

A Systematic Review of Medical Treatments for Children With Autism Spectrum Disorders

abstract

CONTEXT: As many as 1 in every 110 children in the United States has an autism spectrum disorder (ASD). Many medical treatments for ASDs have been proposed and studied, but there is currently no consensus regarding which interventions are most effective.

OBJECTIVE: To systematically review evidence regarding medical treatments for children aged 12 years and younger with ASDs.

METHODS: We searched the Medline, PsycInfo, and ERIC (Education Resources Information Center) databases from 2000 to May 2010, regulatory data for approved medications, and reference lists of included articles. Two reviewers independently assessed each study against predetermined inclusion/exclusion criteria. Studies of secretin were not included in this review. Two reviewers independently extracted data regarding participant and intervention characteristics, assessment techniques, and outcomes and assigned overall quality and strength-of-evidence ratings on the basis of predetermined criteria.

RESULTS: Evidence supports the benefit of risperidone and aripiprazole for challenging and repetitive behaviors in children with ASDs. Evidence also supports significant adverse effects of these medications. Insufficient strength of evidence is present to evaluate the benefits or adverse effects for any other medical treatments for ASDs, including serotonin-reuptake inhibitors and stimulant medications.

CONCLUSIONS: Although many children with ASDs are currently treated with medical interventions, strikingly little evidence exists to support benefit for most treatments. Risperidone and aripiprazole have shown benefit for challenging and repetitive behaviors, but associated adverse effects limit their use to patients with severe impairment or risk of injury. *Pediatrics* 2011;127:e1312–e1321

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KEY WORDS

autism spectrum disorders, antipsychotics, risperidone, aripiprazole, serotonin-reuptake inhibitors, citalopram, fluoxetine, psychostimulants

ABBREVIATIONS

ASD—autism spectrum disorder
SRI—serotonin-reuptake inhibitor
RCT—randomized controlled trial
RUPP—Research Units on Pediatric Psychopharmacology
ABC-C—Aberrant Behavior Checklist Community Version
ABC-C-I—ABC-C irritability/agitation/crying subscale
ABC-C-H—ABC-C hyperactivity/noncompliance subscale
ABC-C-S—ABC-C stereotypy subscale
CY-BOCS—Children's Yale-Brown Obsessive Compulsive Scale

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(Continued on last page)

As many as 1 in every 110 children in the United States has an autism spectrum disorder (ASD).¹ Affected children have multiple symptoms that can be reduced into 3 broad categories: social impairment; communication impairment; and repetitive behavior.²⁻⁵ Comorbidity with other conditions is common, including intellectual disability, seizure disorders, hyperactivity, and anxiety.^{1,2,4,5} Many treatments have been proposed and studied, including behavioral, educational, medical, allied health, and complementary medicine interventions, but there is currently no global consensus regarding which intervention strategy is most effective.^{6,7} Given the lifelong nature of ASDs, most patients are exposed to multiple interventions that address different target symptoms.

Medical treatments are primarily directed toward comorbid symptoms, rather than core symptoms, in children with ASDs. As part of a systematic review of therapies for children younger than 12 with ASDs,⁸ we reviewed the literature on antipsychotic, serotonin-reuptake inhibitor (SRI), and stimulant medications (Table 1). All other medical treatments except secretin (see accompanying review⁹) had insufficient evidence for an evaluation of their possible benefits in children with ASDs; information about these and other therapies addressed in the full review⁸ can be found at www.effectivehealthcare.ahrq.gov.

METHODS

Search Strategy

We searched Medline via the PubMed interface, PsycINFO (psychology and psychiatry literature), and ERIC (Education Resources Information Center) (educational literature) from 2000 to May 2010 by using relevant controlled vocabulary terms and key terms related to ASDs (eg, autistic disorder) and therapy-related terms (eg, thera-

TABLE 1 Description of Medical and Related Interventions Addressed in the Report

Intervention	Description
Antipsychotic medications	Pharmacologic agents including risperidone, aripiprazole, and haloperidol that act primarily on the dopamine and serotonin systems; outside of ASDs, primarily used to treat psychotic and mood disorders; within ASDs, primarily studied for effects on challenging behaviors including irritability, aggression, and self-injurious behavior
SRI	Pharmacologic agents including fluoxetine and citalopram that act on the serotonin system; outside of ASDs, primarily used to treat depression, anxiety, and obsessive-compulsive disorder; within ASDs, studied for potential to ameliorate repetitive and problem behaviors
Stimulants and other medications for hyperactivity	Pharmacologic agents including methylphenidate, amphetamine, and dextroamphetamine that act primarily on the dopamine system; outside of ASDs, primarily used to treat hyperactivity and inattention in patients with attention-deficit/hyperactivity disorder; within ASDs, studied to treat hyperactivity

peutics). We also hand-searched the reference lists of all included articles to identify additional studies, reviewed clinical trials related to therapies for ASDs to identify corresponding articles, and reviewed regulatory information on drugs approved for the treatment of irritability in patients with ASDs (aripiprazole and risperidone).

Study Selection

We developed inclusion and exclusion criteria in consultation with an expert panel of clinicians and educators involved in ASD care. We included all study designs and required that studies of medical interventions include at least 30 participants with ASDs younger than the age of 13 years. We also required that studies be published in the year 2000 or later, after the publication of the *Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition*² and the widespread implementation of gold-standard ASD assessment tools including the Autism Diagnostic Observation System¹⁰ and the Autism Diagnostic Interview-Revised.¹¹

Data Extraction

Using standardized forms, 2 investigators independently extracted data regarding study design; descriptions

of the study populations, intervention, and comparison groups; and baseline and outcome data, as well as data about harms or adverse effects. We also captured data on the conduct and timing of assessments to inform the assessment of quality. Principal outcomes of interest included effects on core symptoms of ASDs or common comorbid symptoms including sleep, anxiety, hyperactivity, and challenging behavior (eg, irritability/agitation).

Study-Quality Assessment

Two investigators independently assessed each study by using a quality-assessment form developed by the review team with input from experts in the field. We evaluated the following elements with a series of yes/no questions in each domain (eg, were outcomes coded and assessed by people blinded to the intervention status of the participants?):

- study design;
- diagnostic approach;
- participant ascertainment and characterization;
- intervention description;
- outcomes measurement; and
- statistical analysis.

TABLE 2 Domains Used to Assess Strength of the Evidence

Risk of bias: Reflects issues in study design and conduct that could result in biased estimates of effect
Consistency: Reflects similarity of effect sizes seen across studies; consistency cannot be assessed when only 1 study is available
Directness: Reflects the relationship between the intervention and the ultimate health outcome of interest
Precision: Reflects the level of certainty around the effect observed

Disagreements between assessors were resolved through discussion to reach consensus. Overall assessment of quality was determined by using a prespecified algorithm that is available in the full report.⁸

We assessed the strength of evidence of the current research by using methods established in the Evidence-Based Practice Centers' methods guide for effectiveness and comparative effectiveness reviews.¹² Assessments were based on consideration of 4 domains: risk of bias; consistency in direction of the effect; directness in measuring intended outcomes; and precision of effect (Table 2). We determined the strength of evidence separately for major intervention-outcome pairs by using a prespecified approach that is described in detail in the full review.⁸

Data Synthesis

Given considerable heterogeneity in the interventions and outcome measures used in studies that met our inclusion criteria, we did not conduct any meta-analyses. We summarized characteristics of study populations and interventions and used descriptive statistics to report study outcomes.

RESULTS

Figure 1 outlines the flow of articles retrieved for the review, and Table 3 summarizes the study characteristics. Eighteen unique studies addressed the

medical interventions listed above for children with ASDs. Of these studies, 10 were randomized controlled trials (RCTs). We located 9 studies that addressed antipsychotic medications,^{13–29} 5 studies that addressed SRI medications,^{30–34} and 4 studies that evaluated stimulant medications.^{35–40} Table 4 summarizes the study results.

Antipsychotics

Two of the 4 RCTs of risperidone targeted challenging behavior as the primary outcome.^{18,23} The first study^{13,14,16–21} was sponsored by the National Institute of Mental Health as part of the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network. The second study was sponsored by the manufacturer of risperidone (Risperdal [Ortho-McNeil-Janssen Pharmaceuticals, Inc, Titusville, NJ]).²²

There were 89 subjects in risperidone arms and 91 subjects in placebo arms. Both studies used a graduated-dose-titration design over 8 weeks; the average risperidone dose ranged from 1.5 to 1.8 mg/day, and dosing was primarily once²³ or twice^{13,14,16–21} daily. In these 2 studies, baseline ratings of challenging behavior, as measured by the Aberrant Behavior Checklist Community Version irritability/agitation/crying subscale (ABC-C-I), were similar between the risperidone and placebo arms. Scores on subscales of the Aberrant Behavior Checklist can range from 0 to 48 with higher scores indicating greater behavioral impairment. Decreases in ABC-C-I scores were significantly greater for subjects in the risperidone arms in both studies (mean decreases: 12.1–14.9) compared with those in the placebo arms (mean decreases: 3.6–6.5).

Similar improvements were seen on the ABC-C hyperactivity/noncompliance subscale (ABC-C-H) in both trials, which indexes both hyperactivity and challenging behavior. Baseline ABC-C-H ratings were similar in both treat-

ment groups, with significantly greater decreases for subjects in the risperidone arms (mean decreases: 14.8–14.9) compared with those in the placebo arms (mean decreases: 4.7–7.4).

Secondary outcomes in the 2 RCTs of risperidone included measures of repetitive behavior including the ABC-C stereotypy subscale (ABC-C-S). Baseline ABC-C-S ratings were similar between the risperidone and placebo arms, and there were significantly greater decreases for subjects in the risperidone arm compared with those in the placebo arm in 1 RCT (mean decreases: 4.8 vs 1.7)¹⁸ but would not have been significant after correction for multiple testing in the other RCT (mean decreases: 4.3 vs 2.4).²³ One study^{16,18} also used the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) modified for pervasive development disorder to assess repetitive behavior and found no baseline differences between the groups but a significantly greater decrease in subjects in the risperidone arms compared with those in the placebo arms (mean decreases: 3.9 vs 1.0). A number of other outcomes were measured in these studies, but none outside of challenging behavior, hyperactivity, and repetitive behavior would have yielded statistically significant findings once corrected for multiple comparisons.

Two additional RCTs did not provide specific numerical ratings on either challenging or repetitive behavior.^{15,24} One of these studies was an 8-week drug-discontinuation RCT with risperidone and placebo arms¹⁵ after positive response during 4 months of open-label risperidone treatment.¹⁸ This study indexed "relapse" by using a composite measure of the ABC-C-I and clinician ratings¹⁵ and found significantly less "relapse" in subjects in the risperidone arm (2 of 16) compared with those in the placebo arm (10 of 16).

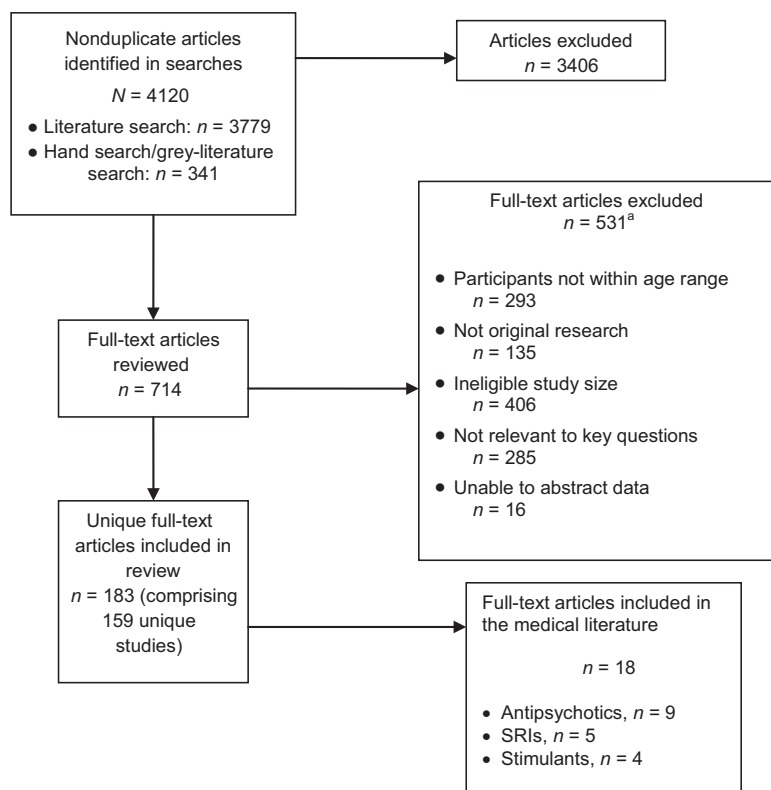


FIGURE 1

Location of studies that addressed medical interventions. ^a The total number of articles in the exclusion categories exceeded the number of articles excluded, because most of the articles fit into multiple exclusion categories.

The last RCT was a 6-month study with risperidone and placebo arms that used a variety of general rating scales to assess response.²⁴ The study authors only reported median Childhood Autism Rating Scale ratings for those participants with at least a 20% response, and more improvement was reported for subjects in the risperidone arms (11.1) than for those in the placebo arms (2.5).²⁴

Reports of all the risperidone RCTs also provided data on adverse events or adverse effects. All study authors reported on weight gain,^{14,15,18,22–24} which was greater for subjects in the risperidone arms (mean weight gain: 2.7–2.8 kg) than for those in the placebo arms (mean weight gain: 0.8–1.7 kg).^{14,18,22,23} Authors of 3 of the RCTs^{14,15,18,22,23} provided data on other adverse events in both the risperidone and placebo arms. Somnolence or

drowsiness was the most common adverse event in 2 of these studies, occurring in 53 of 89 subjects in the risperidone arms and 9 of 91 subjects in the placebo arms, but there was some improvement in somnolence over time.^{14,18,22,23} From both of these studies, more extrapyramidal symptoms, including tremor, dyskinesia, and rigidity, were reported in the risperidone arm compared with the placebo arm, but these events were categorized differently between the 2 studies and did not clearly show a statistically significant difference between treatment arms.^{14,18,22,23}

The RUPP study¹⁸ authors also reported a greater rise in prolactin levels in subjects in the risperidone arm (mean increase: 27.7 ng/mL) compared with those in the placebo arm (mean increase: 0.8 ng/mL),²¹ although they did not report clinical events,

such as gynecomastia or galactorrhea, that could be related to elevated prolactin levels. The RUPP study specifically assessed cognitive function in a subset of subjects and found no worsening and some evidence of improvement on risperidone that would not be statistically significant after correction for multiple testing.^{13,18}

We identified two 8-week RCTs of aripiprazole in children with ASDs,^{26,27} both of which were sponsored by the manufacturer of aripiprazole (Abilify [Otsuka America Pharmaceutical, Inc., Tokyo, Japan]). The primary outcome for these studies was challenging behavior indexed by the ABC-C-I. These studies included a total of 213 subjects in the aripiprazole arms and 103 subjects in the placebo arms.

One study used a fixed-dose design with 1 placebo arm and 3 arms corresponding to 5, 10, and 15 mg/day of aripiprazole²⁶; all subjects began at 2 mg/day with forced titration weekly until they reached their goal dose. The other study used a dose-titration schedule with weekly progression from 2 to 15 mg/day following clinical judgment.²⁷ In these 2 studies, baseline ABC-C-I ratings were similar among the subjects in the aripiprazole and placebo arms; there were greater decreases for subjects in the aripiprazole arms (mean decrease: 12.4–14.4) in comparison with those in the placebo arms (mean decrease: 5.0–8.4). The trial with differing set doses of aripiprazole revealed increasing response with increasing dose.²⁶ Overall, the results of the trial that used titration following clinical judgment were more pronounced.²⁷

Similar improvements for the ABC-C-H were reported across both trials. Baseline ratings were similar among subjects in the aripiprazole and placebo arms; there were greater decreases for subjects in the aripipra-

TABLE 3 Overview of Studies of Medical Interventions

Characteristic	RCTs (N = 10), n	Prospective Case Series (N = 3), n	Retrospective Case Series (N = 5), n	Total Literature (N = 18), n
Intervention				
Antipsychotic medications	7	2	0	9
SRIs	2	1	2	5
Stimulants and other medications for hyperactivity	1	0	3	4
Diagnostic approach				
Clinical DSM-IV diagnosis + ADI-R and/or ADOS	7	1	0	8
Other approaches ^a	3	2	5	10
Treatment duration				
>1 to ≤3 mo	7	1	0	8
>3 to ≤6 mo	3	0	0	3
>6 to ≤12 mo	0	2	2	4
>12 mo	0	0	3	3
Study population				
United States	6	1	5	12
Europe	0	2	0	2
Other	4	0	0	4
Total No. of participants	720	123	558	1401

The numbers shown indicate the number of unique studies with each characteristic. ADI-R indicates Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; DSM-IV, *Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition*.

^a Clinical DSM-IV diagnosis + other diagnostic tool or ADOS + other diagnostic tool or only clinical DSM-IV diagnosis or only ADOS.

zole arms (mean decrease: 12.7–16.3) than for those in the placebo arms (mean decrease: 2.8–7.7).

Secondary outcomes in the 2 major RCTs of aripiprazole included measures of repetitive behavior.⁴¹ Both studies included the ABC-C-S. Baseline ratings of stereotypy were similar among subjects in the aripiprazole and placebo arms. Decreases in ABC-C-S scores were greater for subjects in the aripiprazole arms (mean improvements: 4.2–4.8) compared with those in the placebo arms (mean improvements: 1.8–2.0). Both studies also used the CY-BOGS modified for pervasive development disorder⁴¹ to assess repetitive behavior and found no baseline differences between the groups but a greater decrease in subjects in the aripiprazole arms compared with those in the placebo arms (mean decreases: 2.4–3.8 vs 0.8–1.7). The ABC-C inappropriate-speech subscale, which corresponds primarily to repetitive speech, also revealed significant im-

provement in 1 study²⁷ and a supportive trend in the other.²⁶

The 2 aripiprazole RCTs also provided data on adverse effects. The authors of both studies reported on weight gain,^{26,27} which was greater in subjects in the aripiprazole arms (mean weight gain: 1.3–2.0 kg) than in those in the placebo arms (mean weight gain: 0.3–0.8 kg), and a statistically significant difference was reported from both of the studies.^{26,27} Somnolence and sedation were the most common adverse events in both of these studies (66 of 210 subjects in the aripiprazole arms; 8 of 101 subjects in the placebo arms).^{26,27} The authors of both studies also reported more extrapyramidal symptoms including tremor, dyskinesia, and rigidity (44 of 210 subjects in the aripiprazole arms; 10 of 210 subjects in the placebo arms).^{26,27} Both studies found a statistically significant decrease in prolactin levels in subjects in the aripiprazole arms in contrast with those in the placebo arms.^{26,27}

One 8-week RCT with 40 participants compared the addition of cyproheptadine versus placebo to haloperidol.²⁸ The medication doses were titrated up from some starting point to cyproheptadine 0.05 mg/kg per day and haloperidol 0.2 mg/kg per day, but no details were provided. The ABC-C scores shown were markedly lower than the total ABC-C scores obtained at baseline in other medication trials,^{18,23,26,27} which suggests that a subscale may have been administered, although it is not stated.²⁸ The response to placebo plus haloperidol was smaller²⁸ than the response found in previous haloperidol trials.^{42,43} The improvement in ABC-C score in the cyproheptadine-plus-haloperidol arm was larger (mean decrease: 10.9) than the improvement in the placebo-plus-haloperidol arm (mean decrease: 3.7).²⁸

Serotonin-Reuptake Inhibitors

We reviewed citalopram and escitalopram together, because escitalopram is the active component (enantiomer) of citalopram. We reviewed fluoxetine separately. We identified a 12-week RCT of citalopram³² that focused on repetitive-behavior outcomes. Subjects were begun on 2.5 mg of citalopram daily with weekly increases up to a maximum dose of 20 mg/day.³²

No significant difference among subjects in the citalopram ($n = 73$) and placebo ($n = 76$) arms was seen in measures of repetitive behavior; there were similar baseline scores on the CY-BOGS modified for pervasive development disorder and similar improvements (mean decreases: 2.0 vs 1.9) in each arm. The other measures of repetitive behavior, including the Repetitive Behavior Scale-Revised, also resulted in similar baseline scores and similar improvements in each arm and no evidence for an effect of citalopram.³²

TABLE 4 Summary of Results of Studies

Intervention	Study Design/Quality	Study Results and Overall Strength of Evidence
Antipsychotic medications		
Risperidone vs placebo	4 RCTs/1 of good quality, ^{13,14,16-21} 3 of fair quality ^{15,22-24} 2 prospective case series ^{25,29}	Improvements in challenging and repetitive behaviors; strength of evidence for reducing challenging and repetitive behaviors is moderate Strength of evidence for adverse events is high on the basis of results of RCTs and case series; common adverse effects included weight gain, sedation, and extrapyramidal effects
Aripiprazole vs placebo	2 RCTs/good quality ^{26,27}	Improvements in challenging and repetitive behaviors; strength of evidence for reducing challenging and repetitive behaviors is high; strength of evidence for adverse events is high; common adverse effects included weight gain, sedation, and extrapyramidal effects
Cyproheptadine added to haloperidol vs haloperidol and placebo	1 RCT/fair quality ²⁸	Behavioral improvement reported but without indicating specific domains in 1 study; strength of evidence is insufficient
SRLs		
Citalopram or Escitalopram vs placebo	1 RCT/good quality ³² 1 prospective case series ³³	No significant difference between the groups on repetitive behavior in 1 study; significant but clinically small reduction in challenging behavior in the treatment group compared with the placebo group Strength of evidence for effect of citalopram or escitalopram to reduce repetitive or challenging behavior is insufficient; strength of evidence for adverse events is insufficient
Fluoxetine vs placebo	1 RCT/fair quality ³⁰ 1 retrospective case series ³¹	Greater change in repetitive behavior with fluoxetine compared with placebo; strength of evidence for fluoxetine to decrease repetitive behavior is insufficient Strength of evidence for adverse events is insufficient
Various SRLs (including sertraline, citalopram, paroxetine, fluvoxamine)	1 retrospective case series ³⁴	40 of 89 subjects were ranked as "much improved"; strength of evidence for the effect of SRLs to reduce repetitive behavior is insufficient; strength of evidence for adverse events is low when SRLs are considered as a class
Psychostimulants	1 RCT/good quality ³⁵⁻³⁷ 3 retrospective case series ³⁸⁻⁴⁰	Improvement in hyperactivity and noncompliance in 1 study; adverse events included increases in challenging behavior and loss of appetite Strength of evidence for effectiveness in reducing hyperactivity is insufficient; strength of evidence around adverse events is insufficient

One secondary measure in this study, the ABC-C-I, revealed an advantage for citalopram. The baseline ratings were not statistically different between the citalopram and placebo arms, but more improvement was seen in the scores of subjects in the citalopram arm (mean decrease: 3.2) than in those in the placebo arm (mean decrease: 0.9).³²

Adverse effects in this study included a marked increase in "activation" symptoms, including increased energy, disinhibition, and decreased sleep, in subjects in the citalopram arm in comparison with those in the placebo arm.³² Diarrhea and dry or itchy skin were also more common in subjects in the citalopram arm.

One prospective case series of escitalopram also met our criteria.³³ This 10-week study sought to identify pharmacogenetic modifiers of treatment

response in the challenging-behavior domain as measured by the ABC-C-I. Fifty-eight subjects underwent a forced-dose titration of escitalopram from 2.5 mg/day increasing weekly up to 20 mg; most of the subjects did not tolerate the full dose. It is unfortunate that the data were presented in figures only; raw values could not be inferred. It is evident, however, that the ABC-C-I for all subjects was similar at baseline and that improvements were ~10 points for 3 of the 4 genotype groups.³³

One randomized controlled crossover trial of fluoxetine with two 8-week treatment periods separated by a 4-week washout period³⁰ randomly assigned 19 subjects to fluoxetine followed by placebo and 20 to placebo followed by fluoxetine. During each phase of the study, subjects began the first week at 2.5 mg/day

fluoxetine or placebo, followed as clinically indicated to 0.8 mg/kg per day for weeks 4 to 8.

Subjects in the first fluoxetine group showed an improvement of 1.2 on the CY-BOCS, and those in the first placebo arm showed an improvement of 0.5. These differences were not statistically significant when considered alone. Subjects in the second fluoxetine arm showed an improvement of 1.2, and those in the second placebo arm showed a worsening of 0.1. When analyzed together with the first treatment period in a repeated-measures design, the CY-BOCS score change for subjects in the fluoxetine arms was significantly greater than for those in the placebo arms. No adverse events were significantly more frequent in the fluoxetine group, although more subjects on fluoxetine had their dose reduced because of agitation.³⁰

Psychostimulants

The RUPP Autism Network's double-blind crossover trial^{35–37} of methylphenidate included 72 children who received a 1-day placebo followed by 2 days at each of 3 (low, medium, high) test doses of methylphenidate; doses ranged from 7.5 to 50.0 mg/day. The subjects who tolerated methylphenidate ($n = 66$) moved on to a 4-week, double-blind crossover phase. Subjects with a positive response in the double-blind phase ($n = 34$) completed an 8-week open-label continuation phase at their best dose. The primary outcome measure was hyperactivity/noncompliance as assessed by the teacher-rated ABC-C-H. Blinded clinicians also assessed participants by using the Clinical Global Impression of Improvement scale; this subscale and the ABC parent- and teacher-rated hyperactivity subscales were combined to assess response.

In the double-blind crossover phase, all methylphenidate doses demonstrated mean effects that were statistically superior to placebo, and effect sizes favored the medium dose for parent ratings and the high dose for teacher ratings. Mean parent ratings on the ABC-C lethargy/social withdrawal subscale significantly worsened during the high dose of methylphenidate compared with placebo. Irritability was the most frequent reason for discontinuation (18%) of treatment. Other adverse effects reported included appetite and sleep changes, anxiety, depression, headache, and diarrhea.

DISCUSSION

Assessment of the Literature

Although many children with ASDs are currently treated with medical interventions,^{44–46} strikingly little evidence exists to support clear benefit for most medications. Nonetheless, a few medications have shown benefit for chal-

lenging behavior as well as repetitive behavior and hyperactivity.

Medications to address challenging behavior have the strongest evidence to support their use. Risperidone and aripiprazole are the 2 best-studied medications for ASDs, and the corresponding pharmaceutical companies have funded at least 1 RCT for each. Each medication has at least 2 RCTs that have revealed improvement in parent-reported measures of challenging behavior and measures of hyperactivity. Although it was not the primary target behavior addressed in these studies, repetitive behavior also showed improvement with both risperidone and aripiprazole. We rated the strength of evidence for the effect on challenging and repetitive behaviors to be moderate for risperidone and high for aripiprazole, which means that future research is unlikely to change our assessment of the benefit of these antipsychotic medications.

Both medications also cause significant adverse effects including marked weight gain, sedation, and risk of extrapyramidal symptoms. Strength of evidence around adverse events is high for both risperidone and aripiprazole. When considered in aggregate, risperidone and aripiprazole are efficacious but are associated with significant adverse effects that limit their use to patients with severe impairment or risk of injury.

The SRI fluoxetine showed benefit for repetitive behavior in a single crossover RCT; although this effect was driven primarily by the second arm of the study.³⁰ An RCT of the SRI citalopram³² revealed no benefit for repetitive behavior but possible improvement in challenging behavior. With only 1 good-quality RCT available and an additional RCT of fair quality, we consider the strength of evidence for the ability of SRI medications to reduce repetitive or challenging behavior

to be insufficient. Evidence of adverse effects with SRIs (decreased sleep and increased energy) had insufficient strength of evidence (2 RCTs, 1 of which was of good quality) with variability in how the outcomes were measured. The strength of evidence for the effect of stimulants on hyperactivity and challenging behavior was also insufficient on the basis of 1 good-quality RCT.

Future Directions

At present, the literature surrounding medication for children with ASDs lacks properly designed, appropriately powered RCTs of a number of medical interventions that have been inadequately studied to date. Most of the medical interventions that are currently being applied for children with ASDs^{44–46} have insufficient strength of evidence to evaluate either their potential benefit or adverse effects. Some of the strongest study results to support the use of medical interventions have been funded by pharmaceutical companies or device manufacturers that profit from the treatment. The National Institutes of Health have funded 2 published large-scale studies of medical interventions, but more publicly funded studies of medications for ASDs are warranted.

It is important to note that the marked improvements in challenging behaviors seen with risperidone and aripiprazole support the study of other antipsychotic medications that do not cause as much weight gain or liability to develop metabolic disorders. In addition, medications for hyperactivity and inattention symptoms deserve further scrutiny in subjects with ASDs. Dosing information remains inadequate in the stimulant literature and is particularly important for balancing positive outcomes with potential harms. The data on SRIs are scattered and contradictory, and there is a particular need to consider modifiers

such as age and pharmacogenetics.³⁵ The largest published trial of citalopram found no effect at all on repetitive or compulsive behavior but found a possible effect on challenging behavior (ABC-C-I).³² A number of medical treatments have been evaluated in single studies or in small sample sizes that did not meet criteria for our review,^{47–51} and larger well-controlled studies are necessary to evaluate their potential benefit. On the basis of available evidence, new treatments are urgently needed to treat both core symptoms and associated symptoms in patients with ASDs.

Finally, this literature lacks comparisons of medical interventions with behavioral interventions and combinations of the 2, despite the fact that most children are undergoing multiple concurrent treatments. This approach has proven crucial in studies of obsessive-compulsive disorder, depression, and anxiety,^{52–54} but only 2 studies of adequate size have considered combination treatment with ris-

peridone and behavioral treatment, and these studies lacked an arm that considered behavioral treatment alone, in addition to their lack of a placebo control.

CONCLUSIONS

A few medications have shown benefit for challenging or repetitive behaviors, and the clearest evidence favors risperidone and aripiprazole. Significant adverse-effect profiles, however, make it clear that although these drugs are efficacious, caution is warranted regarding their use in patients without severe impairments or risk of injury. Insufficient evidence is available to judge the potential benefit or adverse effects of all other medical interventions currently used to treat autism.

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