

Pharmacological Therapies for Autism Spectrum Disorder: A Review

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INTRODUCTION

Autism spectrum disorder (ASD) comprises a group of neurodevelopmental disabilities. The *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (*DSM-5*) includes autism, Asperger's disorder, and "pervasive personality disorder not otherwise specified" under the umbrella heading of ASD.¹ The symptoms of ASD generally appear between the ages of 2 and 3 years.^{2,3} All children with the disorder experience difficulty in developing social, speech, and behavioral skills. Therefore, behavioral therapy is usually the first-line treatment, with pharmacological therapies added to help patients function in their daily activities.²

This review discusses approved and off-label pharmacotherapeutic options for the various symptoms of ASD.

TREATMENT OF IRRITABILITY AND AGGRESSION

Risperidone

Risperidone (Risperdal, Janssen, and generics), a second-generation antipsychotic, was the first drug approved by the Food and Drug Administration (FDA) to treat autism-related irritability.⁴ Its 2006 approval applied to children 5 years of age and older.

McCracken et al. conducted an eight-week, randomized, double-blind, placebo-controlled trial of risperidone (0.5 to 3.5 mg daily) in 101 children 5 to 17 years of age.⁵ This study showed improvements in the number of tantrums, aggressive episodes, and self-injurious behaviors in children with ASD treated with risperidone compared with those given placebo, as measured by the irritability scale of the Aberrant Behavior Checklist (ABC) and by the Clinical Global Impressions–Improvement (CGI–I) scale ($P < 0.001$). The most common adverse effects (AEs) observed in the risperidone arm included increased appetite, dizziness, drooling, drowsiness, and fatigue ($P < 0.05$ versus placebo for each). The authors noted that the study's short duration did not allow tardive dyskinesia—a potential consequence of risperidone therapy—to occur.

Troost and colleagues conducted a 32-week placebo-discontinuation trial to assess the long-term efficacy and safety of risperidone in children (ages 5 to 17 years) with ASD accompanied by severe tantrums, aggression, or self-injurious behavior.⁶ Thirty-six subjects received eight weeks of open-label treatment with risperidone. The responders ($n = 26$) continued treatment for another 16 weeks, followed by a double-blind discontinuation phase ($n = 24$) consisting of either three weeks of taper and five weeks of placebo only or continuing use of risperidone. Daily doses of risperidone ranged from 0.5 to 3.5 mg.

Patients treated with risperidone showed decreased levels

of irritability ($P = 0.0001$), social withdrawal ($P = 0.0001$), stereotypy ($P = 0.047$), hyperactivity ($P = 0.033$), and inappropriate speech ($P = 0.033$) compared with those given placebo. Risperidone was also superior to placebo in preventing the relapse of ASD ($P = 0.049$). Weight gain, increased appetite, anxiety, and fatigue were the most common AEs.

Sharma et al.⁷ conducted a meta-analysis of 16 open-label and six placebo-controlled studies of risperidone in children with ASD published after 2000. The authors calculated effect sizes for each reported measure within a study to determine an average effect size per study. They found that the trials' outcome measures demonstrated a mean improvement in problematic behaviors equaling one standard deviation, thus supporting the effectiveness of risperidone in managing behavioral problems and symptoms in children with ASD. In all of the studies, rapid weight gain was the most common AE associated with risperidone.

Aripiprazole

The FDA approved the psychotropic drug aripiprazole (Abilify, Bristol-Myers Squibb, and generics) in 2009 for the treatment of irritability in children (ages 6 to 17 years) with ASD.⁸ The drug is also indicated for the treatment of schizophrenia, bipolar I disorder, major depressive disorder, and Tourette's syndrome. Its mechanism of action is unknown but may involve a combination of partial agonist activity at dopamine type 2 (D2) and serotonin type 1A (5-HT_{1A}) receptors and antagonist activity at 5-HT_{2A} receptors.⁹

The safety and tolerability of aripiprazole were evaluated in a 52-week, open-label study involving 330 children (ages 6 to 17 years) with ASD who were treated for irritability.¹⁰ All of the subjects were started on a dosage of 2 mg per day and were then titrated to target dosages of 5, 10, or 15 mg per day. AEs occurred in 87% of the subjects. The most common AEs included weight increase, vomiting, nasopharyngitis, increased appetite, pyrexia, upper respiratory tract infection, and insomnia. Discontinuations due to AEs occurred in 11% of the subjects, mostly because of weight gain and aggression.

A *post hoc* analysis of two eight-week, controlled clinical studies focused on the effects of aripiprazole on health-related quality of life during treatment for irritability in 316 children (ages 6 to 17 years) with ASD.¹¹ Aripiprazole was associated with significantly greater improvement than placebo in Pediatric Quality of Life Inventory scores. The most common AEs included fatigue, somnolence, sedation, extrapyramidal symptoms, and weight gain.

These eight-week clinical trials were also the subject of a meta-analysis by Ching and colleagues.¹² The authors reported a mean improvement of 6.17 points on the ABC irritability

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subscale, 7.93 points on the ABC hyperactivity subscale, and 2.66 points on the stereotypy subscale in children treated with aripiprazole compared with those given placebo. Children treated with aripiprazole had a greater increase in weight, with a mean gain of 1.13 kg, compared with the placebo group. Aripiprazole-treated children also had a higher risk ratio for sedation (4.28) and tremor (10.26).

Clozapine

Before the approval of risperidone and aripiprazole for the treatment of ASD symptoms, the second-generation antipsychotic agent clozapine (Clozaril, Novartis, and generics) had been used for aggression and tantrums.⁶⁷

Clozapine is indicated for the treatment of schizophrenia and for reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder. Its therapeutic efficacy in schizophrenia is believed to be mediated through antagonism of the D2 and 5-HT_{2A} receptors. The drug also acts as an antagonist at adrenergic, cholinergic, histaminergic, and other dopaminergic and serotonergic receptors.¹³

The effectiveness of clozapine in limiting ASD-related disruptive behaviors was the subject of a retrospective analysis by Beherec and colleagues.¹⁴ They found that treatment with clozapine resulted in a significant twofold decrease in the number of days with aggression, a decrease in the number of psychotropic drugs used, and a decrease in the dose of the antipsychotic drugs. The authors also found, however, that clozapine was associated with significant weight gain, metabolic syndrome, and tachycardia. Other studies have reported extrapyramidal symptoms and the need for frequent hematological monitoring. Further, clozapine may cause seizures at high doses. For these reasons, it is seldom used as a first-line treatment in children.¹⁵

Haloperidol

Haloperidol (Haldol, Janssen/Ortho-McNeil, and generics) belongs to the butyrophenone class and is a highly potent and selective D2 receptor antagonist.¹⁶ It is indicated for use in the treatment of schizophrenia and in the control of the tics and vocal utterances of Tourette's syndrome.¹⁷ Haloperidol has a long track record of effective use for the treatment of acute agitation, such as that seen in drug- or alcohol-using patients or in disruptive emergency patients. It is by far the most common first-generation antipsychotic used to treat agitation in the acute setting.^{18,19}

In an early study, Faretra and colleagues²⁰ reported that haloperidol was more effective than the second-generation antipsychotic fluphenazine at reducing aggression in children with autism, although the AEs of treatment included acute dystonic reactions, akathisia, and sedation.

Similarly, Perry et al.²¹ found that haloperidol remained effective in 60 autistic children (2 to 8 years of age) during six months of treatment. Those with prominent symptoms of irritability, anger, and uncooperativeness were the best responders.

Remington and colleagues²² compared haloperidol with the tricyclic antidepressant clomipramine in the treatment of irritability and other deficits in children and adults (ages 10 to 36 years) with ASD. They, too, reported that the results

favored haloperidol. Thirty-six subjects were treated with haloperidol (mean daily dose, 1.3 mg) or clomipramine (mean daily dose, 128.4 mg) for seven weeks. Although clomipramine was comparable with haloperidol in terms of improvement versus baseline, significantly fewer subjects in the clomipramine group compared with those in the haloperidol group were able to complete the study (37.5% versus 69.7%, respectively) because of AEs and efficacy or behavior problems. Moreover, only haloperidol proved superior to baseline on a global measure of autistic symptom severity at the end of the study.

As with all antipsychotic agents, haloperidol has been associated with persistent dyskinesias. In addition, extrapyramidal symptoms have been reported frequently during administration of the drug, often during the first few days of treatment.¹⁷

Sertraline

Sertraline (Zoloft, Pfizer/Roerig, and generics), a selective serotonin reuptake inhibitor (SSRI),²³ was shown to improve separation anxiety disorder in an 11-year-old girl with Asperger's disorder.²⁴ In this case report, sertraline was up-titrated over a six-month period to a dosage of 150 mg per day.

No large, well-designed trials have been conducted to support the use of sertraline for the treatment of irritability or aggression in adolescents. In general, SSRIs are not well tolerated in young people because of the drugs' AEs, which can include increased energy, impulsivity, decreased concentration, diarrhea, and insomnia.²⁵

TREATMENT OF ABERRANT SOCIAL BEHAVIOR

Risperidone Versus Haloperidol

In an eight-week, double-blind, prospective study, Miral and colleagues²⁶ compared risperidone and haloperidol in 30 children and teenagers (ages 8 to 18 years) with ASD. Both treatments were administered in a once-daily dosage regimen of 0.01 to 0.08 mg/kg per day. Risperidone achieved significant ($P < 0.05$) reductions from baseline in the sensory motor and language subscales of the Ritvo-Freeman Real-Life Rating Scale. Moreover, compared with haloperidol, treatment with risperidone resulted in a significantly greater reduction in ABC and Turgay DSM-IV Pervasive Developmental Disorder (PDD) scores ($P < 0.05$ and $P < 0.01$, respectively). Importantly, risperidone was more effective than haloperidol in treating social behavior, although both drugs had significant effects on the change from baseline ($P = 0.0032$ and $P = 0.0111$, respectively). The haloperidol group had significantly ($P = 0.0477$) more reports of the development or worsening of extrapyramidal symptoms.

In an open-label extension of the study by Miral et al., researchers compared the efficacy and safety of risperidone and haloperidol during 12 weeks of treatment in 28 children and teenagers with ASD.²⁷ In this trial, risperidone (1.2 to 3.8 mg per day) was shown to improve scores on behavioral rating scales, including the ABC and the CGI-I, to a greater degree than haloperidol (0.01 to 0.08 mg per day); the differences, however, were not statistically significant ($P = 0.0594$). Weight gain occurred more often with haloperidol. The authors concluded that risperidone was more efficacious and better tolerated than haloperidol in the long-term maintenance treatment of ASD.

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Oxytocin

Oxytocin (Pitocin, Par Sterile Products, and generics) is an endogenous hormone best known for its role in lactation and parturition.²⁸ It has also been found to play a major role in relationship formation and social functioning in both humans and animals.²⁹ Since ASD is associated with impaired social interaction and impaired communication, among other symptoms,¹ investigators have looked at the ability of intranasal oxytocin to reduce these deficits.²⁹

Using magnetic resonance imaging, Gordon and colleagues measured changes in brain activity during judgments of socially and nonsocially meaningful pictures in 17 children with ASD after treatment with intranasal oxytocin.³⁰ The investigators found that oxytocin enhanced brain function in these subjects and appeared to improve their evaluations of the socially meaningful stimuli.

Preti and colleagues conducted a systematic review of all randomized controlled trials (RCTs) of intranasal oxytocin in subjects with ASD published from 1990 to 2013.³¹ Their research yielded seven RCTs involving a total of 101 subjects with the disorder. The authors concluded that these studies provided “potentially promising” findings in measures of emotion recognition and eye gaze, which are impaired early in the course of ASD and might disrupt the learning of social skills in developing children.

In a double-blind, crossover, placebo-controlled study, Guastella et al. demonstrated an improvement in emotional recognition in 16 male youths (ages 12 to 19 years) with ASD treated with intranasal oxytocin.³² The subjects' treatment responses were evaluated with the Reading the Mind in the Eyes Test, a widely used test of emotion recognition. In comparison with placebo, oxytocin significantly improved performance on this test ($P = 0.03$).

In a case report from Japan, Kosaka et al.³³ described a 16-year-old girl whose social behavior improved after long-term administration of intranasal oxytocin. After six months of treatment, the patient's ABC score decreased from 69 to 7. The authors concluded that long-term oxytocin nasal spray appeared to be a promising treatment for the social impairments of ASD.

Secretin

Secretin, another endogenous hormone, regulates exocrine secretions in the stomach, pancreas, and gallbladder. It also acts as a neuropeptide in the central nervous system (CNS).³⁴

A report from the Agency for Healthcare Research and Quality identified eight publications that addressed treatment with human, porcine, or biologic secretin in children with ASD.³⁵ According to the authors, none of these trials demonstrated significantly greater improvements in measures of language, cognition, or autistic symptoms compared with placebo.

Similarly, Williams and colleagues³⁶ reviewed data from 16 clinical trials of intravenous secretin in a total of 900 children with ASD and found no evidence that the hormone was effective in that setting. They concluded that secretin should not be recommended or administered as an ASD treatment.

TREATMENT OF HYPERACTIVITY AND INATTENTION

Methylphenidate

Methylphenidate (Ritalin, Novartis; Concerta, Janssen; and generics) is a mild CNS stimulant indicated for attention-deficit disorders and narcolepsy.^{37,38} The drug is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and to increase the release of these monoamines into the extraneuronal space.³⁸

Handen et al. evaluated methylphenidate in a double-blind, placebo-controlled, crossover study of 13 children (6 to 11 years old) with autism and symptoms of attention-deficit/hyperactivity disorder (ADHD).³⁹ Methylphenidate was administered at doses of 0.3 and 0.6 mg/kg. Eight of the subjects showed significant improvements in hyperactivity and impulsivity, as measured by the Conners Hyperactivity Index. However, no changes were found on the Childhood Autism Rating Scale (CARS). More than 50% of the subjects in each dosage arm experienced decreased appetite, increased irritability, social withdrawal, and restlessness.

In another blinded crossover study, Posey and colleagues⁴⁰ evaluated methylphenidate in 66 children (mean age, 7.5 years) with pervasive developmental disorders (PDDs) and significant hyperactive-inattentive symptoms. Methylphenidate was administered at doses of 0.125, 0.25, or 0.5 mg/kg at 8 A.M. and at noon, with an additional half dose late in the afternoon. Subjects in all three treatment arms showed significant improvements in ADHD symptoms ($P < 0.04$, $P < 0.001$, and $P < 0.001$, respectively). However, only the medium and high doses of methylphenidate significantly improved inattention ($P = 0.15$, $P < 0.001$, and $P < 0.001$) and hyperactivity/impulsivity ($P = 0.80$, $P < 0.001$, and $P < 0.001$). There were no significant effects on oppositional defiance disorder or stereotyped and repetitive behavior. The most common AE was irritability.

The Research Units on Pediatric Psychopharmacology Autism Network⁴¹ evaluated methylphenidate in 72 children (5 to 14 years of age) with PDDs accompanied by moderate-to-severe hyperactivity. Treatment was based on weight and ranged from 7.5 mg per day to 50 mg per day in divided doses. Subjects who tolerated the test dose ($n = 66$) were assigned to receive placebo for one week and then three methylphenidate doses in random order during a double-blind crossover phase. Children who responded to methylphenidate then entered eight weeks of open-label treatment at the individually determined best dose.

Methylphenidate was superior to placebo on the teacher-rated hyperactivity subscale of the ABC (the trial's primary outcome measure). Thirty-five of the 72 enrolled subjects (49%) were classified as methylphenidate responders. AEs led to treatment discontinuation in 13 of the 72 subjects (18%).

Venlafaxine

Venlafaxine (Effexor, Pfizer/Wyeth, and generics) is a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of major depressive disorder, generalized anxiety disorder, social anxiety disorder, and panic disorder.⁴²

In three clinical cases described by Carminati et al.,⁴³ all of the subjects responded to low-dose venlafaxine (18.75 mg per day), as determined by their CGI scores. The first case

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involved a 17-year-old boy with autism and severe behavioral symptoms, including aggression, self-injurious behavior, and hyperactivity; the second case involved a 23-year-old woman with autism hyperactivity; and the third case involved a 17-year-old girl with the same disorder. The subjects were followed for 18, 36, and six months after treatment initiation, respectively. The authors concluded that low-dose venlafaxine, in addition to the patient's current antipsychotic regimen, could improve self-injurious behavior and ADHD-like symptoms.

TREATMENT OF REPETITIVE BEHAVIORS

Fluoxetine

Fluoxetine (Prozac, Lilly, and generics) is a selective serotonin reuptake inhibitor (SSRI) indicated for acute and maintenance treatment of major depressive disorder; acute and maintenance treatment of obsessive compulsive disorder; acute and maintenance treatment of bulimia nervosa; and acute treatment of panic disorder, with or without agoraphobia.⁴⁴

Hollander and colleagues²² reported improvement in repetitive behaviors among adults with ASD treated with fluoxetine (20 to 80 mg per day). Thirty-seven adults (18 to 60 years of age) were treated with fluoxetine ($n = 22$) or placebo ($n = 15$) for 12 weeks. The fluoxetine dosage started at 10 mg per day and was increased, as tolerated, up to 80 mg per day. Repetitive behaviors (obsessive-compulsive symptoms) showed improvement in 50% of the fluoxetine group compared with 8% of the placebo group. The most common treatment-related AEs were mild-to-moderate insomnia, headache, and dry mouth.

In the Study of Fluoxetine in Autism (SOFIA), however, a low-dose, melt-in-the-mouth formulation of the drug was found to be no more effective than placebo in treating repetitive behaviors in children and adolescents (5 to 17 years of age) with ASD.⁴⁵

Citalopram

Citalopram (Celexa, Forest Pharmaceuticals, and generics) is an SSRI indicated for the treatment of depression.⁴⁶

In a randomized, placebo-controlled trial, King and colleagues⁴⁷ found that citalopram was ineffective in treating children (5 to 17 years old) with ASD, including Asperger's disorder and unspecified developmental disorders. A total of 149 subjects received either citalopram 10 mg ($n = 73$) or placebo ($n = 76$) for 12 weeks. There was no significant difference between citalopram and placebo in the rate of positive response on the CGI-I subscale (32.9% versus 34.2%, respectively). Moreover, citalopram was significantly more likely to be associated with AEs, particularly increased energy level, impulsiveness, decreased concentration, hyperactivity, stereotypy, diarrhea, insomnia, and dry skin or pruritus.

Bumetanide

Bumetanide (generics) is a potent loop diuretic indicated for the treatment of edema associated with congestive heart failure, hepatic disease, and renal disease (including nephrotic syndrome).⁴⁸

A small, double-blind, randomized, placebo-controlled study conducted in Europe and the U.S. evaluated 60 children (3 to 11 years of age) with ASD who were treated with bumetanide 1 mg or placebo for three months.⁴⁹ Bumetanide was associated

with significantly reduced scores on the CARS ($P < 0.004$) and the CGI ($P < 0.017$).

The only AE of active treatment was occasional mild hypokalemia, which was treated with supplemental potassium.⁴⁹ Bumetanide, however, is known to cause profound diuresis, with water and electrolyte depletion. Therefore, careful medical supervision is required during treatment, and the dose and dosage schedule must be adjusted to the individual patient's needs.⁴⁸

TREATMENT OF COGNITIVE DISORDERS

Memantine

Memantine (Namenda, Forest Pharmaceuticals, and generics) is an *N*-methyl-D-aspartate (NMDA) receptor antagonist indicated for the treatment of moderate-to-severe dementia of the Alzheimer's type. Persistent activation of NMDA in the CNS is believed to contribute to the symptoms of Alzheimer's disease.⁵⁰

Owley and colleagues⁵¹ evaluated memantine (0.04 mg/kg) in an eight-week, open-label pilot study of 14 children (ages 3 to 12 years) with PDDs. Twelve children completed the study. A significant improvement from baseline was noted on the Children's Memory Scale Dot Learning Subtest, a memory evaluation ($P = 0.021$). However, there were no significant differences from baseline on measures of expressive language, receptive language, and nonverbal IQ. Several ABC subscales, including hyperactivity, lethargy, and irritability, also failed to show significant improvements from baseline. Four of the 14 enrolled subjects showed minimal improvement on the CGI-I test, and none was judged to be "much improved" or "very much improved."

Rivastigmine

The acetylcholinesterase inhibitor rivastigmine (Exelon, Novartis, and generics) is indicated for the treatment of mild-to-moderate dementia of the Alzheimer's type and mild-to-moderate dementia associated with Parkinson's disease. Although the drug's precise mechanism of action is unknown, it is thought to exert its therapeutic effects by enhancing cholinergic function.⁵²

Rivastigmine was evaluated in 32 children (ages 3 to 12 years) with ASD to determine whether its use would improve cognition in these patients.⁵³ During the 12-week, open-label study, the subjects received an oral solution of rivastigmine 0.4 mg twice daily. At six weeks, significant improvements from baseline in cognition were seen in the CARS scores and in the Conners' Parent Rating Scale (both $P = 0.001$). In addition, significant improvements in cognition were evident at week 12 in the Gardner's Expressive One-Word Picture Vocabulary test ($P = 0.001$). AEs were similar to those reported in adults treated with rivastigmine (e.g., nausea, diarrhea, irritability, and hyperactivity).

TREATMENT OF INSOMNIA

Mirtazapine

Mirtazapine (Remeron, Merck, and generics) is an oral tetracyclic antidepressant that enhances central noradrenergic and serotonergic activity.⁵⁴ In general, antidepressants have been associated with an increased risk, compared with placebo,

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of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies of subjects with major depressive disorder and other psychiatric disorders. Therefore, this risk must be balanced with the patient's clinical need when mirtazapine (or any other antidepressant) is used in children, adolescents, or young adults.⁵⁴

In an open-label study, Poe and colleagues showed that mirtazapine (dosage range, 7.5 to 45 mg per day) was effective in improving insomnia (CGI severity rating, $P < 0.004$) in 26 children, adolescents, and young adults (4 to 24 years of age) with ASD and other developmental disorders.⁵⁵ The treatment also significantly improved aggression, self-injury, and irritability scores on the CGI. AEs included increased appetite and transient sedation.

Melatonin

Cortesi et al.⁵⁶ evaluated a controlled-release formulation of the sleep-promoting hormone melatonin⁵⁷ in a randomized, placebo-controlled trial involving 160 children (ages 4 to 10 years old) with ASD. Melatonin 3 mg per day (combined with cognitive-behavioral therapy) was compared with placebo for 12 weeks. Treatment was administered at 9 P.M. each day. The active therapy significantly reduced insomnia compared with placebo ($P < 0.001$), as assessed by the Children's Sleep Habits Questionnaire. Sleep-onset latency of less than 30 minutes was achieved by 85% of the melatonin-treated patients.

In an open-label, dose-escalation study, Malow and colleagues⁵⁸ measured sleep latency by actigraphy in 24 children with ASD. The subjects initially received melatonin at a dose of 1 mg 30 minutes before bedtime. The children were evaluated at three-week intervals, and if they did not show a sufficient response (defined as falling asleep within 30 minutes five or more nights per week), the melatonin dose was increased to 3 mg. This process was repeated up to a dose of 6 mg.

Melatonin improved sleep latency as early as one week into the 14-week study, and this improvement was maintained until the end of the trial. Of the 24 children studied, seven obtained a satisfactory response at a dose of 1 mg, 14 at 3 mg, and three at 6 mg.

CURRENT RESEARCH

Aside from Roche,⁵⁹ pharmaceutical companies have generally shied away from investing in treatments for autism and other ASDs.⁵⁷ In particular, the pharmaceutical industry has shown risk aversion with regard to conducting research in autism, a disorder with a hazy pathophysiology, a high level of heterogeneity, few clear biomarkers, and poorly developed outcome measures for clinical studies.⁶⁰

Nevertheless, according to data from the National Institutes of Health,⁶¹ approximately 20 clinical trials are evaluating current or potential ASD treatments in the U.S. (Table 1). Oxytocin nasal spray appears to be the most popular therapeutic approach, with at least five early- or mid-stage studies in progress at U.S. centers. Other interesting drugs under investigation for the treatment of ASD include the following:

- Acamprosate (Campral, Forest Pharmaceuticals), a synthetic compound with a chemical structure similar to that

of the endogenous amino acid homotaurinate, approved for the maintenance of alcohol abstinence⁶²

- Atomoxetine (Strattera, Lilly USA), an SNRI indicated for the treatment of ADHD⁶³
- Intrathecal baclofen (Gablofen, Mallinckrodt), a gamma-aminobutyric acid (GABA)-ergic agonist indicated for use in the management of severe spasticity of cerebral or spinal origin⁶⁴
- DMXB-A, a derivative of the nemertine toxin anabasein,⁶⁵ which is being studied for the treatment of severe ASD-associated tactile defensiveness⁶¹
- EPI-743 (vincerinone, Edison Pharmaceuticals), a member of the para-benzoquinone class of drugs, which was originally developed for the treatment of patients with inherited mitochondrial diseases⁶⁶
- RG7314 (Roche), an investigational small-molecule antagonist of the V1A vasopressin receptor, which has been implicated in modulating emotional processing and social deficits in patients with ASD⁵⁹

DISCUSSION

Although numerous medications are used to treat the symptoms of ASD, such as irritability, aggression, and aberrant social behavior, only risperidone and aripiprazole are FDA-approved for ASD patients. Limited clinical data have supported treatment with SSRIs, CNS stimulants, NMDA-receptor antagonists, and other agents, but well-designed trials in larger cohorts are needed.

Irritability and Aggression

Risperidone and aripiprazole are FDA-approved for the treatment of irritability in children with ASD.^{4,8} Although clozapine can reduce aggression in ASD patients,¹⁴ its adverse effects—including significant weight gain, metabolic syndrome, and tachycardia—have limited its use in that setting.¹⁵ Haloperidol has been shown to be effective in treating ASD-related irritability and aggression,^{20,22} but treatment has been associated with persistent dyskinesias and extrapyramidal symptoms.¹⁷

Aberrant Social Behavior

In comparison studies,^{26,27} risperidone was generally more effective than haloperidol in treating aberrant social behavior in ASD patients, with fewer adverse effects. Oxytocin nasal spray has been shown to improve measures of emotion recognition and eye gaze as well as social impairments in patients with ASD.²⁸⁻³⁰ Secretin, on the other hand, showed no clinical benefit in numerous ASD trials and is not recommended for this indication.^{35,36}

Hyperactivity and Attention

Studies of methylphenidate in patients with ADHD and PDDs showed improvements in attention, hyperactivity, and impulsivity.³⁹⁻⁴¹ Similarly, venlafaxine improved attention and self-injurious behaviors in a series of case reports.⁴³

Repetitive Behaviors

Standard fluoxetine improved repetitive behaviors (obsessive-compulsive symptoms) in adults with ASD,²⁵ but a melt-in-the-mouth formulation of the drug was no more effective

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Table 1 Ongoing U.S. Clinical Trials in Autism Spectrum Disorder (ASD)⁶¹

Intervention	Study	Sponsor(s)	Description	Start Date	Estimated Completion Date
Acamprosate (Campral, Forest Pharmaceuticals)	Study of Acamprosate in Autism	Children's Hospital Medical Center, Cincinnati, Ohio	26-week, randomized, double-blind, placebo-controlled, phase 2 trial in 36 patients (ages 5–17 years)	April 2013	February 2016
Atomoxetine (Strattera, Lilly)	Effectiveness of Atomoxetine in Treating ADHD Symptoms in Children and Adolescents With Autism	Massachusetts General Hospital, Boston, Massachusetts	8-week, randomized, double-blind, placebo-controlled, cross-over, phase 3 trial in 86 patients (ages 5–15 years)	July 2007	October 2015
Autologous umbilical-cord blood infusion	Autologous Umbilical Cord Blood Infusion for Children With ASD	Duke University, Durham, North Carolina	52-week, prospective, phase 1 trial in 20 patients (ages 2–6 years)	June 2014	July 2016
Baclofen, intrathecal (Gablofen, Mallinckrodt)	Open-Label Treatment of Severe Tactile Defensiveness and ASD With Intrathecal Baclofen	University of Missouri, Columbia	Open-label trial in 5 patients (ages 10–65 years)	September 2014	June 2017
DMXB-A (nicotinic agonist)	Phase I Nicotinic Agonist Treatment Trial for Autism	University of Colorado, Denver	Open-label, phase 1 trial in 20 patients (ages 18–50 years)	August 2015	August 2018
Buspirone	Open-Label Trial of Buspirone for Treatment of Anxiety in Youth With ASD	Massachusetts General Hospital, Boston, Massachusetts	Exploratory 8-week pilot study in 40 patients (ages 6–17 years)	July 2013	April 2016
Dextromethorphan hydrobromide/quinidine sulfate (Nuedexta)	Nuedexta for Treatment of Adults With Autism	Sutter Health, Sacramento, California	8-week, randomized, double-blind, placebo-controlled, cross-over, phase 2 trial in 20 patients (ages 18–60 years)	June 2012	September 2015
Divalproex	Treatment of Children With ASDs and Epileptiform EEG With Divalproex Sodium	Children's Hospital, Boston, Massachusetts	12-week, randomized, double-blind, placebo-controlled, cross-over, phase 2 trial in 30 patients (ages 4–8 years)	April 2014	April 2016
Donepezil	Trial of the Drug Donepezil for Sleep Enhancement and Behavioral Change in Children With Autism	National Institute of Mental Health	Randomized, double-blind, placebo-controlled, phase 2 trial in 90 patients (ages 22–44 months)	June 2013	September 2017
EPI-743 (vincerinone)	Exploratory Open-Label Study of EPI-743 (Vincerinone) in Children With ASD	Edison Pharmaceuticals, California	24-week, open-label, phase 2 trial in 20 patients (ages 3–14 years)	October 2014	January 2016
Folinic acid	Folinic Acid Intervention for ASDs	University of Arkansas, Little Rock	12-week, randomized, double-blind, placebo-controlled, phase 2 trial in 192 patients (ages 3–14 years)	May 2012	September 2015
Mecasermin (Increlex, Ipsen)	Treatment of Rett Syndrome With Recombinant Human IGF-1	Children's Hospital, Boston, Massachusetts	40-week, randomized, double-blind, placebo-controlled, phase 2 trial in 30 patients (ages 2–10 years)	January 2013	December 2015
Memantine	Multi-Site Double-Blind Placebo-Controlled Trial of Memantine Versus Placebo in Children With Autism Targeting Memory and Motor Planning (MEM)	Mount Sinai School of Medicine; Rush University Medical Center; Nationwide Children's Hospital; Ohio State University	24-week, randomized, double-blind, placebo-controlled, phase 2 trial in 60 patients (ages 6–12 years)	December 2011	August 2015

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Table 1 Ongoing U.S. Clinical Trials in Autism Spectrum Disorder (ASD)⁶¹ (continued)

Intervention	Study	Sponsor(s)	Description	Start Date	Estimated Completion Date
Methylphenidate (extended release)	Methylphenidate ER Liquid Formulation in Adults With ASD and ADHD	Massachusetts General Hospital, Boston, Massachusetts	6-week, open-label, phase 4 trial in 40 patients (ages 18–25 years)	May 2014	July 2015
	Dose Response Effects of Quillivant XR in Children With ADHD and Autism: A Pilot Study	Seattle Children's Hospital, Seattle, Washington	6-week, randomized, single-blind, phase 4 trial in 25 patients (ages 6–16 years)	September 2014	December 2016
Oxytocin nasal spray	Intranasal Oxytocin and Learning in Autism	Children's Hospital of Philadelphia, Pennsylvania	12-day, randomized, double-blind, placebo-controlled, phase 2 trial in 68 patients (ages 12–17 years)	September 2011	April 2015
	Randomized, Controlled Trial of Intranasal Oxytocin as Adjunct to Behavioral Therapy for ASD	Massachusetts General Hospital, Boston, Massachusetts	Randomized, placebo-controlled, phase 2 interventional trial in 150 patients (ages 18–30 years)	April 2014	September 2016
	Open-Label Trial of Oxytocin in Adolescents With ASD		8-week, open-label trial in 40 patients (ages 11–17 years)	October 2013	November 2016
	Study of Oxytocin in Autism to Improve Reciprocal Social Behaviors (SOARS-B)	University of North Carolina, Chapel Hill	Randomized, double-blind, placebo-controlled, phase 2 trial in 300 patients (ages 3–17 years)	August 2014	October 2017
	Brain Imaging of Intranasal Oxytocin Treatment in Autism		Randomized, double-blind, phase 1 trial in 28 patients (ages 6–18 years)	September 2014	February 2018
Rapalogues (sirolimus or everolimus)	Rapalogues for Autism Phenotype in Tuberous Sclerosis Complex (TSC): A Feasibility Study (RAPT)	Hugo W. Moser Research Institute, Baltimore, Maryland	53-week, open-label, phase 2 trial in 3 patients (ages 2–30 years)	July 2013	December 2015
RG7314 (vasopressin V1A receptor antagonist)	Study of RG7314 to Investigate Efficacy and Safety in Individuals With ASDs	Hoffmann-LaRoche	12-week, randomized, double-blind, parallel-group, placebo-controlled, proof-of-concept trial in 155 patients (ages 18–45 years)	September 2013	August 2015
Riluzole	Pilot Study of Riluzole for Drug-Refractory Irritability in ASD	Children's Hospital Medical Center, Cincinnati, Ohio	14-week, randomized, double-blind, placebo-controlled, crossover, phase 2/3 trial in 12 patients (ages 12–25 years)	June 2013	July 2015
STX209 (arbaclofen)	Magnetoencephalographic (MEG) Study of STX209	Children's Hospital of Philadelphia, Pennsylvania	Randomized, double-blind, placebo-controlled trial in 8 patients (ages 14–17 years); five weekly visits	October 2014	December 2016
Vitamin D ₃	Open Label Clinical Trial of Vitamin D in Children With Autism	University of California, San Francisco	Open-label, phase 2/3 trial in 20 patients (ages 3–8 years)	February 2012	December 2015

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than placebo in children.⁴⁵ Citalopram provided no benefit in a randomized controlled trial of children with ASD,⁴⁷ but bumetanide showed some efficacy in a small European trial.⁴⁸ The latter drug, a loop diuretic, can cause profound diuresis.⁴⁸

Cognition

Memantine was found to be ineffective in improving cognition in children with ASD.⁵¹ Rivastigmine, on the hand, provided significant improvements in this setting.⁵²

Insomnia

Mirtazapine improved insomnia in children and adults with ASD and other developmental disorders.⁵⁵ Similarly, a controlled-release formulation of melatonin, in addition to cognitive-behavioral therapy, improved sleep latency as early as one week in a 14-week study.⁵⁶

CONCLUSION

While risperidone and aripiprazole remain the mainstays of ASD treatment, they are FDA-approved only for managing the irritability associated with the disorder. Clinical trials, therefore, have evaluated an array of pharmacological treatments in patients with ASD and related PDDs, and have provided clinicians with numerous off-label options. These treatments should be administered based on individual patient need, with due consideration being given to potential risks as well as benefits.

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