

Pharmacologic Treatment of Behavioral Symptoms in Autism and Pervasive Developmental Disorders

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Autism and other pervasive developmental disorders (PDDs) are associated with various dysfunctional and problematic behaviors, in addition to the core features of language and social skills dysfunction that define these conditions. Although there is currently no pharmacologic cure for the core features of PDDs, some of the behavioral symptoms may be treated pharmacologically. In addition to relieving some of the daily stress in the lives of patients and their families, improvement of these behavioral symptoms, which include hyperactivity, aggression, tantrums, and self-injury, removes some of the hindrances to other rehabilitative efforts. This article discusses the efficacy and tolerability of various medications and alternative interventions in addressing the symptoms of autism and other PDDs.
(J Clin Psychiatry 2005;66[suppl 10]:26-31)

The core aspects of autism and the other pervasive developmental disorders (PDDs) include the early childhood onset of impairments in language and social skills. In addition to these core features, many patients with a PDD also experience behavioral symptoms, such as hyperactivity, aggression, tantrums, self-injury, and other problematic behaviors, at various times throughout their lives. Although autism and its related disorders cannot be cured with medication, pharmacologic agents of various classes may be efficacious in treating the dysfunctional behavioral symptoms that may be interfering with rehabilitative efforts and that may be causing impairment or distress.¹

Psychotropic medications may be effective in treating various behavioral symptoms of autism and PDD, including hyperactivity, lack of attention, agitation, insomnia, aggression, self-injury, irritability, tantrums, repetitive and compulsive behaviors, anxiety, and hyperarousal. Medications have also been used in hopes of improving expressive speech and reducing rituals, stereotypies, overadherence to routines, impulsivity, affective lability, and social withdrawal. These medications are reviewed in this article. Special care should be used when prescribing any psychotropic for children. Potential benefits of any medication should be weighed against its side effects and risks.

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This article is derived from the teleconference series "The Management of Autism and Its Related Disorders," which was held February 10–April 21, 2005, and supported by an educational grant from Janssen Medical Affairs, L.L.C.

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In recent years, the use of dietary and other alternative treatments for autism and PDD has become popular; however, such treatments have not been clearly established as efficacious.¹

REVIEW OF PHARMACOLOGIC AGENTS

Stimulants

Amphetamines. Amphetamines (specifically dextroamphetamine and levoamphetamine) were studied in the 1970s as a possible treatment for preschool children, but they were not associated with significant clinical benefit.^{2,3} The side effects of these drugs included an increase in stereotypy and irritability.

Methylphenidate. Methylphenidate is a stimulant that is commonly prescribed for children and adolescents with autism and other PDDs. The small number of controlled studies⁴⁻⁶ conducted with methylphenidate shows varying degrees of improvement in hyperactivity, impulsivity, and attention. Methylphenidate was reported to have some of the same side effects as amphetamines, including increased stereotypies and irritability, and some subjects experienced other side effects such as increased dysphoria, social withdrawal, and crying.^{4,5} Some initial insomnia, anorexia, aggression, tics, and agitation were also reported with the use of methylphenidate.⁴⁻⁶

α_2 -Agonists

α_2 -Agonists may have a role in treating hyperactivity related to autism and other PDDs; however, large-scale, methodologically-stringent studies are still lacking.

Clonidine. Small, controlled studies^{7,8} of oral or transdermal clonidine, an α_2 -adrenergic receptor, have shown some improvement in hyperactivity and agitation in autism. Although clonidine was generally well tolerated by

trial subjects, sedation was common and hypotension was observed in some subjects.

Guanfacine. A 2004 retrospective chart review⁹ by Posey and colleagues found some benefit from guanfacine for children and adolescents with PDDs. The review of 80 subjects, aged 3 to 18 years, included 46 patients with autistic disorder, 6 patients with Asperger's disorder, and 28 patients with PDD not otherwise specified (PDD-NOS). Taking an average dose of 2.6 mg/day, 23.8% of subjects responded to guanfacine, showing improvements in hyperactivity, inattention, insomnia, and tics. Patients with Asperger's or PDD-NOS responded more often (38%) than patients with autistic disorder (13%), and patients with comorbid mental retardation responded at a lower rate (18%) than those patients without comorbid mental retardation (38%). Transient sedation was common among subjects taking guanfacine; hypotension was not reported as an adverse effect.

Antidepressants

Tricyclic antidepressants. In a 1966 study¹⁰ of nortriptyline in 10 autistic children, Kurtis found some benefit for hyperactivity, aggressiveness, and antisocial behavior. Some subjects experienced side effects of restlessness, confusion, and weight gain.

A 1971 study¹¹ of imipramine in preschool children by Campbell and colleagues found that it was generally unsuitable for treatment of autism and that it was not well tolerated. In 1994, a case study¹² of imipramine in a patient with Asperger's disorder described marked improvement; however, it was unclear whether the imipramine was treating the symptoms associated with Asperger's disorder or an accompanying mood or anxiety disorder.

Clomipramine. The use of the serotonin reuptake blocker clomipramine to treat children and adults with PDDs has been met with varying success and adverse effects. In a study¹³ of 35 adults with PDDs, clomipramine reduced total repetitive thoughts and behaviors as well as aggression and improved some aspects of social relatedness (including eye contact and verbal responsivity) in 18 subjects (51%). However, seizures did occur in 3 subjects, including 2 subjects with a history of seizures who were taking anticonvulsants. A study¹⁴ of 24 autistic subjects aged 6 to 18 years found clomipramine to be superior to placebo and the antidepressant desipramine in improving autistic symptoms, anger, and compulsive and ritualized behaviors. Clomipramine and desipramine were equally efficacious and superior to placebo in reducing hyperactivity. A study¹⁵ of young autistic patients 3 to 8 years of age found that clomipramine was not therapeutic for autism and produced adverse effects such as sedation and a worsening of behaviors such as aggression, irritability, and hyperactivity. Clomipramine appears to be less well tolerated and less effective in younger children than in adults or adolescents.

Trazodone. The support for trazodone as a treatment for symptoms of autism comes primarily from case studies. A case study¹⁶ of trazodone used to treat the behavioral symptoms of autism in an adolescent male patient with mental retardation found that trazodone reduced the daily number of minutes of aggression, including hitting episodes and self-injurious movements. However, another case study¹⁷ showed that long-term trazodone use in a patient with autism caused the adverse effect of priapism.

Selective serotonin reuptake inhibitors. Various selective serotonin reuptake inhibitors (SSRIs) have been used to treat the symptoms of autism and other PDDs.

Fluoxetine treatment has been studied in children and adults with autism and related disorders and has shown several possible benefits, including reductions in rituals, stereotypies, repetitive behaviors, and overadherence to routines.¹⁸⁻²² Adverse effects associated with fluoxetine treatment include disinhibition, hypomania, agitation, and hyperactivity. In a double-blind, placebo-controlled, crossover trial¹⁸ of fluoxetine in 45 children and adolescents, Hollander and colleagues found that fluoxetine was superior to placebo in treating compulsive and repetitive behaviors associated with autism and that fluoxetine was generally well tolerated.

Case reports²³ and an open trial²⁴ focused on fluvoxamine treatment of autism and other PDDs in children and adolescents have shown that fluvoxamine treatment has similar potential benefits and adverse effects as fluoxetine treatment. A double-blind, placebo-controlled trial²⁵ of fluvoxamine treatment in 30 adults (aged 18 to 53 years) with autistic disorder found fluvoxamine to be generally well tolerated (with some instance of sedation and nausea) and to ameliorate compulsive and repetitive behaviors and aggression. After 12 weeks of 277 mg/day of fluvoxamine, 8 (53%) of 15 subjects experienced beneficial response, compared with 0 responders among the 15 placebo-treated patients.

Several other SSRIs, including sertraline,²⁶⁻²⁸ paroxetine,^{29,30} citalopram,^{31,32} and escitalopram,³³ have been used with some success to treat the symptoms of autism. They tend to have the same potential benefits and adverse effects as fluoxetine and fluvoxamine.

Venlafaxine. A retrospective cases series³⁴ examining the use of venlafaxine in 10 children, adolescents, and young adults (mean age = 10 years) reported improvement of repetitive behaviors and restricted interests, social deficits, communication and language, inattention, and hyperactivity associated with autism and other PDDs. Taking a mean dose of 24 mg/day, 6 (60%) of 10 subjects responded to venlafaxine treatment. Although the medication was generally well tolerated, hyperactivity and agitation were the most common adverse effects.

Mirtazapine. In a 2001 study³⁵ by Posey and colleagues, 26 subjects (aged 3.8 to 23.5 years old) with PDDs participated in a naturalistic, open-label trial of

mirtazapine. Treated with an average daily dose of 30.3 mg/day, 20 subjects had autistic disorder, 1 had Asperger's disorder, 1 had Rett's disorder, and 4 had PDD-NOS. The medication had limited effectiveness, with 9 (35%) of 26 subjects responding to treatment and showing improvement in various symptoms, including aggression, self-injury, irritability, hyperactivity, anxiety, depression, and insomnia. Minimal adverse side effects included irritability, increased appetite, and transient sedation.

Mood Stabilizers and Anticonvulsants

Divalproex sodium. Divalproex sodium can be prescribed as a mood stabilizer for patients with bipolar disorders. For this reason it has been used to treat the symptoms of PDDs, which can include mood instability. A retrospective pilot study³⁶ of 14 patients (aged 5 to 40 years) with PDDs found that divalproex sodium could improve affective instability, impulsivity, and aggression. Of the 14 patients, 10 (71%) experienced sustained response to the medication, and all of the subjects with a history of seizures or an abnormal electroencephalograph (EEG) were responders. However, 2 patients who began the trial discontinued after the first 14 days because of activation symptoms.

Lamotrigine. Although an open-label case series³⁷ of lamotrigine treatment of epilepsy in children found that autistic symptoms decreased in 8 (62%) of the 13 autistic subjects, a double-blind, placebo-controlled study³⁸ of 35 patients (aged 3 to 11 years) with autistic disorder found no significant difference between placebo-treated and lamotrigine-treated patients.

Levetiracetam. In an open-label, prospective study³⁹ of levetiracetam treatment, Rugino and Samsoc found that it may be useful in reducing hyperactivity, impulsivity, aggression, and affective lability. Levetiracetam was generally well tolerated by the 12 subjects.

Typical Antipsychotics

Typical antipsychotics have long been studied and used to treat autism and other PDDs, with haloperidol being the best studied.⁴⁰⁻⁴⁴ Although haloperidol has shown efficacy in ameliorating the symptoms of irritability, aggression, hyperactivity, and tantrums, there have been serious concerns about the potential neurologic side effects, including abnormal involuntary movements and other extrapyramidal side effects (EPS). Other reports of neuroleptics include chlorpromazine, fluphenazine, pimozide, thioridazine, trifluoperazine, and thiothixene and indicate that these agents have similar benefits and risks as haloperidol.^{40,44,45} Because of the concern over EPS and tardive dyskinesia, clinicians and researchers have shifted their focus from typical antipsychotics to the atypical antipsychotics, which have a reduced likelihood of producing neurologic side effects.

Atypical Antipsychotics

Clozapine. Clozapine has been described in case reports⁴⁶⁻⁴⁸ as having potential symptom amelioration for treatment-resistant autistic children, adolescents, and adults. Although it is reported to improve aggression and hyperactivity, it has a limited usage because of the hematological safety monitoring that is necessary for patients taking the medication and a potential lowering of the seizure threshold in a population with a high occurrence of seizures.

Risperidone. Risperidone treatment of autism and other PDDs has been the focus of much research, with benefits being suggested by several case studies and open prospective trials.⁴⁹⁻⁵¹ Superiority to placebo was also confirmed in 3 double-blind, placebo-controlled trials.⁵²⁻⁵⁴

In a study⁵² of adults with autistic disorder and PDD-NOS, McDougle and colleagues found that risperidone was superior to placebo in treating aggression, irritability, repetitive behavior, depression, anxiety, and nervousness. In the 12-week, double-blind, placebo-controlled, parallel-arms study, 31 patients with a mean age of 28 years (17 subjects with autistic disorder and 14 subjects with PDD-NOS) participated. Taking a mean dose of 2.9 mg/day, 8 (57%) of 14 subjects responded to risperidone, and 0 of 16 responded to placebo. Except for mild, transient sedation, risperidone was well tolerated, showing no evidence of EPS, cardiac events, or seizures.

A risperidone trial⁵³ by the Research Units on Pediatric Psychopharmacology (RUPP) included 101 young subjects (mean age = 8.8 years) with autistic disorder treated for 8 weeks in parallel groups, at a mean risperidone dose of 1.8 mg/day. Risperidone subjects responded at a significantly higher rate (34 of 49, or 69%) than placebo subjects (6 of 52, or 12%), showing improvement in irritability and a rating of "much improved" or "very much improved" on the Clinical Global Impressions-Improvement scale. Subjects taking risperidone did have a significantly greater average weight gain (2.7 kg) than subjects taking placebo (0.8 kg). Other side effects included increased appetite, fatigue, drowsiness, dizziness, and drooling. There were no EPS.

Shea and colleagues⁵⁴ studied risperidone treatment in a double-blind, placebo-controlled, parallel-group trial with 79 children with PDD (aged 5 to 12 years). Receiving an average daily dose of 1.2 mg/day, 54% of risperidone patients responded to treatment, compared with 18% responding among the placebo group. The average weight gain of the risperidone group (2.7 kg) was also higher than that of the placebo group (1.0 kg) in this study, and other noted risperidone side effects included somnolence and increased appetite. There were no between-group differences in mean extrapyramidal rating scale scores.

Olanzapine. Olanzapine is another atypical antipsychotic that has been considered and studied as a treat-

ment for PDD, but there have been no methodologically-stringent, double-blind, placebo-controlled studies. The case series and small, prospective, open-label studies that have been reported indicate that there is some potential benefit.⁵⁵⁻⁵⁸ The risk of EPS seems low, and weight gain and sedation seem to be the most common side effects. Controlled studies of olanzapine are indicated.

Quetiapine. Two open-label studies^{59,60} of quetiapine have suggested suboptimal effectiveness in treating PDD. Modest benefit of the drug was noted in a chart review study.⁶¹ Controlled studies are needed to determine the value of quetiapine in treating PDD.

Ziprasidone. A retrospective case series study⁶² of ziprasidone in 12 subjects (mean age = 11.6 years) suggested that the drug has some benefit for patients with PDD. Taking a mean dose of 59.23 mg/day, half of the subjects (6 of 12) responded, according to Clinical Global Impressions scale measures. Patients had no significant weight gain or other significant adverse effect.

Aripiprazole. In a case series⁶³ of 5 patients with autistic disorder, aged 5 to 18 years, 100% of subjects responded to aripiprazole treatment. Taking an average dose of 12 mg/day, patients experienced improvement in aggression, self-injury, and irritability. There were no EPS, but 2 subjects did experience mild, transient sedation. Blinded, placebo-controlled trials are necessary to establish whether or not aripiprazole is an efficacious treatment for PDDs.

Other Compounds

Buspiron. Several small, prospective studies⁶⁴⁻⁶⁶ have suggested that buspirone may benefit anxiety, irritability, tantrums, and hyperactivity in patients with autism and PDD-NOS. Subjects of the studies (aged 6 to 17 years) were taking doses between 10 and 45 mg/day.

Propranolol. A case series⁶⁷ examined the use of propranolol, a β -blocker, in 8 adults with autistic disorder. The drug ameliorated symptoms of aggression, anxiety, and hyperarousal.

Amantadine. King and colleagues⁶⁸ conducted a double-blind, placebo-controlled study of the use of amantadine in children (N = 39) with autistic disorder and found that it brought about modest improvement in hyperactivity. The subjects, aged 5 to 15 years, took 5 mg/kg/day for 3 weeks; amantadine was generally well tolerated.

D-Cycloserine. A single-blind, placebo-controlled case series⁶⁹ of D-cycloserine in 10 subjects with autistic disorder noted some improvement in social responsiveness, and it was generally well tolerated. More methodologically rigorous studies are warranted.

Cholinesterase inhibitors. Preliminary data⁷⁰⁻⁷² of treatment of PDDs with cholinesterase inhibitors (including donepezil, galantamine, and rivastigmine) show some benefit for dysfunctional behaviors, hyperactivity, and expressive speech in this patient population. However, there

have been no placebo-controlled studies of these medications, so more research is needed.

Naltrexone. Naltrexone has been extensively studied as a potential treatment for PDD because initial open trial data⁷³ suggested effectiveness and therapeutic benefit. It was suspected that opioid system abnormalities might be responsible for some of the dysfunctional behaviors seen in patients with autistic disorder and naltrexone might be able to help correct those abnormalities.⁷³ Subsequent controlled studies⁷⁴⁻⁷⁷ suggested that naltrexone had some salutary effects on hyperactivity but not on self-injurious behavior or learning. Currently, naltrexone is not commonly prescribed for PDDs.^{78,79}

Alternative Interventions

Secretin. Secretin has received a substantial amount of scientific attention because of a 1998 case series⁸⁰ of 3 children that suggested benefit. Subsequently, however, multiple randomized, controlled trials⁸¹⁻⁸³ have consistently failed to demonstrate any efficacy for secretin in patients with autistic disorder.

Vitamins and nutritional supplements. Patients diagnosed with PDD often receive vitamins and nutritional supplements from their clinicians. However, neither pyridoxine (vitamin B₆)⁸⁴ nor dimethylglycine (DMG)^{85,86} has proved to be superior to placebo in treating PDDs. Dimethylaminoethanol (DMAE) has not been studied.

CONCLUSION

Various pharmacologic treatments may have a role in ameliorating the dysfunctional behavioral symptoms of autistic disorder and other PDDs. Clinicians should be guided by the extant scientific literature on these medications in order to make evidence-based decisions about what to prescribe for their patients. More research into current and emerging medications is needed to ensure that clinicians are able to provide the best possible treatment for autism and related disorders.

Drug names: amantadine (Symmetrel and others), aripiprazole (Abilify), buspirone (BuSpar and others), chlorpromazine (Thorazine, Sonazine, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), clonidine (Catapres, Duraclon, and others), clozapine (Clozaril, Fazaclon, and others), cycloserine (Seromycin), desipramine (Norpramin and others), dextroamphetamine (Dexedrine, Dextrostat, and others), divalproex sodium (Depakote), donepezil (Aricept), escitalopram (Lexapro), fluoxetine (Prozac and others), fluphenazine (Prolixin and others), galantamine (Reminyl), guanfacine (Tenex and others), haloperidol (Haldol and others), imipramine (Tofranil and others), lamotrigine (Lamictal), levetiracetam (Keppra), methylphenidate (Ritalin, Methylin, and others), mirtazapine (Remeron and others), naltrexone (Revia and others), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), pimozide (Orap), propranolol (Inderal, Innopran, and others), quetiapine (Seroquel), risperidone (Risperdal), rivastigmine (Exelon), secretin (Chirhostim and Secremax), sertraline (Zoloft), thiothixene (Navane and others), trazodone (Desyrel and others), trifluoperazine (Stelazine and others), venlafaxine (Effexor), and ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, amantadine, aripiprazole, buspirone, chlorpromazine, citalopram, clomipramine, clonidine, clozapine, D-cycloserine, desipramine, dextroamphetamine, divalproex, donepezil, escitalopram, fluoxetine, fluphenazine, galantamine, guanfacine, imipramine, lamotrigine, levetiracetam, methylphenidate, mirtazapine, naltrexone, nortriptyline, olanzapine, paroxetine, pimozone, propranolol, quetiapine, risperidone, rivastigmine, secretin, sertraline, thiothixene, trazodone, trifluoperazine, venlafaxine, ziprasidone, fluvoxamine, haloperidol, levoamphetamine, and thioridazine are not approved by the U.S. Food and Drug Administration for the treatment of autism/pervasive developmental disorders.

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