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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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abstract

BACKGROUND AND OBJECTIVE: Hyperactivity, impulsivity, and inattention (referred to as "ADHD [attention-deficit/hyperactivity disorder] symptoms") occur in 41% to 78% of children with autism spectrum disorders (ASDs). These symptoms often affect quality of life, interfering with learning or interventions that target primary ASD symptoms. This practice pathway describes the guidelines for evaluation and treatment of children and adolescents with ASD and comorbid ADHD symptoms.

METHODS: Current research in this area is limited, and, therefore, these recommendations are based on a systematic literature review and expert consensus in the Autism Speaks Autism Treatment Network Psychopharmacology Committee.

RESULTS: The recommended practice pathway includes the Symptom Evaluation Pathway for systematic assessment of ADHD symptoms across settings; examination for comorbid sleep, medical, or psychiatric comorbidities that may contribute to symptoms; and evaluation of behavioral interventions that may ameliorate these symptoms. For children for whom medication is being considered to target the ADHD symptoms, the medication choice pathway provides guidance on the selection of the appropriate agent based on a review of available research, assessment of specific advantages and disadvantages of each agent, and dosing considerations.

CONCLUSIONS: These recommendations provide a framework for primary care providers treating children who have ASD and ADHD symptoms. Our systematic review of the current evidence indicates the need for more randomized controlled trials of the medications for ADHD symptoms in ASD. There will also be a need for studies of the effectiveness of these practice pathways in the future. *Pediatrics* 2012;130: S125–S138

Children with autism spectrum disorders (ASDs) frequently experience medical or neurologic comorbidities, including gastrointestinal symptoms, sleep difficulties, and seizures.[1–3] Similarly, co-occurring behavioral or mental health symptoms occur in the majority of children who have ASD,[4] with individual children often showing symptoms of ≥2 comorbid disorders.[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.[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.[11] These symptoms often lead parents and caregivers to seek medical evaluation and treatment.[12] Conversely, autistic features have been reported in children who have ADHD, especially in those with the combined type.[13,14] Medical providers often prescribe medications targeting ADHD symptoms in ASD, recognizing the significant impairment that results if these symptoms are left untreated.[15,16]

Children may manifest all ADHD symptoms as outlined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV)[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.[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,[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.

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.

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, α-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[23] and Autism Diagnostic Observation Schedule[24]) were rarely applied before this time. Four primary reviewers graded the research by using a system adapted from GRADE.[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.[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
Amphetamine
Lisdexamfetamine dimesylate
Dextroamphetamine
Methylphenidate
Dexmethylphenidate
• 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 end points 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, α_2-agonists). Among these medications, most evidence was available for stimulant medications (only methylphenidate), with 3 RCTs, including 1 study of preschool-aged children.[24] Non-RCTs included studies of stimulant medications (only methylphenidate), atomoxetine, α_2-agonists (primarily guanfacine), atypical antipsychotic agents (risperidone, aripiprazole, ziprasidone, and olanzapine), and others (memantine and levetiracetam).

TABLE 3 Summary of Grading Criteria

Quality	Measures the quality of the study design, such as blinding, random assignment, patient selection, and measures used
Consistency	Measures the quality of patient selection, such as ASD diagnosis/definition, homogenous population in terms of disease and progression, and adjustment for confounders.
Directness	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 "real life"
Effect size	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

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.*

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

Pathway 1: Symptom Evaluation

Routine screening for ADHD symptoms by primary care clinicians should follow the American Academy of Pediatrics' 2011 guideline.[25] 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.[20,26,27] 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[28] and the Vanderbilt ADHD Diagnostic Scales.[29,30] (Figure 1, Boxes 1 and 2) 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.

†Narrative available at www.autismspeaks.org/atn.

TABLE 4 Systematic Literature Review Results (RCTs)

Study Medication/ Study Type/ Grade	Population	Intervention	Measures	Results	Conclusion
Stimulants					
MPH Posey et al, 2005[32] RCT category II	Included: 72 children aged 5 to 14 y with ASD (DSM-IV)	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	ABC-H, CGI-I, SNAP-IV	All MPH doses improved both teacher and parent ratings on the ABC-H: low (parent, $P = .03$; teacher, $P = .03$), medium (parent, $P < .001$; teacher, $P = .008$), and high (parent, $P = .003$; teacher $P = .002$) with best signal for the "optimal dose" (parent, $P < .001$; teacher, $P < .001$). Effect sizes ranged from 0.20 to 0.89	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
MPH Ghuman et al, 2009[24] RCT category II	Included: 20 preschool-aged children aged 3 to 5 y with PDD or ID	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	Parent rating of DSM-IV-ADHD symptoms, CPRS-R, N-H	MPH improved parent ratings on CPRS-Rand DSM-IV-ADHD ($P = .005$ for the PDD subgroup). Estimated effect sizes ranged from 0.5 to 0.95. Only 14 children completed the crossover phase	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
MPH Handen et al, 2000[41] RCT category II	Included: 13 children with autistic disorder or PDD-NOS	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	Conners Teacher Scale; IOWA Conners Teacher Scale; ABC-H; CARS; Childhood Autism Rating Scale side effects checklist	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 ($P = .003$)	MPH was often efficacious in treating ADHD symptoms in children with ASD
ATX					
ATX Arnold et al, 2006[34] RCT category I	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 Handen et al, 2008[38] RCT category II	Included: 11 children aged 5 to 9 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 4 Continued

Study Medication/ Study Type/ Grade	Population	Intervention	Measures	Results	Conclusion
Antipsychotic agent[a]					
Risperidone McCracken et al, 2002[39] RCT category I	Included: 101 children (82 boys and 19 girls) (mean age, 8.8 ± 2.7 y) with autistic disorder and irritability/aggression symptoms	Risperidone in randomized controlled design compared with placebo for 8 wk (dose range, 0.5– 3.5.5 mg/d)	ABC-H; various scales for other symptoms	Risperidone was superior to placebo on the parent ABC-H ($P < .001$; effect size, 1.0)	Risperidone improved multiple symptoms, including hyperactivity, in children with autism disorder and irritability/agitation
Risperidone Aman et al, 2008[42] RCT category I	Included: 38 children, aged 5 to 17 y with ASD and severe behavioral disturbance	Risperidone in randomized, controlled design, 0.25 or 0.5 mg to 2.5 or 3.5 mg/day, compared with placebo	Cancellation Task (for attention span) and Classroom Analog Task (timed math task)	No declines in either measure of attention were noted at weeks 4 and 8. ANOVA indicated significant improvement on Cancellation Task ($P = .05$)	Risperidone does not seem to have a detrimental effect on cognitive performance
Risperidone Troost et al, 2005[43] RCT category I	Included: 24 children (22 males; 2 females) aged 5 to 17 y, with ASD	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	ABC-H; various scales for other symptoms	Nonsignificant increase in parent ABC-H ($P = .118$ but large effects size, $z = -1.56$)	No conclusion is possible, perhaps due to low power
Risperidone Shea et al, 2004[44] RCT category II	Included: 79 children (61 males, 18 females), aged 5 to 12 y, with ASD and irritability/ agitation	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	ABC-H; N-H; various scales for other symptoms	Risperidone was superior to placebo for ABC-H ($P < .001$) and N-H ($P < .05$)	Risperidone improved multiple symptoms, including hyperactivity, in children with ASD and irritability/agitation
Risperidone Nagaraj et al, 2006[45] RCT category II	Included: 40 children with autism, aged 2 to 9 y	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	Parent Questionnaire/Report	Risperidone was superior to placebo for hyperactivity (7 of 19 responders; $P = .002$)	Risperidone reduced hyperactivity in children with ASD
Aripiprazole Owen et al, 2009[40] RCT category I	Included: 98 patients aged 6 to 17 y (86 males, 12 females) with autistic disorder and irritability/aggression symptoms	Aripiprazole in a randomized, controlled design, dose range of 5 to 15 mg/day, compared with placebo	ABC-H; various scales for other symptoms	Aripiprazole was superior to placebo on the parent ABC-H ($P < .01$)	Aripiprazole improved multiple symptoms, including hyperactivity, in children with autism and irritability/ agitation
Aripiprazole Marcus et al, 2009[46] RCT category I	Included: 218 children aged 6 to 17 y (50% males) with autistic disorder and irritability/ aggression symptoms	Aripiprazole in a randomized, placebo-controlled, fixed-dose design with doses of 5, 10, or 15 mg/day for 8 wk	ABC-H; various scales for other symptoms	All doses showed improvement compared with placebo on ABC-H (5 mg, $P \leq .005$; 10 mg, $P \leq .05$; 15 mg, $P \leq .001$)	Aripiprazole improved multiple symptoms, including hyperactivity in children with autistic disorder and irritability and agitation

TABLE 4 Continued

Study Medication/ Study Type/ Grade	Population	Intervention	Measures	Results	Conclusion
Other[b]					
Adjunctive pentoxifylline Akhondzadeh et al, 2010[47] RCT category I	Included: 40 children (29 boys, 11 girls) aged 4 to 12 y with autistic disorder and irritability/agitation	Pentoxifylline versus placebo added to risperidone in randomized, controlled design. Risperidone was titrated up to 2 or 3 mg/day for the first 3wk. Pentoxiphylline was started at 200 mg and titrated to a maximum of 400 or 600 mg/day, depending on weight	ABC-H; various scales for other symptoms	Adjunctive pentoxifylline was superior to placebo on ABC-H ($P < .0001$) when added to risperidone	Adjunctive pentoxifylline may improve hyperactivity symptoms when added to risperidone in children with autistic disorder and irritability/agitation
Adjunctive topiramate Rezaei et al, 2010[48] RCT category I	Included: 40 children aged 4 to 12 y with ASD and irritability/ agitation	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	ABC-H; various scales for other symptoms	Adjunctive topiramate was superior to placebo on ABC-H ($P < .0001$) when added to risperidone	Adjunctive topiramate may improve hyperactivity symptoms when added to risperidone in children with ASD and irritability/agitation
Tianeptine Niederhofer et al, 2003[49] RCT category II	Included: 12 boys with autistic disorder (ages 4–14 y)	Tianeptine in randomized, controlled crossover study, 37.5 mg daily for 12 wk compared with placebo	ABC-C; various measures of other symptoms	Tianeptine was superior to placebo for ABC-H ($P = .035$)	Tianeptine may be helpful for hyperactivity in ASD

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.

[a] Hyperactivity was not a primary endpoint in any RCT of an antipsychotic, and findings are not corrected for multiple comparisons.

[b] Hyperactivity was not a primary endpoint in any RCT and findings are not corrected for multiple comparisons.

For children who have ASD and symptoms of ADHD who show a discrepancy in symptoms across settings, educational or behavioral interventions may be beneficial (Figure 1, Box 5). Some children may have a decrease in their overall ADHD symptoms with a more structured environment and schedule in school, whereas others may have more difficulty due to excessively demanding school routines. ADHD symptoms occurring only at home might respond to behavioral or family-oriented interventions.

When ADHD symptoms occur primarily in school, parents should request incorporation of a behavioral intervention plan into a Section 504 plan or Individualized Educational Program. Successful behavioral interventions may include functional behavioral assessment, identification of successful teaching styles, accommodations for learning disorders, tailored curriculum to the developmental and adaptive level of the child, or provision of related services (eg, speech and language therapy, occupational therapy). Comprehensive psychoeducational testing and/or neuropsychological testing help to evaluate the child's cognitive strengths/weaknesses, which, in turn, will aid in designing an appropriate individualized educational plan.

Once medical, mental health, and educational/behavioral interventions have been optimized, the symptoms of ADHD can be reevaluated to assess the necessity of a medication trial for ADHD as a target symptom domain, depending on the severity of the symptoms and their effect on daily functioning.

Importantly, some children who have ASD and severe ADHD symptoms may require simultaneous evaluation and treatment across multiple steps in the symptom evaluation pathway. The process for implementing the pathway

TABLE 5 Nonrandomized Studies of Medications for Hyperactivity/Impulsivity/Inattention Symptoms in ASD

Study Medication/Reference/Study Type and Category	Population	Intervention	Results/Conclusions[a]
MPH Di Martino et al, 2004[50] Pre/post without control, category III	Included: 13 children and adolescents with ASD aged 5 to 17 y	Open-label administration of MPH 0.5 ± 0.2 mg/kg single dose and ongoing treatment over 3 mo	Some children with ASD showed improved ADHD symptoms with MPH. Five of 13 subjects had adverse events with single dose
MPH or DEX Santosh et al, 2006[51] Case series, category III	Included: 88 total patients with DSM-IV diagnosed ASD + ADHD compared with 138 patients with ADHD alone	Mixed retrospective and prospective data on MPH 10 to 50 mg/day or DEX 5 to 30 mg/day	Children with ASD + ADHD showed a similar pattern of response and adverse events compared with those diagnosed with ADHD alone
ATX Posey et al, 2006[52] Pre/post without control, category III	Included: 16 children and adolescents aged 6 to 14 y with ASD	Prospective open-label study of ATX increasing from 0.5 to 1.2 mg/kg per day for 6 wk	Some children and adolescents with ASD showed improved ADHD symptoms on open-label ATX
ATX Zeiner et al, 2011[53] Pre/post without control, category III	Included: 14 boys aged 7 to 17 y with ASD (DSM-IV)	Open-label ATX starting at 0.5 to 1.4 mg/kg per day for 10 wk	Some children and adolescents with ASD showed improved ADHD symptoms on open-label ATX, which was well tolerated
Guanfacine Scahill et al, 2006[54] Pre/post without control, category III	Included: 25 children aged 5 to 14 y with ASD who did not improve with MPH	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	Some children with ASD showed improved hyperactivity symptoms with guanfacine
Clonidine Ming et al, 2008[55] Case series, category IV	Included: 19 children aged 4 to 16 y with ASD (DSM-IV)	Clonidine starting at 0.5 mg qhs and titrated further based on clinician judgment	Some children with ASD showed improved sleep with clonidine, with fewer children showing benefit for ADHD symptoms
Risperidone Aman et al, 2010[56] Pre/post without control, category I	Included: 124 children, aged 4 through 13 y, with ASD and irritability/agitation	Risperidone open-label treatment with 0.5 to 3.5 mg/day. Randomized parent-training behavioral treatment	Some children with ASD showed improved hyperactivity with risperidone, with larger improvements seen in the group that also received behavioral therapy (d = 0.55; P = .04)
Risperidone Malone et al, 2002[57] Pre/post without control, category III	Included: 22 children, aged 2 to 16 y, with autistic disorder	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	Some children with ASD showed improved hyperactivity with risperidone
Risperidone Masi et al, 2001[58] Pre/post without control, category III	Included: 21 boys and 3 girls, aged 3 to 6 y with autistic disorder or PDD-NOS	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	Some young children with ASD showed decreased hyperactivity with risperidone
Risperidone RUPP, 2005[59] Pre/post without control, category III	Included: 63 children aged 5 to 17 y with for autistic disorder and irritability/agitation	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	Some children and adolescents with autism showed persistent improvement in hyperactivity with risperidone
Risperidone Gagliano et al, 2004[60] Pre/post without control, category III	Included: 20 children aged 3 to 10 y diagnosed with autistic disorder	Risperidone open-label treatment with 0.75 to 2 mg/day. A 12-wk phase first, followed by continuation phase	Some children with autism showed persistent improvement in hyperactivity with risperidone
Aripiprazole Kim et al, 2010[61] Case series, category III	Included: 14 children and adolescents, aged 7 to 17 y, with ASD	Aripiprazole retrospective chart review with dose range of 5 to 15 mg/day extending over an average of 183 days of treatment	Some children showed improvement in multiple poorly defined symptom domains, including hyperactivity
Olanzapine Kemner et al, 2002[62] Pre/post without control, category III	Included: 23 children aged 6 to 16 y with ASD and irritability/agitation	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	Some children with ASD showed decreased hyperactivity with olanzapine
Ziprasidone Malone et al, 2007[63] Pre/post without control, category III	Included:15 adolescents (mean age, 14.5 ± 1.8 y) with autistic disorder and irritability/agitation	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	Some children with autism and irritability/agitation showed decreased hyperactivity with ziprasidone

TABLE 5 Continued

Study Medication/Reference/Study Type and Category	Population	Intervention	Results/Conclusions[a]
Olanzapine Fido et al, 2008[64] Pre/post without control, category III	Included: 40 male children, aged 7–17 y, with autistic disorder	Olanzapine open-label treatment beginning at 2.5 mg BID, titrated up to a maximum dose of 10 mg/day	Some children with autism showed decreased hyperactivity with olanzapine
Memantine Erickson et al, 2007[65] Pre/post without control, category III	Included: 18 children and adolescents, aged 6 to 19 y, with ASD	Memantine open-label treatment beginning at 2.5 or 5 mg daily, depending on weight, titrated up to maximum dose of 20 mg/day	Some children showed improvement in hyperactivity with memantine
Levetiracetam Rugino and Samsock, 2002[66] Pre/post without control, category III	Included: 12 children, aged 4 to 10 y, with ASD and irritability/agitation	Levetiracetam open-label treatment at 13 mg/kg divided twice daily	Some children showed improvement in hyperactivity and impulsivity with levetiracetam

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.

[a] Non-RCTs cannot demonstrate treatment-specific effects.

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.[31] 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,[19] there is 1 large RCT of methylphenidate in children with ASD.[32,33] 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.[32] 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.[21,22]

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[34]; this study produced a 50% response rate with

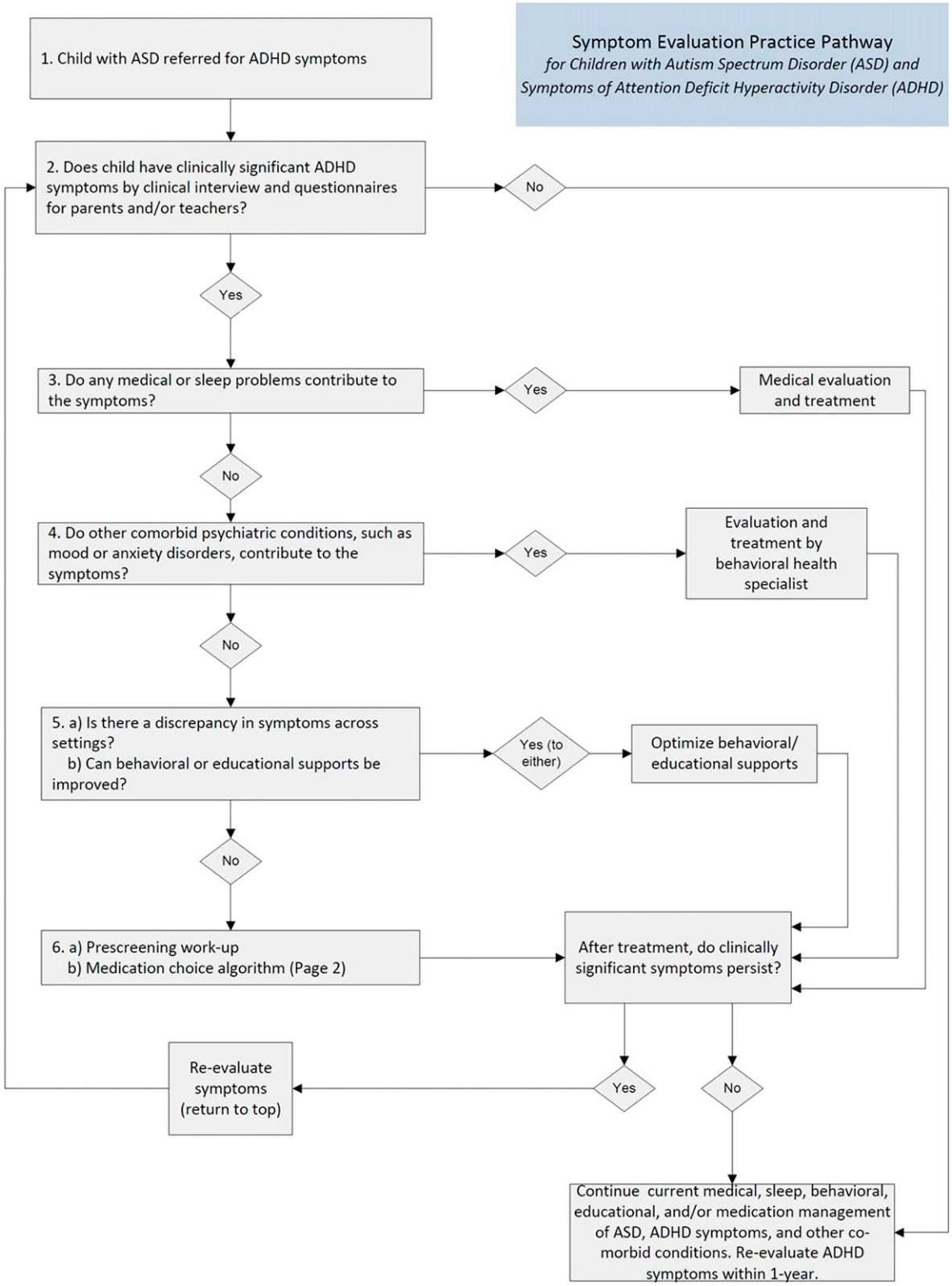

FIGURE 1
ADHD symptom evaluation practice pathway.

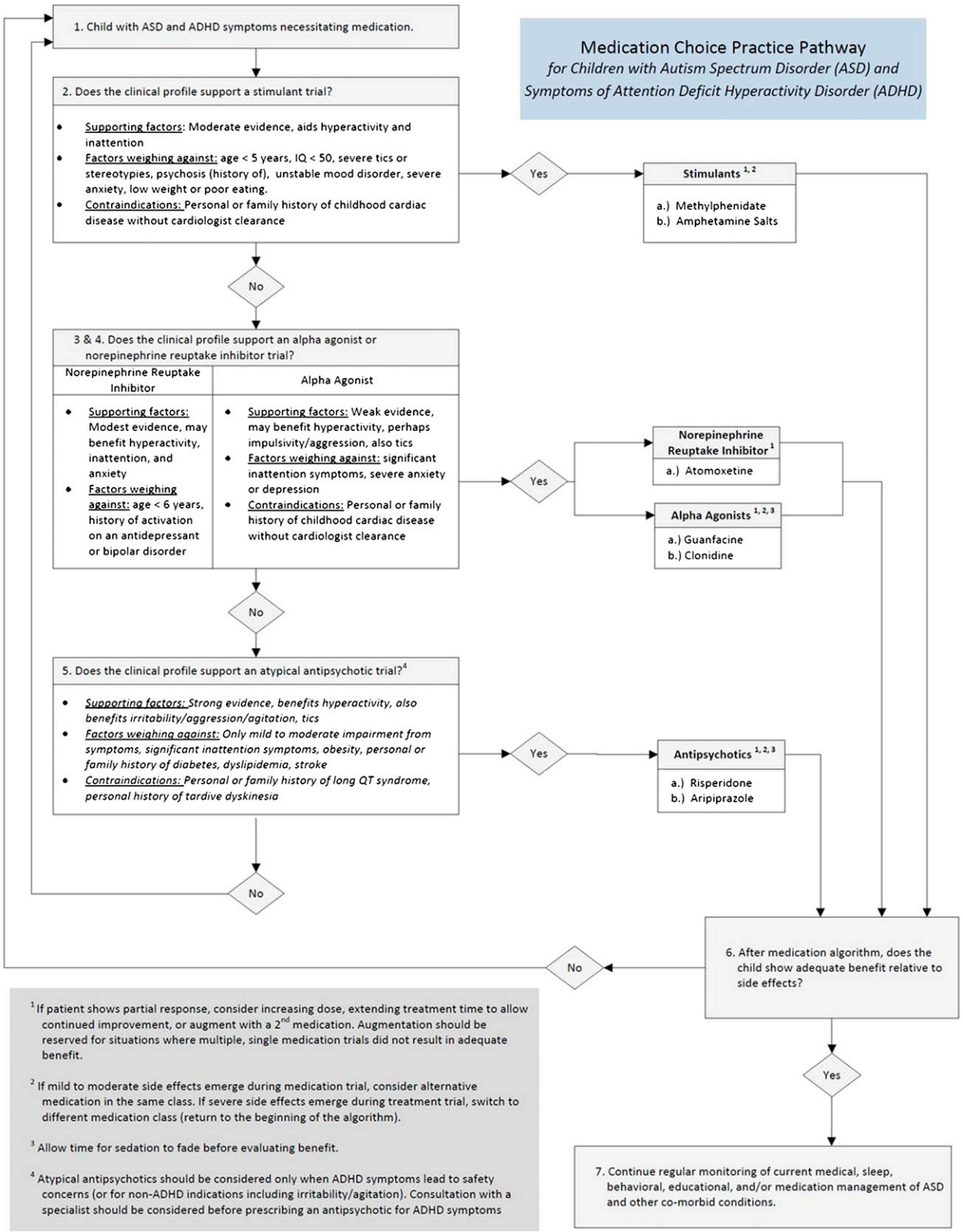

FIGURE 2
ADHD symptom medication choice practice pathway.

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,[36] although this agent has not been evaluated in those with ASD.

Guanfacine and clonidine are 2 available α_2-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.[36] 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).[37] RCTs of these medications have included very small sample sizes.[38] 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 cooccurring irritability and agitation.[39,40] 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,[40] 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.[39,40]

DISCUSSION

Assuming an accurate ASD diagnosis, in most cases, the symptom evaluation pathway (Fig 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 (Fig 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 cooccurring 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

‡Detailed narrative at www.autismspeaks.org/atn for reference.

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

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