Effective Health Care Program

Medical Therapies for Children With Autism Spectrum Disorder—An Update

Executive Summary

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder broadly defined by impaired social communication as well as restricted or repetitive patterns of behavior and interest. As defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5), specific features of ASD include deficits in social and emotional reciprocity (e.g., atypical social approaches, conversational impairment, atypical sharing of interests, attention, and affect); deficits in nonverbal communication (e.g., poorly integrated verbal and nonverbal communication, atypical body-language and gesture use, deficits in use and understanding of nonverbal communication), and deficits in maintaining appropriate relationships (e.g., challenges with peer interest, vulnerabilities forming friendships, difficulties adjusting behavior to suit social contexts) as well as restricted and repetitive patterns of behavior such as stereotyped speech, motor movements, or use of objects; excessive adherence to routine or insistence on sameness; intense interest patterns; and atypical sensory interests or responses. Symptoms of the disorder impair and limit everyday functioning and are thought to be evident in early childhood; although they may not be fully evident until later ages. Although not core symptoms, many children with ASD may also have significant cognitive and language impairments.

Purpose of Review

To assess effectiveness and safety of medical interventions for children with autism spectrum disorder.

Key Messages

- Despite many randomized trials, confidence in reported improvements (strength of evidence, SOE) remains low for most interventions.

  - Risperidone and aripiprazole improved challenging behaviors in the short term (<6 months, high SOE), but side effects include weight gain and extrapyramidal symptoms.

  - Methylphenidate and atomoxetine improved hyperactivity; SOE is low, with few studies addressing each agent. Side effects include behavior and appetite changes.

  - Omega-3 fatty acids, N-acetylcysteine, and tetrahydrobiopterin did not improve outcomes in small short-term studies (low SOE).

  - Data are inadequate to draw conclusions about other agents due to variation in interventions and outcomes.

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Treatment of ASD

The manifestation and severity of symptoms of ASD differ widely, and treatments include a range of behavioral, psychosocial, educational, medical, and complementary approaches[1-4] that vary by a child's age and developmental status. The goals of treatment for ASD typically focus on improving core deficits in communication, social interactions, or restricted behaviors, as changing these fundamental deficits may help children develop greater functional skills and independence.[5] Treatment frequently is complicated by symptoms or comorbidities that may warrant targeted intervention. Individual goals for treatment vary for different children and may include combinations of approaches such as behavioral and medical therapies; parents may also pursue complementary and alternative medicine therapies.

The antipsychotics risperidone (Risperdal) and aripiprazole (Abilify) have been specifically approved by the U.S. Food and Drug Administration (FDA) for treatment of irritability and challenging behaviors in ASD. Many other medications are used off –label to manage behavioral symptoms such as anxiety and hyperactivity. In addition, devices such as hyperbaric oxygen chambers may be used to treat symptoms of ASD.

Scope and Key Questions (KQs)

Scope of the Review

This review updates findings reported in the 2011 AHRQ review Therapies for Children with ASD[6] with a focus on studies of medical interventions. We defined medical interventions broadly as interventions involving the administration of external substances to the body or use of external, nonbehavioral procedures to treat symptoms of ASD, which includes pharmacologic agents, diet therapies, vitamins and supplements, chelating agents, electroconvulsive therapy, transcranial magnetic stimulation and hyperbaric oxygen, among other modalities. We used this broad definition, developed with input from our clinical experts, in order to capture the landscape of medically-related interventions used to treat children with ASD. A companion review updating findings related to interventions targeting sensory challenges is available on the AHRQ Effective Health Care Web site.

Key Questions

We developed KQs in consultation with Key Informants and Task Order Officers. KQs were posted for review to the AHRQ Effective Health Care Web site.

KQs were as follows:

KQ1: Among children ages 2-12 with ASD, what is the comparative effectiveness (benefits and harms) of medical treatments?

a. **What are the effects on core symptoms (e.g., deficits in social communication and interaction; restricted, repetitive patterns of behavior, interests, or activities including hyper- or hypo- reactivity to sensory input or unusual interest in sensory aspects of the environment) in the short term (<6 months)?**

b. **What are the effects on commonly associated symptoms (e.g., motor, medical, mood/anxiety, irritability, and hyperactivity) in the short term (<6 months)?**

c. **What are the longer term effects (≥6 months) on core symptoms (e.g., social deficits, communication deficits, and repetitive behaviors)?**

d. **What are the longer term effects (≥6 months) on commonly associated symptoms (e.g., motor, medical, mood/anxiety, irritability, and hyperactivity)?**

KQ2: Among children ages 2-12 with ASD, what are the modifiers of outcome for different medical treatments?

a. **Is the effectiveness of the therapies reviewed affected by the frequency, duration, intensity, or dose of the intervention?**

b. **Is the effectiveness of the therapies reviewed affected by co-interventions or prior treatment, or the training and/or experience of the individual providing the therapy?**

c. **What characteristics (e.g., age, symptom severity), if any, of the child modify the effectiveness of the therapies reviewed?**

d. **What characteristics, if any, of the family modify the effectiveness of the therapies reviewed?**

KQ3: What is the time to effect of medical interventions?

KQ4: What is the evidence that effects measured at the end of the treatment phase predict long-term functional outcomes of medical interventions?

**KQ5: Is the effectiveness of medical interventions maintained across environments or contexts (e.g., people, places, materials)?**

KQ6: What evidence supports specific components of treatment with medical interventions as driving outcomes, either within a single treatment or across treatments?

Analytic Framework

The analytic framework (Figure A) illustrates the population, interventions, and outcomes that guided the literature search and synthesis.

Figure A. Analytic framework
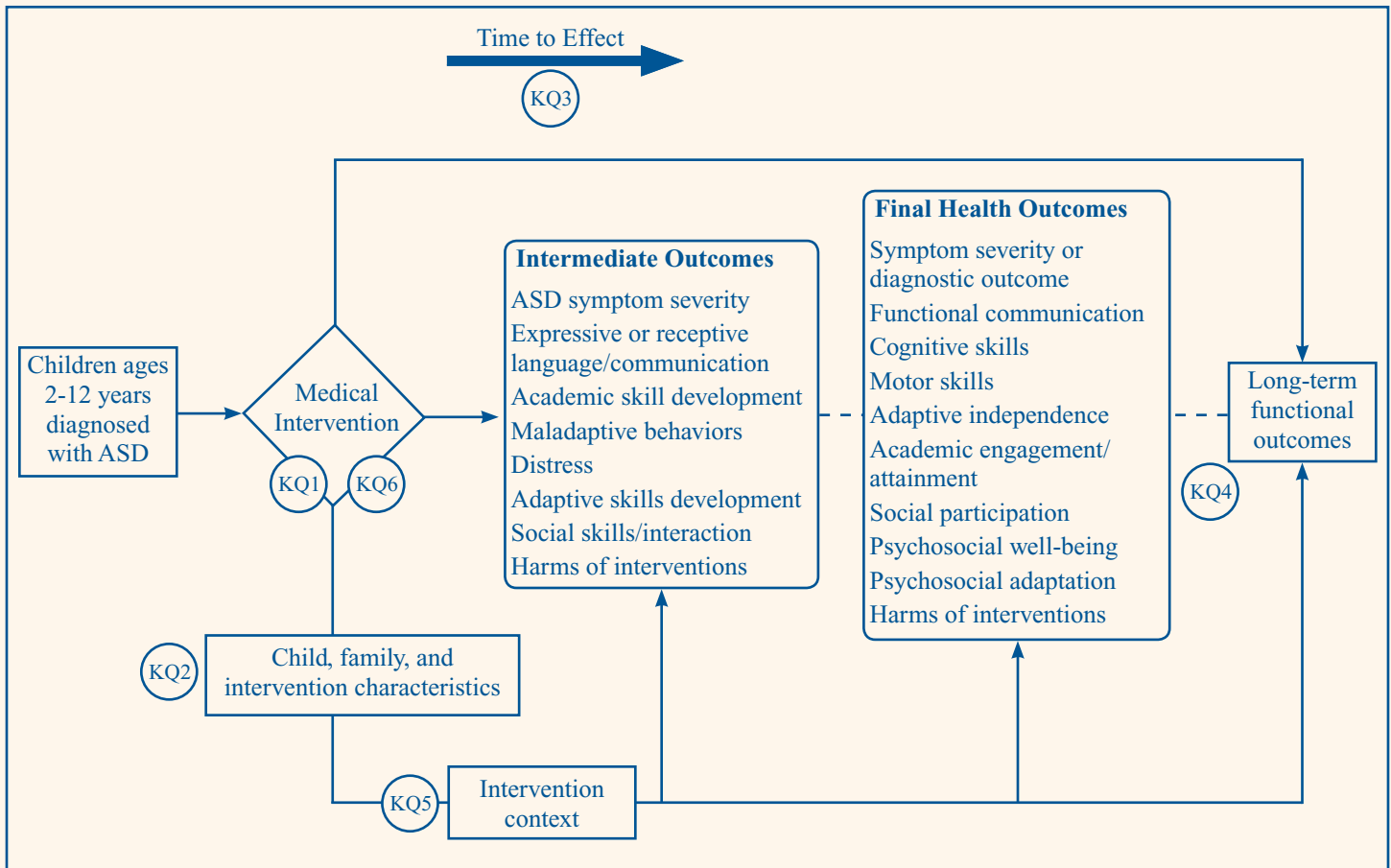
ASD=autism spectrum disorder; KQ=Key Question

Methods

Topic Surveillance

The topic for a 2011 report on therapies for children with ASD[6] was nominated by Autism Speaks in a public process using the Effective Health Care Web site. AHRQ published an update addressing behavioral interventions in 2014.[7] We conducted a surveillance process to assess the need to update the earlier report by contacting topic experts about the relevance of the KQs and new evidence that may address them. In consultation with clinical experts and stakeholders, and based on our preliminary scan of the literature and surveillance findings, we focused the review update on medical approaches and approaches to address sensory challenges (reported in a separate update). These areas reflect both areas of clinical relevance and sufficient newly published literature for a review update.

Literature Search Strategy

To ensure comprehensive retrieval of relevant studies of medical therapies for children with ASD, we used four key databases: the MEDLINE® medical literature database via the PubMed® interface; EMBASE (Excerpta Medica Database); the Cumulative Index of Nursing and Allied

Health Literature (CINAHL); and PsycINFO®. Search strategies applied a combination of controlled terms and key words. We last conducted searches for the review in September 2016.

We hand searched the reference lists of recent systematic reviews or meta-analyses of studies addressing therapies for ASD. The investigative team also scanned the reference lists of studies included after the full-text review phase for additional potentially relevant studies.

Inclusion Criteria

Table A lists our inclusion criteria. We focused the review on children between 2 and 12 years of age. We chose to limit the age range to this span because a) diagnosis of ASD earlier than age 2 is less established and b) adolescents likely have substantially different challenges and would warrant different interventions than children in the preschool, elementary, and middle school age groups.

Table A. Inclusion criteria

Category	Criteria
Study population	Children ages 2-12 with ASD (mean age plus standard deviation is ≤ 12 years and 11 months)
Publication languages	English only
Admissible evidence (study design and other criteria)	**Admissible designs** Randomized controlled trials, prospective and retrospective cohort studies with comparison groups, and nonrandomized controlled trials **Other criteria** Original research studies published from 2010—present and not addressed in prior reviews Studies must have relevant population and ≥20 participants with ASD (non-RCTs) or at least 10 total participants (RCTs) Studies must address one or more of the following for ASD: • Outcomes of interest • Treatment modality of interest • Predictors or drivers of treatment outcomes (e.g., biomarkers, clinical changes) • Maintenance of outcomes across environments or contexts • Sufficiently detailed methods and results to enable data extraction • Reporting of outcome data by target population or intervention

ASD = autism spectrum disorder; RCT = randomized controlled trial

Study Selection

Two reviewers independently assessed each abstract and the full text of studies proceeding to full text review. A senior reviewer adjudicated disagreements in full text review .

Data Extraction and Synthesis

Data were initially extracted by one team member and reviewed for accuracy by a second. We summarized data for KQs qualitatively using summary tables as studies were too heterogeneous to allow for meta-analyses.

Risk-of-Bias Assessment of Individual Studies

We evaluated the overall methodologic risk of bias of individual studies using the ASD-specific assessment approach developed and used in our prior reviews of interventions for ASD and informed by the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[8] Two senior investigators assessed each included study independently with disagreements resolved through discussion. Appendix D of the main report includes ratings for each study.

Strength of the Body of Evidence

Two senior investigators graded the strength of the evidence (SOE) for key intervention/outcome pairs using methods based on the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[8] We assessed the domains of study limitations (low, medium, high level of limitation), consistency (inconsistency not present, inconsistency present, unknown), directness (direct, indirect), precision (precise, imprecise), and reporting bias (detected, unsuspected). The full team reviewed the final SOE designations. The possible grades were:

- High: High confidence that the evidence reflects the true effect. Further research is unlikely to change estimates.
- Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low: Low confidence that the evidence reflects the true effect. Further research is likely to change confidence in the estimate of effect and is also likely to change the estimate.
- Insufficient: Evidence is either unavailable or does not permit a conclusion.[9]

Applicability

We assessed the applicability of findings reported in the included literature addressing our KQs to the general population of children with ASD by determining the population, intervention, comparator, and setting in each study and developing an overview of these elements for each intervention category. We anticipated that areas in which applicability would be especially important to describe would include ASD severity, comorbidities, age at treatment, and intervention characteristics such provider, dosing/intensity, and setting. Applicability tables are in Appendix E of the full report.

Results

We identified 6583 nonduplicative titles or abstracts with potential relevance, with 554 proceeding to full text review. We excluded 469 studies at full text review. We included 68 unique studies (85 publications) in the review. In addition to these 68 studies published since the completion of our original review of therapies for children with ASD in 2011, we include 12 comparative studies addressed in the 2011 review that also addressed an agent reported on in the current review. Four studies included in the 2011 review now include followup analyses published since the

completion of that report; thus we describe a total of 76 studies in the review.

The 76 studies included in the review comprised 72 randomized controlled trials (RCTs), 2 nonrandomized trials, and 2 retrospective cohort studies. Studies addressed the following categories:

- **Antipsychotics**: 11 RCTs and one retrospective cohort study (n=1055 children) with low (n=7) and moderate (n=5) risk of bias.
- **Medications to treat attention deficit hyperactivity disorder (ADHD)**: Five RCTs (n=265 children) with low (n=4) and moderate (n=1) risk of bias.
- **Combination medical and behavioral treatment**s: Three RCTs and two nonrandomized trials (n=419 children) with low (n=2), moderate (n=1) and high (n=2) risk of bias.
- **Nutritional supplements and dietary interventions**: 19 RCTs (n=732 children) with low (n=4), moderate (n=10), and high (n=5) risk of bias.
- **Risperidone adjuncts**: 14 RCTs (n =561 children) with low (n=12) and moderate (n=2) risk of bias.
- **Hyperbaric oxygen therapy**: Three RCTs (n=150 children) with low (n=2) and moderate (n=1) risk of bias.
- **N-acetylcysteine**: Two RCTs (n=123 children) with low and moderate risk of bias.
- **Tetrahydrobiopterin**: Two RCTs (n=56 children) with low and moderate risk of bias.
- **Other interventions**: 13 RCTs and 1 retrospective cohort study (n=829 children) with low (n=6), moderate (n=7), and high (n=1) risk of bias. We categorized studies as "other" if we could not assess strength of evidence for interventions and outcomes reported (i.e., insufficient strength of evidence) and the studies did not fall under a broader category of intervention such as diet or nutritional supplements.

Overall, 39 studies had low, 29 had moderate, and 8 had high risk of bias. Despite the high number of low and moderate risk of bias studies, few studies addressed the same interventions or outcomes, and most studies included few participants, evaluated only in the short term (<6 months). Thus, evidence for many agents remains insufficient. Because few studies addressed subquestions under Key Questions (KQ) 1 and 2, we present results in the aggregate under each of these KQ.

KQ1. Benefits and Harms of Medical Treatments

Antipsychotics. Studies of antipsychotics addressed either risperidone or aripiprazole and reported significant improvements in measures of challenging behavior in the short term (<6 months) in children receiving the medications compared with those receiving placebo. Harms of these agents, including extrapyramidal symptoms and weight gain, were also clinically significant. Studies reporting longer term followup (up to 21 months for risperidone) reported continued effectiveness in most children but did not include control groups.

Medications to treat ADHD. RCTs of methylphenidate, atomoxetine, and guanfacine reported improvements in hyperactivity and other challenging behaviors with treatment compared with placebo. Clinically significant side effects were associated with methylphenidate including aggressive behavior and appetite changes. Harms reported with atomoxetine and guanfacine included irritability, gastrointestinal symptoms, drowsiness, and decreased appetite.

Studies of combined medical and behavioral treatments. In three of the five studies of combined medical and behavioral treatments, the addition of a behavioral therapy (e.g., cognitive behavioral therapy, parent training) did not increase effectiveness over medical therapy alone. In two small trials, bumetanide plus applied behavior analysis improved symptom severity more than applied behavioral analysis alone and stem cell transplantation plus rehabilitation therapy improved symptom severity, lethargy, and stereotypy more than umbilical cord blood cell transplant plus rehabilitation therapy or rehabilitation therapy alone.

Diet and nutritional supplements. Omega-3 fatty acid supplementation did not affect challenging behaviors and was not associated with clinically significant harms. Seven studies addressed variations of the gluten-free diet, but studies addressed different outcomes and different approaches to restricted and control diets. Similarly, a number of RCTs with low or moderate risk of bias addressed other agents, but studies were small and few addressed the same agent or outcomes.

Risperidone adjuncts. Study medications added to risperidone included celecoxib, minocycline, *Ginkgo biloba*, memantine, topiramate, riluzole, buspirone, N-acetylcysteine (addressed in 2 studies), amantadine , pioglitazone, pentoxifylline, galantamine, and piracetam. Most studies (12 of 14) reported improvements in irritability measured on the Aberrant Behavior Checklist (ABC) in the adjunct groups compared with placebo plus risperidone.

Hyperbaric oxygen therapy. Three RCTs of hyperbaric oxygen used different doses and reported inconsistent outcomes and harms.

N-acetylcysteine. N-acetylcysteine had no effect on social skills outcomes in two small RCTs. Harms of this agent were not clinically significant.

Tetrahydrobiopterin. Tetrahydrobiopterin had no effect on symptom severity and was not associated with clinically significant harms.

Other medical interventions. Few studies addressed the same agent or outcomes. Studies of donepezil, melatonin, bumetanide, citalopram, amantadine, divalproex, prednisolone, and transcranial stimulation reported some positive effects on outcomes including symptom severity, language, and sleep. Studies of oxytocin and mecamylamine reported no statistically significant effects. Harms reported in studies comparing these interventions were diverse, and their clinical significance is difficult to determine.

KQ2. Modifiers of Treatment Outcomes

Few studies reported modifiers, and few were likely adequately powered to detect effects. In one subanalysis, higher baseline irritability was associated with greater improvement in irritability than was low severity in improvement with risperidone. Greater weight gain was associated with less irritability improvement in the risperidone group. In another study of risperidone, younger age and better communication skills were associated with greater gains in communication but not with gains in daily living skills or socialization.

Studies of stimulants identified no significant phenotypic predictors of effects (e.g., baseline cognitive skills, age, IQ), but one genetic analysis identified seven genetic variations that predicted response to methylphenidate. Modifiers reported in studies of other agents were varied and included cognitive skills, age, and symptom severity. No characteristics had consistent effects.

KQ3. Time to Effect of Interventions

While several studies reported changes in the number of children responding to a given agent over time, studies typically did not provide data to determine the initiation of effects.

KQ4. Evidence that Effects Measured at the End of Treatment Predict Long-Term Functional Outcomes

Few studies had longer term followup and those with more than 6 months of treatment or followup typically did not report functional outcomes. In one study, risperidone use was not associated with changes in IQ: changes from baseline to the end of study in class assignment (e.g., special education, regular classroom) were not significant.

KQ5. Effectiveness Across Environments or Contexts

Seven studies reported teacher ratings of outcome measures that provide some information to address this KQ, but the limited results preclude conclusions. One RCT of omega-3 fatty acids reported no significant group differences in teacher ratings of challenging behaviors (parents also rated few measures as improved), while another RCT of docosahexaenoic acid (DHA) supplementation versus placebo reported improvement in parent-rated social skills in children receiving placebo vs. those receiving DHA, while teachers rated communication as more improved in the treatment group compared with placebo. An RCT of challenge foods introduced to a gluten-free diet reported no statistically significant changes in behavior as rated by parents or teachers on the Connors scale. An RCT of levetiracetam vs. placebo reported no significant group differences on any parent- or teacher- rated measures but also noted that teachers, but not parents, rated children in the placebo arm as more improved on irritability compared with the levetiracetam group.

RCTs of methylphenidate reported general agreement between parent and teacher ratings of hyperactivity. In one RCT, both parents and teachers considered hyperactivity and impulsive behavior to be significantly improved in the treatment group compared with placebo, but teachers (vs. parents) reported no significant group differences in inattention or oppositional behavior. Finally, one RCT of atomoxetine reported significant teacher-rated improvements in hyperactivity in the atomoxetine group compared with placebo but teacher ratings of cognitive problems/inattention, oppositional behavior, or overall ADHD symptoms did not differ between groups. In another RCT comparing atomoxetine alone, atomoxetine + parent training , placebo alone, and placebo + parent training, parents, but not teachers, rated children in active treatment groups as significantly improved on measures of ADHD, inattention, hyperactivity, and oppositional behavior.

KQ6. Drivers of Treatment Outcomes

We did not identify any studies that provided data to address this KQ.

Discussion

State of the Literature

We identified a total of 76 unique comparative studies, primarily (n=72) RCTs, addressing medical interventions. Most studies were small (median 40 total participants/study) and addressed variable agents. Most studies had placebo comparators, while five compared a pharmaceutical agent to behavioral treatment or combined pharmaceutical and behavioral treatment. Studies were typically of short duration (<6 months, range 4 days to 24 months), with few studies reporting longer term followup after the immediate intervention period.

The methodologic rigor of studies has increased substantially compared with those studies reported in our 2011 review of therapies for children with autism spectrum disorder (ASD).[6] However, while studies were generally well conducted, evidence remains insufficient for most interventions due to small sample sizes, lack of long term followup, and heterogeneous agents and populations.

Despite the number of new studies, we can make few conclusions beyond those reached in our 2011 review. Evidence supports the effectiveness of antipsychotics in improving challenging behaviors, but with significant harms. Methylphenidate also improves hyperactivity but with significant harms. Evidence is promising for the ADHD medication atomoxetine. More studies have addressed combination approaches, but data are inadequate to draw conclusions. Data were limited and inconsistent for other interventions.

Strength of Evidence

KQ1. Benefits and Harms of Medical Treatments

Antipsychotics. Our confidence in the conclusion that risperidone and aripiprazole improve challenging behaviors in the short term (<6 months), with clinically significant harms, is high (high strength of evidence). Behaviors improved in the longer term (≥6 months) with these agents compared with placebo, but our confidence in this conclusion is low (low strength of evidence) as only five studies had ≥6 months followup. In studies comparing risperidone and aripiprazole, BMI increased with both drugs over treatment durations of 6 months to more than 2 years, but group differences were not significant. We have low confidence that effects on BMI do not differ between

agents given the few studies addressing this outcome (low strength of evidence). Other outcomes (e.g., challenging behaviors, attention) were not consistently addressed; thus we considered strength of evidence insufficient for all other intervention/outcome pairs. Table B outlines findings for all comparisons with greater than insufficient strength of evidence.

Medications to treat ADHD. Methylphenidate versus placebo improved hyperactivity and was associated with clinically significant harms (Table B). Our confidence in these conclusions is low as studies were small and short term (low strength of evidence). Data were inadequate to assess effects on social communication and oppositional behavior (insufficient strength of evidence). Findings for oppositional behavior were inconsistent in two studies; thus, we could not assess the strength of evidence (insufficient). We considered the evidence inadequate to comment on potential effects on social communication or oppositional behavior (insufficient strength of evidence).

We found positive effects of atomoxetine compared with placebo on hyperactivity in children with ASD and ADHD in the short term (<6 months), with effects maintained over the longer term (≥6 months) (Table B). Our confidence in this conclusion is low (low strength of evidence). Atomoxetine was associated with harms considered to be clinically moderate, and our confidence in this conclusion is low (low strength of evidence). Data were inadequate to assess effects on inattention as studies reported inconsistent findings (insufficient strength of evidence).

Data were inadequate in a small study of guanfacine to draw conclusions about effects on any outcomes (insufficient strength of evidence).

Studies of combination medical and behavioral treatments. Given that combination therapies were investigated in single studies, we could not make conclusions about their effects on any outcomes (insufficient strength of evidence).

Nutritional supplements and dietary interventions. Omega-3 fatty acid supplementation and placebo did not affect challenging behaviors. Our confidence in this conclusion is low (low strength of evidence for no effect) (Table B). We also have low confidence in the conclusion that omega-3 supplementation was associated with minimal harms (low strength of evidence).

Despite the number of RCTs with low or moderate risk of bias addressing other agents, evidence was inadequate to make conclusions about all clinical efficacy and harms outcomes because few, small, underpowered studies addressed each diet or supplement (insufficient strength of

evidence). Data in two small studies of methyl-B12 were inadequate to draw conclusions (insufficient strength of evidence). While seven studies addressed variations of the gluten-free diet, studies addressed different outcomes and different approaches to restricted and control diets; thus, data were inadequate to make conclusions about the body of evidence (insufficient strength of evidence). Data were inadequate to allow conclusions about the relative effectiveness of other dietary interventions (e.g., camels' milk, challenge foods containing gluten) compared with placebo (insufficient strength of evidence).

Risperidone adjuncts. Data were inadequate to assess effects of risperidone plus adjunctive agents including amantadine, buspirone, celecoxib, memantine, riluzole, *Gingko biloba*, pioglitazone, or topiramate on any outcome assessed as no study addressed the same adjunctive agent (insufficient strength of evidence). While two RCTs addressed risperidone plus N-acetylcysteine, data are inadequate to comment on effects given the small number of participants and high attrition (insufficient SOE).

Hyperbaric oxygen therapy. Three RCTs of hyperbaric oxygen used different doses and reported inconsistent results. We considered SOE to be insufficient to assess effects.

N-acetylcysteine. N-acetylcysteine had no effect on social skills outcomes in two small RCTs; harms of this agent were not clinically significant. Our confidence in these conclusions is low (low strength of evidence) (Table B). Data were inadequate to assess effects on other outcomes given inconsistent findings in these two studies (insufficient strength of evidence).

Tetrahydrobiopterin. Tetrahydrobiopterin had no effect on symptom severity and was not associated with clinically significant harms. Our confidence in these conclusions is low (low strength of evidence) (Table B). Data were inadequate to assess effects on other outcomes (insufficient strength of evidence).

Studies of other medical interventions. Data were inadequate to make conclusions about the effects of amantadine, bumetanide, divalproex, oxytocin, mecamylamine, prednisolone, citalopram, melatonin, and neurostimulation vs. placebo as few studies addressed the same agents or outcomes (insufficient strength of evidence).

Table B. Summary of evidence in studies addressing medical interventions for children with ASD

Intervention and comparator	Number/Type of Studies (Total N Participants)	Key Outcome(s)	Strength of Evidence (SOE) Grade	Findings
Antipsychotics				
Risperidone vs. placebo	3 RCT (274)	Challenging behavior (<6 months)	High SOE	Significant improvement in treatment group vs. placebo in 3 RCTs with 6-8 week treatment phases; improvement maintained in 2 RCTs with 6 months of treatment
	3 RCT (118)	Challenging behavior (≥6 months)	Low SOE	Improvement maintained in 1 RCT with 6 months of treatment and in one open label extension with no comparison group with mean 21 months treatment duration; in another open label extension, more children relapsed with placebo vs. risperidone
	9 RCT (262) 1 Retrospective cohort (72)	Harms	High SOE for clinically significant harms associated with risperidone	Harms including weight gain, appetite changes, drowsiness, fatigue, extrapyramidal symptoms, drooling/hypersalivation, and gastrointestinal symptoms consistently reported
Aripiprazole vs. placebo	2 RCT (316)	Challenging behavior (<6 months)	High SOE	Significant improvements in 2 short-term RCTs in treatment groups
	2 RCT (415)	Challenging behavior (≥6 months)	Low SOE	In longer term followup, no differences in time to relapse of symptoms between aripiprazole and placebo groups in one 16 week RCT and continued improvements in ABC in one 52-week open label continuation with no control arm
	4 RCT (422) 1 Retropective chort (70)	Harms	High SOE for clinically significant harms associated with aripiprazole	Harms including weight gain, appetite changes, somnolence, extrapyramidal symptoms, drooling/hypersalivation, infection, and gastrointestinal symptoms consistently reported
Risperidone vs. aripirazole	1 RCT (37) 1 Retropective cohort (142)	BMI change	Low SOE for no difference in effects	BMI increased with both drugs over treatment durations of 6 months to more than 2 years, but group differences were not significant

Table B. Summary of evidence in studies addressing medical interventions for children with ASD (continued)

Intervention and comparator	Number/Type of Studies (Total N Participants)	Key Outcome(s)	Strength of Evidence (SOE) Grade	Findings
Medications to treat ADHD				
MPH vs. placebo	2 RCT (90)	Hyperactivity	Low SOE	Significant improvement with MPH compared with placebo on parent and teacher-rated measures; differential effect of dose not clear (little effect on 1 study and linear effect in another); SOE is low given small sample size and lack of long-term followup
	2 RCT (90)	Oppositional behavior	Low SOE for no effect	Significant improvement with MPH on parent-rated measure at medium dose level only in 1 RCT; no differences on teacher-rated measures. No differences in teacher-, parent-, or clinician-rated measures in another RCT
	2 RCT (90)	Harms	Low SOE for association of MPH with clinically significant harms	Rates of children experiencing harms ranged from 0-75%; higher rates reported for repetitive behaviors or speech, loss of appetite, and irritability. Irritability responsible for withdrawals (n=6) in one RCT; SOE is low given small sample size
Atomoxetine vs. placebo	2 RCT (113)	Hyperactivity (≤ 3 months)	Low SOE for improvements in the short-term	Significant improvements in rating of hyperactivity in treatment group compared with placebo in both studies
	3 RCT (241)	Harms	Low SOE for clinically moderate harms associated with atomoxetine	No serious adverse events reported; most harms attenuated over open label extension phase
Other agents				
Omega-3 supplementation vs. placebo	3 RCT (119)	Challenging behaviors	Low SOE for no effect	No significant differences between groups in three small, short-term RCTs
		Harms	Low SOE for minimal harms	No clinically significant harms reported in any study
N-acetylcysteine vs. placebo	2 RCT (127)	Social skills	Low SOE for lack of effect	No significant effects in either small, short-term RCT
		Harms	Low SOE for minimal harms	No study reported harms considered clinically important
Tetra-hydrobiopterin vs. placebo	2 RCT (54)	Symptom severity	Low SOE for lack of effect	No significant effects in either small, short-term RCT
		Harms	Low SOE for minimal harms	No study reported harms considered clinically important

ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorder; BMI = body mass index; MPH = methylphenidate; RCT = randomized controlled trial; SOE = strength of evidence

Other Key Questions

Few studies reported modifying characteristics, and no characteristics were consistent modifiers. Few studies reported data to assess time to effect of interventions. Few studies had longer-term followup and those few with 6 months or more of treatment or followup typically did not report functional outcomes; thus our understanding of whether effects at the end of treatment predict functional outcomes is limited. Four studies reported teacher ratings of outcome measures that provide some information to address effectiveness of treatments across environments or contexts, but the limited results preclude conclusions. Finally, we did not identify studies that provided data to address drivers of treatment outcomes.

Applicability

Study participants were generally recruited from specialty clinical service programs and represent non–primary care populations. As such, families of these children may be seeking a higher level of care than those of the broader population of children with ASD based upon more severe or acute symptoms, including aggression or other challenging behaviors. Most studies of medical interventions targeted elementary school aged and older children with autism, with little data on the treatment of younger children. Most studies included majority male populations (consistent with the male prevalence of ASD).

Studies also included children with highly variable severity of challenging behaviors, ASD symptom severity, and cognitive impairment. Studies of pharmacological agents often sampled children with high levels of specific symptom patterns (e.g., children with severe challenging behavior at baseline where parents may be willing to pursue pharmacologic intervention and trial participation) who may not reflect the wider population of children with ASD in whom these challenges may not be present. Most of the studies reported including children with at least moderate level of severity of ASD. Studies of stimulants included children with cognitive impairment and with comorbidities including attention deficit hyperactivity disorder, oppositional defiant disorder, and obsessive compulsive disorder. Studies of other approaches had similarly heterogeneous populations. Dietary and nutritional studies included some younger children, with severity of autism not well described or the degree of intellectual functioning not well characterized in most studies. This heterogeneity in population characteristics may limit the generalizability of findings to children with differing levels of symptom expression or comorbidities

but likely reflects the heterogeneity of the broader population of children with ASD.

Studies addressed a variety of agents and typically reported use of concurrent medications or other therapies. Most agents studied are accessible in the United States albeit with few receiving FDA approval for use. Comparators among nonplacebo controlled studies varied, and few studies assessed the effect of concomitant behavioral or other therapies, though many children with ASD receive multiple interventions. The treatments studied may not adequately reflect the broad range of treatment combinations used in the general population of children with ASD.

As noted, few studies evaluated longer term treatment (≥6 months); short treatment and followup periods limit our ability to understand potential longer term outcomes such as academic achievement or longer term harms.

Overall, the heterogeneity of these studies parallels the heterogeneity of children with ASD, and some findings may be more applicable to children with specific levels of baseline severity or comorbidities. These limitations to generalizability likely reflect both the significant heterogeneity of ASD itself as well as its associated features, such as irritability. Thus, while there is a growing evidence base for treating certain symptoms in certain populations, these findings underscore the continued need for individualized treatment approaches that are informed by the emerging evidence base for benefits as well as harms of medical intervention, with careful consideration of symptom presentation and functioning level relative to study populations and applicability of the known literature.

Limitations of the Comparative Effectiveness Review Process

We included studies published in English only and did not include unpublished data. In our scan of a random sample of 150 non-English abstracts retrieved by our MEDLINE search, only two studies appeared to meet inclusion criteria; thus, given the high percentage of ineligible items in this scan (99%), we concluded that excluding non-English studies would not introduce significant bias into the review. We recognize that this preliminary scan did not address the entire corpus of ASD literature in other languages.

We also included only comparative studies of medical interventions with at least 10 children with ASD. To ensure comprehensive coverage of the literature, we included comparative studies with a smaller sample size that would

have been excluded in our 2011 review (which required a sample size of 30) in the present report. We did not conduct a de novo search for such studies but re-examined the excluded studies from the prior review. This approach may have overlooked relevant studies.

Given heterogeneity in treatment regimens, outcomes addressed in each study, and patient populations, we were limited in our ability to meta-analyze findings or identify potential subgroups that may respond more favorably to specific treatments. Finally, we used a nonvalidated tool to assess risk of bias, though we note that the tool evaluates similar constructs to those assessed in tools such as that used by the Cochrane Collaboration, with the addition of ASD-specific domains.

Limitations of the Evidence Base

As noted, studies in the review had small sample sizes and typically limited duration of intervention and followup after intervention, despite significant improvements in study design and execution over time. Populations across studies were heterogeneous in terms of challenging behaviors, ASD symptom severity, age, and comorbidities. Few studies addressed the same agent and outcomes, and few assessed potential factors that may modify effectiveness or drive effects of interventions. Many (n=63) studies also explicitly noted that concomitant interventions were held steady during the study treatment period; however, few studies reported specific analyses to control for or assess the effects of additional treatments.

Despite these limitations, investigators have made significant improvements in incorporating commonly used measures of symptom severity and behavior to facilitate comparisons across studies. Studies also typically described interventions fully, used standardized diagnostic processes and blinded assessors, and reported on the use or restriction of concomitant interventions.

Implications for Clinical and Policy Decisionmaking

This review provides some evidence for decisionmaking about medical interventions for children with ASD. The clearest evidence favors the use of the antipsychotics risperidone and aripiprazole to address challenging behaviors in the short-term (<6 months); however, clinicians and caregivers must balance the significant harms of these agents. The significant side effect profiles make it clear that although these drugs are efficacious, caution is warranted regarding their use in patients without severe impairments or risk of injury. Few studies addressed

longer term effects of these agents; thus, our confidence in longer term (≥6 months) effectiveness is low. Studies of adjuncts to risperidone typically reported positive effects on challenging behaviors, but few studies addressed the same agents, precluding our ability to draw conclusions about their effectiveness.

Some evidence supports the use of methylphenidate and atomoxetine for hyperactivity, but few comparative studies addressed each agent, so our confidence in effects is limited. Given that many children with ASD are currently treated with medical interventions, strikingly little evidence exists to support clear benefit for most medical interventions, especially in the realm of interventions such as restrictive diets and supplements. Studies of nutritional supplements or specialized diets were typically underpowered and provided little evidence of effects of these approaches. Several agents were addressed in single studies, which limits conclusions about their effects.

Decisional dilemmas remain regarding characteristics of the child, family, or intervention that may modify effectiveness or predict which children may be most likely to benefit from a given approach. Similarly, the literature base is currently insufficient to inform our understanding of the time to effect of interventions, longer term effectiveness of interventions, generalizability of effects outside the treatment context, effectiveness and applicability to broader ASD populations, and components that may drive effectiveness.

Research Gaps and Areas for Future Research

Improving research in this area should include methodologic considerations of power and sample size and durability of effects. Sample size and participant followup were frequently insufficient to allow firm conclusions. Duration of treatment and followup were generally short (<6 months); those studies with longer duration of treatment were typically open label extensions of RCTs and lacked control arms. While duration was typically short, retaining participants in studies, especially in placebo arms, is difficult when parents or children perceive little improvement in symptoms. Longer duration of treatment, however, is also important to rule out meaningful improvements in placebo groups and help inform our understanding of the placebo effect.

Few studies provided data on long-term outcomes after cessation of treatment. Future studies should extend the followup period and assess the degree to which outcomes are durable in "real world" situations. The literature

includes many single studies of various agents. Studies of adjuncts to risperidone, for example, examined different adjunct agents, with some positive effects on challenging behaviors reported with most. Understanding which agents should be examined further is lacking. Another critical area for further research is identifying which children are likely to benefit from particular interventions. To date, studies have provided limited characterization of the subpopulation of children who experience positive response to medical interventions and limited characterization of the extent or type of behavioral challenges children experience at baseline.

Children with ASD also typically receive multiple types of therapies, but few studies addressed combinations of medical and behavioral or other categories of interventions or a medical treatment compared with a nonmedical treatment. Few attempted to account for potential effects on ongoing interventions. This not only limited our ability to interpret the effects of medical treatments in isolation but represents a significant gap for families and providers in choosing additional treatments that may bolster (or impair) the effects of behavioral, medication, or other therapies. Few studies (n=10) compared active treatments, and future research to assess comparative effectiveness of antipsychotics, ADHD medications, and other medications is necessary.

In addition, much of the medical intervention literature relies on baseline and outcome measures that have specific limits in understanding individualized response. Future research attempting to elucidate potential biobehavioral markers of response may prove useful. Research in understanding outcomes of importance to patients and caregivers, such as quality of life, is also lacking.

Harms reporting varied across studies; some studies amply described how harms were tracked, while others listed harms with no indication of how they were assessed (e.g., parent recall, checklist, clinician assessment during followup). This lack of reporting makes comparing harms across studies difficult. For instance, while studies of atomoxetine generally reported fewer harms than did studies of methylphenidate in children with ADHD symptoms, exploring differences in safety profiles is an important area for additional research.

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Conclusions

Risperidone and aripiprazole ameliorated challenging behaviors in the short term (<6 months), but had clinically significant side effects. Methylphenidate and atomoxetine were also associated with improvements in hyperactivity in small, short-term RCTs (with uncontrolled open label extensions). Atomoxetine plus parent training was not more effective for hyperactivity than atomoxetine alone. Omega-3 fatty acid supplementation was not associated with improvements in challenging behaviors, and N-acetylcysteine and tetrahydrobiopterin were not associated with improvements in social skills and symptom severity, respectively. Some positive effects were reported with other agents studied (risperidone adjuncts, melatonin), but few studies addressed the same agent or outcomes. Data on longer term (≥6 months) results and harms of interventions are lacking. Similarly, more research is needed to understand characteristics of the child or treatment that modify outcomes and whether effectiveness of interventions generalizes across different settings such as the home or school. Current evidence also does not inform our understanding of components of interventions that may drive effects. Some therapies hold promise and warrant further study, and the conduct of studies has improved considerably over time (i.e., growing number of RCTs and use of standardized measures). However, additional studies with larger, well-characterized populations over longer time frames, and that utilize transparent and rigorous methods that permit comparison across studies, would further inform decisionmaking.

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