treating certain features of autism and they are both serotonergic in their mechanisms of action,[44,77,78] there is clinical support for a serotonin dysregulation component of autism.[79-81]

A genetic polymorphism has been identified for the serotonin transporter (5-HTTLPR) in patients with autism, lending further support for the use of serotonergic agents.[82,83] Genetic abnormalities on the chromosome 7q31 region may be associated with language disorders, but they are also related to the serotonin 2A receptor ($5HT_{2A}$) *HTR2A* gene.[84] Dysregulation of the $5HT_{2A}$ receptor and the subsequent blockade of that receptor by AAs may support the outcomes observed in clinical trials with these agents showing selected benefits in autism.[85-87]

The strong serotonin receptor antagonism demonstrated by most AAs and the recognized efficacy of members of this class of agents, such as risperidone, supports the ongoing hypothesis of serotonin dysregulation as a factor in some patients with autism.[31,77,78]

2.3.2 Dopamine

Dopamine neurotransmitter dysregulation 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.[83] Dopamine antagonism is a principle mechanism of many antipsychotics and may be part of their ability to reduce agitated and aggressive behaviors. The dopamine D_2 receptor is a common target of both older antipsychotics and newer atypical ones. The AAs are usually more potent at $5HT_{2A}$ antagonism than D_2 receptor antagonism and this may contribute to their lower risk for extrapyramidal adverse effects.[78]

Blockade of the D_2 receptor in mesolimbic areas may reduce symptoms of aggression and agitation; however, this antagonism may not be a beneficial action in the frontal cortex. Increasing dopamine activity in the pre-frontal cortex may be a preferential benefit of the atypical agents over the older conventional agents. This occurs either by selectivity for other dopamine receptors, such as D_1 or D_4 receptors, or by indirect enhancement or efflux through serotonin antagonism.[88-90]

2.3.3 Norepinephrine (Noradrenaline)

Elevated norepinephrine plasma levels have also been reported in autism.[73] Therefore, norepinephrine dysregulation could be a factor in certain aspects of the symptoms of autism. However, psychostimulants and clonidine (noradrenergic agents) may offer certain symptomatic improvements, through different mechanisms of action, in terms of inattention in some patients, or aggression and irritability, respectively, in others.

Some AAs such as clozapine, risperidone, and quetiapine have α-1 and α-2 receptor antagonism as part of their pharmacologic profile and these properties may contribute, to an unknown degree, to their observed efficacy.[73,91]

Lending some support to the efficacy and relationship of the AAs to more than one, if not all, of these neurotransmitter systems is the US FDA approval in October 2006 of risperidone, the first agent for the treatment of irritability and aggression in autism. This agent has the combined qualities of serotonin, dopamine, and norepinephrine receptor antagonism. It thus supports the proposition that a multi-transmitter dysregulation is occurring in autism, or at the least, that these systems are interrelated and therefore targeting one or more of these neurotransmitters may improve certain symptoms of autism.[92]

3. Discussion

Based on the reviewed literature, AAs can play a role in the treatment of children with PDDs. They can be used to control symptoms such as aggression, irritability, hyperactivity, and some stereotypic behavior. However, there is more favorable evidence for the use of risperidone than for other AAs.

Risperidone has been studied in five double-blind, placebo-controlled trials and nine open-label trials all with similar results of improvement in symptoms. One open-label trial has shown that olanzapine is as effective as haloperidol, but other open-label trials have failed to show efficacy with this agent in PDDs. Quetiapine does not seem to be effective either. This may be due to its fast disassociation at dopamine receptors. There is only a small amount of data for ziprasidone and aripiprazole but these data are promising. More trials are warranted with these two medications. The use of clozapine is limited because of its incidence of agranulocytosis and its potential for lowering the seizure threshold.

The adverse effect of weight gain is a concern with AAs. The clinical trials with risperidone, olanzapine, and quetiapine all showed significant weight gain, with weight gain being slightly greater with olanzapine. Ziprasidone and aripiprazole did not cause weight gain, and some patients lost weight while receiving these medications. Although this may have been due to discontinuation of a previous AA rather than to a property of ziprasidone or

aripiprazole, these agents do not seem to cause the same amount of weight gain that the other AAs do.

AAs also increase the risk of metabolic syndrome.[30] Risks and monitoring recommendations have been provided in a consensus statement published by several associations, including the American Diabetes Association and the American Psychiatric Association.[30] Metabolic syndrome includes hyperglycemia and dyslipidemia as well as weight gain. None of the trials in our review mentioned the results of these laboratory values; some of the studies were performed before the consensus statement was published. More research needs to be done on this subject to evaluate the long-term effects these medications may have on children with PDDs. However, since evidence has shown that AAs can increase the risk of metabolic syndrome, children receiving AAs should be monitored for hyperglycemia and dyslipidemia, as well as weight gain. The consensus statement provides guidelines on the frequency of monitoring.[30]

Sedation was the most commonly seen adverse event in all of the trials. Patients should be informed that sedation may be transient, and will improve after a short time on medication. Oversedation can lead to a loss of productivity at school, impacting other therapy options.

On October 2006, risperidone (Risperdal®)[1] was approved in the USA for the treatment of irritability associated with autistic disorder in children (aged 5–16 years), including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. This makes risperidone the first drug ever approved for use in children for symptoms related to autism. The use of risperidone in children aged <5 years has not been extensively studied; results of the one available study were not robust.[37]

4. Conclusion

The AAs provide a treatment option for children with autism and other PDDs. Clinical trials have shown them to be efficacious in decreasing irritability, aggression, and self-injurious behavior. Risperidone has the most published literature to support its use, including an FDA approval in children (aged 5–16 years) for the treatment of irritability, aggression, self-injurious behavior, temper tantrums, and quickly changing moods associated with autistic disorder. All the other AAs are used off-label in the PDD population. Caution must be taken when prescribing these medications; monitoring for adverse effects, particularly metabolic syndrome, is necessary. Using appropriate pharmacotherapy can enable other treatment options, such as speech therapy and applied behavior analysis, to be more effective.

Acknowledgments

There was no funding necessary for this review article. Benjamin Chavez, Mapy Chavez-Brown, and Michael A. Sopko Jr have no conflicts of interest. Jose A. Rey is a consultant for Bristol-Myers Squibb, Ortho-McNeil Neurologics, Janssen Pharmaceutical, and AstraZeneca; has received honoraria from Janssen Pharmaceutical; and owns stock/options for Bristol-Myers Squibb.

References

1. Diagnostic and statistical manual of mental disorders. 4th ed, text revision. Washington, DC: American Psychiatric Association, 2000
2. Corsello CM. Early intervention in autism. Infants Young Child 2005; 18: 74-85
3. Heward WL. Exceptional children. 8th ed. Upper Saddle River (NJ): Pearson/Merrill Prentice Hall, 2006
4. Frith U. Autism: explaining the enigma. 2nd ed. Oxford: Blackwell, 2003
5. Baron-Cohen S, Wheelwright S. The friendship questionnaire (FQ): an investigation of adults with Asperger's syndrome or high functioning autism, and normal sex differences. J Autism Dev Disor 2003; 33: 509-17
6. Baron-Cohen S, Wheelwright S. The empathy quotient (EQ): an investigation of adults with Asperger's syndrome or high functioning autism, and normal sex differences. J Autism Dev Disor 2004; 34: 163-75
7. Centers for Disease Control and Prevention [online]. Available from URL: http://www.cdc.gov/ncbddd/autism/asd_common.htm [Accessed 2006 Oct 1]
8. Connor DF, Meltzer BM. Pediatric psychopharmacology fast facts. New York: W.W. Norton & Company, 2006
9. National Institutes of Health. 'Autism fact sheet' NINDS. Bethesda (MD): National Institutes of Health, 2006 Apr. NIH publication no. 06–1877
10. Griffith EM, Pennington BF, Wehner EA, et al. Executive function in young children with autism. Child Dev 1999; 70: 817-32
11. Mostofsky S, Dubey P, Jerath VK, et al. Developmental dyspraxia is not limited to imitation in children with autism spectrum disorders. J Int Neuropsychol Soc 2006; 12: 314-26
12. Zhao Y, Shen H, Amini R, et al. Control of hippocampal morphogenesis and neuronal differentiation by the LIM homeobox hene Lhx5. Science 1999; 284 (5417): 1155-8
13. Happe F, Ronald A, Plomin R. Time to give up on a single explanation for autism. Nat Neurosc 2006; 9: 1218-20
14. Williams DL, Goldstein G, Minshew NJ. The profile of memory function in children with autism. Neuropsychol 2006; 20 (1): 21-9
15. Durand CM, Betancur C, Boeckers TM, et al. Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. Nat Genet 2007; 39: 25-7
16. Brune CW, Kim SJ, Salt J, et al. 5-HTTLPR genotype-specific phenotype in children and adolescents with autism. Am J Psychiatry 2006; 163: 2148-56
17. The Agency for Toxic Substances and Disease Registry. Contaminants of concern [online]. Available from URL: http://www.atsdr.cdc.gov/HAC/pha/bri/bri_p4.html#a [Accessed 2006 Oct 1]
18. Geier MR, Geier DA. Thimerosal in childhood vaccines, neurodevelopment disorders, and heart disease in the United States. J Am Physicians Surgeons 2003; 8 (1) [online]. Available from URL: http://www.jpands.org/jpands0801.htm [Accessed 2007 Jul 4]
19. Institute of Medicine of the National Academies. Immunization safety review: vaccines and autism [online]. Available from URL: www.nap.edu/catalog.php?.record_id=10997#toc [Accessed 2006 Oct 1]
20. Taylor B. Vaccines and the changing epidemiology of autism. Child Care Health Dev 2006; 32: 511-9
21. Fombonne E, Zakarian R, Bennett A, et al. Pervasive developmental disorders in Montreal, Quebec, Canada: prevalence and links with immunizations. Pediatrics 2006; 118: e139-50
22. Uchiyama T, Kurosawa M, Inaba Y. MMR-vaccine and regression in autism spectrum disorders: negative results presented from Japan. J Autism Dev Disord 2007; 37: 210-7

1 The use of trade names is for product identification purposes only and does not imply endorsement.

23. National Institute of Neurological Disorders and Stroke. NINDS pervasive development disorders information page [online]. Available from URL: http://www.ninds.nih.gove/disorders/pdd/pdd.htm [Accessed 2007 Feb 14]
24. Smith T, Eikeseth S, Klevstrand M, et al. Intensive behavioral treatment for preschoolers with severe mental retardation and pervasive developmental disorder. Am J Ment Retard 1997; 102: 238-49
25. Eikeseth S, Smith T, Jahr E, et al. Intensive behavioural treatment at school for 4 to 7 year old children with autism: a one year comparison controlled study. Behav Modif 2002; 26: 49-68
26. Smith T. Outcome of early intervention for children with autism. Clin Psychol Sci Pract 1999; 6: 33-49
27. Jensen VK, Sinclair LV. Treatment of autism in young children: behavioral intervention and applied behavioral analysis. Infants Young Child 2002; 14: 42-52
28. Sloam L. Use of medication in pervasive developmental disorders. Psychiatr Clin North Am 1991; 14 (1): 165-82
29. Mikkelsen EJ. Efficacy of neuroleptic medication in pervasive developmental disorders of childhood. Schizophr Bull 1982; 8 (2): 320-32
30. American Diabetes Association. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004; 27: 596-601
31. Chavez B, Chavez-Brown M, Rey JA. Role of risperidone in children with autism spectrum disorder. Ann Pharmacother 2006; 40: 909-16
32. Research Units on Pediatric Psychopharmacology Autism Network. Risperidone in children with autism and serious behavioral problems. N Engl J Med 2002; 347: 314-21
33. Research Units on Pediatric Psychopharmacology Autism Network. Risperidone treatment of autistic disorder: longer-term benefits and blinded discontinuation after 6 months. Am J Psychiatry 2005; 162: 1361-69
34. Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. Pediatrics 2004; 114: 634-41
35. Nagaraj R, Singhi P, Malhi P. Risperidone in children with autism: randomized, placebo-controlled, double-blind study. J Child Neuro 2006; 21 (6): 450-5
36. Troost PW, Lahuis BE, Steenhuis MP, et al. Long-term effects of risperidone in children with autism spectrum disorders: a placebo discontinuation study. J Am Acad Child Adolesc Psychiatry 2005; 44: 1137-44
37. Luby J, Mrakotsky C, Stalets MM, et al. Risperidone in preschool children with autistic spectrum disorders: an investigation of safety and efficacy. J Child Adolesc Psychopharmacol 2006; 16: 575-87
38. Hollander E, Wasserman S, Swanson EN, et al. A double-blind placebo-controlled pilot study of olanzapine in childhood/adolescent pervasive developmental disorder. J Child Adolesc Psychopharmacol 2006; 16: 541-8
39. Aman MG, Arnold LE, McDougle CJ, et al. Acute and long-term safety and tolerability of risperidone in children with autism. J Child Adolesc Psychopharmacol 2005; 15: 869-84
40. Hellings JA, Zarcone JR, Crandall K, et al. Weight gain in a controlled study of risperidone in children, adolescents and adults with mental retardation and autism. J Child Adolesc Psychopharmacol 2001; 11 (3): 229-38
41. Anderson GM, Scahill L, McCracken JT, et al. Effects of short- and long-term risperidone treatment on prolactin levels in children with autism. Biol Psychiatry 2007; 61: 545-50
42. Findling RL, Kusumakar V, Daneman D, et al. Prolactin levels during long-term risperidone treatment in children and adolescents. J Clin Psych 2003; 64: 132-69
43. McDougle C, Scahill L, Aman M, et al. Risperidone for the core symptom domains of autism: results from the study by the autism network of the research units on pediatric psychopharmacology. Am J Psychiatry 2005; 162: 1142-8
44. Williams SK, Scahill L, Vitiello B, et al. Risperidone and adaptive behavior in children with autism. J Am Acad Child Adolesc Psychiatry 2006; 45 (4): 431-9
45. Rausch JL, Sirota EL, Londino DL, et al. Open-label risperidone for the Asperger's disorder: negative symptoms spectrum response. J Clin Psychiatry 2005; 66: 1592-7
46. Malone RP, Maislin G, Choudhury MS, et al. Risperidone treatment in children and adolescents with autism: short- and long-term safety and effectiveness. J Am Acad Child Adolesc Psychiatry 2002; 41 (2): 140-7
47. Diler RS, Firat S, Avci A. An open-label trial of risperidone in children with autism. Curr Ther Res Clin Exp 2002; 63: 91-102
48. Zuddas A, DiMartino A, Muglia A, et al. Long-term risperidone for pervasive developmental disorder: efficacy, tolerability, and discontinuation. J Child Adolesc Psychopharmacol 2000; 10 (2): 79-90
49. Nicolson R, Awad G, Sloman L. An open trial of risperidone in young autistic children. J Am Acad Child Adolesc Psychiatry 1998; 37 (4): 372-6
50. Findling RL, Maxwell K, Wiznitzer M. An open clinical trial of risperidone monotherapy in young children with autistic disorder. Psychopharmacol Bull 1997; 33 (1): 155-9
51. McDougle CL, Holmes JP, Bronson MR, et al. Risperidone treatment of children and adolescents with pervasive developmental disorders: a prospective open-label study. J Am Acad Child Adolesc Psychiatry 1997; 36 (5): 685-93
52. Horrigan JP, Barnhill LJ. Risperidone and explosive aggressive autism. J Autism Development Dis 1998; 27 (3): 313-23
53. Fisman S, Steele M. Use of risperidone in pervasive developmental disorders: a case series. J Child Adolesc Psychopharmacol 1996; 6 (3): 177-90
54. Malone RP, Cater J, Sheikh RM, et al. Olanzapine versus haloperidol in children with autistic disorder: an open pilot study. J Am Acad Child Adolesc Psychiatry 2001; 40: 887-94
55. Kemner C, Willemsen-Swinkels SH, DeJonge M, et al. Open-label study of olanzapine in children with pervasive developmental disorder. J Clin Psychopharmacol 2002; 22: 455-60
56. Potenza M, Holmes JP, Kanes SJ, et al. Olanzapine treatment of children, adolescents, and adults with pervasive developmental disorders: an open-label pilot study. J Clin Psychopharmacol 1999; 19: 37-44
57. Martin A, Koenig K, Scahill L, et al. Open-label quetiapine in the treatment of children and adolescents with autistic disorder. J Child Adolesec Pyschopharmacol 1999; 9: 99-107
58. Findling RL, McNamara NK, Gracious BL, et al. Quetiapine in nine youths with autistic disorder. J Child Adolesc Psychopharmacol 2004; 14: 287-94
59. McDougle CJ, Kem DL, Posey DJ. Case series: use of ziprasidone for maladaptive symptoms in youths with autism. J Am Acad Child Adolesc Psychiatry 2002; 41: 921-7
60. Stigler KA, Posey DJ, McDougle CJ. Aripiprazole for maladaptive behavior in pervasive developmental disorders. J Child Adolesc Psychopharmacol 2004; 14: 455-63
61. Stigler KA, Diener JT, Kohn AE, et al. A prospective, open-label study of aripiprazole in youth with Asperger's disorder and pervasive developmental disorder not otherwise specified [poster]. New Clinical Drug Evaluator Unit 47th annual meeting; 2007 Jun 11–14; Boca Raton (FL)
62. Geodon® [package insert]. New York: Pfizer, 2007 Mar [online]. Available from URL: http://www.pfizer.com/pfizer/download/uspi_geodon.pdf [Accessed 2007 Jul 18]
63. Zuddas A, Ledda MG, Fratta A, et al. Clinical effects of clozapine on autistic disorder [letter]. Am J Pscyhiatry 1996; 153: 738
64. Chang NC, Bedair HS, McKay B, et al. Clozapine in the treatment of aggression in an adolescent with autistic disorder. J Clin Psychiatry 2001; 62: 479-80
65. Casaer P, Walleghem D, Vandenbussche I, et al. Pharmacokinetics and safety of risperidone in autistic children [abstract]. Pediatr Neurol 1994; 11 (2): 89
66. Grothe DR, Calis KA, Leslie J, et al. Olanzapine pharmacokinetics in pediatric and adolescent inpatients with childhood-onset schizophrenia. J Clin Psychopharmacol 2000; 20: 220-5
67. McConville BJ, Arvantis LA, Thyrum PT, et al. Pharmacokinetics, tolerability, and clinical effectiveness of quetiapine fumerate: an open-label trial in adolescents with psychotic disorders. J Clin Psychiatry 2000; 61: 252-60
68. Sallee FR, Miceli JJ, Tesnfeldt T, et al. Single-dose pharmacokinetics and safety of ziprasidone in children and adolescents. J Am Acad Child Adolesc Psychiatry 2006; 45: 720-8
69. Findling RL, Blumer JL, Kaufman R, et al. Aripiprazole in pediatric conduct disorder: a pilot study [poster]. Presented at the 16th Congress of the European College of Neeuropsychopharmacology Meeting; 2003 Sep 20–24; Prague
70. Findling RL, Kaufman R, Batterson J, et al. Tolerability of aripiprazole in children and adolescent with major psychiatric diagnoses [poster]. Presented at the American Academy of Child and Adolescent Psychiatry Meeting; 2005 Oct 18–23; Toronto (ON)
71. Frazier JA, Cohen LG, Jacobsen L, et al. Clozapine pharmacokinetics in children and adolescents with childhood-onset schizophrenia. J Clin Psychopharmacol 2003; 23: 87-91

72. Anderson GM. Genetics of childhood disorders: XLIV. Autism, part 4: serotonin in autism. J Am Acad Child Adolesc Psychiatry 2002; 41: 1513-6
73. Cook EH. Autism: review of neurochemical investigation. Synapse 1990; 6: 292-308
74. Anderson GM, Freedman DX, Cohen DJ, et al. Whole blood serotonin in autistic and normal subjects. J Child Psychol Psychiatry 1987; 28: 885-900
75. Schain RJ, Freedman DX. Studies on 5-hydroxyindole metabolism in autistic and other mentally retarded children. J Pediatr 1961; 58: 315-20
76. Burgess NK, Sweeten TL, McMahon WM, et al. Hyperserotoninemia and altered immunity in autism. J Autism Dev Disord 2006; 36: 697-704
77. Aman MG, Madrid A. Atypical antipsychotics in persons with developmental disabilities. MRDD Res Rev 1999; 5: 253-63
78. Richelson E. Preclinical pharmacology of neuroleptics: focus on new generation compounds. J Clin Psychiatry 1996; 57 Suppl. 11: 4-11
79. Hunsinger DM. Nguyen T, Zebraski SE, et al. Is there a basis for novel pharmacotherapy of autism? Life Sci 2000; 67: 1667-82
80. McDougle CJ, Naylor ST, Cohen DJ, et al. A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. Arch Gen Psychiatry 1996; 53: 1001-8
81. Tuchman R. Autism. Neurol Clin North Am 2004; 21: 915-32
82. Anderson GM, Cook EH. Pharmacogenetics: promise and potential in child and adolescent psychiatry. Child Adolesc Psychiatr Clin North Am 2000; 9: 23-42
83. Palermo MT, Curatolo P. Pharmacologic treatment of autism. J Child Neurol 2004; 19: 155-64
84. Veenstra-VanderWeele J, Kim SJ, Lord C, et al. Transmission disequilibrium studies of the serotonin 5-HT2A receptor gene (HTR2A) in autism. Am J Med Genet 2002; 114: 277-83
85. Klauck SM, Poustka F, Lesch KP, et al. Serotonin transporter (5-HTT) gene variants associated with autism. Hum Mol Genet 1997; 6: 2233-8
86. Nurit Yurmiya N, Pilowsky T, Nemanov L, et al. Evidence for an association with the serotonin transporter promoter region polymorphism and autism. Am J Med Genet 2001; 105: 381-6
87. Murphy DL, Lerner A, Rudnick G, et al. Serotonin transporter gene: gene, genetic disorders, and pharmacogenetics. Mol Inter 2004; 4: 109-23
88. Meltzer HY. An overview of the mechanism of action of clozapine. J Clin Psychiatry 1994; 55 (9 Suppl. B): 47-52
89. Moghaddam B. Preferential activation of cortical dopamine neurotransmission by clozapine: functional significance. J Clin Psychiatry 1994; 55 (9 Suppl. B): 27-9
90. Pehek EA, Meltzer HY, Yamamoto BK. Local administration of ritanserin on ICS 205,930 enhances dopamine and serotonin efflux in rat prefrontal cortex [abstract]. Neurosci Abstr 1993; 19: 302
91. Leysen JE, Gommeren W, Eens A, et al. Biochemical profile of risperidone, a new antipsychotic. J Pharmacol Exp Ther 1988; 247: 661-70
92. McDougle CJ, Posey D. Genetic of childhood disorders: XLIV. Autism, part 3: psychopharmacology of autism. J Am Acad Child Adolesc Psychiatry 2002; 41: 1380-3

Correspondence: Dr *Benjamin Chavez*, Ernest Maio School of Pharmacy, 160 Frelinghuysen Rd, Piscataway, NJ 08854, USA.
E-mail: bchavez@rci.rutgers.edu