Title: Psychopharmacological Interventions in Autism Spectrum Disorder

Activity Date: This activity will be available as an online learning module starting March 10, 2014, and will be available for one year.

Activity Location: Online

Target Audience Statement: This CME activity is intended for physicians.

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Learning Objectives: After completing this activity, the learner should be better able to:

- Prescribe the appropriate psychotropic medication to treat symptoms of autism spectrum disorder.
- Identify the side effects of the psychotropic medications used to treat autism spectrum disorder.

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**Method of Physician Participation in the Learning Process/Evaluation Method**

Successful completion of this activity includes reading the entire article and successfully completing the post-quiz and an evaluation form.

**Getting the Most out of the Activity**

As you prepare to participate in this activity, please reflect on your practice and your patients and identify clinical challenges you hope to have addressed.

While participating in the training, identify ways you can use newly acquired knowledge, strategies, and skills to enhance patient outcomes and your own professional development.

**Disclaimer**

Clinicians should ensure that all diagnostic and therapeutic modalities are prescribed and used appropriately, based on accepted standards of care. Use of any drugs, devices, and imaging techniques should be guided by approved labeling/full prescribing information, best available evidence, and professional judgment.

Faculty have been instructed that their content should be fair balanced and based on best available evidence. The information presented in this activity is the responsibility of the faculty and does not reflect the opinions of the provider.
Psychopharmacological Interventions in Autism Spectrum Disorder
Laura C. Politte, MD, Charles A. Henry, MD, and Christopher J. McDougle, MD

Learning Objectives: After participating in this educational activity, the physician should be better able to
1. Prescribe the appropriate psychotropic medication to treat symptoms of ASD.
2. Identify the side effects of the psychotropic medications used to treat ASD.

Autism spectrum disorders (ASDs) are characterized by core deficits in social communication and language, and restrictive and repetitive behaviors that cause significant functional impairment and distress for affected individuals and their caregivers. The increasing prevalence of ASD, most recently estimated as 1 in 88 children, presents an ever-increasing burden on families, schools, medical systems, and society at large. Individuals with ASD commonly present for treatment of associated emotional and behavioral disturbances that include anxiety, symptoms of ADHD, compulsions and other repetitive behaviors, mood lability, irritability, aggression, and sleep disturbance. Psychotropic medications are widely utilized in alleviating these symptoms, though rigorous clinical trials in ASD are lacking for most areas of impairment. Strong evidence from randomized, placebo-controlled trials supports the use of atypical antipsychotics, particularly risperidone and aripiprazole, for managing severe irritability and aggression in ASD. Serotonin reuptake inhibitors are commonly used to treat anxiety and compulsions, though reports of efficacy in the literature are mixed, and behavioral side effects in children are common. Minimal evidence supports the utility of anticonvulsants and traditional mood stabilizers in managing mood lability and aggression. Stimulant and nonstimulant ADHD medications can be effective for reducing hyperactivity, inattention, and impulsivity, though to a lesser degree than in ADHD populations without ASD and with greater risk of adverse effects. Psychopharmacological interventions in development for core symptoms of autism include those that target the glutamatergic and GABAergic neurotransmitter systems and the neuropeptide oxytocin. Further research is needed to establish evidence-based interventions in ASD populations.

Keywords: anticonvulsants, antidepressants, atypical antipsychotics, autism, autism spectrum disorders, mood stabilizers, oxytocin, pervasive developmental disorders, psychopharmacology, stimulants
Though it remains uncertain whether the rising prevalence of ASD is driven primarily by increased awareness and higher detection rates or by a true rise in the prevalence of these disorders, there is no question that the burden on families, schools, health care systems, and individuals is significant and ongoing.4–6 As more children with ASD transition into adulthood, the need for comprehensive services for adults with autism will also increase.7,8

The treatment of individuals with ASD is complex and typically includes behavioral therapy, language and communication training, occupational therapy, special education, vocational training and support, and management of associated medical conditions, such as seizure disorders and gastrointestinal symptoms. While there is no single, definitive treatment for ASD, early intensive behavioral interventions can reduce core autistic symptoms and improve developmental outcomes.9 Psychiatric comorbidity is common in ASD,10 and the presence of additional diagnoses such as attention-deficit/hyperactivity disorder (ADHD) and intellectual disability substantially increases health care expenditures compared to children who have ASD without such comorbidities.9 Furthermore, psychiatric symptoms can impede progress in educational and therapeutic settings and cause significant distress for patients and their families.

When psychiatric symptoms or maladaptive behaviors lead to distress and impairment above and beyond core autistic symptoms, psychopharmacological treatment is often employed. In a database analysis of children with ASD aged 2–17 years, 27% of all participants took at least one psychotropic medication, with greatest rates of use (66%) in adolescents.11 Eighty percent of children diagnosed with a comorbid psychiatric disorder were taking at least one psychotropic medication. Common targets of medication management in ASD include anxiety, ADHD symptoms (inattention, impulsivity, and hyperactivity), compulsions and interfering repetitive behaviors, sleep disturbance, and irritability, which can include mood lability, severe tantrums, self-injurious behavior, and aggression. In higher-functioning children and adolescents with ASD, depression is also common.12–14 The thorough assessment of individuals with ASD should include an inventory of these symptom domains in addition to a detailed developmental and medical history. Physicians who evaluate patients with ASD should also be mindful that many patients and their families will choose to seek out natural remedies and treatments that may include vitamins, supplements, and oral chelating agents that have the potential to interact with prescribed medications; inquiry about complementary and alternative strategies should be included in every assessment. A review of supplemental treatment strategies is beyond the scope of this article, though there is substantial support for the efficacy of melatonin for sleep dysregulation in ASD, particularly delayed sleep onset.15–23

This article aims to review the literature pertaining to the use of psychotropic medications in treating the psychiatric symptoms in ASD. For most medications, limited data are available regarding efficacy in ASD populations, owing in part to small sample sizes, heterogeneity within the disorder, and methodological difficulties in organizing multicenter trials. Currently, only two medications—risperidone and aripiprazole—have U.S. Food and Drug Administration (FDA) indication for use in autism, specifically for the treatment of severe irritability. Many psychiatric medications are prescribed off-label, however, for interfering symptoms associated with ASD. Benzodiazepines are excluded from this review as no clinical trials of these medications in ASD have been published, and the existing literature is primarily limited to case reports of benzodiazepines used to treat catatonia occurring in the context of autism.

Novel medications that show promise in ASD but are still under development, particularly oxytocin and agents affecting glutamate transmission, are also reviewed. Translational research holds the promise of targeted, neurobiologically sound treatments for core symptoms of autism. Some researchers advocate early pharmacological intervention during critical windows of brain development to enhance plasticity and experience-dependent change, or to potentially correct derangements in neurotransmission.24 Pharmacological studies in very young children present ethical and practical challenges, however, and few studies have included participants younger than five years old, in whom brain plasticity is at its peak. Animal studies of novel treatments will be helpful in identifying potential critical windows for intervention and also in determining long-term side effects, which are largely unknown for commonly used medications.24

The authors have chosen to organize this review by classes of medication (e.g., atypical antipsychotics), as opposed to target symptom clusters (e.g., irritability) due to the broad range of measures frequently employed in the study of any particular medication in this population. Broad measures reflect an initially limited understanding of how individual medications will affect those with ASD, and results often cross categories of associated symptoms (e.g., an atypical antipsychotic may reduce both irritability and hyperactivity). Reporting the results of individual medication trials by category of medication is intended to reduce overlap in the description of results.

METHODS
A literature search was conducted using the PubMed database for articles in English language pertaining to the use of psychiatric medications in ASD. In addition to “autism spectrum disorders,” search terms included general classes of medication (e.g., atypical antipsychotics) and individual medication names (e.g., risperidone). Particular weight was given to randomized, controlled trials, though due to limited publications for most medications, case reports and the results of open-label studies are also included. Reference sections of relevant articles were reviewed for additional pertinent publications.

Harvard Review of Psychiatry
SEROTONERGIC AGENTS

Given the core compulsive and repetitive behaviors present in ASD and frequent comorbid anxiety symptoms, treatment with serotonin reuptake inhibitors and tricyclic antidepressants is an obvious option. Results from early case series and open trials with clomipramine have been mixed. Positive reports noted improvements in repetitive behaviors, aggression, social engagement, language, adventitious movements, and adaptive behavior. Two of these participants had a preexisting seizure disorder that had been stabilized on anticonvulsants, and 1 experienced a new onset tonic-clonic seizures. Two of the open-label trials in children reported difficulties with agitation and aggression. Examining blinded controlled trials in clomipramine, two trials, each with 12 participants, reported improvement in overall autistic symptoms and also in compulsive behaviors and anger as compared to both placebo and desipramine. Clomipramine's differential effect on these measures over desipramine seems to implicate clomipramine's serotonergic action. Both clomipramine and desipramine were helpful in decreasing hyperactivity, an outcome that might be consistent with the common noradrenergic effect of both medications. Side effects in these studies were minimal, with clomipramine not differing from placebo, though in the second report, one participant had a prolonged QTc interval (0.45 seconds), and another became tachycardic (resting heart rate 160–170 beats per minute). These effects resolved after dose reduction. One individual treated with clomipramine suffered from a grand mal seizure.

Looking at selective serotonin reuptake inhibitors (SSRIs), open trials in children and adults with ASD have been mostly positive, with notable improvements in obsessive-compulsive symptoms, anxiety, depressive symptoms, aggression, and overall symptom severity. Difficulty with activation side effects and agitation were frequent in some reports. The two placebo-controlled trials in adults have shown efficacy in important outcome measures. A 12-week double-blind investigation of fluvoxamine in 30 adults with ASD noted improvement in repetitive thoughts and behaviors, aggression, language function, and maladaptive behavior. Treatment with the mean dose of 276.7 mg/day was overall well tolerated, with side effects mostly limited to nausea and sedation. A similarly designed, more recent study of 37 adults treated with fluoxetine also noted improvements, specifically with measures of repetitive behavior and overall global functioning. Again, side effects were minimal at a moderately high mean dose of 64.76 mg/day. Peak dosing was reached by week 8 of the study.

Placebo-controlled trials of SSRIs in children have been mostly discouraging. In the first investigation, only 1 of 18 children with ASD treated with fluvoxamine showed improvement in established target symptoms. Side effects were common, including trouble with agitation and aggression. Dosing was modest, with a mean dose of 106.9 mg/day. In a second study, 45 children with ASD randomized to an eight-week placebo-controlled, crossover study were treated with fluoxetine. Improvement was noted in repetitive behavior as measured by the Children’s Yale-Brown Obsessive Compulsive Scale, with a moderate to large effect size. The mean dose of 9.9 mg per day was low.

The two most recent placebo-controlled studies of SSRIs in children with ASD have been negative. Results from a 12-week National Institute of Mental Health–funded, multicenter, placebo-controlled study of citalopram (mean dose, 16.5 mg daily) in 149 children with ASD found no difference in repetitive behaviors or global improvement compared to placebo. Participants did demonstrate statistically significant improvement in irritability as measured by the Aberrant Behavior Checklist (ABC), though the improvement was modest and not thought to be clinically meaningful. Activation side effects were common in the treatment group, with significantly greater rates of impulsivity, hyperactivity, distractibility, stereotypy, and insomnia. Two children in the citalopram group had seizure episodes. Finally, an industry-sponsored, placebo-controlled trial of a fluoxetine preparation developed by Neuropharm was tested in 158 children with autism. Though details of the study have not been published, the released findings indicated no improvement in repetitive behaviors compared to placebo.

In summary, despite the positive placebo-controlled trials with SSRIs in autism, findings in children have been mostly negative. In particular, the negative results of two large placebo-controlled studies are difficult to ignore. Age-related differences in serotonin functioning in those with autism may be a factor in the limited efficacy of, and the vulnerability to side effects with, SSRIs treatment in children. Unfortunately, alternative treatment options are not readily available for repetitive/compulsive symptoms in those with autism. Because of the limited alternatives and sometimes severe repetitive and compulsive behaviors that often impair functioning, a trial with an SSRI in children and adolescents might be considered. Low initial dosing with slow titration would be recommended, with close monitoring of activation side effects and treatment-emergent aggression.

Buspirone and mirtazapine are serotoninergic agents with unique profiles that may also be useful alternatives to SSRIs for treating anxiety and irritable mood associated with ASD. Buspirone is a partial serotonin receptor type 1A agonist with anxiolytic and antidepressant effects that has been associated with improved anxiety, irritability, and hyperactivity in ASD in a few case reports and one open-label study with 22 participants. Buspirone has a relatively mild side-effect profile in comparison to SSRIs and neuroleptics, and the authors of this article often utilize buspirone to treat anxiety in patients who have tolerated SSRIs poorly. In a few reports, mirtazapine, a serotonin reuptake inhibitor at low doses with noradrenergic effects ($\alpha_2$ antagonism) at higher doses, has
shown promise for treating problematic sexual behaviors associated with autism. An open-label study of mirtazapine for treating a variety of symptoms associated with ASD reported significant overall improvement in 34.6% but no improvement in core autistic features. As with buspirone, the authors have used mirtazapine in clinical practice for patients who have difficulty tolerating SSRIs, particularly those with prominent anxiety accompanied by sleep disturbance.

**STIMULANTS AND NONSTIMULANTS FOR TREATING ADHD SYMPTOMS**

Although ADHD could not be co-diagnosed with a pervasive developmental disorder according to DSM-IV criteria, ADHD-related symptoms are common in ASD. This co-diagnosis is allowed in DSM-5. Treatment of such symptoms has been investigated with psychostimulants and other medications used for ADHD. Some initial reports suggested that the psychostimulants were ineffective for individuals with ASD, with common side effects including increased tics, stereotypies, and agitation. Other uncontrolled studies, however, reported improved attention, hyperactivity, impulsivity, and stereotypies, with minimal side effects.

Initial small placebo-controlled, crossover studies with methylphenidate (n = 10 and n = 13) in children with autism noted improved hyperactivity. Side effects of social withdrawal and irritability were evident at higher doses in some children.

In a large double-blind, placebo-controlled, crossover trial conducted by the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, the effects of methylphenidate 0.125–0.5 mg/kg/day were investigated in 72 children with ASD over one-week periods. Improvement in the ABC-Hyperactivity subscale score was reported, with a small to medium effect size. Forty-nine percent of children were determined to be responders by a combined measure of improvement in hyperactivity and global severity, as determined by the Clinical Global Impressions–Improvement scale (CGI-I). Side effects of note included social withdrawal (particularly at higher doses) and irritability. The response rate was lower than the 70%–80% response observed in the Multisite Multimodal Treatment of Children with ADHD study, and side effects were more common.

Eighteen percent of the participants discontinued the trial, most frequently due to irritability. Of note, a small placebo-controlled, crossover trial of 14 preschool-aged children with developmental delay or PDD reported a similar response rate and side-effect profile.

Given the evidence from the controlled trials, psychostimulants are an option in treating ADHD symptoms in ASD. Caution should be advised for the well-known adverse events that are noted in non-autistic populations. For example, those with ASD are at risk for developing psychotic symptoms, and evidence of psychotic changes may be difficult to detect due to communication impairments, potentially presenting as irritability. In the reviewed trials, irritability is a particular vulnerability with psychostimulant use in ASD. Given the rapid onset of effect and side effects, short trials might be used to readily clarify potential treatment response. Such an approach was taken in the RUPP study, which used a closely monitored test-dose phase to screen for initial tolerance.

Alpha-2 agonists have demonstrated effectiveness in reducing ADHD symptoms and also oppositionality in children. An open-label trial with clonidine in 19 children with ASD noted improved sleep and, to a lesser extent, ADHD symptoms, aggression, and mood instability. Two small placebo-controlled studies (n = 8 and n = 9 participants) also reported positive findings, with improved irritability, hyperactivity, inappropriate speech, oppositionality, stereotypy, sensory reactivity, and global illness severity. In the smaller sample study, however, no benefit for clonidine over placebo was identified based on clinician ratings.

A chart review of 80 youth with ASD treated with guanfacine demonstrated effectiveness in 24% of participants, with specific improvements in hyperactivity, inattention, insomnia, and tics. Many of the participants had nonresponders to a prior trial of methylphenidate or had been unable to tolerate it. Those with Asperger’s disorder or PDD not otherwise specified and those without mental retardation showed a higher response rate. A prospective open study of 25 children with ASD also noted improvement in hyperactivity. Forty-eight percent were considered responders by improvement in global illness severity. Daytime sedation and mid-cycle awakenings were noted, along with irritability and constipation. A small placebo-controlled, crossover study of 11 children with developmental disorders (the majority of whom had ASD diagnoses) treated with guanfacine demonstrated improved hyperactivity, with 48% determined to be responders by a 50% reduction in hyperactivity symptoms. Drowsiness and irritability were noted. None of these investigations found significant changes in blood pressure or heart rate. A National Institute of Mental Health-funded, placebo-controlled trial of guanfacine extended-release (Intuniv) for treating hyperactivity in children aged 5–17 years with ASD is currently under way, though results are not yet available (www.clinicaltrials.gov).

Atomoxetine has also been investigated in children with ASD. A retrospective study noted a 60% response rate as determined by a rating of “much improved” or “very much improved” on the CGI-I. Specific improvements were noted in conduct, hyperactivity, inattention, and learning. Three open-label studies of children with ASD noted a decrease in ADHD symptoms, with one of the studies reporting improved irritability, stereotypies, repetitive speech, and social withdrawal. By contrast, one open study of children with severe ASD was negative, showing no change in the primary outcome measure of hyperactivity. One large placebo-controlled trial of atomoxetine (dosed at 1.2 mg/kg/day) in 97 children with ASD found improved ADHD symptoms. Eighty-one percent versus 65% with
placebo reported side effects, with nausea, decreased appetite, and mid-cycle awakenings reported at significantly higher rates in the atomoxetine group. No serious adverse events were noted. Finally, in a smaller placebo-controlled, crossover study of 16 children with ASD, a decrease in hyperactivity was noted, though the improvement in attention only approached statistical significance. One individual was hospitalized secondary to severe difficulty with aggression.

Finally, a placebo-controlled study of 39 children with autism investigated the effects of amantadine, dosed at 0.5 mg/kg/day. Improvements were noted in clinician-rated measures of hyperactivity and inappropriate speech, though the improvement in parent ratings did not reach statistical significance. Side effects were minimal.

**ATYPICAL ANTIPSYCHOTICS**

Atypical antipsychotics are among the most extensively studied and widely used medications for treating severely disruptive behavior in individuals with ASD. To date, risperidone and aripiprazole are the only two medications with FDA indications specifically in autism; both are approved for managing irritability in children and adolescents.

Of the atypical antipsychotics, risperidone has been most thoroughly investigated, with evidence for its efficacy in treating severe irritability associated with ASD established in two large randomized, placebo-controlled trials, leading to FDA approval in 2006. In 2002, the RUPP Autism Network published results of a multisite, controlled trial of risperidone in children with autism and severe behavioral disturbance (n = 101; age range, 5–17 years) that included an eight-week active treatment phase followed by a four-month open-label continuation phase and two-month discontinuation phase. Sixty-nine percent of the participants in the risperidone group met responder status (≥25% reduction in ABC-Itr irritability [ABC-I] subscale score and CGI-I rating of “much improved” or “very much improved”) compared to 12% in the placebo group. Two-thirds of participants maintained this benefit at six months in the open-label phase, and a similar proportion number (62.5%) relapsed with placebo substitution during the blinded discontinuation phase, leading to elimination of this latter phase for ethical reasons. A subsequent eight-week controlled trial in a Canadian sample of youth with ASD generated a slightly lower response rate for risperidone (54%) and higher placebo response rate (18%) based on the same response criteria, though reductions in ABC-I subscale scores were similar across studies (−56.9% vs. −64%). Additional open-label and controlled trials of risperidone in children with ASD and severe irritability have generally supported short-term response rates in the range of 57% to 72%. Improvement has also been observed in secondary measures of restrictive, repetitive, and stereotyped behaviors; adaptive functioning; hyperactivity; social withdrawal; and communication. A follow-up study conducted by the RUPP Autism Network found that the addition of manualized parent training to risperidone resulted in improved outcome scores and lower risperidone doses during combination treatment than with risperidone alone.

Common side effects observed across studies of risperidone included sedation, increased appetite, weight gain, and elevated prolactin levels. Sedation was reported at a rate of 37% and 72% in the two largest controlled trials, though this side effect had abated for most participants by eight weeks. In both treatment groups, participants gained an average of 2.7 kg in eight weeks, substantially more than their placebo-group counterparts. At six months, participants had gained an average of 5.6 kg, representing an average 16.7% absolute weight increase and 10.6% BMI increase. Hyperprolactinemia tends to peak during acute treatment and decline with chronic treatment, though remained double the baseline level at two years in the RUPP study; the clinical significance of asymptomatic elevation in prolactin levels has yet to be determined. No significant differences in extrapyramidal symptoms (EPS) were reported between treatment arms in the largest studies. The authors of those studies did not include reports of blood sugar levels or lipid levels, though hyperglycemia and hyperlipidemia have been associated with the use of antipsychotics in other clinical populations.

In 2009, aripiprazole became the second agent approved by the FDA for managing irritability in children 6–17 years old with autism—a decision based on positive results from two multisite, industry-sponsored, randomized, double-blind, placebo-controlled trials. In the first trial, 218 youth with ASD and significant irritability were treated for eight weeks with fixed doses of aripiprazole 5, 10, or 15 mg daily. All groups demonstrated significant improvement on primary outcome measures (ABC-I and CGI-I scores), though response rate (defined as ABC-I reduction ≥25% and CGI-I of “much improved” or “very much improved,” as in the RUPP risperidone trial) separated from placebo only for the 5 mg treatment arm. Response rate for the 5 mg group was 55.8%, compared to an unusually large placebo response rate of 34.7%. In the second controlled trial—of 98 youth with autism—aripiprazole was flexibly dosed up to 15 mg/day for eight weeks, with most participants (74%) ultimately taking 5–10 mg/day at study endpoint. The overall treatment response rate of 52.2% mirrors the response rate found for the 5 mg treatment group in its companion study, and placebo response was lower at 14.3%. ABC-I subscale scores declined by a mean of 12.9 points for all treatment groups compared to 5 points for placebo, for an effect size of 0.87. Clinically significant residual symptoms presumably persisted for many individuals, however, as the mean endpoint ABC-I subscale score was only slightly lower than the minimum entrance-criterion score of 18 (indicating irritability of at least moderate severity).

In both studies, sedation and somnolence were the most commonly reported adverse effects, resolving in a median of
An advantage included weight neutrality or weight loss for sedation. By contrast, two chart reviews employing retrospective assignment of CGI-I scores found response rates of 40%–60%, though as great as that observed in the risperidone studies. Treatment-emergent EPS occurred at rates of 14.9%–23% in treatment groups compared to 8%–11.8% in placebo groups. Vomiting was twice as common with active treatment (13.7%) as with placebo in pooled data (6.9%). In a 52-week open-label extension study in 330 individuals, mean weight increase was 6.3 kg, corresponding to a change in BMI z-score of 0.31; weight gain tended to plateau over time. High-density lipoprotein levels declined in 30% of individuals, though clinically significant elevations of total cholesterol (5.2%), low-density lipoproteins (6.5%), triglycerides (4.6%), and serum glucose (1.9%) were less common. Mean serum prolactin levels declined from baseline to endpoint. EPS-related events were reported in 14.5% of subjects, leading to drug discontinuation in half of this group. Aripiprazole has not been associated with significant QTc interval prolongation or other abnormal ECG findings in children with ASD.

Other atypical antipsychotics have not been as thoroughly investigated in children with autism, and the studies have typically yielded mixed results. Two small open-label trials of olanzapine reported high response rates (6/7 and 5/6 participants), though results from an additional two studies were less robust (3/25 participants and 12/40 participants were responders). A small randomized, controlled trial of 11 patients found a treatment response rate of 50% (3 of 6). Weight gain was substantial across studies and greater than observed with risperidone and aripiprazole; in one study, participants gained an average of 4 kg in six weeks of treatment. Mild, transient sedation was also common in all studies.

Open-label studies of quetiapine have generally found minimal efficacy and poor tolerability due to excessive sedation, weight gain, and increased aggression or agitation, though one study suggested quetiapine may be helpful for sleep disturbance and aggression (possibly reduced secondary to sedation). By contrast, two chart reviews employing retrospective assignment of CGI-I scores found response rates of 40%–60%, though susceptibility to bias with this study design limits conclusions.

Aripiprazole has shown promise in the treatment of irritability, aggression, hyperactivity, and impulsivity in autism, though published data are limited to one open-label study, one case series, and two case reports. Significant overall improvement, defined as a CGI-I rating of “much improved” or “very much improved,” was reported in 50% and 75% of participants in the case series and open-label study, respectively (each consisting of 12 participants). An advantage included weight neutrality or weight loss for those patients discontinuing an alternative antipsychotic.

Initial sedation was common, and in two patients with comorbid bipolar disorder, symptoms were rated as “much worse” with ziprasidone. QTc intervals were found to increase by 14.7 milliseconds from baseline; ECG monitoring during ziprasidone treatment is recommended.

Information regarding the efficacy of paliperidone, the extended-release active metabolite of risperidone, in patients with ASD is limited to one open-label study and three case reports. Results from a study of 25 adolescents with autism and severe irritability are encouraging, with 84% of participants showing significant improvement in irritability. Weight gain and increased serum prolactin were common, and mild to moderate EPS were reported in 4 individuals.

As in other disorders, clozapine is not considered a first-line agent for severe irritability, given its potentially serious side effects of agranulocytosis, seizures, and cardiomyopathy. The need for frequent blood draws is a major limiting factor for many individuals with autism, some of whom experience intense anxiety with needlesticks. Case reports indicate that clozapine may be useful in cases of severe aggression and self-injury that have not responded to other antipsychotic and mood-stabilizing agents.

Recently approved second-generation antipsychotics, including asenapine, iloperidone, and lurasidone, have not been studied in autism or pediatric populations, though further investigation may be warranted, given their potentially more favorable metabolic profiles.

In summary, atypical antipsychotics, particularly risperidone and aripiprazole, are considered first-line agents for treating severe irritability and aggression in children and adults with ASD. Clinicians must carefully weigh the risks and benefits of those agents, however, as they carry a significant potential side-effect burden. Weight gain is more common than not with all atypical antipsychotics except ziprasidone, and while metabolic derangements such as dyslipidemia and hyperglycemia have not been well established in clinical trials with ASD populations, they are known risks from studies of other neuropsychiatric disorders. Furthermore, caregivers may find that aggression is more difficult to contain and safely manage in a heavier child. Hyperprolactinemia is common with all agents except aripiprazole, and the long-term effects of elevated prolactin in the absence of clinical stigmata are largely unknown.

### MOOD STABILIZERS/ANTICONVULSANTS

Anticonvulsants with mood-stabilizing properties have been investigated as potential treatments for core symptoms of autism and for affective dysregulation, aggression, and impulsivity in ASD, with mixed results.

Divalproex sodium has been the most extensively studied medication in this class. It gained early attention from case reports of substantial improvement in language and maladaptive behaviors in children with autism and with clinical seizures.
or abnormal EEGs. However, small sample sizes, heterogeneity within samples, and, in one study, a large placebo response limit the ability to draw definitive conclusions about the efficacy of divalproex sodium for this population. In a pilot study of 14 children and adults with ASD treated with divalproex sodium (mean dose, 768 ± 582 mg/day; mean peak valproate level, 75.8 ± 12.6 μg/mL), 10 (71%) showed substantial improvement in retrospectively assigned CGI-I scores. Areas of subjective improvement included autistic symptoms, aggression, impulsivity, and mood lability. In two subsequent randomized, double-blind, placebo-controlled trials of divalproex sodium in relatively small samples of children and adolescents with ASD (n = 50; n = 27), one study reported significant improvement in irritability (62.5% responder status in active treatment group vs. 9% in placebo group), whereas the other did not find between-group differences for aggression and irritability. Both trials used CGI-I, ABC-I, and Overt Aggression Scale scores as outcome measures and reported similar valproate blood levels, though full-scale intelligence quotient scores were somewhat higher in the study with positive findings (means: 63.3 vs. 54). Divalproex sodium was associated with improved repetitive behaviors as measured by the Children's Yale-Brown Obsessive Compulsive Scale in a randomized, placebo-controlled trial of 13 individuals with autism. Another small study suggested that divalproex sodium may be effective in preventing irritability associated with fluoxetine treatment in children with ASD. Though divalproex sodium is generally well tolerated, side effects of behavioral activation, rash, sedation, nausea and vomiting, and weight gain may be limiting factors for some. Divalproex should not be considered a first-line medication for young women of child-bearing potential, given the increased risks of fetal malformations in the event of pregnancy and of developing polycystic ovarian syndrome. Monitoring valproate blood levels and administering liver function tests periodically can also present a challenge in children with ASD.

Lamotrigine was studied in a randomized, double-blind, placebo-controlled trial for treating core autistic symptoms and associated aberrant behaviors in 28 children (aged 3–11 years) with autistic disorder, titrated to 5 mg/kg/day over eight weeks and maintained for four weeks. The group receiving lamotrigine did not differ from placebo on any ABC subscales, Vineland Adaptive Behavior Scales, or measures of autistic behaviors, and outcome assessors were unable to predict who was assigned to which group. The researchers conducted the study based on previous clinical observation of benefit for inattention, hyperactivity, and stereotypy in six children with autism and epilepsy, and while this study suggests that lamotrigine is not effective for children with ASD who do not have seizures, a subset of children with ASD and comorbid seizure disorder may show behavioral improvement with treatment.

Levetiracetam has been studied in two small samples of children with autism, with conflicting results. In an open-label study of ten young boys with autism and no seizure history, levetiracetam was associated with significant improvement in measures of ADHD symptoms, emotional lability, and aggression, though individuals who had been weaned from medications prescribed for aggression upon study entry (risperidone, carbamazepine, desipramine) demonstrated worsened aggression during the course of the study. A double-blind, placebo-controlled trial in 20 children failed to support these earlier, positive findings; individuals treated with levetiracetam did not show significant improvement in global scores of autism, aggression, affective instability, repetitive behaviors, hyperactivity, or impulsivity. Both studies were limited by the small sample size and lack of selection for patients with high scores on measures of target symptoms.

Reports of oxcarbazepine use for irritability in ASD populations are limited to a retrospective case series of 30 youth and a case report of 3 patients. Subjective improvement in maladaptive behaviors was reported in the 3 patients. In the case series, 14 patients (47%) were retrospectively rated as “much improved” on the CGI-I (mean CGI-I response, 2.9), though 7 patients (23%) terminated treatment due to significant adverse events, including hypotension, seizures, allergy, and, most commonly (n = 4), worsened irritability. In the absence of controlled trials, the efficacy of oxcarbazepine for irritability in ASD cannot be determined and, caution is recommended because of the risk of adverse events.

Topiramate has not been evaluated in controlled trials as a behavioral treatment in individuals with ASD. A small case series (n = 5) and retrospective chart review (n = 15) reported response rates for overall improvement (CGI-I rating of 1 or 2) of 40% and 53%, respectively; side effects in a minority included mild sedation (n = 2), cognitive difficulties (n = 2), and rash (n = 1). In a study of ten youth with ASD treated with topiramate for weight reduction in conjunction with atypical antipsychotic use, weight loss was inconsistent, and four patients discontinued due to adverse behavioral side effects.

To date, beyond individual case reports, no studies have been published concerning the traditional mood stabilizer lithium in individuals with ASD.

In general, response rates for improved maladaptive behaviors with anticonvulsants are lower than with the atypical antipsychotics risperidone and aripiprazole. Anticonvulsants should be considered, however, in certain subsets of ASD populations, including those with poor response or tolerability to treatment with atypical antipsychotics or with concurrent seizure disorders. Controlled trials would be necessary to draw stronger conclusions regarding their effectiveness.

**OXYTOCIN**

Oxytocin (OT), a nine-amino-acid neuropeptide synthesized in the hypothalamus and widely circulated systemically and in the central nervous system, is involved in mammalian...
social behavior, including affiliation, attachment, and social cognition.\textsuperscript{151} Below-average plasma OT levels have been associated with autism,\textsuperscript{152} and in a subset of individuals with autism, social impairment may be related to dysfunction of the OT system, likely due to genetic variation in system components.\textsuperscript{153} In healthy adult volunteers, intranasal OT administered in a single dose improved the ability to infer the affective mental state of others (theory of mind) on the most difficult items of the Reading the Mind in the Eyes (RMET) task.\textsuperscript{154}

OT has been investigated in a number of small samples as a possible therapeutic agent for treating core social deficits in autism, with encouraging results.\textsuperscript{155–158} In a randomized, placebo-controlled, within-subject study, 15 adults with autism or Asperger’s disorder received single intravenous infusions of either OT or placebo, followed by infusions of the other a week later.\textsuperscript{157} In post-infusion testing, participants who received OT during the first condition showed superior retention of affective speech comprehension compared to those receiving placebo first. A subsequent controlled trial in 19 adults with ASD found that OT 24 IU administered intranasally twice a day for six weeks led to significant improvements in social cognition on the RMET task and in overall quality of life, though with no significant change, compared to placebo, on primary outcome measures of social ability (Diagnostic Analysis of Nonverbal Accuracy) and repetitive behaviors (Repetitive Behavior Scale Revised).\textsuperscript{155} In a sample of adolescent boys (12–19 years old), a single dose of intranasal OT (18 or 24 IU) improved emotion recognition on the RMET task,\textsuperscript{156} and OT intranasal administration for two months to a 16-year-old girl with autism improved social communication and irritability.\textsuperscript{158}

In a randomized, double-blind study, based on findings from animal studies showing a link between OT dysregulation and repetitive behaviors, Hollander and colleagues\textsuperscript{159} administered a four-hour intravenous infusion of synthetic OT (Pitocin) to 15 male adults with ASD, with each participant receiving both placebo and OT. During the OT infusion, 86.7\% (n = 13/15) of participants showed a decline in repetitive behaviors from beginning to endpoint, compared to 40\% (n = 6/15) during the placebo phase. No serious adverse effects were reported in these studies.

Limitations of published reports include small sample sizes, which limit the power to detect anything but large effects, and exclusion of individuals with intellectual disability, a common comorbid condition in ASD. Lower-functioning individuals have largely been excluded from OT trials due to difficulty in administering social-cognition tasks in this group, as the measures typically require language-based responses. The effects of long-term administration of OT remain unknown. Numerous clinical trials are currently under way to further characterize the efficacy of OT in treating core social impairment in autism, including three placebo-controlled trials in children and two controlled trials in adults with ASD.\textsuperscript{150}

One trial of note will include children as young as three years old, including those with comorbid intellectual disability, with plans for data collection on potential biomarkers: OXT mRNA expression, OXTR methylation, and OXTR mRNA expression (NCT01308749). OT is not currently commercially available for the treatment of ASD. The therapeutic potential of OT may be limited in part by its short half-life and low ability to penetrate the blood-brain barrier; non-peptide oxytocin receptor agonists, currently under investigation in animal models, may be a promising alternative in the future.\textsuperscript{161}

### AGENTS MODULATING GLUTAMATE TRANSMISSION

Given that glutamate is the major excitatory neurotransmitter in the central nervous system, dysregulation within the glutamate system has been proposed as a possible neurobiological mechanism of disease in autism.\textsuperscript{162} Several medications modulating glutamate neurotransmission are under investigation for treating core autistic features and also related behavioral symptoms.

Memantine is a noncompetitive antagonist of the N-methyl-D-aspartate receptor (NMDAR; an ionotropic glutamate receptor), marketed for the treatment of cognitive impairment associated with Alzheimer’s dementia. Data from mouse models of fragile X syndrome, a single-gene disorder with associated symptoms of autism, suggests that memantine may exert its effect by correcting abnormal synaptic formation and growth of dendritic spines.\textsuperscript{163} Open-label use of memantine in 151 pediatric and young adult patients with ASD (mean age, 9 years; range, 2.5–26 years) to treat core autistic symptoms led to overall improvement (as determined by clinician-rated CGI-I scores) in language in 70\% of participants, social functioning in 70.7\% of participants, and repetitive behaviors in 12.1\% of participants.\textsuperscript{164} The mean daily dose was 12.67 mg and ranged from 2.5 to 30 mg/day. Side effects included increased irritability, hyperactivity, and “manic-type behaviors.” A retrospective review of 18 children with ASD (mean age, 11.4 years; range, 6–19 years) treated with open-label memantine (mean dose, 10.1 mg/day; range, 2.5–20 mg/day) for social communication impairment and inattention yielded similar results, with 61\% rated as “much improved” or “very much improved” on the CGI-I.\textsuperscript{165} Adverse effects occurred in 39\%, most commonly irritability (n = 4/18), though irritability improved in a comparable number of children (n = 4/18) during the course of treatment. Memantine was reported to significantly reduce disruptive behavior and social withdrawal in the single case of a 23-year-old man with autism.\textsuperscript{166} Multisite, placebo-controlled trials are currently under way to determine the efficacy of memantine for social communication deficits in children with autism.\textsuperscript{160}

Riluzole is a glutamate-modulating agent approved by the FDA for treating amyotrophic lateral sclerosis, with preliminary evidence suggesting a benefit for psychiatric disorders with presumed glutamatergic dysfunction, including obsessive-compulsive disorder, treatment-resistant
Hardan and colleagues conducted a 12-week randomized, depression, and fragile X syndrome. Though the exact mechanism of action is unknown, riluzole is thought to reduce glutamate-induced excitotoxicity by enhancing glutamate reuptake into presynaptic cells and inhibiting presynaptic glutamate release. Limited case reports of individuals with autism treated with riluzole for severe repetitive or compulsive behaviors suggest a benefit for this particular symptom cluster. Notable side effects have included anemia, pancreatitis, and elevation in live function tests.

D-cycloserine, an NMDAR partial agonist that binds to the regulatory glycine binding site on NMDARs, has been shown to normalize aberrant NMDAR function in a mouse model of autism and to improve social interaction. In a prospective, single-blind study of ten individuals with autism (mean age, 10 years; range, 5.1–27.6 years) treated with ascending doses of D-cycloserine for eight weeks, 40% showed significant overall improvement, notably in severity of social withdrawal. D-cycloserine has been investigated in other neuropsychiatric disorders with proposed glutamatergic dysfunction, including schizophrenia, but with less promising results, possibly due to the agent’s relatively low affinity for the glycine binding site. The related compound D-serine is a full agonist at the glycine site and may exert a more therapeutic effect, though no results from studies of D-serine in humans have yet been reported. A preclinical trial of a newly developed NMDAR glycine-site partial agonist, GLYX-13, has also suggested improvement in autistic-like social communication deficits in mice and is being investigated as an augmentative treatment in major depressive disorder.

N-acetylcysteine (NAC), a glutamate transmission modulator and antioxidant-promoting agent, is a prodrug of cysteine primarily used to minimize liver damage in the setting of acetaminophen overdose and as a mucolytic in cystic fibrosis. Recent trials suggest that NAC may also reduce symptom burden as an augmenting agent in various neuropsychiatric disorders, including bipolar disorder, schizophrenia, and disorders of impulse control such as obsessive-compulsive disorder, trichotillomania, and pathological gambling. Hardan and colleagues conducted a 12-week randomized, placebo-controlled trial of NAC in 33 children with autism, finding significant reduction on the ABC-Irritability subscale for NAC compared to placebo. Nonsignificant improvement in repetitive behaviors and stereotypy was also observed, though social communication symptoms as measured by the Social Responsiveness Scale did not change. NAC was well tolerated, with few side effects, primarily gastrointestinal upset. These findings have not yet been replicated in larger controlled trials.

Arbaclofen (also known as STX209; developed by Seaside Therapeutics) is a GABA<sub>B</sub> receptor agonist that inhibits presynaptic release of glutamate and thereby reduces glutamate transmission postsynaptically. A recently published randomized, controlled trial of arbaclofen in individuals with fragile X syndrome reported improved social withdrawal and irritability, most significantly in those most severely affected by the disorder. Headaches and sedation were the most commonly reported side effects. Seaside Therapeutics has preliminarily reported improved irritability, social withdrawal, and overall symptom severity in an open-label, Phase II study of arbaclofen in 32 children with ASD, though full results have not yet been published. At a May 2013 conference, the company also reported preliminary results from a Phase 2 placebo-controlled trial of arbaclofen in 150 children aged 5–21 years with ASD. While no improvement was seen in the primary outcome measure of social withdrawal, arbaclofen-treated participants showed significant overall improvement, as measured by CGI-Severity scores.

**CONCLUSIONS**

ASD requires comprehensive care across the lifespan and frequently includes pharmacotherapy for associated emotional problems and maladaptive behaviors, symptoms that may appear different at different developmental stages. Screening for these symptom clusters—particularly sleep disturbance, anxiety, ADHD symptoms, irritability, repetitive behaviors, and compulsions—may reveal significant distress and impairment that could be amenable to improvement with thoughtful medication management. Pharmacological interventions have the potential, when effective, to enhance individuals’ participation in behavioral and educational therapies, leading to better outcomes and overall quality of life.

In general, however, response rates to traditional psychotropic medications in ASD populations have been lower than those observed in studies of disorders with some shared clinical features, such as ADHD and obsessive-compulsive disorder. Methylphenidate, for example, may be effective for some children with ASD and symptoms of ADHD, though not as many respond positively as in ADHD without ASD. Similarly, improvement in repetitive behaviors and compulsions with SSRIs has been modest in comparison to improvements seen in obsessive-compulsive disorder. This variability likely reflects a different underlying neurobiology in autism that has yet to be fully understood, and highlights the complexity of constructs such as attention and repetitive behavior. Medications may also be more efficacious and better tolerated at different points in development, perhaps indicating that changing neurotransmission patterns influence response. SSRIs, including fluoxetine and fluvoxamine, are generally associated with greater efficacy and lower side-effect burden in adults than in children with ASD, possibly due to differential serotonergic activity observed during these stages. Atypical antipsychotics, particularly risperidone and aripiprazole, stand out as well-characterized treatments with large effect sizes for managing irritability in ASD. Metabolic side effects are common, however, and pose a risk to overall health, generally limiting their use to those with the most severe symptoms. Table 1 summarizes findings from the largest available randomized, controlled trials for medications studied in ASD populations. It is
<table>
<thead>
<tr>
<th>Publication</th>
<th>Medication</th>
<th>Mean dose</th>
<th>Sample size (n)</th>
<th>Age range (years)</th>
<th>Study design</th>
<th>Outcomes</th>
<th>Areas of improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>McDougle et al. (1996)</td>
<td>Fluvoxamine</td>
<td>276.7 mg/day</td>
<td>30</td>
<td>18–53</td>
<td>12 weeks</td>
<td>8/15 (53%) fluvoxamine responders</td>
<td>Repetitive thoughts/behavior</td>
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<td></td>
<td>Parallel</td>
<td>Fluvoxamine &gt; placebo</td>
<td>Maladaptive behavior</td>
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<td>groups</td>
<td></td>
<td>Aggression</td>
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<td></td>
<td>Social relatedness (especially language usage)</td>
</tr>
<tr>
<td>McDougle et al. (1998)</td>
<td>Risperidone</td>
<td>2.9 mg/day</td>
<td>31</td>
<td>18–43</td>
<td>12 weeks</td>
<td>8/14 (57%) risperidone responders</td>
<td>Autistic symptoms</td>
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<td>Parallel</td>
<td>Risperidone &gt; placebo</td>
<td>Repetitive behaviors</td>
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<td>groups</td>
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<td>Depression</td>
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<td>Aggression</td>
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<tr>
<td>King et al. (2001)</td>
<td>Amantadine</td>
<td>5 mg/kg/day</td>
<td>39</td>
<td>5–19</td>
<td>4 weeks</td>
<td>Amantadine = placebo on parent-rated ABC</td>
<td>Hyperactivity</td>
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<td></td>
<td>Parallel</td>
<td>Amantadine &gt; placebo on clinician-rated ABC, CGI</td>
<td>Inappropriate speech</td>
</tr>
<tr>
<td>McCracken et al. (2002)</td>
<td>Risperidone</td>
<td>1.8 mg/day</td>
<td>101</td>
<td>5–17</td>
<td>8 weeks</td>
<td>34/49 (69%) risperidone responders</td>
<td>Irritability</td>
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<td>Parallel</td>
<td>Risperidone &gt; placebo</td>
<td>Repetitive behaviors</td>
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<td>groups</td>
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<td>Stereotypy</td>
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<td>Hyperactivity</td>
</tr>
<tr>
<td>Shea et al. (2004)</td>
<td>Risperidone</td>
<td>1.17 mg/day</td>
<td>79</td>
<td>5–12</td>
<td>8 weeks</td>
<td>25/39 (64%) risperidone responders</td>
<td>Irritability</td>
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<td></td>
<td>Parallel</td>
<td>Risperidone &gt; placebo</td>
<td>Hyperactivity</td>
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<td>groups</td>
<td></td>
<td>Inappropriate speech</td>
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<td>Social withdrawal</td>
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<td></td>
<td>Stereotypy</td>
</tr>
<tr>
<td>Hellings et al. (2005)</td>
<td>Divalproex</td>
<td>20 mg/kg/day</td>
<td>30</td>
<td>6–20</td>
<td>8 weeks</td>
<td>Divalproex = placebo</td>
<td>Aggression (improved in a minority of subjects)</td>
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<td></td>
<td></td>
<td></td>
<td>Parallel</td>
<td></td>
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<tr>
<td>Hollander et al. (2005)</td>
<td>Fluoxetine</td>
<td>9.9 mg/day</td>
<td>45</td>
<td>5–16</td>
<td>8 weeks</td>
<td>Fluoxetine &gt; placebo (effect size = 0.76)</td>
<td>Repetitive behaviors/compulsions</td>
</tr>
</tbody>
</table>

Continued on next page
noteworthy that well-designed, placebo-controlled studies of behavioral medications in ASD are scarce; more rigorous, multisite trials are needed to guide sound, evidence-based care. Clinicians treating individuals with ASD should keep in mind that families are often wary of the allopathic medical approach to the treatment of autism; increasing the body of evidence to support these interventions will lead to better care and increased credibility with the general public.

Given the frequently poorer tolerability and lower response rates of many psychotropic medications in ASD

<table>
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<tr>
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<th>Study design</th>
<th>Outcomes</th>
<th>Areas of improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUPP Autism Network (2005)</td>
<td>Methylphenidate</td>
<td>0.125 mg/kg TID, then 0.25 mg/kg TID, then 0.5 mg/kg TID</td>
<td>72</td>
<td>5–14</td>
<td>1 week Crossover</td>
<td>35/72 (49%) methylphenidate responders Methylphenidate &gt; placebo</td>
<td>Hyperactivity</td>
</tr>
<tr>
<td>King et al. (2009)</td>
<td>Citalopram</td>
<td>16.5 mg/day</td>
<td>149</td>
<td>5–17</td>
<td>12 weeks Parallel groups</td>
<td>33% citalopram responders 34% placebo responders Citalopram = placebo</td>
<td>None observed</td>
</tr>
<tr>
<td>Marcus et al. (2009)</td>
<td>Aripiprazole</td>
<td>5, 10, or 15 mg/day, fixed doses</td>
<td>218</td>
<td>6–17</td>
<td>8 weeks Parallel groups (placebo, fixed doses of 5, 10, and 15 mg/day)</td>
<td>Aripiprazole &gt; placebo</td>
<td>Irritability Hyperactivity Stereotypy Compulsions (15 mg/day) Inappropriate speech (15 mg/day)</td>
</tr>
<tr>
<td>Owen et al. (2009)</td>
<td>Aripiprazole</td>
<td>2, 5, 10, or 15 mg/day, flexibly dosed</td>
<td>98</td>
<td>6–17</td>
<td>8 weeks Parallel groups (placebo, fixed doses of 5, 10, and 15 mg/day)</td>
<td>52% aripiprazole responders Aripiprazole &gt; placebo</td>
<td>Irritability Hyperactivity Stereotypy Inappropriate speech</td>
</tr>
<tr>
<td>Hollander et al. (2012)</td>
<td>Fluoxetine</td>
<td>64.76 mg/day</td>
<td>37</td>
<td>18–60</td>
<td>12 weeks Parallel groups</td>
<td>7/20 (35%) improved overall with fluoxetine 10/20 (50%) responders for repetitive behaviors</td>
<td>Repetitive behaviors/ compulsions</td>
</tr>
<tr>
<td>Harflerkamp et al. (2012)</td>
<td>Atomoxetine</td>
<td>1.2 mg/kg/day</td>
<td>97</td>
<td>6–17</td>
<td>8 weeks Parallel groups</td>
<td>Atomoxetine &gt; placebo on ADHD Rating Scale Atomoxetine = placebo on CGI-I</td>
<td>ADHD symptoms, especially hyperactivity</td>
</tr>
<tr>
<td>Hardan et al. (2012)</td>
<td>N-acetylcysteine</td>
<td>900 mg/day, 900 mg BID, or 900 mg TID (all for 4 weeks)</td>
<td>33</td>
<td>3–10</td>
<td>12 weeks Parallel groups</td>
<td>N-acetylcysteine &gt; placebo on ABC-Irritability subscale</td>
<td>Irritability</td>
</tr>
</tbody>
</table>

ABC, Aberrant Behavior Checklist; ADHD, attention-deficit/hyperactivity disorder; BID, twice a day; CGI-I, Clinical Global Impression-Improvement; TID, three times a day.
populations, medications with novel mechanisms of action need to be more actively investigated—both medications in development and those already in use for related disorders. As with other neuropsychiatric disorders, the future of care for individuals with autism lies in better understanding its neurobiological underpinnings, allowing for the development of targeted interventions. Currently, oxytocin and agents that modulate glutamate transmission show promise, but further study is needed to determine their utility. Genetic and neuroimaging studies comparing individuals with ASD who respond positively to particular medications with those who do not could help determine endophenotypes within the autism spectrum and aid in developing more tailored interventions in the future.

More controlled trials in ASD populations are needed to determine parameters and guidelines for using all classes of psychotropic medications. In the meantime, distress and impairment from associated symptoms can be profound, and trials of psychotropic medications are often undertaken in clinical practice when symptom burden is determined to outweigh the risk of potential side effects. A cautious approach is recommended, starting at low doses and increasing slowly according to tolerability. Though much remains unknown about the etiology of autism, emerging rational approaches to pharmacotherapy hold promise for the future.

Declaration of interest: Dr. Henry is a consultant to Beacon Health Strategies. The authors have disclosed that the U.S. Food and Drug Administration has not approved the use of any medication, except aripiprazole and risperidone, for the treatment of autism spectrum disorder as discussed in this article. Please consult the product’s labeling for approved information.

REFERENCES


