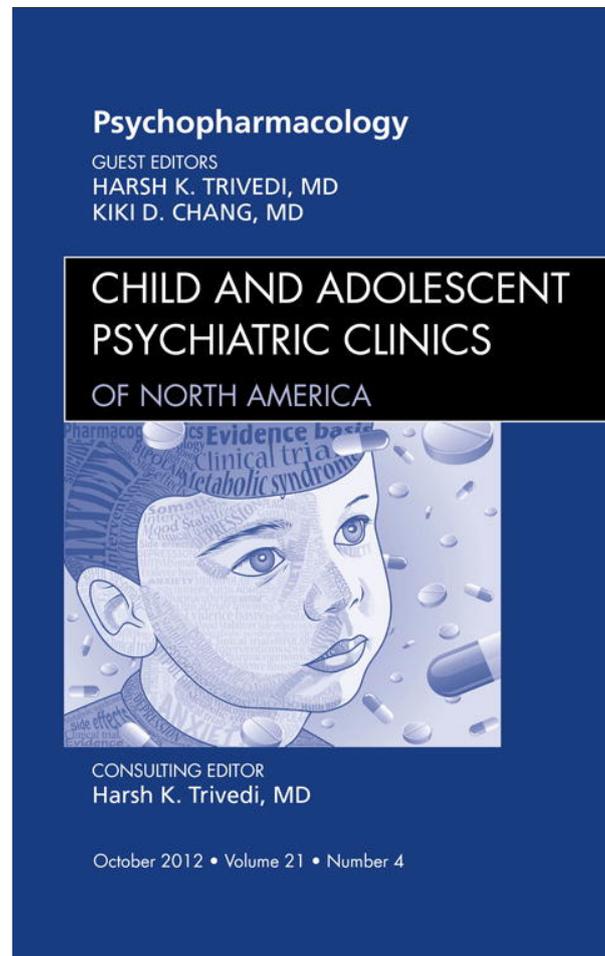


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# Psychopharmacology of Autism Spectrum Disorder: Evidence and Practice

Matthew Siegel, MD<sup>a,b,c,\*</sup>

## KEYWORDS

- Autism spectrum disorder • Comorbid psychopathology • Psychopharmacology
- Symptom-specific treatment

## KEY POINTS

- Children with autism spectrum disorder (ASD) present with high rates of behavioral symptoms and comorbid psychopathology.
- No medications have shown efficacy for the core symptoms of ASD.
- Successful treatment depends on careful dissection of etiologic factors, only some of which may be responsive to psychopharmacologic intervention.
- The controlled evidence base provides important guidance for pharmacologic treatment choices.

## INTRODUCTION

The ASDs—autistic disorder, Asperger syndrome, and pervasive developmental disorder not otherwise specified (PDD-NOS)—share core impairments in the domains of social communication and restricted, repetitive interests and behaviors. Increased identification of children with ASD, now estimated at 1 in 88 by the Centers for Disease Control and Prevention,<sup>1</sup> and the prevalence of comorbid psychiatric and behavioral disorders in the population have contributed to increased exposure of children with ASD to psychotropic medication.

Over the past 3 decades the number and quality of randomized controlled trials (RCTs) of psychotropic medications in children with ASD have increased substantially (**Fig. 1**). Despite this burgeoning evidence base, it remains the case that there is no medication that has shown efficacy for treating the core impairments of ASD. Psychotropic treatment approaches, therefore, currently center on the amelioration of associated symptoms or identifiable comorbid psychiatric disorders.

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<sup>a</sup> Department of Psychiatry, Tufts University School of Medicine, 800 Washington Street, Boston, MA 02111, USA; <sup>b</sup> Developmental Disorders Program, Spring Harbor Hospital, 123 Andover Road, Westbrook, ME 04092, USA; <sup>c</sup> Center for Outcomes Research and Evaluation, Maine Medical Center Research Institute, 509 Forest Avenue, Portland, Maine 04103, USA

\* Developmental Disorders Program, Spring Harbor Hospital, 123 Andover Road, Westbrook, ME 04092.

E-mail address: [siegem@springharbor.org](mailto:siegem@springharbor.org)

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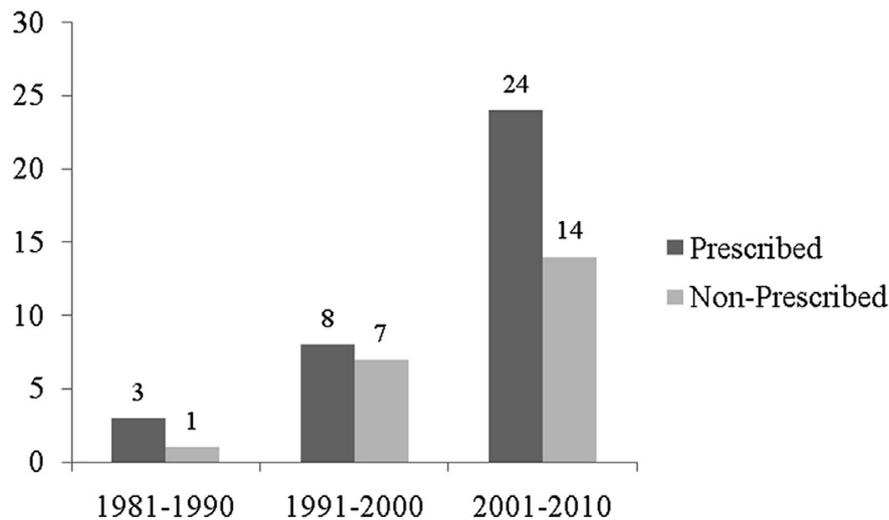


Fig. 1. RCTs of medications in children with ASD.

Two recent systematic reviews graded the controlled evidence base for medications in ASD. The first review included antipsychotics, serotonin reuptake inhibitors, and stimulants in children under 12 years.<sup>2</sup> The second review included those medication classes as well as  $\alpha_2$ -agonists, mood stabilizers, norepinephrine reuptake inhibitors, opioid receptor antagonists, and other medications in children up to 18 years old.<sup>3</sup> Both studies found moderate to strong/established evidence for risperidone and aripiprazole for challenging and repetitive behaviors, and the Siegel and Beaulieu<sup>3</sup> study also found established evidence for haloperidol for hyperactivity and stereotypy, promising evidence for methylphenidate for hyperactivity, and preliminary evidence for atomoxetine and naltrexone for hyperactivity.

This article focuses on the controlled evidence base, discussing uncontrolled data when necessary. Because the evidence for psychopharmacology is limited and the presenting problems typically have a multifactorial cause, successful treatment of children with ASD requires a broad differential diagnostic approach, incorporation of multidisciplinary interventions, and the use of targeted psychopharmacology based on the best evidence for treatment of specific symptoms or syndromes. Symptom specific approaches are presented.

### CURRENT USE OF PSYCHOTROPICS IN THE ASD POPULATION

Studies of local and nationally representative populations in the United States in the past decade have consistently reported that 30% to 60% of children with ASD use at least 1 psychotropic medication.<sup>4-7</sup> In several studies,<sup>8</sup> more severe autistic symptoms and older age have been associated with greater likelihood of prescription medication use. In a Medicaid-enrolled sample, Mandell and colleagues<sup>6</sup> examined more than 60,000 claims and found that increasing age, Asperger syndrome as opposed to autistic disorder, presence of a comorbid psychiatric condition, and greater intellectual disability were correlated with psychotropic medication use. Among the children in the sample, 58% were prescribed at least 1 psychotropic medication. As a Medicaid sample, however, the findings may reflect a disproportionately poor and severely affected group.

In a study of more than 5000 children with ASD with varying insurance status enrolled in a voluntary Web-based parent report registry, 35% used at least 1 psychotropic medication and almost 10% reported 3 or more concurrent psychotropic medications. Those who were insured by Medicaid were more likely to use 3 or more psychotropic medications.<sup>9</sup> The most common medication classes were stimulants, antipsychotics, and antidepressants. The majority of children received psychotropic

prescriptions from psychiatrists (48%) and neurologists (20%), followed by developmental pediatricians (12%) and pediatricians (10%); 39% of respondents reported 1 or more psychiatric comorbidities. As the study showed that insurance status and prescriber specialty affect medication use, it suggests that non-clinical factors may contribute to exposure to psychotropic medications.

The economic impact of medication use in ASD is large. The global market for autism therapeutics has been estimated at \$2.2 billion to \$3.5 billion.<sup>10</sup> Children with ASD incurred 8 to 9 times higher medication costs than children without ASD in a large group-model health plan, accounting for 27% of annual health care expenditures for these children.<sup>11</sup>

### COMORBID PSYCHOPATHOLOGY IN ASD

A strong predictor of medication use in children with ASD is the presence of comorbid psychopathology. Diagnosing comorbid psychopathology in children with ASD, particularly in children at a minimal or non-verbal communication level, is a complex endeavor. Assessments must take into account whether children's symptoms are typical of ASD, normal for their developmental age, serve a specified adaptive function, and/or are modeled or reinforced in their environment, among other considerations. An additional complexity is that most epidemiologic samples of children with ASD report the presence of intellectual disability in at least 50% of subjects.

Children with ASD usually perform in an aberrant fashion on standard psychiatric diagnostic instruments that are designed for the neurotypical population. This can lead to overidentification of comorbid psychiatric disorders. For example, a 2001 study revealed that half of the individuals with ASD assessed with the Structured Clinical Interview met criteria for schizophrenia.<sup>12</sup> Similarly, De Bruin and colleagues<sup>13</sup> used the Diagnostic Interview Schedule for Children Version IV<sup>14</sup> to diagnose comorbidity in 94 children with PDD-NOS and reported that more than 80% of the sample had a comorbid psychiatric disorder, including 61% with a disruptive behavior disorder and 55% with an anxiety disorder. Even higher rates were reported among children with ASD who were referred to a pediatric psychopharmacology clinic and diagnosed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children.<sup>15</sup> This study identified an average of 6.4 comorbid diagnoses in each child, and 95% of the sample met criteria for 3 or more comorbid diagnoses.<sup>16</sup>

Less dramatic findings were obtained by Simonoff and colleagues,<sup>17</sup> who used the Child and Adolescent Psychiatric Assessment to diagnose a population-derived sample of 112 children (ages 10–14 years) with PDD-NOS or autistic disorder identified by parent interview. They found at least 1 comorbid psychiatric disorder in 70% of the sample and 2 or more in 41% of the sample. Most common were social phobia, attention-deficity/hyperactivity disorder (ADHD), and oppositional defiant disorder. Although it likely over-identified psychopathology, the strength of this study was the use of a population-derived sample, suggesting that comorbid disorders occur with some frequency in the general ASD population, not just in clinically referred samples.

Several investigators have worked to develop diagnostic measures of psychopathology specific to children with ASD. Leyfer and colleagues<sup>18</sup> modified the Schedule for Affective Disorders and Schizophrenia for School-Age Children<sup>19</sup> to account for symptoms typical of autism and for how psychiatric symptoms may present in children with ASD, producing the Autism Co-morbidity Interview—Present and Lifetime Version. The instrument was piloted in a sample of 109 children who had at least some spoken language and a performance IQ greater than 65 who were diagnosed with an ASD using the Autism Diagnostic Observation Schedule<sup>20</sup> and the Autism Diagnostic Interview—Revised.<sup>21</sup> The sample was 94% male, and 72% of participants

were diagnosed with at least 1 comorbid *DSM-IV* disorder. The most common disorders included

- Specific phobia: 44% (one-third of which were fear of needles or crowds)
- Obsessive-compulsive disorder (OCD): 37%
- ADHD: 31% (two-thirds inattentive type)
- Separation anxiety disorder: 12%
- Major depressive episode: 10%

The study was limited by a sample that was mostly male, verbal, and higher functioning as well as by the use of parental reports as the sole data source.

Sukholdolsky<sup>22</sup> modified the 26-item Child and Adolescent Symptom Inventory<sup>23</sup> to create a 20-item parent-rated screening tool to detect symptoms across 8 anxiety disorders, attempting to take into account typical ASD and ADHD symptoms. At least 10 of the items required children to provide verbal evidence. A total of 172 medication-free children with ASD (ages 5–17 years) with either high levels of aggression, tantrums, and self-injury or high levels of hyperactivity were screened. The sample included a full range of cognitive ability, from average intelligence to profound intellectual disability. Screening items included statements, such as “has difficulty controlling worries” and “has nightmares about being separated from parents.” In this pilot study, 43% of subjects met the screening criteria for at least 1 anxiety disorder, twice the estimated rate for the neurotypical child population. The specific disorders that screened positive differed by level of intellectual disability, with those reliant on verbal articulation by the patients of their internal experience—generalized anxiety disorder, somatization disorder, separation anxiety disorder, and panic disorder—detected at significantly lower rates in the group with IQ less than 70. Because the instrument was likely somewhat insensitive to the sample with lower cognitive ability or verbal limitations, it is possible that the reported rate of anxiety disorders is an underestimate for that group.

Several investigators have provided evidence that psychiatric comorbidity is common in children with ASD, in particular anxiety and attention/impulsivity disorders. At this time, ASD-specific comorbidity measures have been confined primarily to the higher functioning, verbal population and have yet to develop into a scale brief enough for clinical practice. The absence of a gold standard diagnostic tool for psychiatric comorbidity in ASD has been a barrier to clinical efficacy, targeted research trials, and the ability to rationally extend the large literature on psychopharmacology in neurotypical children to those with ASD. In this context, clinicians are best served by accumulating experience with typical presentations of different subpopulations of children with ASD and taking a broad approach to presenting problems.

#### **DIFFERENTIAL DIAGNOSIS OF PROBLEM BEHAVIORS: DEVELOPING THE WHOLE FROM A PART**

Psychiatric comorbidity is just one of the potential causes of the problem behaviors that are prevalent in the general population of children with ASD. Using the Nisonger Child Behavior Rating Form,<sup>24</sup> an instrument developed for assessing young people with developmental disabilities, LeCavalier<sup>25</sup> conducted a survey of the parents and teachers of 487 school children receiving educational services for ASD. This survey of a non-clinically referred community sample revealed high rates of

- Easy frustration: 60%
- Inattention: 50%
- Hyperactivity: 40%
- Temper tantrums: 30%

Other symptoms included

- Irritability: 20%
- Fearfulness/anxiety: 13%
- Harming self: 11%
- Destroying property: 11%
- Physical fighting: 5%

Success in treating problem behaviors is likely to increase if a broad differential diagnostic approach is used based on a multidisciplinary consideration of causes. In the broadest sense, symptoms should be analyzed in terms of whether environmental (operant) conditions or intrinsic factors are responsible for maintenance of the presentation. Whether the symptoms are best explained by environmental reinforcement, such as the removal of task demands when a child strikes an educational aide, or as neurobiologically mediated, such as aggression that arises when a severely anxious child experiences stimuli flooding, can be considered.

For any given symptom or symptom constellation, clinicians should consider etiologic domains that include

- Medical: pain, seizure, nutrition
- Genetic: fragile X syndrome
- Communication
- Sensory-related
- Psychological: family dynamics, individuation
- Psychopathologic: anxiety, depression, ADHD
- Behavioral operant
- Iatrogenic: polypharmacy, sedation
- And others (**Tables 1** and **2**)

Only a few of these causes are likely to be responsive to psychotropic medication.

<b>Table 1 ASD presenting problem differential diagnosis</b>	
<b>Etiologic Domains</b>	<b>Examples of Potential Factors</b>
Medical	Pain Seizure Nutrition Constipation
Genetic	Fragile X, 22q11.2 deletion syndrome
Communication	Absence of functional communication system
Sensory-related	Hypersensitivities or hyposensitivities
Cognitive	Intellectual disability
Psychological	Family dynamics Individuation
Psychopathologic	Anxiety Depression ADHD
Behavioral operant	Environmental maintenance
Iatrogenic	Polypharmacy Sedation Prompt dependence
Others	

<b>Table 2</b>			
<b>Evidence for medication by target symptom/disorder</b>			
<b>Target Symptom</b>	<b>Agent</b>	<b>Dosing Studied</b>	<b>Level of Evidence</b>
Aggression/ irritability	Aripiprazole	5–15 mg/d	Established evidence
	Risperidone	0.5–3.5 mg/d (mean dose 1.8 mg/d)	Established evidence
	Haloperidol	0.25–4 mg/d	Established evidence (in 2–7 y olds)
	Divalproex sodium	Mean level of 75–90 µg/mL	Insufficient evidence (conflicting results)
	Levitiracetam	20–30 mg/kg/d	Insufficient evidence
	Olanzapine	10 mg/d average	Insufficient evidence
	Lamotrigine	5 mg/kg/d	Evidence of no effect
Anxiety/OCD	Buspirone	15–45 mg qd	Insufficient evidence
	Sertraline	25–50 mg qd	Insufficient evidence
Hyperactivity	Methylphenidate	0.25–0.30 mg/kg/dose best response	Promising evidence
	Aripiprazole	5–15 mg/d	Promising evidence
	Risperidone	0.5–3.5 mg/d (mean dose 1.8 mg/d)	Promising evidence
	Haloperidol	0.25–4 mg qd	Promising evidence (in 2–7 y olds)
	Atomoxetine HCl	20–100 mg divided bid (mean 44 mg/d)	Preliminary evidence
	Naltrexone	0.5–1 mg/kg/d	Preliminary evidence
	Clomipramine	100–150 mg/d (mean 128.4 mg/d)	Insufficient evidence
	Clonidine Guanfacine	0.15–0.20 mg/d 1–3 mg/d divided tid	Insufficient evidence Insufficient evidence
Insomnia	Melatonin	1–3 mg/d	Preliminary evidence
Repetitive behavior/stereotypy	Risperidone	0.5–3.5 mg/d (mean dose 1.8 mg/d)	Established evidence
	Haloperidol	0.25–4 mg/d	Established evidence (in 2–7 y olds)
	Aripiprazole	5–15 mg/d	Established evidence
	Divalproex Sodium	500–1500 mg/d	Insufficient evidence
	Fluoxetine	9.9 mg/d mean	Insufficient evidence
	Clomipramine	100–150 mg/d (mean 128.4 mg/d)	Evidence of no effect
	Citalopram	16.5 mg/d mean	Evidence of no effect
Self-injury	Naltrexone	Approximately 1 mg/ kg/d	Insufficient evidence (conflicting results)
Social communication/ emotional regulation	Methylphenidate	0.25–0.30 mg/kg/ dose best response	Insufficient evidence
	Risperidone	0.5–3.5 mg/d (mean dose 1.8 mg/d)	Insufficient evidence

Data from Siegel M, Beaulieu A. Psychotropic medications in children with autism spectrum disorders: a systematic review and synthesis for evidence-based practice. *J Autism Dev Disord* 2012;42:1592–605.

### MEASURING CHANGE DURING PHARMACOTHERAPY

Because many children with ASD exhibit variations in symptom severity on a daily to weekly basis, reflecting the multifactorial etiology of most problem behaviors, it is vital

to use behavioral data or rating instruments in a longitudinal fashion to drive treatment decision making. Relying solely on parent report, which may reflect only the most recent or most severe data, contributes to abbreviated treatment trials and increases the risk of polypharmacy.

The most widely used standardized outcome measure for children with ASD is the Aberrant Behavior Checklist (ABC).<sup>26</sup> The ABC is a 58-item parent or teacher-rated measure validated for children with developmental disabilities that produces 5 subscale scores in the domains of

1. Irritability
2. Lethargy/Social Withdrawal
3. Stereotypy
4. Hyperactivity
5. Inappropriate speech

The Irritability subscale comprises items that primarily reflect aggression, self-injury, and tantrums and has been used in multiple RCTs. Significant decreases in the irritability subscale contributed to the FDA approval for risperidone and aripiprazole in the treatment of irritability in ASD. Caution is advised, however, in applying the term, *irritability*, too freely to presenting symptoms, because 1 study found that only 20% of children with ASD were rated by parents and teachers as irritable.<sup>25</sup>

The Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS) modified for PDDs<sup>27</sup> is an adaptation of the CYBOCS, designed to better characterize compulsions in the setting of ASD. The symptom checklist was expanded to include spinning objects, twirling, staring, and repetitive communications, and the informant was changed from the child to the parent. Whether the repetitive behaviors commonly seen in ASD represent obsessive-compulsive phenomena, which are typically egodystonic, or are better conceptualized as self-stimulatory actions that maintain sensorial equilibrium or provide self-reinforcing pleasurable feedback has not been established. Finally, several measures designed to assist in diagnosing autism have been used to evaluate response to treatment, including the Childhood Autism Rating Scale (CARS),<sup>28</sup> Gilliam Autism Rating Scale (GARS),<sup>29</sup> Autism Diagnostic Observation Schedule, though the validity of their use for this purpose has not been well established.

At this point there is no comprehensive scale for assessing change in the full range of maladaptive behaviors seen in children with ASD. Definition and recording of target behavior occurrences in educational and home treatment settings has become more common, providing an important source of data.

## EVIDENCE BASE FOR PSYCHOTROPIC TREATMENT

### *Aggression and Irritability*

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Aggression, irritability, and self-injury are prevalent in the ASD population and treatments for some of these symptoms have the strongest evidence in ASD psychopharmacology. The most common outcome measure for this symptom cluster, the ABC Irritability subscale, contains 15 items that individually probe physical aggression toward others, self-injurious behavior, and irritability of mood or tantrum behaviors. Because the individual irritability subscale item data are not typically presented in published reports, further parsing of the symptom cluster has been limited.

In a recent report, the author of the instrument performed a line-item analysis of the irritability subscale data from 2 RCTs of aripiprazole in children with ASD. The ABC Irritability score was significantly improved, but individual item improvement was confined to the aggression and tantrum behavior items – self-injury items did not

show statistically significant improvement.<sup>30</sup> For maximal clinical utility, this article groups aggression and irritability together and separately examines the few trials that have specifically targeted self-injury.

Risperidone and aripiprazole have the best evidence for reducing irritability and aggression, as shown in multiple RCTs. In the groundbreaking Research Units on Pediatric Psychopharmacology (RUPP)<sup>31</sup> RCT in 101 children ages 5 to 17 with ASD, risperidone (at an average of 1.8 mg/d) produced a significant improvement. In the treatment group, there was a 57% decrease in the ABC Irritability score compared with a 14% reduction in the placebo group. Responders in the blinded portion of the trial were enrolled in an open-label continuation phase for an additional 16 weeks, followed by an 8-week randomized, double-blinded discontinuation phase. In the open-label continuation, 51 of 63 initial responders remained stable, and of the 32 individuals who participated in the discontinuation study, 10 (62.5%) in the placebo group relapsed versus 2 (12.5%) in the medication group. A second RCT, performed by a separate investigative group, produced results largely similar to the treatment phase.<sup>32</sup>

In the preschool population, 2 RCTs of risperidone have been conducted. Luby and colleagues<sup>33</sup> performed an RCT in 24 children, ages 2.5 to 6 years, who received concurrent applied behavior analysis. At doses of 0.5 mg/d to 1.5 mg/d, the most common adverse events were sedation, sialorrhea, and increased appetite. Because the CARS and GARS diagnostic measures were the primary outcome measures, results are difficult to interpret but showed no effect on core symptom domains—although effects may have been muted by the lack of symptomatic entry criteria. A second RCT in preschoolers demonstrated some efficacy at 1 mg/d on the Children's Global Assessment Scale and the CARS.<sup>34</sup>

The RCTs of risperidone in school-aged children have shown mean weight gain in the medication group of 2.7 kg to 2.8 kg more than in the placebo group. Somnolence was the most common side effect, and the risperidone group had more extrapyramidal symptoms (EPS) reported than the placebo group. Cognitive effects of risperidone were assessed in the RUPP study and no significant adverse changes were detected.

Two pharmaceutical industry-sponsored large RCTs of aripiprazole showed efficacy for reduction of irritability. The first trial enrolled 98 children ages 6 to 17 years<sup>35</sup> and the second examined 218 children.<sup>36</sup> ABC Irritability subscale scores decreased 12.4 to 14.4 points in the medication group, compared with 5 to 8.4 points in the placebo group; 52.2% to 55.8% of subjects were considered responders. As with risperidone, somnolence was the most common side effect, EPSs were more common in the medication group than the placebo group, and 10.6% of the aripiprazole group discontinued the medication. Weight gain was less dramatic than in the risperidone studies but subjects taking aripiprazole did have a mean increase of 1.3 kg to 2 kg compared with 0.3 kg to 0.8 kg in the placebo group.

Haloperidol was reported as equivalent to risperidone in a study with methodologic and reporting issues.<sup>37</sup> An earlier crossover design RCT that included 24 children ages 10 to 18 years; however, found no difference on the ABC Irritability subscale between the placebo group and those treated with haloperidol at an average of 1.3 mg/d.<sup>38</sup> Results from the latter study need to be interpreted in light of a sample not selected for aggression or irritability, possible carryover effects between groups, and a low dosing scheme. Two older RCTs of haloperidol by Anderson<sup>39,40</sup> reported reduction in aggression, among several other symptoms, in mid-sized samples of 2-year-old to 7-year-old children with ASD. Despite the evidence for efficacy, use of haloperidol is best reserved for treatment of refractory cases due to the side-effect profile, which includes risks of dyskinesia and dystonia.

Mood stabilizers have been studied in several RCTs for reducing irritability/aggression and have yet to produce consistent evidence of benefit. Two RCTs of divalproex sodium targeting global clinical irritability or ABC-defined irritability have produced conflicting results. In 30 individuals with ASD, ages 6 to 20 years, Hellings and colleagues<sup>41</sup> found no significant difference on the ABC Irritability subscale between medication and placebo groups, with a mean trough level of 77.8 µg/mL. The study also described high intersubject variability and a large placebo effect. Hollander and colleagues<sup>42</sup> used more severe symptom entry criteria to reduce intersubject variability and showed a significant difference between divalproex sodium and placebo in favor of divalproex, particularly for those who obtained serum levels of 87 µg/mL to 110 µg/mL.

RCTs on lamotrigine and levitirecetam produced no significant effect on irritability.<sup>43,44</sup> There is insufficient evidence for olanzapine based on 1 small RCT, which showed improvement confined to the CGI,<sup>45</sup> and both ziprasidone and quetiapine have only uncontrolled data thus far. In addition, there is marginal evidence that methylphenidate can be helpful for reducing aggression in children with ASD and high degrees of impulsivity.<sup>46,47</sup>

Given the multifactorial etiology of most presenting problems, recent studies have begun to examine the efficacy of combining medication with behavioral management. The first enrolled 124 children with ASD (4–13 years old) and demonstrated greater reduction in the ABC Irritability score for patients who received an average dose of risperidone of 1.98 mg/d and 10.9 parent training sessions than the group who received risperidone at a mean dose of 2.26/d without parent training.<sup>48</sup> A recently published secondary analysis of adaptive behavior outcomes in this study demonstrated modestly greater gains (effect size [ES] = 0.14–0.35) in the socialization and communication domains for the risperidone plus parent training group.<sup>49</sup> Although early, these results are intriguing given the small investment required in providing 11 parent training sessions and the currently widespread use of behavioral management strategies in educational and treatment settings.

### **Anxiety/OCD**

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Despite multiple diagnostic surveys reporting anxiety disorders as the most common psychiatric comorbidity in children with ASD, there have been no controlled trials of pharmacologic treatment targeting anxiety in the population. The most frequently reported anxiety disorders are simple phobias, generalized anxiety disorder, separation anxiety disorder, and OCD.<sup>50</sup> Because anxiety is prevalent across the range of functioning in ASD, the need for better assessment tools of anxiety in both verbal and minimal or non-verbal children is urgent.

Perhaps related to the lack of assessment tools, studies targeting anxiety are restricted to small, uncontrolled trials and scattered case reports. Sertraline was studied in an uncontrolled trial of 9 children, 6 to 12 years old, with transition-induced behavioral deterioration, which was interpreted as related to transition anxiety.<sup>51</sup> Eight of the 9 subjects were reported to experience clinically significant improvement at 25 mg/d to 50 mg/d, based on parent report without standardized outcome measures. This pilot report has not been followed-up with a controlled trial.

Buspirone was the subject of an open label, uncontrolled trial in 22 children with ASD ages 6 to 17 years who were given 15–45 mg/d.<sup>52</sup> The investigators reported qualitative reduction of “overwhelming anxiety,” although the primary outcome measure was only the CGI, which was reported as much/very much improved in 16 of 22 subjects. Side effects included oral-buccal movements in 1 subject.

Little is known about treating anxiety and OCD with riluzole, a compound that has complex effects on glutamate activity. There is currently a double-blind, placebo-controlled trial of riluzole being conducted by the National Institute of Mental Health in

which riluzole or placebo is being given to youths ages 7 to 17 years who have treatment refractory moderate to severe OCD. Half of the enrolled subjects can also have ASD.

### ***Hyperactivity-Impulsivity and Inattention***

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Symptoms of inattention, hyperactivity, or impulsivity are common in children with ASD. Concerns based on smaller uncontrolled studies regarding poor response or high rates of adverse events for the developmental disorders population have not been fully supported by controlled studies.

One large RCT has been performed targeting hyperactivity in children with ASD. Low (0.125 mg/kg), medium (0.25 mg/kg), and high (0.5 mg/kg) doses of methylphenidate were given twice a day, with a smaller third dose in the late afternoon, to 72 children (ages 5–14 years) with ASD (65% autistic disorder) and significant hyperactivity-impulsivity scores on the SNAP-IV ADHD scale.<sup>49</sup> A few subjects (8.3% of the sample) did not proceed beyond a test dose. Based on parent ratings, 49% of children were responders on the ABC hyperactivity subscale, with the greatest ES (.54) seen at the medium dose. 18% of subjects exited the study due to side effects. A smaller RCT was performed by Handen and colleagues on 13 children with ASD (69% autistic disorder) and ADHD symptoms, ages 5 to 11 years.<sup>48</sup> The study compared low (0.3 mg/kg/d) and high (0.6 mg/kg/d) doses of methylphenidate divided 2 or 3 times a day. On the ABC hyperactivity subscale, the high dose outperformed placebo, and both doses outperformed placebo on the Conners' Abbreviated Symptom Questionnaire, as rated by teachers. The most common adverse events across the 2 studies included irritability, emotional outbursts, social withdrawal, sadness, or dullness. A recent small RCT of methylphenidate in 12 preschoolers with ASD and ADHD showed a 50% response rate (ES = 0.97) on the Conners' Parent Rating Scale (CPRS)–Revised ADHD subscale but also demonstrated higher side-effect rates than in studies of methylphenidate in older children.<sup>53</sup>

Atomoxetine has been subjected to 1 small, double-blind RCT in 16 children ages 5 to 15 years with ASD and ADHD symptoms.<sup>54</sup> Atomoxetine produced an ES of 0.90 on the primary outcome measure, the ABC hyperactivity subscale, and 56% of subjects were considered responders. As with methylphenidate, the primary gains were in hyperactivity and impulsivity rather than inattentive symptoms; 18% of the sample exited the study and side effects were primarily gastrointestinal.

Risperidone has also been shown to reduce hyperactivity in children with ASD in at least 3 RCTs, the strongest of which is the RUPP 2002 study,<sup>29</sup> which showed 69% of subjects as responders on the ABC hyperactivity subscale (ES = 1.0) at the 8-week endpoint. Aripiprazole was tested in 2 large RCTs and demonstrated efficacy in reducing the ABC hyperactivity score of children with ASD by 12.7 to 16.3 points compared with a mean decrease of 2.8 to 7.7 points in the placebo group.

Naltrexone has been evaluated in 5 RCTs in children with ASD, primarily to test efficacy for reducing self-injury, but was found to have significant effects on hyperactivity. The largest of these studies produced significant reductions in the CPRS hyperactivity factor among 41 children 3 to 8 years old given 0.5 mg/kg/d to 1 mg/kg/d of naltrexone, and reported side effects of sedation, decreased appetite, and vomiting in the medication group.<sup>55</sup> Other treatments have included haloperidol, which demonstrated efficacy in reducing hyperactivity on the CPRS in 2 medium-sized RCTs in 40 to 45 children ages 2 to 7 years old.<sup>39,40</sup> Because sedation, irritability, and EPS were significant side effects, haloperidol is not a preferred choice for treatment of ADHD symptoms.

Guanfacine and clonidine have undergone small controlled studies targeting ADHD symptoms in ASD. Handen and colleagues<sup>56</sup> performed the only published RCT of guanfacine, targeting inattention and hyperactivity in 11 children with ASD ages 5 to

9 years; 45% of the sample showed more than a 50% reduction in the ABC hyperactivity score and approximately 45% of participants exhibited drowsiness. Approximately 27% of participants, experienced a level of drowsiness, irritability, or enuresis that prevented titration to the maximum dosage. A few open-label studies have been performed and a large RCT of long-acting guanfacine is currently under way. Two small RCTs of clonidine have been performed, each of which showed mixed results based on the reporter, and significant rates of sedation and hypotension.<sup>57,58</sup>

Clomipramine and desipramine seemed to show some efficacy in reducing hyperactivity in children with ASD.<sup>59</sup> A later RCT on clomipramine, however, evaluated 31 children and found no significant difference between clomipramine and placebo on the ABC hyperactivity subscale. In addition, twice as many participants receiving clomipramine stopped the study medication due to side effects or lack of efficacy than those on placebo.<sup>39</sup>

Based on these data, methylphenidate produces a somewhat lower response rate in children with ASD and ADHD symptoms (50%–60%) than it does in the neurotypical population (70%–90%). The evidence for methylphenidate is significantly stronger than that for atomoxetine, with best average results seen at a methylphenidate dose of approximately 0.25 mg/kg to 0.30 mg/kg given 2 to 3 times a day. Naltrexone has shown some efficacy in reducing hyperactivity. Risperidone and aripiprazole also appear efficacious for reducing hyperactivity, although their side-effect profile makes them a second-line choice for targeting hyperactivity.

### ***Repetitive Behavior/Stereotypy***

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The domain of repetitive/stereotypic behaviors can be a treatment target when these symptoms interfere with educational programming or family life.

Risperidone has the best evidence for reducing repetitive behaviors, as shown in the large RUPP RCT<sup>31</sup> (discussed previously). In this trial, risperidone, at an average of 1.8 mg/d, produced a decrease in mean ABC stereotypy subscale scores from a baseline of 10.6 to an endpoint of 5.8 at 8 weeks of treatment. A decrease was also found in a modified, parent-rated Ritvo-Freeman Real Life Rating Scale sensory-motor subscale that included many repetitive behaviors. Decreased repetitive behavior was further evidenced by decreases in a modified CYBOCS, altered to better capture repetitive behaviors in nonverbal children, with a change from 15.51 at baseline to 11.65 at the 8-week endpoint (ES = 0.55). The RCTs of aripiprazole have also demonstrated significant reductions in the ABC stereotypy subscale.<sup>36,37</sup> Haloperidol demonstrated strong evidence for efficacy in reducing stereotypy on the CPRS in 2 moderately sized RCTs in 40 to 45 children ages 2 to 7 years old.<sup>40,41</sup> Sedation, irritability, and EPS were significant side effects and relegate haloperidol to being a second-line agent for use in stereotypy.

SRIIs have proved disappointing when subjected to rigorous RCTs to evaluate effects on repetitive behavior. King and colleagues<sup>10</sup> demonstrated no significant difference between placebo and citalopram at a mean dose of 16.5 mg/d in 145 children with ASD (ages 5–17) on the CYBOCS-PDD. Side effects seen in the citalopram group included increased energy levels, impulsiveness, decreased concentration, hyperactivity, and stereotypy, among others. An RCT of fluoxetine in 39 children 5 to 17 years old used a crossover design and showed a 1.3-point, clinically insignificant, decrease on the 20-point CYBOCS.<sup>60</sup> The crossover design for an ultra-long-acting compound and the relatively low dosing scheme may have affected results. Clomipramine was initially reported to have positive effects on repetitive behavior in open-label and small controlled studies, whereas a medium-sized RCT of clomipramine showed no separation from placebo on the ABC stereotypy subscale.<sup>39</sup>

Finally, a small RCT of divalproex sodium in 13 children with ASD showed no clinically significant effect on repetitive behaviors as measured by an approximately 1-point decrease in the 20-point CYBOCS with a mean divalproex level of 58.<sup>61</sup>

### ***Self-Injury***

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Naltrexone has been the subject of at least 5 RCTs examining self-injury, which have produced conflicting results and have suffered from methodologic problems. Initially, it was hoped that naltrexone would be efficacious in children with self-injurious behavior (SIB) based on the theory that the SIB is maintained through endogenous opioid release. The largest study was of 41 children with ASD ages 3 to 8 years, who were given naltrexone (1 mg/kg for 2 weeks) and found no significant difference between medication and placebo groups for self-injury or aggression.<sup>54</sup> Another RCT was performed on 20 children with ASD (ages 3–7 years) using a single higher dose (mean 1.96 mg/kg) in a crossover design.<sup>62</sup> This study produced a significant reduction in the ABC Irritability subscale score in the medication group. The same investigator then performed an RCT with an 8-week crossover design (4 weeks in each arm) with an average daily dose of 0.98 mg/kg/d.<sup>63</sup> Parent and teacher ratings on the ABC Irritability subscale, which includes aggression and self-injury, were conflicting, although the study sample was not selected for children with significant SIB. Despite the generally disappointing results, some investigators reported impressive effects in several subjects and noted that the selected populations were heterogeneous. In practice, when faced with a child with moderate to severe self-injury for whom behavioral and other interventions have failed, a trial of naltrexone is likely warranted.

### ***Sleep Disturbance***

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Insomnia is reported to be highly prevalent in children with ASD, occurring in 44% to 86%.<sup>64</sup> Other sleep disturbances may include irregular sleep-wake patterns, early awakening, and poor sleep routines. The evaluation and treatment of sleep disturbance is multifactorial. In the author's clinical experience admitting many children with ASD to a specialized inpatient psychiatric unit, parent-reported sleep difficulties that are observed in the home frequently cease on entry to the hospital, suggesting that environmental factors are prominent.

Melatonin is the only compound that has been subjected to controlled study for use in sleep disturbance in children with ASD. At least 2 small RCTs have been performed, showing modest efficacy for melatonin in the population. An RCT of controlled-release melatonin (5 mg) included 16 children with ASD who had not responded to sleep hygiene interventions. The study reported a significant reduction in sleep latency and longer nighttime sleep in the children with ASD.<sup>65</sup> A small RCT of immediate release melatonin in 7 children with ASD showed reduction in sleep latency of 0.85 hours and increase in total sleep time of 1.09 hours compared with the placebo group.<sup>66</sup> Other potential sleep enhancing options, such as trazodone, mirtazapine, clonazepam, or diphenhydramine, have not been studied for this indication in ASD.

### ***Social Communication, Hyperarousal, and Self-Regulation***

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Deficits in social communication and emotional regulatory mechanisms are persistent features in individuals across the ASD spectrum. Evidence from controlled trials of compounds targeting these areas is currently limited to secondary outcome analyses.

Jahromi and colleagues<sup>67</sup> performed a secondary analysis of the RUPP methylphenidate sample to examine a subgroup of 33 children with ASD and hyperactivity

between the ages of 5 and 13 years, with mental ages less than 9 years. Using a validated procedure to assess joint attention initiations, response to bids for joint attention, self-regulation, and affective state, significant improvements were seen in the methylphenidate group. Parameters were measured repeatedly by blinded observer ratings of video recordings of both a scripted, semi-structured social communication task and a parent-child interaction. The investigators describe this as a pilot investigation, because it is a secondary analysis using a novel assessment strategy.

Risperidone demonstrated possible evidence for improvements in social communication in a secondary analysis of the RUPP 2002<sup>29</sup> data, which revealed significant improvement on the Ritvo-Freeman Real Life Rating Scale-affective reactions subscale, although there were no significant changes on the relationship to people or language subscales.<sup>68</sup> Other marginal evidence comes from an RCT of risperidone that showed a 63% decrease in the ABC social withdrawal subscale versus a 40% reduction for the placebo group.<sup>30</sup> One or more RCTs of secretin,<sup>69</sup> naltrexone,<sup>61</sup> and donepezil<sup>70</sup> have refuted earlier uncontrolled reports that suggested improved social interaction or significant cognitive enhancement could be seen with these agents.

The secondary analyses discussed raise the intriguing question as to whether methylphenidate's well-described effects on executive functioning or risperidone's effects on the dopaminergic reward system and other areas may lead directly or indirectly to improved social communication and emotional regulation in children with ASD.

## SUMMARY

Children with ASD have high rates of problem behaviors and comorbid psychiatric disorders, which are associated with use of psychotropic medications. Accurate assessment of presenting symptoms requires a broad differential diagnostic approach and recognition of the multitude of factors that may pertain, only some of which are likely responsive to psychotropic medication. Psychopharmacology should be based on the best evidence for efficacy in ameliorating the target symptom or syndrome, balanced against the risk and severity of side effects.

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