Clinical Practice Pathways for Evaluation and Medication Choice for Attention-Deficit/Hyperactivity Disorder Symptoms in Autism Spectrum Disorders

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**KEY WORDS**
ADHD symptoms, autism spectrum disorders, hyperactivity, impulsivity, inattention

**ABBREVIATIONS**
- ADHD—attention-deficit/hyperactivity disorder
- ASD—autism spectrum disorder
- ATN-PC—Autism Treatment Network Psychopharmacology Committee
- DSM-IV—Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
- RCT—randomized controlled trial

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Children with autism spectrum disorders (ASDs) frequently experience medical or neurologic comorbidities, including gastrointestinal symptoms, sleep difficulties, and seizures.\textsuperscript{1–3} Similarly, co-occurring behavioral or mental health symptoms occur in the majority of children who have ASD,\textsuperscript{4} with individual children often showing symptoms of ≥2 comorbid disorders.\textsuperscript{5–7} Recent systematic analyses of comorbidity in ASD indicate that behavioral or mental health conditions increase the need for multiple resources, extra assistance in schools, and therapeutic interventions.\textsuperscript{8–10}

Symptoms of hyperactivity and impulsivity, with or without inattention (attention-deficit/hyperactivity disorder [ADHD] symptoms), are common in children who have ASD. Rates vary from 41% to 78% in large samples.\textsuperscript{11} These symptoms often lead parents and caregivers to seek medical evaluation and treatment.\textsuperscript{12} Conversely, autistic features have been reported in children who have ADHD, especially in those with the combined type.\textsuperscript{13,14} Medical providers often prescribe medications targeting ADHD symptoms in ASD, recognizing the significant impairment that results if these symptoms are left untreated.\textsuperscript{15,16}

Children may manifest all ADHD symptoms as outlined in the \textit{Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition} (DSM-IV)\textsuperscript{17} criteria for ADHD; however, the DSM-IV does not allow the concurrent diagnosis of ADHD and ASD. The fifth edition of the DSM is anticipated to allow a concurrent diagnosis of the 2 conditions.\textsuperscript{18} In the interim, we refer to hyperactivity, impulsivity, and inattention in ASD as “ADHD symptoms” to reflect the DSM-IV criteria. Although guidelines exist for evaluating and treating ADHD symptoms in typically developing children,\textsuperscript{19–22} there are no such guidelines for children with ASD who may have these symptoms. In addition, the evaluation and treatment, although based on guidelines and evidence for the typically developing children, are not always successful because of the multidimensional difficulties that children who have ASD experience. Psychotropic medications, although used commonly for these symptoms, may not be as effective for children who have ASD as in typically developing children. Moreover, children who have ASD are more sensitive to the side effects of these medications. With these considerations, clinicians often seek specialist opinion, which may not be readily available, given the variability in such access regionally. The present effort provides an attempt to address the need for a clinical pathway for practitioners, specifically for evaluating and treating symptoms of ADHD in children who have ASD.

Within the behavioral symptom domains, the Autism Speaks Autism Treatment Network Psychopharmacology Committee (ATN-PC) Medication Choice Subcommittee, composed of specialists in the treatment of children with ASD and comorbid conditions, was charged with the task of developing practice pathways for the symptom evaluation and use of psychotropic medications for target symptoms in children who have ASD. The current practice pathways provide clinicians with critical steps in evaluation of ADHD symptoms and with guidance on the choice of appropriate medications.

\section*{METHODS}

Because of the limited evidence base for evaluation and treatment of ADHD symptoms in children who have ASD, we were forced to rely primarily on collective clinical experience, complemented, where possible, with such evidence as does exist, as well as previously available guidelines in ADHD and ASD. Based primarily on group consensus, the ATN-PC Medication Choice Subcommittee developed 2 practice pathways related to ADHD: 1 for the evaluation of ADHD symptoms and 1 for the choice of medication for individuals whose symptoms merit a medication trial. After refinement of the practice pathways, accompanying narratives were composed for each step in the pathway. Individual members drafted narrative subsections corresponding to single steps in the pathway. These drafts underwent further review by 1 or 2 other members of the subcommittee. The entire ATN-PC Medication Choice Subcommittee then discussed and revised each step in detail before the integration for final review by members of the larger ATN-PC.

\section*{Systematic Literature Review}

To ensure there were no omissions of relevant evidence from the pathway, we conducted a systematic literature review to identify evidence for the benefits and adverse effects of stimulants, atomoxetine, \(\alpha\)-agonists, antipsychotic agents, and other medications on ADHD symptoms in ASD. The searches were conducted in Ovid, CINAHL, Embase, Database of Abstracts and Review, and the Cochrane Database of Systematic reviews (Tables 1 and 2) and were limited to research conducted with humans, published in the English language, involving children aged 0 to 18 years, and published between January 2000 and July 2010. The year 2000 was used as a cutoff because the standard diagnostic instruments for ASD (Autism Diagnostic Interview-R\textsuperscript{23} and Autism Diagnostic Observation Schedule\textsuperscript{24}) were rarely applied before this time. Four primary reviewers graded the research by using a system adapted from GRADE.\textsuperscript{25} The system systematically assigned numerical values (26 points possible across 16 questions) based on the quality, consistency, directness, and effect size demonstrated (Table 3). Those scoring <40% were removed from the evidence base.\textsuperscript{23}
TABLE 1 Literature Review Questions

- What are the indications for the following medicines in treating ADHD symptoms in ASD/PDD?
- What are the side effects of the following medicines in treating ADHD symptoms in ASD/PDD?

PDD, pervasive developmental disorder.

TABLE 2 Medication Medical Subject Headings and Key Words

- Stimulants
  - Amphetamines
  - Dextroamphetamine
  - Methylphenidate
  - Dexamfetamine
- α-Agonists
  - Clonidine
  - Guanfacine
- Antipsychotic/neuroleptic agents
  - Risperidone
  - Aripiprazole
  - Atomoxetine
  - Antidepressant
  - Nortriptyline

RESULTS

Results of the Literature Review

The search identified 1255 articles. After removing review articles, commentaries, studies including <10 subjects, nonintervention trials, and articles that did not measure ADHD symptoms, 31 articles remained. These were organized into 2 tables (Tables 4 and 5), 1 for the randomized controlled trials (RCTs) and another for the non-RCT studies (non-RCTs). Based on the review, atypical antipsychotic agents (primarily risperidone) had the most RCTs, although ADHD symptoms were not the primary endpoints in these studies. These medications were being studied for irritability and behavioral symptoms; the benefit for ADHD was a secondary outcome, with improvement reported primarily in hyperactivity. Surprisingly, there were fewer RCTs for the ADHD-focused studies, with medications commonly used in clinical practice to target these symptoms (eg, stimulant medications, atomoxetine, α2-agonists). Among these medications, most evidence was available for stimulant medications (only methylphenidate), with 3 RCTs, including 1 study of preschool-aged children. Non-RCTs included studies of stimulant medications (only methylphenidate), with 3 RCTs, including 1 study of preschool-aged children. Non-RCTs included studies of stimulant medications (only methylphenidate), with 3 RCTs, including 1 study of preschool-aged children.

TABLE 3 Summary of Grading Criteria

<table>
<thead>
<tr>
<th>Quality</th>
<th>Measures the quality of the study design, such as blinding, random assignment, patient selection, and measures used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistency</td>
<td>Measures the quality of patient selection, such as ASD diagnosis/definition, homogenous population in terms of disease and progression, and adjustment for confounders.</td>
</tr>
<tr>
<td>Directness</td>
<td>Measures the external validity of the study, such as representative of the gender distribution, loss to follow-up due to treatment demands, and applicability to &quot;real life&quot;</td>
</tr>
<tr>
<td>Effect size</td>
<td>Measures the study's use of statistics to report outcomes/findings. Follows use of confidence intervals, relative risk/odds ratio, and/or P values. Studies were not graded on basis of the value of the statistic presented but instead on presence. Presence of statistics was weighted by a factor of 3 as the absence denotes the paper as more qualitative than quantitative</td>
</tr>
</tbody>
</table>

Results of Guideline Development

Figures 1 and 2 present the recommended ADHD symptom evaluation and medication choice practice pathways for children with ASD. An overview of the accompanying narrative and the systematic review describes the function and flow of evaluation through each step of the 2 practice pathways.*

Pathway 1: Symptom Evaluation

Routine screening for ADHD symptoms by primary care clinicians should follow the American Academy of Pediatrics' 2011 guideline. When a child presents to a clinician with significant ADHD symptoms, along with a suspicion of ASD by the caregivers, an accurate diagnosis of ASD should be made using existing ASD diagnostic guidelines. Language and cognitive testing should be conducted as part of the evaluation for ASD. Educational, speech and language, and behavioral supports should be optimized to target the core ASD symptoms, as well as language or cognitive impairment.

If the child continues to display ADHD symptoms despite these initial steps, a clinical interview focused on ADHD should be conducted, supplemented by commonly used ADHD-focused questionnaires such as the Conners Scale and the Vanderbilt ADHD Diagnostic Scales. Often, children may not exhibit ADHD symptoms on 1 or more clinical visits. Therefore, information about these symptoms in school, home, and community may serve to establish that ADHD symptoms are pervasive and not triggered by a specific environmental context.

Children should also undergo a systemic medical evaluation to rule out any undiagnosed medical problem† that may contribute to the ADHD symptoms, especially if the child has limited ability to communicate (Figure 1, Box 3). For some medical problems, corresponding ATN practice pathways may provide guidance (eg, sleep, constipation). Other comorbid conditions, such as mood or anxiety symptoms, may contribute to the ADHD symptoms (Figure 1, Box 4) and merit assessment and treatment by a mental health provider.

*Full versions of the narrative and practice pathways are available at www.autismspeaks.org/atn.

†Narrative available at www.autismspeaks.org/atn.
<table>
<thead>
<tr>
<th>Study Medication/Study Type/ Grade</th>
<th>Population</th>
<th>Intervention</th>
<th>Measures</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
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<tbody>
<tr>
<td><strong>Stimulants</strong> MPH</td>
<td>MPH Included: 72 children aged 5 to 14 y with ASD (DSM-IV)</td>
<td>MPH in randomized, controlled crossover design. After test dosing to establish tolerability, subjects underwent 1 week at each of three TID doses (0.125, 0.25, and 0.5 mg/kg per dose) versus placebo</td>
<td>ABC-H, CGI-I, SNAP-IV</td>
<td>All MPH doses improved both teacher and parent ratings on the ABC-H: low (parent, P = .03; teacher, P = .03), medium (parent, P &lt; .001; teacher, P = .008), and high (parent, P = .003; teacher P = .002) with best signal for the “optimal dose” (parent, P &lt; .001; teacher, P &lt; .001). Effect sizes ranged from 0.20 to 0.89</td>
<td>MPH was often efficacious in treating hyperactivity in children with ASD, but the effect size is smaller than that seen in pure ADHD, and adverse events are more common</td>
</tr>
<tr>
<td></td>
<td>MPH Included: 20 preschool-aged children aged 3 to 5 y with PDD or ID</td>
<td>MPH in randomized, controlled crossover design. Dose range from 1.25 mg BID to 10 mg BID. Single-blind titration followed by a randomized, double-blind phase of 2 wk of placebo with 2 wk at child’s best dose</td>
<td>Parent rating of DSM-IV-ADHD symptoms, CPRS-R, NH</td>
<td>MPH improved parent ratings on CPRS-Rand DSM-IV-ADHD (P = .005 for the PDD subgroup). Estimated effect sizes ranged from 0.3 to 0.95. Only 14 children completed the crossover phase</td>
<td>MPH was often efficacious in treating ADHD symptoms in preschool-aged children with PDD, although the response was smaller than in older, typically developing children and adverse events are more common</td>
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<tr>
<td></td>
<td>MPH Included: 13 children with autistic disorder or PDD-NOS</td>
<td>MPH in controlled, crossover design with MPH doses of 0.3 and 0.6 mg/kg BID or TID for 1 week versus placebo. Lower MPH preceded higher dose or interspaced with placebo</td>
<td>Conners Teacher Scale; IOWA Conners Teacher Scale; ABC-H; CARS, Childhood Autism Rating Scale side effects checklist</td>
<td>8 of 13 children were MPH responders (minimum 50% decrease on Conners scale between one MPH dose and placebo). Significant decreases between placebo and one or both of the MPH doses for Conners (P = .000), IOWA Conners (P = .004), ABC-H (P = .003)</td>
<td>MPH was often efficacious in treating ADHD symptoms in children with ASD</td>
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</table>
| **
ATX**                           | ATX Included: 16 children/adolescents aged 5 to 15 y with ASD | ATX in randomized, controlled, cross-over design. Split doses, starting at 0.25 mg/kg per day and increased every 4 to 5 days by increments of 0.3 to 0.4 to maximum dose of 1.4 mg/kg per day or 100 mg/day total | DSM-IV-ADHD, ABC-H, CGI-S | ATX was superior to placebo on DSM-IV ADHD hyperactive/impulsive symptoms (P = .005, d = 1.27), with a trend on inattentive symptoms (P = .053, d = 0.89) | In this small pilot study, ATX was often efficacious in treating ADHD symptoms in children with ASD, with infrequent intolerable adverse events |
| **
α-Agonist** Guanfacine          | Guanfacine Included: 11 children aged 5 to 8 y with ASD | Guanfacine in randomized, controlled, crossover design over 6 wk. Titrated to a maximum of 3 mg/day (1 mg TID) | Parent and teacher-rated ABC-H; CGI-S | Guanfacine was superior to placebo on parent and teacher ABC-H (P = .025, P = .005, respectively) | Guanfacine was efficacious and well tolerated for hyperactivity symptoms in this small pilot study |
<table>
<thead>
<tr>
<th>Study Medication/Study Type/ Grade</th>
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</tr>
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<tbody>
<tr>
<td>Antipsychotic agent&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Risperidone McCracken et al, 2002&lt;sup&gt;20&lt;/sup&gt; RCT category I</td>
<td>Included: 101 children (82 boys and 19 girls) (mean age, 8.8 ± 2.7 y) with autistic disorder and irritability/aggression symptoms</td>
<td>Risperidone in randomized controlled design compared with placebo for 8 wk (dose range, 0.5–3.5 mg/d)</td>
<td>ABC-H; various scales for other symptoms</td>
<td>Risperidone was superior to placebo on the parent ABC-H (P &lt; .001; effect size, 1.0)</td>
<td>Risperidone improved multiple symptoms, including hyperactivity, in children with autism disorder and irritability/agitation</td>
</tr>
<tr>
<td>Risperidone Aman et al, 2008&lt;sup&gt;21&lt;/sup&gt; RCT category I</td>
<td>Included: 38 children, aged 5 to 17 y with ASD and severe behavioral disturbance</td>
<td>Risperidone in randomized, controlled design, 0.25 or 0.5 mg to 2.5 or 3.3 mg/d, compared with placebo</td>
<td>Cancellation Task (for attention span) and Classroom Analog Task (timed math task)</td>
<td>No declines in either measure of attention were noted at weeks 4 and 8. ANOVA indicated significant improvement on Cancellation Task (P = .03)</td>
<td>Risperidone does not seem to have a detrimental effect on cognitive performance</td>
</tr>
<tr>
<td>Risperidone Troost et al, 2005&lt;sup&gt;22&lt;/sup&gt; RCT category I</td>
<td>Included: 24 children (22 males; 2 females) aged 5 to 17 y with ASD</td>
<td>Risperidone 24-wk open-label treatment with up to 2.5 or 3.5 mg, followed by a randomized placebo substitution, with 3 wk of taper and 5 wk of placebo only or continuing use of risperidone</td>
<td>ABC-H; various scales for other symptoms</td>
<td>Nonsignificant increase in parent ABC-H (P = .118 but large effect size, z = −1.56)</td>
<td>No conclusion is possible, perhaps due to low power</td>
</tr>
<tr>
<td>Risperidone Shea et al, 2004&lt;sup&gt;23&lt;/sup&gt; RCT category II</td>
<td>Included: 79 children (61 males, 18 females), aged 5 to 12 y, with ASD and irritability/agitation</td>
<td>Risperidone in a randomized, controlled design, beginning at 0.01 mg/kg per day titrated up to a maximum of 0.06 mg/kg per day, compared with placebo</td>
<td>ABC-H; N-H; various scales for other symptoms</td>
<td>Risperidone was superior to placebo for ABC-H (P &lt; .001) and N-H (P &lt; .05)</td>
<td>Risperidone improved multiple symptoms, including hyperactivity, in children with ASD and irritability/agitation</td>
</tr>
<tr>
<td>Risperidone Nagaraj et al, 2006&lt;sup&gt;24&lt;/sup&gt; RCT category II</td>
<td>Included: 40 children with autism, aged 2 to 9 y</td>
<td>Risperidone in a randomized, controlled design, beginning at 0.5 mg daily and increased to 1 mg daily for a total of 6 mo, compared with placebo</td>
<td>Parent Questionnaire/Report</td>
<td>Risperidone was superior to placebo for hyperactivity (7 of 19 responders; P = .002)</td>
<td>Risperidone reduced hyperactivity in children with ASD</td>
</tr>
<tr>
<td>Aripiprazole Owen et al, 2009&lt;sup&gt;25&lt;/sup&gt; RCT category I</td>
<td>Included: 98 patients aged 6 to 17 y (86 males, 12 females) with autistic disorder and irritability/aggression symptoms</td>
<td>Aripiprazole in a randomized, controlled design, dose range of 5 to 15 mg/day, compared with placebo</td>
<td>ABC-H; various scales for other symptoms</td>
<td>Aripiprazole was superior to placebo on the parent ABC-H (P &lt; .01)</td>
<td>Aripiprazole improved multiple symptoms, including hyperactivity, in children with autism and irritability/agitation</td>
</tr>
<tr>
<td>Aripiprazole Marcus et al, 2009&lt;sup&gt;26&lt;/sup&gt; RCT category I</td>
<td>Included: 219 children aged 6 to 17 y (90% males) with autistic disorder and irritability/aggression symptoms</td>
<td>Aripiprazole in a randomized, placebo-controlled, fixed-dose design with doses of 5, 10, or 15 mg/d, for 8 wk</td>
<td>ABC-H; various scales for other symptoms</td>
<td>All doses showed improvement compared with placebo on ABC-H (5 mg, P ≤ .003; 10 mg, P ≤ .05; 15 mg, P = .001)</td>
<td>Aripiprazole improved multiple symptoms, including hyperactivity in children with autistic disorder and irritability/agitation</td>
</tr>
</tbody>
</table>
### TABLE 4 Continued

<table>
<thead>
<tr>
<th>Study Medication/Study Type/Grade</th>
<th>Population</th>
<th>Intervention</th>
<th>Measures</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
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<tbody>
<tr>
<td><strong>Other</strong>&lt;sup&gt;a&lt;/sup&gt; &lt;br&gt;Adjunctive pentoxifylline &lt;br&gt;Akhondzadeh et al, 2010&lt;sup&gt;16&lt;/sup&gt; &lt;br&gt;RCT category I</td>
<td>Included: 40 children (29 boys, 11 girls) aged 4 to 12 y with autistic disorder and irritability/agitation</td>
<td>Pentoxifylline versus placebo added to risperidone in randomized, controlled design. Risperidone was titrated up to 2 or 3 mg/day for the first 3 wk. Pentoxifylline was started at 200 mg and titrated to a maximum of 400 or 600 mg/day, depending on weight</td>
<td>ABC-H; various scales for other symptoms</td>
<td>Adjunctive pentoxifylline was superior to placebo on ABC-H (&lt;i&gt;P&lt;/i&gt; &lt; .0001) when added to risperidone</td>
<td>Adjunctive pentoxifylline may improve hyperactivity symptoms when added to risperidone in children with autistic disorder and irritability/agitation</td>
</tr>
<tr>
<td><strong>Adjunctive topiramate</strong> &lt;br&gt;Rezaei et al, 2010&lt;sup&gt;21&lt;/sup&gt; &lt;br&gt;RCT category I</td>
<td>Included: 40 children aged 4 to 12 y with ASD and irritability/agitation</td>
<td>Topiramate versus placebo added to risperidone in randomized, controlled design. Risperidone was titrated up to 2 or 3 mg/day for the first 3 wk. Topiramate was then titrated up to 100 or 200 mg/day, depending on weight</td>
<td>ABC-H; various scales for other symptoms</td>
<td>Adjunctive topiramate was superior to placebo on ABC-H (&lt;i&gt;P&lt;/i&gt; &lt; .0001) when added to risperidone</td>
<td>Adjunctive topiramate may improve hyperactivity symptoms when added to risperidone in children with ASD and irritability/agitation</td>
</tr>
<tr>
<td><strong>Tianeptine</strong> &lt;br&gt;Niederhofer et al, 2003&lt;sup&gt;14&lt;/sup&gt; &lt;br&gt;RCT category II</td>
<td>Included: 12 boys with autistic disorder (ages 4–14 y)</td>
<td>Tianeptine in randomized, controlled crossover study 37.5 mg daily for 12 wk compared with placebo</td>
<td>ABC-C; various measures of other symptoms</td>
<td>Tianeptine was superior to placebo for ABC-H (&lt;i&gt;P&lt;/i&gt; = .055)</td>
<td>Tianeptine may be helpful for hyperactivity in ASD</td>
</tr>
</tbody>
</table>

**Grade Categories:** category I, 80% to 100% of ideal methodology met; category II, 60% to 79.99% of ideal methodology met; category III, 40% to 59.99% of ideal methodology met; and category IV, <39.99% of ideal methodology met. ABC-H, Aberrant Behavior Checklist- Hyperactivity Subscale; ATX, atomoxetine; BID, twice daily; CARS, Childhood Autism Rating Scale; CGI-I, Clinical Global Impression of Improvement; CGI-S, Clinical Global Index of Severity; CPRS-R, Conners Parent Rating Scale- Revised; MPH, methylphenidate; ID, intellectual disability; N-H, Nisonger Child Behavior Rating Form- Parent-Hyperactive Subscale; PDD, pervasive developmental disorder; SNAP-IV, Teacher- and parent-rated Swanson, Nolan, and Pelham Questionnaire; TID, 3 times daily. <sup>a</sup> Hyperactivity was not a primary endpoint in any RCT of an antipsychotic, and findings are not corrected for multiple comparisons. <sup>b</sup> Hyperactivity was not a primary endpoint in any RCT and findings are not corrected for multiple comparisons.
**TABLE 5** Nonrandomized Studies of Medications for Hyperactivity/Impulsivity/Inattention Symptoms in ASD

<table>
<thead>
<tr>
<th>Study Medication/Reference/Study Type and Category</th>
<th>Population</th>
<th>Intervention</th>
<th>Results/Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPH</td>
<td>Included: 13 children and adolescents with ASD aged 5 to 17 y</td>
<td>Open-label administration of MPH 0.5 ± 0.2 mg/kg single dose and ongoing treatment over 3 mo</td>
<td>Some children with ASD showed improved ADHD symptoms with MPH. Five of 13 subjects had adverse events with single dose</td>
</tr>
<tr>
<td>Di Martino et al, 2004&lt;sup&gt;49&lt;/sup&gt; Pre/post without control, category III</td>
<td>Included: 88 total patients with DSM-IV diagnosed ASD + ADHD compared with 138 patients with ADHD alone</td>
<td>Mixed retrospective and prospective data on MPH 10 to 50 mg/day or DEX 5 to 30 mg/day</td>
<td>Children with ASD + ADHD showed a similar pattern of response and adverse events compared with those diagnosed with ADHD alone</td>
</tr>
<tr>
<td>MPH or DEX</td>
<td>ATX</td>
<td>Included: 16 children and adolescents aged 6 to 14 y with ASD</td>
<td>Prospective open-label study of ATX increasing from 0.5 to 1.2 mg/kg per day for 6 wk</td>
</tr>
<tr>
<td>Santosh et al, 2006&lt;sup&gt;51&lt;/sup&gt; Case series, category III</td>
<td>ATX</td>
<td>Included: 14 boys aged 7 to 17 y with ASD (DSM-IV)</td>
<td>Open-label ATX starting at 0.5 to 1.4 mg/kg per day for 10 wk</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Guanfacine</td>
<td>Included: 25 children aged 5 to 14 y with ASD who did not improve with MPH</td>
<td>Open-label guanfacine starting at 0.25 to 0.5 mg qhs titrated up to 3.5 to 5 mg/day in divided TID doses</td>
</tr>
<tr>
<td>Zeiner et al, 2011&lt;sup&gt;53&lt;/sup&gt; Pre/post without control, category III</td>
<td>Guanfacine</td>
<td>Included: 19 children aged 4 to 16 y with ASD (DSM-IV)</td>
<td>Clonidine starting at 0.5 mg qhs and titrated further based on clinician judgment</td>
</tr>
<tr>
<td>Gagliano et al, 2004&lt;sup&gt;60&lt;/sup&gt; Pre/post without control, category I</td>
<td>Risperidone</td>
<td>Included: 124 children, aged 4 through 13 y, with ASD and irritability/agitation</td>
<td>Risperidone open-label treatment with 0.5 to 3.5 mg/day. Randomized parent-training behavioral treatment</td>
</tr>
<tr>
<td>Aman et al, 2010&lt;sup&gt;56&lt;/sup&gt; Pre/post without control, category I</td>
<td>Risperidone</td>
<td>Included: 22 children, aged 2 to 16 y, with autistic disorder</td>
<td>Risperidone open-label treatment beginning at 0.5 mg/day and titrated to maximum of 6 mg/day. Continued for 6 mo followed by 1 mo discontinuation</td>
</tr>
<tr>
<td>Malone et al, 2002&lt;sup&gt;47&lt;/sup&gt; Pre/post without control, category III</td>
<td>Risperidone</td>
<td>Included: 21 boys and 3 girls, aged 3 to 6 y with autistic disorder or PDD-NOS</td>
<td>Risperidone open-label treatment beginning at 0.25 mg qhs and titrated up to a maximum dose of 0.04 mg/kg or 0.75 mg/day</td>
</tr>
<tr>
<td>Masi et al, 2001&lt;sup&gt;58&lt;/sup&gt; Pre/post without control, category III</td>
<td>Risperidone</td>
<td>Included: 63 children aged 5 to 17 y with for autistic disorder and irritability/agitation</td>
<td>Risperidone open-label extension after RCT with risperidone up to 3.5 or 4.5 mg/day, depending on weight, followed by randomized, controlled discontinuation, but hyperactivity measures not reported for discontinuation</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Olanzapine</td>
<td>Included: 20 children aged 3 to 10 y diagnosed with autistic disorder</td>
<td>Risperidone open-label treatment with 0.75 to 2 mg/day. A 12-wk phase first, followed by continuation phase</td>
</tr>
<tr>
<td>RUPP, 2005&lt;sup&gt;48&lt;/sup&gt; Pre/post without control, category III</td>
<td>Olanzapine</td>
<td>Included: 14 children and adolescents, aged 7 to 17 y, with ASD</td>
<td>Aripiprazole retrospective chart review with dose range of 5 to 15 mg/day extending over an average of 183 days of treatment</td>
</tr>
<tr>
<td>Gagliano et al, 2004&lt;sup&gt;60&lt;/sup&gt; Pre/post without control, category III</td>
<td>Olanzapine</td>
<td>Included: 23 children aged 6 to 16 y with ASD and irritability/agitation</td>
<td>Olanzapine open-label treatment beginning at 2.5 mg every other day, titrated to a maximum dose of 15 or 20 mg/day, depending on weight</td>
</tr>
<tr>
<td>Malone et al, 2007&lt;sup&gt;52&lt;/sup&gt; Pre/post without control, category III</td>
<td>Ziprasidone</td>
<td>Included: 15 adolescents (mean age, 14.5 ± 1.8 y) with autistic disorder and irritability/agitation</td>
<td>Ziprasidone open-label treatment beginning at 20 mg every other day, titrated to a maximum dose of 40 to 160 mg/day, depending on weight</td>
</tr>
</tbody>
</table>
may be sequential or simultaneous across multiple steps for different children, as determined by severity of symptoms and/or availability of resources. Our intention is to provide guidance on the comprehensive medical, psychiatric, and behavioral domains that should be considered when evaluating and treating a child who has ADHD symptoms.

Pathway 2: Medication Choice

As indicated in the systematic review, most of the medications used to treat ADHD symptoms have not been studied in sufficient depth in ASD to allow for accurate assessment of the treatment effects. Therefore, this pathway (Figure 2) represents consensus expert clinician opinion and is based on (1) existing research in ASD; (2) treatment of ADHD in the non-ASD population for which there have been considerably more research studies; and (3) clinical experience. These opinions serve as broad recommendations, and the clinician should continue to use judgment in selecting medications. These are not a substitute for medication handouts or desk references and do not list all the precautions, potential adverse effects, or risks of using a particular medication. For detailed recommendations, including those for initial evaluation and for initiation of individual medications, monitoring for side effects and adverse events, and maintenance on these medications, please see the narrative.

Pathway 2 assumes that the child has been determined to need a medication trial for the ADHD symptoms (Figure 2, Box 1).

Stimulant medications (Figure 2, Box 2) include methylphenidate and amphetamine preparations. They enhance dopaminergic transmission by inhibiting or reversing dopamine reuptake and act, to a lesser degree, on the noradrenergic system. Generally, methylphenidate preparations are the first choice for treating ADHD symptoms in ASD because (1) there is extensive clinical experience with them over the past several decades; and (2) they have a relatively well-documented safety record and side effect profile. Compared with typically developing children with ADHD, children who have ASD, as in other developmental disabilities (including intellectual disabilities, fragile X syndrome, and head trauma), seem to have lower effect sizes with these medications and are more sensitive to side effects, including emotionality and agitation. Although best studied in typically developing children with ADHD, there is 1 large RCT of methylphenidate in children with ASD. Only 49% of children in this study displayed a therapeutic response compared with 69% in the Multimodal Treatment Study of Children with ADHD (MTA) study. In addition, 18% of the children discontinued participation due to adverse events, especially irritability, compared with 1.4% in children with ADHD.

We recommend beginning stimulant treatment with a methylphenidate formulation because of greater evidence in both ASD and ADHD. It is often preferable to start with a short-acting formulation to gauge side effects before switching to the corresponding long-acting formulation. Amphetamine salts are an option for children who do not benefit sufficiently from methylphenidate or who experience dose-limiting side effects. We recommend following the American Academy of Pediatrics’ guidelines for screening for cardiac problems before initiating treatment with stimulant medications.

Atomoxetine (Figure 2, Box 3) is a selective norepinephrine reuptake inhibitor. There is limited evidence of its effectiveness in treating ADHD symptoms in ASD, with 1 small, randomized crossover pilot study; this study produced a 50% response rate with

### TABLE 5 Continued

<table>
<thead>
<tr>
<th>Study Medication/Reference/Study Type and Category</th>
<th>Population</th>
<th>Intervention</th>
<th>Results/Conclusions†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine Fido et al, 2008 Pre/post without control, category III</td>
<td>Included: 40 male children, aged 7–17 y, with autistic disorder</td>
<td>Olanzapine open-label treatment beginning at 2.5 mg BID, titrated up to a maximum dose of 10 mg/day</td>
<td>Some children with autism showed decreased hyperactivity with olanzapine</td>
</tr>
<tr>
<td>Memantine Erickson et al, 2007 Pre/post without control, category III</td>
<td>Included: 18 children and adolescents, aged 6 to 19 y, with ASD</td>
<td>Memantine open-label treatment beginning at 2.5 or 5 mg daily, depending on weight, titrated up to maximum dose of 20 mg/day</td>
<td>Some children showed improvement in hyperactivity with memantine</td>
</tr>
<tr>
<td>Levetiracetam Rugino and Samsock, 2002 Pre/post without control, category III</td>
<td>Included: 12 children, aged 4 to 10 y, with ASD and irritability/agitation</td>
<td>Levetiracetam open-label treatment at 13 mg/kg divided twice daily</td>
<td>Some children showed improvement in hyperactivity and impulsivity with levetiracetam</td>
</tr>
</tbody>
</table>

Grade Categories: category I, 80% to 100% of ideal methodology met; category II, 60% to 79.99% of ideal methodology met; category III, 40% to 59.99% of ideal methodology met; and category IV, <39.99% of ideal methodology met. ATX, atomoxetine; BID, twice daily; DEX, dexamphetamine; MPH, methylphenidate; qhs, every night; RUPP, Research Units on Pediatric Psychopharmacology. Pre/post refers to pre-intervention and post-intervention - in non randomized studies.

† Non-RCTs cannot demonstrate treatment-specific effects.
FIGURE 1
ADHD symptom evaluation practice pathway.

1. Child with ASD referred for ADHD symptoms

2. Does child have clinically significant ADHD symptoms by clinical interview and questionnaires for parents and/or teachers?
   - Yes
   - No

3. Do any medical or sleep problems contribute to the symptoms?
   - Yes
   - Medical evaluation and treatment
   - No

4. Do other comorbid psychiatric conditions, such as mood or anxiety disorders, contribute to the symptoms?
   - Yes
   - Evaluation and treatment by behavioral health specialist
   - No

5. a) Is there a discrepancy in symptoms across settings?
   b) Can behavioral or educational supports be improved?
   - Yes (to either)
     - Optimize behavioral/educational supports
   - No

6. a) Prescreening work-up
   b) Medication choice algorithm (Page 2)

   Re-evaluate symptoms (return to top)

   After treatment, do clinically significant symptoms persist?
   - Yes
   - Continue current medical, sleep, behavioral, educational, and/or medication management of ASD, ADHD symptoms, and other co-morbid conditions. Re-evaluate ADHD symptoms within 1-year.
   - No
FIGURE 2
ADHD symptom medication choice practice pathway.
atomoxetine compared with 25% with placebo. One treatment study in typically developing children who have ADHD found that atomoxetine is effective in children with comorbid anxiety symptoms, although this agent has not been evaluated in those with ASD.

Guanfacine and clonidine are 2 available α2-agonists (Figure 2, Box 4). Originally developed as antihypertensive agents, they primarily target hyperactivity and impulsivity, and are used as adjuncts to stimulant medications, although they are also prescribed as single medications for these symptoms. They are frequently used in the treatment of ADHD symptoms in ASD. Guanfacine has the benefit of being relatively longer-acting and less sedating compared with clonidine. Most studies of these agents have been open-label (Tables 4 and 5). RCTs of these medications have included very small sample sizes. Although these medications have been studied in typically developing children who have ADHD, leading to the recent approval by the US Food and Drug Administration of their extended-release preparations as adjunct agents in the treatment of ADHD, there is currently limited empirical evidence for their effectiveness for ADHD in ASD.

Risperidone and aripiprazole are 2 atypical antipsychotic medications (Figure 2, Box 5) that have received approval by the US Food and Drug Administration for the treatment of irritability and agitation in children who have ASD. These studies have also demonstrated reduction in ADHD symptoms in children with ASD who have co-occurring irritability and agitation. Among all the medications used to treat ADHD symptoms, these antipsychotic agents have the most empirical evidence (including most RCTs). However, children who have ASD are more sensitive than typically developing children to the side effects and adverse events of these medications; their use is limited by the risk of weight gain/metabolic syndrome and movement disorders, including tardive dyskinesia. Therefore, these medications should be reserved only for children who have severe impulsivity leading to safety concerns (eg, dangerous and impulsive running or jumping) or those with comorbid irritability, agitation, or aggression.

Consultation or referral to an autism or mental health specialist should be considered when risperidone, aripiprazole, or another antipsychotic medication is being considered for a child who has ADHD symptoms in ASD. Choice of these medications depends primarily on the side effect profile, with risperidone more likely to lead to weight gain and aripiprazole more likely to lead to a movement disorder.

### DISCUSSION

Assuming an accurate ASD diagnosis, in most cases, the symptom evaluation pathway (Figure 1) may be completed in 1 or 2 visits that begin with a clinical evaluation, obtaining a description of ADHD symptoms in different settings, extend to identifying possible causes or triggers for the ADHD symptoms, and finish with developing a treatment plan. If medication is part of that treatment plan, the practitioner should follow the medication choice pathway (Figure 2), involving the family in the decision-making process so that they can understand the evidence, the target symptoms that may improve, and the potential side effects or adverse events. Because initiating a medication is a significant choice by the family, >1 visit may be necessary to discuss the pros and cons of a given treatment plan. This action may also allow time for medical, behavioral, or educational interventions to be implemented, providing further evidence for or against the need for a medication trial. As part of the discussion, the clinician should explore the caregivers’ beliefs and values related to using medications for ADHD symptoms and provide an evidence-based, realistic appraisal of the risks and benefits of the use of these medications.

Included in any discussion of medication should also be the definition of target symptoms and the time frame during which they can be expected to improve. To prevent potentially beneficial medications from being stopped prematurely at low doses, or inadequate duration of treatment, clinicians should explain that identification of an effective medication usually takes time and careful evaluation. This will also help prevent disappointment with inadequate or lack of response to the medication. Even more concerning, however, are situations in which side effects and adverse events of medications are not recognized or are allowed to continue too long between clinic visits. Families should be carefully educated about potential side effects and adverse events before they emerge, emphasizing both the ones that are most likely and those that are severe and should prompt a call to the clinician’s office. Monitoring for effectiveness and safety of these medications should be done at each visit to gauge their usefulness.

### CONCLUSIONS

Children who have ASD and co-occurring ADHD symptoms should undergo careful symptom evaluation and, if indicated, trials of medications, following the recommended practice pathways as outlined in this article. At all steps, clinical judgment should be used in evaluating ADHD symptoms and choosing an appropriate medication. Stimulant medications are considered

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first, although they have fewer RCTs and a response rate of ~50%, with higher rates of side effects. As shown in our systematic review, atypical antipsychotic medications currently have the most evidence for efficacy in the treatment of ADHD symptoms in ASD. These benefits, however, have only been studied in the context of irritability and agitation and are accompanied by significant adverse effects that should limit their use. This review highlights the need for more RCTs to evaluate medications for ADHD symptoms in children who have ASD, especially as new medications and preparations of the existing medications are added to the available formulary. Future research could also focus on the effectiveness of the recommended practice pathway in clinical practice.

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REFERENCES


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