Draft Comparative Effectiveness Review

Comparative Effectiveness of Therapies for Children with Autism Spectrum Disorders

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

Structured Abstract

Objectives: The Vanderbilt Evidence-based Practice Center systematically reviewed evidence on therapies for children with autism spectrum disorders (ASD). We focused on treatment outcomes, modifiers of treatment effectiveness, evidence for generalization of outcomes to other contexts, and evidence to support treatment decisions in children ages 0-2 at risk for an ASD diagnosis.

Data: We searched MEDLINE®, ERIC, and PsycInfo®.

Review Methods: We included studies published in English from January 2000 to January 2010. We excluded medical studies with fewer than 30 participants and behavioral, educational, and allied health studies with fewer than 10 participants, or lack of relevance to treatment for ASD.

Results: Of 149 unique studies included, 13 were good quality, 49 were fair, and 87 poor. There is evidence to support early and intensive behavioral intervention, including the University of California, Los Angeles (UCLA)/Lovaas and Early Start Denver Model for improving cognitive performance, language skills, and adaptive behavior skills. There is some suggestion that less intensive interventions focusing on providing parent training and cognitive behavioral therapy (CBT) for bolstering social communication skills and managing challenging behaviors may be useful for children with ASD to improve social communication, language use, and potentially symptom severity. No current medical interventions demonstrate clear benefit for social or communication symptoms in ASD. Risperidone and aripiprazole demonstrate improvement in challenging behavior that includes emotional distress, aggression, hyperactivity and self-injury, but have high incidence of harms. The Treatment and Education of Autistic and related Communication-handicapped CHildren (TEACCH) educational program demonstrated some improvements in gross motor, eye-hand coordination, and cognitive measures. Little evidence is available to assess other behavioral interventions, allied health therapies or complementary and alternative medicine. Data are preliminary but promising for intensive intervention in children under age 2. Information is lacking on modifiers of effectiveness, generalization of effects outside the treatment context, components of multi-component therapies that drive effectiveness, and predictors of treatment success.

Conclusions: Data to support therapies for children with autism are sparse, with some support for medical and behavioral approaches. Numerous additional behavioral and educational interventions that vary widely in terms of scope, target and intensity have demonstrated effects, but the lack of consistent data limits our understanding of whether these interventions are linked to specific clinically meaningful changes in functioning. In sum, research to support therapies for children with autism is sparse, with ranging strength of evidence, but the field is developing. The needs are substantial for continuing improvements in methodologic rigor in the field and for larger, multi-site studies of existing interventions that extend our current knowledge. Finally, better characterization, both phenotypically and genotypically, of children in these studies to target treatment plans better, is imperative.

Contents

Executive Summary 1

Evidence Report 7

Chapter 1. Introduction 9
Need for Evidence for Treatment of ASD 9
Behavioral Interventions 9
Educational Interventions 13
Medical and Related Interventions 14
Allied Health Interventions 17
CAM Interventions 19
Importance of this Review 20
This Evidence Report 20
Key Questions and Analytic Framework 21
Key Questions 21
Analytic Framework 21
Organization of this Evidence Report 22
Technical Expert Panel (TEP) 23
Uses of this Report 23
Chapter 2. Methods 25
Literature Review Methods 25
Inclusion and Exclusion Criteria 25
Literature Search and Retrieval Process 27
Literature Synthesis 28
Development of Evidence Tables and Data Abstraction Process 28
Assessing Methodological Quality of Individual Studies 29
Strength of Available Evidence 33
Chapter 3. Results 35
Article Selection 35
KQ1: Effects of Treatment on Core and Commonly Associated Symptoms in Children with ASD: Behavioral Interventions 36
Early Intensive Behavioral and Developmental Interventions 38
Social Skills Interventions 45
Play-/Interaction-based Interventions 50
Behavioral Interventions focused on Associated Behaviors 52
Other Behavioral Interventions 58
KQ1: Effects of Treatment on Core and Commonly Associated Symptoms in Children with ASD: Educational Interventions 60
TEACCH 61
Broad-Based Educational Approaches 63
Computer-Based Educational Approaches 65

KQ1: Effects of Treatment on Core and Commonly Associated Symptoms in Children with ASD: Medical Interventions 68
Antipsychotics 69
Serotonin Reuptake Inhibitors 77
Stimulants and other Medications to Treat Hyperactivity 82
Secretin 83
Dietary and Other Medical Interventions 84
KQ1: Effects of Treatment on Core and Commonly Associated Symptoms in Children with ASD: Allied Health Interventions 87
Language Interventions 88
Sensory and Auditory Focused Interventions 90
Additional Allied Health Interventions 93
KQ1: Effects of Treatment on Core and Commonly Associated Symptoms in Children with ASD: CAM Interventions 94
CAM Interventions 94
KQ2: Modifiers of Treatment Outcomes 97
Behavioral Interventions 97
Educational Interventions 100
Medical Interventions 100
Allied Health Interventions 102
CAM Interventions 103
KQ3: Early Results in the Treatment Phase That Predict Outcomes 103
Early Identifiable Changes Predicting Response/Outcome 103
KQ4: End of Treatment Effects That Predict Outcomes 103
KQ5: Generalization of Treatment Effects 103
KQ6: Drivers of Treatment Effects 104
KQ7: Treatment Approaches in Children under Age Two at Risk for ASD 105

Chapter 4. Discussion 109
Outcomes and Strength of Evidence of Therapies 109
Effectiveness of Behavioral Interventions 109
Effectiveness of Educational Interventions 116
Effectiveness of Medical Interventions 117
Effectiveness of Allied Health Interventions 122
Effectiveness of CAM Interventions 124
Assessment of Domains for Strength of Evidence 125
KQ2: Modifiers of Treatment Outcomes 128
KQ3: Early Results in the Treatment Phase that Predict Outcomes 129
KQ4: End of Treatment Effects that Predict Outcomes 130
KQ5: Generalization of Treatment Effects 130
KQ6: Drivers of Treatment Effects 130
KQ7: Treatment Approaches in Children under Age Two at Risk for ASD 131
Quality Considerations 131
Applicability 131
Behavioral Interventions 131
Medical Interventions 132

Review of Systematic Reviews 133
Future Research 134
State of the Literature 134
Gaps in Areas of Research 134
Methodologic Issues 136
Conclusions 137

References and Included Studies 139

List of Acronyms/Abbreviations 149

Tables

Table 1. Description of behavioral interventions included in the report 12
Table 2. Description of educational interventions included in the report 14
Table 3. Description of medical interventions included in the report 16
Table 4. Description of allied health interventions included in the report 18
Table 5. Description of CAM interventions included in the report 19
Table 6. Inclusion and exclusion criteria 24
Table 7. Categorization of interventions 25
Table 8. Overview of diagnostic tools used in quality scoring hierarchy 29
Table 9. Quality scoring algorithm 32
Table 10. Overview of behavioral studies 37
Table 11. Outcomes of early-developmentally based behavioral interventions 42
Table 12. Outcomes of RCTs of social skills behavioral interventions 49
Table 13. Outcomes of studies assessing play-based interventions 52
Table 14. Studies assessing interventions targeting conditions associated with ASD 55
Table 15. Overview of educational studies 61
Table 16. Overview of studies assessing educational interventions 65
Table 17. Overview of studies of medical interventions 68
Table 18. Outcomes of RCTs of antipsychotic medications 72
Table 19. Outcomes of studies of SRIs 78
Table 20. Harms frequently reported in studies of medical interventions 80
Table 21. Outcomes of studies of stimulants for the treatment of hyperactivity in ASD 83
Table 22. Outcomes of RCTs of dietary supplements for the treatment of ASD 84
Table 23. Outcomes of RCTs of additional medical interventions for the treatment of ASD 85
Table 24. Overview of allied health studies 87
Table 25. Outcomes of RCTs of sensory/auditory interventions for the treatment of ASD 92
Table 26. Overview of CAM studies 94
Table 27. Outcomes of interventions for children at risk for diagnosis of ASD 107
Table 28. Synthesis of results of studies of early intensive/developmental approaches 111
Table 29. Synthesis of results of studies of social skills interventions 112
Table 30. Synthesis of results of play-/interaction-based interventions 113
Table 31. Synthesis of results of studies targeting behaviors associated with ASD 115
Table 32. Synthesis of results of studies of other behavioral interventions 116
Table 33. Synthesis of results of educational interventions 117

Table 34. Synthesis of results of medical interventions 118
Table 35. Synthesis of results of allied health interventions 123
Table 36. Synthesis of results of CAM interventions 124
Table 37. Intervention, strength of evidence domains, strength of evidence for outcomes 125

Figures

Figure 1. Analytic framework for therapies for children with ASD 22
Figure 2. Disposition of articles for therapies for children with ASD 36

Appendices

Appendix A: Exact Search Strings
Appendix B: Sample Data Abstraction Forms
Appendix C: Evidence Tables
Appendix D: List of Excluded Studies
Appendix E: Peer Reviewers
Appendix F: Study Design Categorization
Appendix G: Review of Recent Systematic Reviews
Appendix H: Table of Quality Scores
Appendix I: Applicability Tables

Appendixes and Evidence Tables for this report are provided electronically at
http://www.ahrq.gov/downloads/pub/evidence/pdf/XXX/XXX.pdf

Executive Summary

Introduction

Background

Autism Spectrum Disorders (ASD) are among the most common neurodevelopmental disorders, with an estimated average of one in 110 children in the United States having an ASD.[1] Disorders within the autism spectrum include Autistic Disorder, Asperger Syndrome, and Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS). ASD are characterized by significant impairments in social interaction, behavior, and communication.[2] Goals of treatment often focus on alleviating core deficits in communication, social interactions, or restricted behaviors as ameliorating these fundamental deficits may help children progress toward developing greater functional skills and independence.[3] Treatment must take into account a child's developmental context; however it is frequently complicated by emergent symptoms such as irritability and other common co-morbid conditions that may also warrant targeted treatment. This report focuses on treatments in the following broad treatment categories:

- Behavioral interventions
- Educational interventions
- Medical and related interventions
- Allied health interventions
- Complementary and alternative medicine interventions (CAM)

Key Questions

We addressed the following key questions:

KQ1: Among children ages 2-12 with ASD, what are the short and long-term effects of available behavioral, educational, family, medical, allied health, or CAM treatment approaches? Specifically,

KQ1a: What are the effects on core symptoms (e.g. social deficits, communication deficits and repetitive behaviors), in the short term (≤6 months)?

KQ1b: What are the effects on commonly associated symptoms (e.g. motor, sensory, medical, mood/anxiety, irritability, and hyperactivity) in the short term (≤6 months)?

KQ1c: What are the longer-term effects (>6 months) on core symptoms (e.g. social deficits, communication deficits and repetitive behaviors)?

KQ1d: What are the longer-term effects (>6 months) on commonly associated symptoms (e.g. motor, sensory, medical, mood/anxiety, irritability, and hyperactivity)?

KQ2: Among children ages 2-12, what are the modifiers of outcome for different treatments or approaches?

KQ2a: Is the effectiveness of the therapies reviewed affected by the frequency, duration, and intensity of the intervention?

KQ2b: Is the effectiveness of the therapies reviewed affected by the training and/or experience of the individual providing the therapy?

KQ2c: What characteristics, if any, of the child modify the effectiveness of the therapies reviewed?

KQ2d: What characteristics, if any, of the family modify the effectiveness of the therapies reviewed?

KQ3: Are there any identifiable changes early in the treatment phase that predict treatment outcomes?

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

KQ5: What is the evidence that specific intervention effects measured in the treatment context generalize to other contexts (e.g., people, places, materials)?

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

KQ7: What evidence supports the use of a specific treatment approach in children under the age of two who are at high risk of developing ASD based upon behavioral, medical, or genetic risk factors?

Methods

Topic Development. The topic for this report was nominated in a public process. With input from technical experts, we drafted the initial key questions and, after approval from AHRQ, they were posted to a public Web site. The public was invited to comment on these questions. After reviewing the public commentary, the EPC drafted final key questions and submitted them to AHRQ for approval.

Literature search. We searched three databases: MEDLINE®, PsycINFO, and the Education Resources Information Center (ERIC) database. We hand searched the reference lists of included articles for additional studies. We excluded studies that:

- were not published in English
- included fewer than ten total participants for studies of behavioral, educational, allied health, or CAM interventions or fewer than 30 total participants for medical studies;
- were published prior to the year 2000
- were not original research
- did not present aggregated results (i.e. presented data for each individual participant) or presented only graphical data.

Study selection. Two reviewers separately evaluated each abstract. If one reviewer concluded that the article could be eligible, we retained it. Two reviewers independently read the full text of each included article to determine eligibility. Disagreements were resolved via third-party adjudication.

Quality assessment. Two reviewers independently assessed quality (assessment of study design, diagnostic approach, participant ascertainment, intervention characteristics, outcomes measurement, and statistical analysis) with differences resolved through discussion, review of the publications, and coming to consensus with the team.

Data extraction. All team members entered information into the evidence tables. After initial data abstraction, a second team member reviewed the table and edited entries for accuracy, completeness, and consistency. In addition to outcomes for treatment effectiveness, we abstracted data on harms.

Evidence synthesis. We used summary tables to synthesize studies that included comparison groups.

Literature search yield. Our searches retrieved 3,934 non-duplicate articles. One hundred and seventy three articles, representing 149 unique studies, were included in the review. All articles (n=173, representing 149 unique studies) pertained to key question (KQ) one. Thirty-one articles addressed KQ2, five addressed KQ3, 18 addressed KQ5, four addressed KQ7, and no articles addressed KQ4 or KQ6. The full report details reasons for exclusion.

Results

KQ1: Outcomes of Therapies for ASD in Children ages 2-12

Behavioral interventions. Behavioral interventions include early intensive behavioral and developmental interventions; social skills interventions; play-based interventions; and behavioral interventions focused on associated behaviors. A total of 75 studies were identified.

Despite substantial methodologic challenges, the existing research suggests, with moderate strength of evidence, that intensive UCLA/Lovaas and Early Start Denver Model interventions (greater than 30 hours per week) may confer greater improvements in cognitive performance, language skills, and adaptive behavior skills than the broadly defined eclectic treatments that are often available to children in the community. At present, these approaches have demonstrated effect in RCTs when implemented by both professionals and parents. Not all children receiving early intensive intervention, however, demonstrate rapid gains, with some available data suggesting that many children will continue to display prominent areas of impairment[4] and that subgroups may account for a majority of the changes observed. There are no studies available directly comparing effects of different treatment approaches and there is little evidence of practical effectiveness or feasibility.

There is some suggestion that less intensive interventions focusing on providing parent training for bolstering social communication skills and managing challenging behaviors may be useful to improve social communication, language use, and potentially symptom severity.[5-8]

Although all of the studies of social skills interventions reported some encouraging results, most have not included objective observations of the extent to which social skills improvements generalize and are maintained within everyday peer interactions. In addition, the current research focuses almost exclusively on high functioning children with autism. Evidence is low for the effects of social skills training for older children or play- and interaction-based approaches for younger children.

Several studies suggest that cognitive behavioral therapy (CBT)-based interventions are effective in reducing anxiety symptoms, such that many no longer met diagnostic criteria for anxiety disorders and a significant number in all studies showed reduced anxiety symptoms post-treatment.

Educational interventions. Among educational interventions, the Treatment and Education of Autistic and Related Communication-handicapped Children (TEACCH) program is the most widely studied, but the majority of research on this intervention took place prior to the date cutoff for our review. In newer research, the program continues to demonstrate improvements among children in gross motor, eye-hand coordination, and cognitive measures. A developmental center-based intervention showed improvements over no treatment, and the inclusion of a home-

based component showed greater improvements beyond the center-based instruction alone.

Among the studies evaluating the setting and the type of instructional strategy, one study[9] found that children in both a home-based early intensive behavioral intervention and an autism-based nursery program improved at similar rates, but that there were child characteristics including intelligence quotient (IQ) and receptive language at baseline that were better predictors of progress. An additional study[10] suggested that home-based applied behavior analysis (ABA) teaching interventions were more effective than those in a school-based intervention borrowing from TEACCH, and a home-based portage program. Case series largely support the group design studies, suggesting that ABA methods applied to educational programs may result in improved outcomes. However, a lack of uniformity in intervention descriptions, comparison, and outcome measures makes any assessment preliminary.

Medical interventions. Medical treatments for symptoms of ASD comprise a variety of pharmacologic agents including antipsychotics, psychostimulants, and serotonin reuptake inhibitors (SRIs). Modalities such as therapeutic diets, supplements, hormonal supplements, immunoglobulin, hyperbaric oxygen, and chelating agents have been employed. A total of 39 studies were identified in the medical literature, of which 25 were randomized controlled trials (RCTs). Eight were studies of antipsychotics, five were of SRIs, four of stimulants and other medications to treat hyperactivity, eight of secretin and 14 dietary and other.

Although no current medical interventions demonstrate clear benefit for social or communication symptoms in ASD, a few medications show benefit for repetitive behaviors or associated symptoms. The clearest evidence favors the use of medications to address challenging behaviors. Risperidone and aripiprazole each has at least two RCTs demonstrating improvement in a parent-reported measure of challenging behavior that includes emotional distress, aggression, and self-injury. A parent-reported hyperactivity and non-compliance measure also showed significant improvement. Repetitive behavior also showed improvement with both risperidone and aripiprazole. Both medications also cause significant side effects, however, including marked weight gain, sedation, and risk of extrapyramidal symptoms. Risperidone and aripiprazole are efficacious but associated with significant side effects that limit their use to patients with severe impairment or risk of injury.

A few medical interventions have been studied in single or multiple RCTs that provide adequate evidence that they show little promise for further study. Secretin has been exhaustively studied in multiple RCTs with no evidence for benefit in ASD. Amantadine, N,N-dimethylglycine, oral immunoglobulin, and the chelating agent DMSA showed no benefit in single RCTs. Other medical interventions also have been evaluated in single RCTs and show promise for further study including methylphenidate for hyperactivity, hyperbaric oxygen treatment for general improvement, fluoxetine for repetitive behavior and citalopram for challenging behavior.

Case series or other studies show promise for future research on omega 3 fatty acids, melatonin, L-carnosine, escitalopram, guanfacine, cyproheptadine, and piracetam.

Allied health. The allied health interventions reviewed here were varied and the published research did not provide support for their use. Specifically, all studies of sensory integration were poor, two fair studies of auditory integration showed no improvement associated with treatment, and only one RCT was available on music therapy, although it did suggest benefit. Language and communication interventions (Picture Exchange Communication System (PECS) and Responsive Education and Prelinguistic Milieu Training (RPMT)) demonstrated short term

improvement in word acquisition without effect durability. No other allied health interventions had adequate research.

CAM interventions. Few studies assessed CAM approaches; massage may offer some benefit in sensory measures, and acupuncture showed some effects on language, but research in both is preliminary.

KQ2: Modifiers of Treatment Outcomes

In the medical literature, some characteristics of the family and child were found to be useful in predicting treatment success, including a history of psychiatric diagnoses in the family, early verbal skills in the child,[11] and, potentially, genotype for predicting lack of treatment response.[12] Several studies of stimulant use highlighted differences in effectiveness by diagnosis type[13-17] finding that children with Asperger syndrome were typically more responsive to psychostimulant treatment than those with autistic disorder. The presence of co-morbid intellectual disability was associated with lower treatment response in one study.[17]

Several investigations note that pretreatment IQ and language predicts IQ at follow-up within the context of early intensive behavioral intervention (EIBI)/ABA studies.[18-22] However, other studies have suggested having a lower IQ at initiation of treatment is related to increased change in IQ over time[23] or failed to find a relationship between IQ and change in response to intervention.[24-26]

In contrast to EIBI/ABA methodologies there is evidence within parent training methodologies for teaching early social communication skills that children with lower language levels and/or lower IQ at baseline may actually benefit more from this intervention.[5-6] Baseline language/communication skills may also correlate with treatment success, with studies generally suggesting a benefit for communication skills, including changes in ASD classification associated with baseline language skills in an ABA approach.[21, 24]

Children initiating treatment at earlier ages may benefit more from EIBI intervention;[20, 27] however, other explicit comparisons have not found this same relationship for EIBI/ABA intervention[28] and age at initiation of treatment may in fact be confounded by type of treatment initiated.[27]

KQ3: Early Results in the Treatment Phase That Predict Outcomes

The reviewed literature offers almost no information about what specific changes predict long-term outcomes and response. There is some evidence that early response to both EIBI/ABA and ESDM intervention in terms of changes in IQ over the first year of treatment predicts, or accounts for, longer-term change in IQ.[18, 29] However, findings also suggest that while gains in the cognitive domain might be accounted for primarily within the first year of treatment, changes in adaptive behavior in response to these same interventions may occur over a longer time frame[18, 29-31] if they occur at all.[32]

KQ4: End of Treatment Effects That Predict Outcomes

No studies analyzed the ability of end of treatment outcomes to predict longer term functional outcomes in children

KQ5: Generalization of Treatment Effects

For medical studies, data across classes of medications are likely to be generalizable outside of the clinic setting, primarily because the outcome measures used in these studies rely on parent report of the subjects' behavior in the home and other settings and are augmented in some studies by teacher report. Research supports continued improvements extending to 6 months and beyond, but also with evidence of continued side effects.[33-37]

Most studies in the behavioral interventions targeting associated conditions primarily assessed outcomes using parent, self, and/or teacher report of targeted symptoms (e.g., anxiety, externalizing behaviors) at home, at school, and in the community, suggesting that those interventions conducted in a clinical setting are generalizable in the sense that they achieve outcomes in the "natural setting" of the child. On the other hand, in most cases, these outcomes are parent report and not confirmed with direct observation. Behavioral intervention studies uniformly failed to measure outcomes beyond the intervention period, and therefore, we cannot assume that effects are maintained over time.

KQ6: Drivers of Treatment Effects

No studies were identified to answer this question.

KQ7: Treatment Approaches in Children Under Age Two at Risk for ASD

Research on interventions for very young children (less than 2 years of age) at risk of ASD is preliminary but promising, with only four studies available.

Conclusions

In sum, research to support therapies for children with autism is sparse, with ranging strength of evidence, but the field is developing. The needs are substantial for continuing improvements in methodologic rigor in the field and for larger, multi-site, studies of existing interventions that extend our current knowledge. Finally, better characterization, both phenotypically and genotypically, of children in these studies to target treatment plans better and to move toward better personalization of treatments to achieve maximal outcomes is imperative.

Evidence Report

Chapter 1. Introduction

Need for Evidence for Treatment of Autism Spectrum Disorders in Children

Autism Spectrum Disorders (ASD) are common neurodevelopmental disorders, with an estimated prevalence of one in 110 children in the United States.[1] The etiology of ASD is largely unknown but likely includes a genetic component. Consistent biomarkers or environmental triggers have not been identified, although factors ranging from oxidative stress, advanced parental age,[38] and prenatal drug exposure, among others, have been investigated.[39] Disorders within the autism spectrum include Autistic Disorder, Asperger Syndrome, and Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS).

Individuals with ASD have significant impairments in social interaction, behavior, and communication.[2]These impairments include a lack of reciprocal social interaction and joint attention (i.e. the ability of the child to use non-verbal means like pointing to direct others' attention to something in which the child is interested); dysfunctional or absent communication and language skills; lack of spontaneous or pretend play; intense preoccupation with particular concepts or things; and repetitive behaviors or movements.[3, 40-41] Children with ASD may also have impaired cognitive skills and sensory perception.[1-2] ASD is often accompanied by other conditions such as seizure disorders, hyperactivity, and anxiety.[3, 41] The expression and severity of symptoms of ASD differ widely, and treatments include a range of behavioral, psychosocial, educational, medical, and complementary approaches[42-44] that vary by a child's age and developmental status.

The goals of treatment for ASD focus on improving core deficits in communication, social interactions, or restricted behaviors, with the idea that changing these fundamental deficits may help children develop greater functional skills and independence.[3] In addition, comprehensive treatment programs were developed in the 1980s to target behaviors and development more broadly instead of focusing on a specific behavior of interest;[45] such approaches have shown some positive effects on cognition and language and have led to the suggestion that beginning intensive therapy (25 to 30 hours/week) at an earlier age may lead to greater improvements.[45-47]

Treatment is frequently complicated by emergent symptoms such as irritability and other common co-morbid conditions that may also warrant targeted treatment. There is no cure for ASD and currently no global consensus regarding which intervention strategy is most effective. Chronic management is often required to maximize ultimate functional independence and quality of life by minimizing the core autism spectrum disorder features, facilitating development and learning, promoting socialization, reducing maladaptive behaviors, and educating and supporting families. Individual goals for treatment will vary for different children, and may include combinations of medical and related therapies, behavioral therapies, educational therapies, allied health therapies and complementary and alternative medicine (CAM) therapies.

Behavioral Interventions

Studies of behavioral interventions are addressed in this review in the broad subcategories of early intensive behavioral and developmental interventions; social skills interventions; focal play-based or interaction-based interventions; interventions focused on associated behaviors; and

a small group of other behavioral interventions assessing a variety of targets.

Early intensive behavioral and developmental interventions. In 1987, Ivar Lovaas published findings[48] on a subgroup of children who demonstrated improvements in cognitive abilities and educational placement in response to intensive intervention based on the principles of applied behavior analysis (ABA). As a result, ASD was re-conceptualized, from a largely an untreatable disorder,[49] to a disorder marked by plasticity and heterogeneity, where there was hope for 'recovery' and better outcomes for children receiving appropriate intervention. Subsequent research focused on social communication and behavioral impairments and used a continuum of approaches from highly structured behavioral reinforcement (UCLA/Lovaas, other ABA-based approaches) to naturalistic/developmental approaches that prioritize individual goals and objectives within natural environments (Early Start Denver Model, Floortime, Relationship-based intervention).

The term early intensive behavior intervention (EIBI) has been used for a variety of techniques, including the UCLA/Lovaas method and other applied behavior analysis (ABA)-based approaches. ABA is an umbrella term for principles and techniques used in the assessment, treatment and prevention of challenging behaviors. The goal of ABA is to teach new skills, promote generalization of these skills, and reduce challenging behaviors with systematic reinforcement. The principles and techniques of ABA existed for decades prior to specific application and study within ASD.

Many interventions, including developmental approaches, may apply principles of ABA within different settings and with different emphases. We use the term EIBI/ABA to refer to interventions that share several common elements: the frequent use of high intensity (many hours per week) one-on-one instruction, in highly structured settings, and emphasis on discrete trial ABA techniques with designated structures for incidental teaching (Table 1). This includes the strictly defined UCLA/Lovaas method, which relies heavily on one-on-one therapy sessions during which a trained therapist and a child practice target skills, as well as variants of this method. Other approaches incorporating principles of ABA and structured behavioral reinforcement have focused on key gateway or "pivotal: behaviors (i.e., initiating and organizing activity) in their intervention paradigms and utilized parent training as a modality for delivery (Pivotal Response Training). Such interventions and trainings are seen as different from EIBI/ABA approaches and are reviewed separately.

Interventions on the other end of the continuum include the Early Start Denver Model (ESDM), which blends ABA principles with developmental and relationship-based approaches for young children as well as several interventions that try to enhance social communication skills through parent training (e.g., Hanen More than Words, social pragmatic intervention, etc.).

Social skills interventions. Social impairments are the unifying and core feature of autism spectrum disorders. Decreased interest in the social environment has been reported since the earliest descriptions of the disorder[50] and is the unique and essential aspect of ASD that distinguishes it from other childhood disorders.[2, 51] The social impairments seen in ASD take many different forms, and can vary greatly from one child to the next. Therefore interventions focused on enhancing social behavior and competence in children with ASD should be targeted with respect to the child's age, developmental level, and peer group. Interventions for very young children may focus on teaching parents how to engage their child and encourage back-and-forth play. At preschool and early childhood levels, interventions may focus on playing with peers, understanding emotions, and learning the basics of turn-taking and initiating and responding to

social interactions. In the later elementary years and into adolescence, interventions may focus more on teaching perspective-taking, social problem-solving, and understanding peer group social norms. Given that social impairments are a core feature of ASD, numerous skill-based approaches have tried to address this vulnerability by direct instruction within individual (e.g. Social Stories) or group (e.g. Skillstreaming, Children's Friendship Training) formats. Other approaches aim to foster the development of various social skills solely through structured interactions with peers (e.g. Lego therapy).

Interventions to address social skills (Table 1) include Skillstreaming[52] a comprehensive, structured social skills curriculum for teaching specific social behaviors (e.g., listening, sharing, having a conversation, accepting a compliment, responding to teasing), as well as social cognition (using self-control), and affect (e.g., recognizing and expressing feelings, responding to anger). LEGO therapy, which uses building with Lego blocks as an interactive medium for children and adolescents with ASD to work on social behaviors (sharing, turn-taking, following conduct and social rules) and social cognition (perspective-taking, problem solving) has also been studied, as well as the reading of social stories[53] to or by individuals with ASD in order to identify the behavior expected in specific social situations.

Another intervention, Children's Friendship Training (CFT),[54] includes more typically developing peers with whom the children with ASD can practice social skills. The program includes instruction on rules of social behavior; modeling; coached behavioral rehearsal and performance feedback during treatment sessions; rehearsal at home; homework assignments; and coaching by parents during play with a peer. The Cognitive-Behavioral-Ecological[55] intervention for children with high functioning autism is conducted individually by the child's main teacher in the school in conjunction with a typically developing peer (to practice the learned social skills) and the child's parents (to support and motivate the child).

Play-/Interaction-based interventions. These interventions try to use interactions between children and adults (either parents or researchers) to affect outcomes such as imitation or joint attention skills or the ability of the child to engage in symbolic play. They include teaching parents how to interact differently with their children within daily routines and interactions, often using standard behavior management strategies. They also include foci on generic day-to-day interactions outside of the family (Table 1).

Behavioral interventions focused on associated behaviors. Several behavioral interventions target symptoms like anger and anxiety, which are often present with ASD (Table 1). CBT is a common treatment for anxiety symptoms in otherwise typically developing children, and has more recently been adapted for and applied to children with ASD,[56-59] particularly high-functioning children. The approach focuses on teaching cognitive skills and relaxation strategies, helping children recognize anxious feelings, and providing them with behavioral exposures in which to practice coping skills in the face of anxiety-provoking situations. The goal of treatment is to reduce generalized and specific anxiety symptoms over time.[60]

Challenging behaviors, such as non-compliance, tantrums, self-injury, and aggression, are also common, and parent training protocols are used to teach behavior prevention, intervention, and management strategies. Once trained, parents can act as "co-therapists," shaping behavior to reduce negative behaviors in daily life. Parent training interventions also often have secondary targets of improving parental feelings of self-efficacy and decreasing parental stress.

Table 1. Description of behavioral interventions addressed in the report

Intervention	Brief description
ABA-based Approaches	
Early Intensive Behavioral Intervention (EIBI)	• Intervention approach which primarily employs techniques derived from principles of applied behavior analysis (ABA) within highly structured contexts. Interventions generally include high intensity (many hours per week) one-on-one instruction with primary emphasis on discrete trial techniques which introduce a stimulus (instruction/cue) to which a child may respond. Responses may be reinforced/rewarded, and the trial of stimulus-potential response-reward is repeated to promote mastery; additional emphasis on incidental teaching. • Programs additionally emphasize incidental teaching and parent training in terms of promoting generalization of skills • Includes the UCLA/Lovaas model and other ABA-based variants
Developmental and relational approaches	• Intervention approaches emphasize learning within naturalistic contexts such as caregiving relationships, play, and daily routines • Parents are typically included as co-therapists and there is a primary emphasis on incidental teaching (involves structuring education in line with a child's ongoing/typical activities; parent training to allow parents to continue training at home and in other settings) • Approaches may often employ techniques derived from principles of applied behavior analysis within such contexts (i.e., Early Start Denver Model) and/or focus on developing core play and relationship skills (Floortime, Relationship Development Intervention)
Pivotal Response Training	• Approach based on ABA principles that focuses on altering gateway/pivotal behaviors, considered to be central to broad areas of functioning and in which improvements would lead to collateral improvements in behaviors; pivotal behaviors include motivation to initiate or and respond to stimuli, self-direction of behavior, and responsiveness to cues/stimuli • Typical involves extensive parent/family training components
Joint attention interventions	• Approaches aimed at promoting joint attention (e.g. communication behaviors to share and direct interest in objects/activities in one's environment) abilities in children with ASD. • Joint attention skills are viewed as potential core precursor skills contributing to long term language and social development • May employ ABA principles and parent or peer training
Symbolic play interventions	• Approaches aimed at promoting symbolic play (e.g. pretend play, "make believe" activities) abilities in children with ASD to promote long term language and social skills development • May employ ABA principles and parent or peer training
Parent Training	
Parent Training in Social Communication	• Intervention approach relying on training parents how to facilitate social and communication development within home and other naturalistic settings. Trainings are typically provided at a low intensity (e.g., once per week or month) over extended periods of time with the prospect of parents inserting intervention techniques across many contexts • Includes approaches such as social-pragmatic intervention and the Hanen More than Words program

Table 1. Description of behavioral interventions addressed in the report (continued)

Intervention	Brief description
Social Skills	
Social skills training	• Approaches generally aimed at the primary dimensions of social competence: specific behavioral skills (e.g., conversations, greetings, initiating game play, joint attention), affective understanding (e.g., recognizing emotions in self and others), and social cognition (e.g., theory of mind, which describes the ability to ascribe mental states to oneself and others to understand and forecast behavior; problem-solving; self-regulation) • Vary in focus given a child's developmental context to target areas of relevance to the child (e.g. age, developmental level, and peer group) • Interventions include Skillstreaming, Children's friendship Training (CFT), LEGO therapy, the Cognitive-behavioral-Ecological intervention, and Social Stories
Approaches Aimed at Commonly Associated Symptoms/Additional Approaches	
Cognitive Behavioral Therapy (CBT)	• Approaches aimed at understanding and restructuring patterns of thought and behavior to ameliorate areas of impairment • Often used to treat anxiety, mood, eating, substance abuse, and personality disorders. Application of CBT to ASD populations has primarily focused on teaching coping skills, increasing insight/awareness into behaviors, and systematically providing behavioral exposures to reduce symptoms of anxiety and associated distress
Neurofeedback	• Aims to remediate abnormal brainwave activity associated with disorders such as anxiety, ADHD, and ASD through training individuals to control brain activity patterns • Involves the placement of electrodes to monitor brain activity while participants interact with specially designed computer games or other modalities designed to promote attention or other skills
Sleep interventions	• Aim to improve difficulties associated with sleep including disordered sleep patterns, night waking, and difficulty falling asleep common among children with ASD • Behavioral interventions include sleep workshops which may provide training to parents in dealing with difficult sleep behaviors and establishing sleep routines

Educational Interventions

Education through schools and other community settings (e.g., centers) is the primary treatment for children with ASD. For children with ASD, educational interventions often aim at promoting personal independence and social responsibility.[47]Educational interventions have focused both on traditional areas of academic progression/achievement, as well as on addressing social, cognitive, and behavioral issues in classrooms or through specialized instruction. These interventions include the Treatment and Education of Autistic and Communication related Handicapped Children (TEACCH) program,[61] early intervention center- or classroom-based instruction, and computer-based approaches.

Originally developed in the 1970s at the University of North Carolina at Chapel Hill, TEACCH involves structured teaching and therapeutic techniques that encompass a "whole life" approach. Instruction is based on the idea that individuals on the autism spectrum have difficulty in perception and understanding; the intervention therefore relies heavily on visual supports like

a picture schedule and arranging the physical environment to support the individual.

Classroom and center-based approaches include a blend of teaching strategies that rely on principles and techniques of applied behavior analysis (ABA) including reinforcement-based procedures such incidental teaching, discrete trial training, and Pivotal Response Training (Table 2). Other interventions, such as TEACCH and language development interventions may also be incorporated in center-based treatment. Computer-based programs use technology to deliver behaviorally based teaching in areas like language acquisition and reading skills.

Table 2. Description of educational interventions addressed in the report

Intervention	Brief description
TEACCH	• Approach employing structured teaching, which applies structure to the organization of time, space, and sequences of events within the educational environment to promote learning by making activities clearer and easier to perform • Includes visual supports (e.g. picture schedules) and arranging the physical environment to support individual learning through physically indicating sequences of events and organizing individual tasks to promote developmentally appropriate behaviors that ultimately promote learning
Broad-based approaches	• Approaches generally based in schools or centers and which combine elements of EIBI- and ABA-based interventions • May also incorporate elements of language development interventions and interventions including TEACCH
Computer-based approaches	• Approaches which use technology to deliver behaviorally-based teaching in areas such as language acquisition and reading skills

Medical and Related Interventions

Interventions in this category are those in which a medication, supplement, or other substance is administered to a child with ASD. Medical treatments for symptoms of ASD comprise a variety of pharmacologic agents including antipsychotics, psychostimulants, and serotonin reuptake inhibitors (SRIs) that are generally intended to treat common comorbidities of ASD. Modalities such as therapeutic diets, supplements, hormonal supplements, immunoglobulin, hyperbaric oxygen, and chelating agents also have been employed to treat ASD symptoms (Table 3).

Antipsychotics. Antipsychotic medications all act on the dopamine system.[62-63] The older typical antipsychotic drugs act primarily to block the dopamine D_2 receptor. The newer atypical antipsychotic drugs also act on a variety of other receptors, including the serotonin 5-HT_{2A} receptor.[64-65] Although these medications were developed to treat psychosis, they have also been studied extensively for the treatment of other disorders, including mood disorders,[66-67] obsessive compulsive disorder,[68] and tic disorders.[69]

Among typical antipsychotics, haloperidol has been used since the 1980s to treat challenging behavior in children with ASD.[70] More recently, risperidone, an atypical antipsychotic that acts on both dopamine D_2 and serotonin 5-HT_{2A} receptors,[65] was the first medication to receive FDA approval for the treatment of irritability in children with ASD. Aripiprazole, which has a more complex mechanism of action,[65] also recently received FDA approval for irritability in children with ASD.

Serotonin reuptake inhibitors. Serotonin reuptake inhibitors (SRIs) block the serotonin

transporter to prevent reuptake of serotonin from the synapse.[71] SRIs have come into wide use for the treatment of depression and anxiety and are some of the most commonly prescribed medications for children with ASD.[72-74] SRIs were tested for use in children with ASD [75-76] after it was noted that 30 percent of this population had elevated blood serotonin.[77] Early RCTs of both comipramine[75, 78] and fluvoxamine[79] showed improvements in multiple behavior domains. Open label trials of selective SRIs in the 1990s provided further support for the idea that this class may benefit some children with ASD, but also revealed common side effects including hyperactivity and decreased sleep.[76, 80] Most recent clinical trials in children with ASD have focused on response in the repetitive behavior domain to SRIs with longer half-lives, including fluoxetine, with a half-life of its active metabolite of four to six days, and citalopram or escitalopram, one of two component drugs contained in citalopram, with a half-life of 35 hours.[80]

Stimulants and other medications for hyperactivity. Psychostimulants treat hyperactivity and inattention in patients diagnosed with attention deficit hyperactivity disorder (ADHD). Stimulants studied in ASD include agents such as methylphenidate (MPH), amphetamine, and dextroamphetamine (Table 3). All stimulant medications share a mechanism of action that includes inhibition of dopamine uptake from the synapse. Amphetamine and dextroamphetamine also cause release of dopamine into the synapse.

Other medications for the treatment of ADHD have also been studied for the treatment of hyperactivity in ASD, including atomoxetine, which inhibits norepinephrine reuptake from the synapse[81-83] Guanfacine, a norepinephrine receptor alpha-2a agonist that was originally used for the treatment of high blood pressure, has also been studied for use in ASD.[84-85]

Secretin. Secretin is a gastrointestinal polypeptide used in the treatment of peptic ulcers[86-87] and as a diagnostic tool in the evaluation of pancreatic function. Animal studies have suggested that there is a direct role for secretin in the central nervous system.[88-89] Interest in secretin for the treatment of ASD symptoms derived when three children with ASD were given synthetic intravenous secretin during a routine endoscopy evaluation for gastrointestinal problems.[90] The study reported social, cognitive and communicative gains after the first infusion and after a second infusion given weeks later.

Other medical interventions. Additional studies in the medical literature addressed medical therapies for sleep and gastrointestinal dysfunction as well as the use of hyperbaric oxygen, specialized diets, supplements, and other agents explored to address symptoms of ASD (Table 3).

Management of sleep issues. Melatonin, a hormone associated with regulating circadian rhythms,[91] has been assessed in a number of conditions including ASD for treating sleep dysfunction.[92] Iron supplementation has also been used to address sleep dysfunction in a range of conditions;[93-95] iron has been tried in ASD based on the hypothesis that low serum ferritin, an iron-related compound in the blood, in some ASD patients may be associated with sleep problems.[96]

Management of gastrointestinal symptoms. Gastrointestinal (GI) symptoms may or may not have an increased prevalence in ASD, with some evidence supporting increased difficulty with constipation but not other gastrointestinal symptoms. Oral immunoglobulin has been considered for its potential utility in addressing GI symptoms in ASD.[97-98]

Dietary supplements and restrictive diets for core ASD symptoms. A range of dietary supplements with potential neurologic effects show some benefit in other chronic neurological conditions and have been assessed for use in treatment of ASD (Table 3). Magnesium-vitamin

B6 and two amino acid-related compounds, L-carnosine and dimethylglycine, show some potential anticonvulsant activity in observational studies[99-101] and have been tried in ASD for potential positive behavioral effects. Reduced levels of free polyunsaturated fatty acids (PUFAs) have been reported in a range of neuropsychiatric conditions including ASD.[102-103] Supplementation with agents containing PUFAs, such as fish oil and evening primrose supplements, have been considered for their possible benefits in ASD.

There are some observational data suggesting benefit of a ketogenic diet, a high fat low carbohydrate diet, in some patients with epilepsy and seizures refractory to standard therapy,[104] and this strategy has also been explored in ASD.

Other. Amantadine, an antiviral agent,[105] is thought by some to have neurologic effects that may positively affect behavior problems in ASD. Similarly, the putative cognitive enhancer piracetam has been used in the treatment of dementia[106] and has been considered for potential cognitive benefit in ASD. Hyperbaric therapy, in which oxygen is administered in special chambers that maintain a higher air pressure, has shown possible effects in other chronic neurologic conditions[107-108] and has also undergone preliminary exploration in ASD. Cholinesterase inhibitors, such as donepezil hydrochloride and rivastigmine tartrate, inhibit an enzyme that breaks down the neurotransmitter acetylcholine; these drugs have been used to prevent further cognitive decline in Alzheimer's disease[109] and have similarly been studied for possible benefit in ASD.

Dimercapto succinic acid (DMSA), approved by the FDA to treat lead poisoning,[110] may have similar activity against other heavy metals such as mercury.[111] While there is no clear evidence that mercury or ability to remove mercury from the body is involved in ASD in any way, investigators have evaluated the ability of DMSA to affect ASD symptoms based upon existing off-label use in some children with autism.[112]

Table 3. Description of medical and related interventions addressed in the report

Intervention	Brief description
Antipsychotics	• Pharmacological agents including risperidone, aripiprazole, and haloperidol which act on the dopamine system and may also affect other systems, including the serotonin system • Primarily used to treat psychosis and mood disorders • Within ASD, primarily studied for effects on problem/challenging behaviors including irritability, aggression, and self-injurious behavior
Serotonin Reuptake Inhibitors (SRI)	• Pharmacological agents including fluoxetine and citalopram that act on the serotonin system • Blood serotonin levels are elevated in 30% of children with ASD • Primarily used to treat depression, anxiety, and obsessive compulsive disorder • Studied for potential to ameliorate repetitive behavior and challenging behaviors in ASD
Stimulants and other medications for hyperactivity	• Pharmacological agents methylphenidate (MPH), amphetamine, and dextroamphetamine primarily affect the dopamine systems • Guanfacine primarily affects the norepinephrine system • Primarily used to treat hyperactivity and inattention in patients with attention deficit hyperactivity disorder (ADHD) • Studied to treat hyperactivity in ASD

Table 3. Description of medical and related interventions addressed in the report (continued)

Intervention	Brief description
Secretin	• Gastrointestinal polypeptide used initially to treat peptic ulcers • Use in ASD stems from findings of social and communication gains in an unblinded, uncontrolled cases series of 3 children with ASD receiving secretin during a routine endoscopic evaluation for gastrointestinal problems • Evaluated in multiple studies for potential effects on language, gastrointestinal symptoms, adaptive behavior, cognitive impairments, and social and fine motor skills in ASD
Dietary supplements / restrictive diets	• Pharmacological agents including melatonin, iron, magnesium-vitamin B6,L-carnosine, polyunsaturated fatty acids (PUFA), and dimethylglycine; special diets including the high fat, low carbohydrate ketogenic diet • Some of these agents have been studied in other chronic neurologic conditions • Studied in ASD for potential effects on behavioral symptoms (magnesium-vitamin B6, L-carnosine, dimethylglicine, PUFA, ketogenic diet) and associated comorbidities including sleep difficulties (melatonin, iron)
Other medical interventions	• Pharmacological agents and interventions including antiviral agents (amantadine); nootropic drugs (piracetam); cholinesterase inhibitors (donepezil hydrochloride, rivastigmine tartrate), hyperbaric oxygen; and immunoglobulin • Chelating agents (dimercapto succinic acid) used in ASD given potential activity against heavy metals including mercury based on the unproven hypothesis that ASD may be related to mercury concentrations in the body, although no clear evidence supports this hypothesis • Some of these agents have been studied in other chronic neurologic conditions • Studied in ASD for potential effects on cognition (piracetam, donepezil, rivastigmine), gastrointestinal symptoms (immunoglobulin), and behavior (hyperbaric oxygen, amantadine) in ASD

Allied Health Interventions

Several allied health interventions have been developed to address core symptoms of ASD, as well as associated difficulties and deficits. We broadly divided allied health studies into three categories: sensory or auditory integration techniques including music therapy, those focused on language, and other approaches (including horseback riding and occupational therapy) (Table 4).

Speech and language development. As a core feature of ASD, communication difficulties are an important target of treatment. Frequently, verbal communication is the target of treatment, but establishing functional non-verbal communication for children who do not speak also can be the primary goal. Two approaches to increasing speech and language were identified: Responsive Education and Prelinguistic Milieu Teaching (RPMT), and the Picture Exchange Communication System (PECS). Responsive Education and Prelinguistic Milieu Teaching (RPMT) is a two-component system aimed at both parents and children. It is play-based, and encourages gestural, nonword vocal, gaze use, and later, word use for intentional communication around play, including for turn-taking, requesting and commenting.[113-114] Parents are taught methods of playing with their children that are thought to facilitate communication, in particular

to use linguistic mapping, in which they put into words a child's immediately preceding nonverbal message. Once prelinguistic communication is achieved, Milieu Language Teaching is incorporated, in which prompts are used to encourage verbal imitation and questions are asked to evoke spoken communication.

The Picture Exchange Communication System (PECS) uses pictures or symbols to teach children to communicate spontaneously.[115] The approach relies on behavioral techniques, especially reinforcement techniques. Providers prompt children to pick up and exchange a symbol/picture for a desired object. The process may include fading those prompts until competency is achieved. PECS can be used while intensive work to increase speech is in progress, and may provide an interim or additional means of communication. PECS relies on immediate positive reinforcement with the child obtaining the desired object upon successfully indicating his desire for it with the corresponding picture.

Sensory and auditory integration and music therapy. Although sensory sensitivity and sensory dysfunction are not core features of ASD, they are frequently described as challenges for some children with ASD.[116-117] Sensory Integration (SI) is a specialized occupational therapy model based on the premise that the brain's response to basic sensory input must be normalized before higher-order processes can be addressed.[118] The approach anticipates that a child who is better able to process, modulate, and integrate sensory information will then be better able to acquire higher-order skills.[119] Auditory integration training (AIT) relates specifically to auditory perception. In AIT, children are repeatedly presented with modulated music according to specific protocols with a therapeutic goal of improving auditory processing, lessening auditory hypersensitivities, and increasing concentration.[120-121] Finally, music therapy is at times employed with children with ASD, hinging on speculation that children engage more with music than with speech. This treatment method is improvisational and unstructured, and practitioners purport that it can improve both verbal and non-verbal communication skills including joint attention abilities.[122-123]

Additional allied health interventions. A number of additional interventions including other occupational therapy techniques, horseback riding therapy, assistive devices to facilitate reading or motor skills, and movement therapy are also considered allied health approaches and may target difficulties in sensory processing as well as language and adaptive behavior.

Table 4. Description of allied health interventions addressed in the report

Intervention	Brief description
	Language/communication
Picture Exchange Communication System (PECS)	• Approach using pictures or symbols to teach spontaneous communication • Relies on behavioral techniques through which providers prompt children to pick up and exchange a symbol/picture for a desired object • May include fading or gradually eliminating those prompts until competency is achieved
Responsive Education and Prelinguistic Milieu Teaching (RPMT)	• Approach aimed at parents and children incorporating play and encouraging gestural, non-word vocal, gaze use and word use for intentional communication around play, including for turn-taking, requesting and commenting • Teaches play-based methods thought to facilitate communication to parents • Uses prompts to encourage verbal imitation and questions to evoke spoken communication

Table 4. Description of allied health interventions addressed in the report (continued)

Intervention	Brief description
Sensory/auditory	
Sensory integration	• Occupational therapy approach based on the premise that individuals with ASD process sensory information differently, often exhibiting atypical responses to sensory input (visual, auditory, etc.) • Posits that a child must be able to process, modulate, and integrate sensory information effectively to facilitate acquisition of higher-order skills • Approaches employ controlled sensory experiences aimed at encouraging functional responses to sensory stimulation in individuals with ASD; techniques include weighted vests, swinging, deep pressure touch, and tactile stimulation
Auditory integration	• Approaches presenting children with modulated sound/music according to specific protocols with a therapeutic goal of improving auditory processing, lessening auditory hypersensitivities, and increasing concentration • Interventions include Tomatis Sound therapy and auditory integration training
Music therapy	• Improvisational, unstructured approach hinging on the speculation that children engage more with music than with speech • Targets verbal and non verbal communication skills including joint attention
Other Approaches	
Animal-assisted interventions	• Approaches employing animals within a treatment implementation, typically targeting cognitive, social, and psychological domains • Interventions include therapeutic horseback riding targeting social cognition and animal-assisted occupational therapy focusing on social skills and language use
Movement therapy	• Approaches premised on stimulating pressure receptors in the body to improve ASD symptoms • Includes various techniques including exercise and movement to music

Complementary and Alternative Medicine (CAM) Interventions

Acupuncture is an ancient Chinese medical system based on the balance of energy flows in which imbalance is thought to result in disease (Table 5). Acupuncture therapy aims to manipulate these energies through the insertion of fine needles at highly specific points related to energy flow to specific organs. Like acupuncture, massage therapy is thought to exert effects on the energy field of the body and has been used in ASD to decrease touch aversion and improve autistic behaviors.[124]

Table 5. Description of CAM interventions addressed in the report

Intervention	Brief description
Massage	• Approaches using therapeutic touch and premised on ameliorating imbalances in the energy field of the body • Approaches in ASD include qigong massage and often focus on improving sensory difficulties

Table 5. Description of CAM interventions addressed in the report (continued)

Intervention	Brief description
Acupuncture	• Approaches based on manipulating, through the insertion of fine needles into specific energy points, the balance of energy flows to correct imbalances thought to result in disease • Interventions in ASD include scalp acupuncture and seven star needle stimulation

Importance of This Review

While advances have been made in early diagnosis and the promotion of early intervention for ASD,[40, 125-126] there are few current sources for comparing the benefits and harms of treatment interventions. Clinicians and families are left to choose among the interventions in part based on what is available to them, what is covered by commercial insurance or Medicaid, or what they can afford out of pocket. Sometimes, a clinical course of action is based on the most common or popular treatments at a given time. Many therapies are not covered by insurance, and a primary reason for insurance denial from private insurers is that there are no evidence-based resources for this condition. Additionally, insurers may find it confusing to distinguish among therapies or to sort out which approaches have an evidence base and which are still experimental.

The delivery and organization of care for ASD therefore tends to be fragmented, with pieces scattered about in the primary care, school, and specialty clinical settings, making it especially important for families and caregivers to have clear information on effectiveness of treatment components. Treatment outcomes may be highly variable across diagnostic groups and developmental stages and in the presence or absence of co-morbidities. Family context and the child's home and school environment may also alter the effectiveness of treatment. Therapeutic approaches should therefore be tailored to an individual child to the extent possible to optimize effectiveness.[126-127]

Previous reviews of the literature have noted limited quality and consistency in studies assessing ASD therapies,[43-44, 46, 128-130] and an umbrella review found methodological weaknesses in systematic reviews of psychosocial interventions.[42] While controlled trials seem to be increasing, much research is observational, generally with small sample sizes, limited follow-up, and limited discussion of the durability of treatment gains once active therapy ends. As the prevalence of ASD has increased, the available treatment options have also increased, but evidence overall for many interventions can only be considered preliminary. There is a need for synthesized research that evaluates the evidence base for various treatments and identifies gaps in the current literature that may drive the research agenda.

This Evidence Report

Scope of the Report. Evidence reviews of therapeutics seek to identify and systematically summarize objective information about the evidence related to the:

- Effectiveness of specific, well-defined treatments
- Relative benefit of one treatment over another
- Common side effects and serious risks of a treatment
- Whether individual characteristics help predict who will benefit or be harmed

Key Questions and Analytic Framework

Key Questions

We focused this review on treatments for children ages 2-12 with autism spectrum disorders (ASD). Key questions addressed aspects of treatment for this population as well as treatment approaches in younger children at risk for a diagnosis of ASD. We have synthesized evidence in the published literature to address these key questions:

KQ1: Among children ages 2-12 with ASD, what are the short and long-term effects of available behavioral, educational, family, medical, allied health, or CAM treatment approaches? Specifically,

- **KQ1a:** What are the effects on core symptoms (e.g. social deficits, communication deficits and repetitive behaviors), in the short term (≤6 months)?
- **KQ1b:** What are the effects on commonly associated symptoms (e.g. motor, sensory, medical, mood/anxiety, irritability, and hyperactivity) in the short term (≤6 months)?
- **KQ1c:** What are the longer-term effects (>6 months) on core symptoms (e.g. social deficits, communication deficits and repetitive behaviors)?
- **KQ1d:** What are the longer-term effects (>6 months) on commonly associated symptoms (e.g. motor, sensory, medical, mood/anxiety, irritability, and hyperactivity)?

KQ2: Among children ages 2-12, what are the modifiers of outcome for different treatments or approaches?

- **KQ2a:** Is the effectiveness of the therapies reviewed affected by the frequency, duration, and intensity of the intervention?
- **KQ2b:** Is the effectiveness of the therapies reviewed affected by the training and/or experience of the individual providing the therapy?
- **KQ2c:** What characteristics, if any, of the child modify the effectiveness of the therapies reviewed?
- **KQ2d:** What characteristics, if any, of the family modify the effectiveness of the therapies reviewed?

KQ3: Are there any identifiable changes early in the treatment phase that predict treatment outcomes?

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

KQ5: What is the evidence that specific intervention effects measured in the treatment context generalize to other contexts (e.g., people, places, materials)?

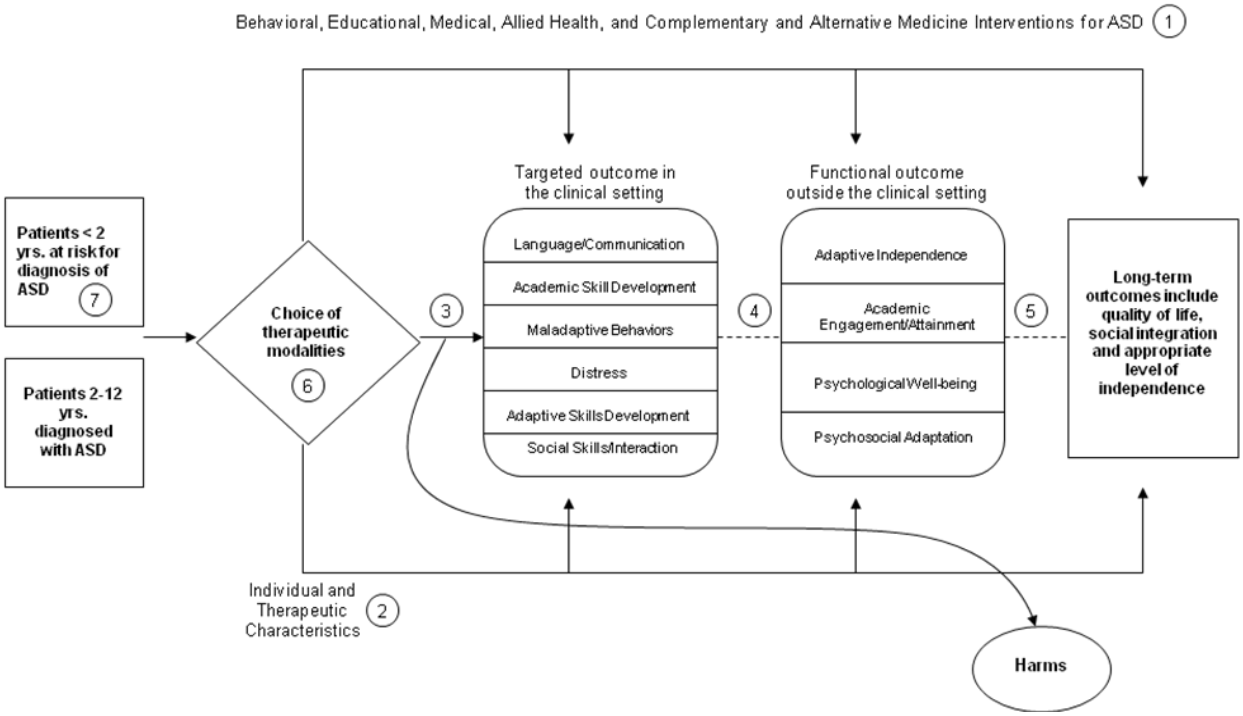
KQ6: What evidence supports specific components of treatment as driving outcomes, either within a single treatment or across treatments?

KQ7: What evidence supports the use of a specific treatment approach in children under the age of two who are at high risk of developing autism based upon behavioral, medical, or genetic risk factors?

Analytic Framework for Therapies for Children with ASD

The analytic framework in Figure 1 summarizes our understanding of ASD treatment and potential outcomes used to guide this systematic review.

Figure 1. Analytic framework for therapies for children with ASD



Alternate text: This figure illustrates how patients with ASD enter into treatment choices, which may be modified by factors related to the therapeutic care as well as related to the child's individual characteristics. Treatments may lead to targeted/short term outcomes in the treatment setting including adaptive and/or academic skills development, distress, language/communication effects, and maladaptive behaviors. Treatment may also lead to functional or long term outcomes outside of the treatment setting including adaptive independence, psychological well-being, academic engagement, and psychosocial adaptation. Treatments may be affected at any point by therapeutic care factors or characteristics of the individual child. Therapies may also lead to longer term outcomes including quality of life, social integration, and an appropriate level of independence and may be associated with harms/adverse effects.

Organization of this Evidence Report

Chapter 2 describes our methods including our search strategy, inclusion and exclusion criteria, approach to review of abstracts and full publications, and our method for extraction of data into evidence tables and compiling evidence. We also describe the approach to grading of the quality of the literature and to describing the strength of the body of evidence.

Chapter 3 presents the results of the evidence report, synthesizing the findings by category of intervention. We report the number and type of studies identified and we differentiate between total numbers of publications and unique studies to bring into focus the number of duplicate publications in this literature in which multiple publications are derived from the same study population. We emphasize the effect of treatment on the core symptoms and commonly associated co-morbidities of ASD. Chapter 4 discusses the results in Chapter 3 and expands on methodologic considerations relevant to each key question. We also outline the current state of the literature and challenges for future research on ASD.

Technical Expert Panel (TEP)

We identified technical experts on the topic of ASD in the fields of developmental disabilities, psychiatry, psychology, occupational therapy and educational research to provide assistance during the project. The TEP contributed to AHRQ's broader goals of (1) creating and maintaining science partnerships as well as public-private partnerships and (2) meeting the needs of an array of potential customers and users of its products. Thus, the TEP was both an additional resource and a sounding board during the project. The TEP included ten members serving as technical or clinical experts, including representatives from our partner organizations (the nominators of the topic), the Medicaid Medical Directors and Autism Speaks. To ensure robust, scientifically relevant work, we called on the TEP to provide reactions to work in progress and advice on substantive issues or possibly overlooked areas of research. TEP members participated in conference calls and discussions through e-mail to:

- Refine the analytic framework and key questions at the beginning of the project;
- Discuss the preliminary assessment of the literature, including inclusion/exclusion criteria;
- Provide input on assessing the quality of the literature.

Because of their extensive knowledge of the literature, including numerous articles authored by TEP members themselves, and their active involvement in professional societies and as practitioners in the field, we also asked TEP members to participate in the external peer review of the draft report.

Uses of This Report

This evidence report addresses the key questions outlined above using methods described in Chapter 2 to conduct a systematic review of published literature including a meta-analysis of effects of pharmacologic treatment. We anticipate that the report will be of value to clinicians treating ASD patients, including general pediatricians, developmental and behavioral pediatricians, neurodevelopmentalists, child neurologists, psychologists, psychiatrists and behavioral experts. In addition, this review will be of use to the National Institutes of Health, Centers for Disease Control and Prevention, Centers for Medicare & Medicaid Services, and the Health Resources and Services Administration–all of which have offices or bureaus devoted to child health issues. This report can bring practitioners up to date about the current state of evidence, and it provides an assessment of the quality of studies that aim to determine the outcomes of therapeutic options for the management of ASD. It will be of interest to families affected by ASD and the general public because of the high prevalence of ASD and the recurring need for families and their health care providers to make the best possible decisions among numerous options. We also anticipate it will be of use to private sector organizations concerned with ASD, as they work to guide research priorities and educate communities about ASD. Researchers can obtain a concise analysis of the current state of knowledge in this field. They will be poised to pursue further investigations that are needed to understand best approaches to therapies for children with ASD.

Chapter 2. Methods

This chapter documents procedures that the Vanderbilt Evidence-based Practice Center used to develop this comprehensive evidence report on the treatment of ASD in children ages 2-12. We first describe our strategy for identifying articles relevant to our key questions, our inclusion/exclusion criteria, and the processes used to abstract relevant information from eligible articles and generate evidence tables. We also discuss our criteria for grading the quality of individual articles and for rating the strength of the evidence as a whole. Finally, we describe the peer review process.

Literature Review Methods

Inclusion and Exclusion Criteria

Our inclusion/exclusion criteria were developed in consultation with the TEP. Criteria are summarized below (Table 6). We worked closely with our TEP to refine our key questions and set our inclusion criteria.

Table 6. Inclusion and exclusion criteria

Category	Criteria
Study population	Children ages 2-12 with ASD or ages 0-2 at risk for diagnosis of ASD
Publication languages	English only
Admissible evidence (study design and other criteria)	Admissible designs RCTs, cohorts with comparison, non randomized controlled trials, case-control studies, and case series Other criteria Original research studies providing sufficient detail regarding methods and results to enable use and aggregation of the data and results Studies must have relevant population & ≥ 10 participants for behavioral, educational, CAM, and allied health studies and ≥ 30 participants for medical studies Studies must address one or more of the following for ASD: Treatment (tx) modality Predictors of treatment outcomes Generalization of tx outcomes to other contexts Drivers of tx outcomes Tx approaches for children 0-2 at risk for an ASD diagnosis Relevant outcomes must be able to be abstracted from data in the papers

ASD=autism spectrum disorders; CAM=complementary and alternative medicine; RCT=randomized controlled trial; tx=treatment

For this review, the relevant population for key questions (KQ) one through six was children with ASD (autism, PDD-NOS, Asperger Syndrome) whose mean age plus standard deviation

was ≤ 12 years and 11 months. Studies needed to provide adequate information to ensure that participants fell within the target age range. Specifically, we chose to limit the age range to 2 – 12 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. We did, however, add one question (KQ7) focusing on children under age 2; children in this age group are not definitively diagnosable, but may be at risk either because they have a sibling with ASD, or they may be exhibiting signs suggestive of a possible ASD diagnosis. Thus, studies of children ages 0 -2 were included for KQ7 only.

We accepted any study designs except individual case reports, and our approach to categorizing study designs is presented in Appendix F. Our interest was in identifying the effectiveness of interventions that target core and commonly associated symptoms of ASD, compared with other intervention or no interventions. We note that if a research study used a comparison group that did not contribute to an estimate of the contrast of interest in our review, we included the one arm of the study that was relevant. For example, an intervention study in which the intervention group is children with ASD and the comparison group is a group of children with Down Syndrome would not provide an estimate of the effect of the intervention for children with ASD. Rather than exclude this study, we include the group of children with ASD as a case series.

As the team lacked translators for potentially relevant non-English studies, we excluded studies that were not published in English. In addition, we excluded studies that:

- did not report information pertinent to the key questions
- included fewer than ten total participants for studies of behavioral, educational, allied health, or CAM interventions or fewer than 30 total participants for medical studies;
- were published prior to the year 2000 (the revision of the Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition (DSM-IV) and widespread implementation of gold standard assessment tools including the Autism Diagnostic Observation System and the Autism Diagnostic Interview – Revised)
- were not original research
- did not present aggregated results (i.e. included data for individual participants only) or presented only graphical data.

We used the following *a priori* taxonomy (Table 7) to group studies into intervention categories.

Table 7. Categorization of interventions

Intervention category	Interventions included:
Behavioral	• Applied behavior analysis (ABA) • Early intensive behavioral and developmental approaches • Parent training • Social skills approaches • Play-based/Interaction-based approaches • Cognitive behavioral therapy (CBT) • Neurofeedback

Table 7. Categorization of interventions (continued)

Intervention category	Interventions included:
Educational	• Treatment and Education of Autistic and Related Communication-handicapped Children (TEACCH) • Special education and classroom-based instruction
Medical	• Pharmaceutical agents • Dietary supplements • Hyperbaric oxygen • Chelating agents • Therapeutic diets • Gastrointestinal therapy (probiotics, digestive enzymes) • Immunotherapy • Antifungals and antibiotics
Allied health	• Speech and language therapy • Sensory and auditory integration approaches • Music therapy • Occupational and physical therapy • Movement therapy • Assistive devices • Adaptive behavior-focused approaches
Complementary and Alternative Medicine (CAM)	• Body manipulation approaches • Acupuncture • Aromatherapy • Chinese medicine • Homeopathy • Naturopathy • Nerve stimulation

As has been previously noted, there is often substantial overlap between ASD intervention categories, and it is difficult to cleanly identify the category into which an intervention should be placed.[131] Where there was uncertainty, we discussed placement of studies as a team. Not all interventions categorized *a priori* were found in the included literature.

We broadly defined medical and related interventions as those that included the administration of external substances to the body in order to treat symptoms of ASD; medical interventions represented in the literature included in this review comprised prescription medications, supplements and enzymes, diet therapies, and treatments such as hyperbaric oxygen. Allied health interventions included therapies typically provided by occupational and physical therapists, including auditory and sensory integration, music therapy and language therapies. We defined behavioral interventions to include early intensive interventions, applied behavior analysis, other general behavioral approaches and therapies such as cognitive behavioral therapy to address concomitant conditions. Educational interventions focus on improving educational and cognitive skills and include programs such as TEACCH.

Literature Search and Retrieval Process

Databases: We employed search strategies provided in Appendix A to retrieve research on the treatment of autism spectrum disorders, including Asperger syndrome and pervasive

developmental disorder, not-otherwise-specified. Our primary literature search employed three databases: MEDLINE® via the PubMed interface, PsycINFO (psychology and psychiatry literature), and ERIC (educational literature), searched from 1980 to the present. We also hand-searched the reference lists of all included articles to identify additional studies for review.

Search terms: Controlled vocabulary terms served as the foundation of our search in each database, complemented by additional keyword phrases to represent ASD in the clinical and educational literature. We also employed indexing terms when possible within each of the databases to exclude undesired publication types (e.g. reviews, case reports, news), items from non-peer-reviewed journals, and items published in languages other than English.

Our searches were executed between May 2009 and January 2010. Appendix A provides our search terms and the yield from each database. After eliminating duplication from the retrieval of the three databases, we had a pool of 3,934 citations for review.

Article selection process. Once we identified articles through the electronic database searches, review articles, and bibliographies, we examined abstracts of articles to determine whether studies met our criteria, including the cutoff date of the year 2000. Two reviewers separately evaluated each abstract for inclusion or exclusion, using an Abstract Review Form (Appendix B). If one reviewer concluded that the article could be eligible for the review based on the abstract, we retained it. The group included 3 expert clinicians (WS, ZW, JV), and two senior health services researchers (MM, RJ). Two reviewers assessed the full text of each included article using a standardized form (Appendix B); disagreements between reviewers were resolved by a third-party adjudicator.

Literature Synthesis

Development of Evidence Tables and Data Abstraction Process

The staff members and clinical experts who conducted this review jointly developed the evidence tables, which were used to abstract data from the studies. We designed the tables to provide sufficient information to enable readers to understand the studies, including issues of study design, descriptions of the study populations (for applicability), description of the intervention, appropriateness of comparison groups, and baseline and outcome data on constructs of interest. We gave particular emphasis to essential information related to our KQs, which were about assessing treatment effectiveness.

The team abstracted several articles into evidence tables and then reconvened as a group to discuss the utility of the table design. We repeated this process through several iterations until we decided that the tables included the appropriate categories for gathering the information contained in the articles. All team members shared the task of initially entering information into the evidence tables. Another member of the team also reviewed the articles and edited all initial table entries for accuracy, completeness, and consistency. The full research team met regularly during the article abstraction period and discussed global issues related to the data abstraction process. In addition to outcomes related to treatment effectiveness, we abstracted all data available on harms. Harms encompass the full range of specific negative effects, including the narrower definition of adverse events.

The final evidence tables are presented in their entirety in Appendix C. Studies are presented in the evidence tables chronologically and alphabetically by the last name of the first author within each year. When possible to identify, analyses resulting from the same study were grouped into a single evidence table. A list of abbreviations and acronyms used in the tables

appears at the end of this report.

Several reporting conventions for describing studies in evidence tables were adopted that warrant explanation, namely those related to practice setting, intervention setting, and assessments. We developed a brief taxonomy of the most common practice settings to reflect where the research was conducted. Practice settings include:

- Academic (comprises academic medical centers and universities)
- Community
- Specialty treatment centers
- Residential centers
- Private practice
- Other (including pharmaceutical companies)

We developed a similar listing for intervention settings to reflect where the intervention was implemented, including home, school, clinic, and residential center. We considered the default setting for drug studies to be the clinic (even if medication was provided by caregivers in the home). Behavioral interventions involving the clinician in both the home and clinic were coded as occurring in both settings.

We captured data on the conduct of assessments in order to inform the evaluation of quality of study conduct and to address questions of applicability of the intervention outcomes data to different populations of children with ASD; data reported include the assessment conducted (e.g. ADOS-R), the context and administrator of the assessment (e.g. administered by study psychologist in the clinic), and the timing (pre-intervention and at the six and eight week study visit, etc.).

Assessing Methodological Quality of Individual Studies

We developed our approach to assessing the quality of individual articles based on our prior experience with conducting systematic reviews, and a focus on evaluating issues of internal and external validity. The individual quality components are described here. Individual quality scores for each study are reported in Appendix H.

In some instances, it was appropriate to apply specific questions only to one body of literature (e.g. to medical literature) and we note those cases where appropriate. Each domain described below was given points based on the number of pluses earned and those points were totaled and weighted as described in the score algorithm below.

Study design:

Studies should use a comparison group in order to make causal inferences. The selected comparison group should be appropriately counterfactual to the intervention group either through good randomization or other approaches. The comparison group should accurately represent the characteristics of the intervention group in the absence of the intervention. Specifically, factors that are likely to be associated with the intervention selected and with outcomes observed should be evenly distributed between groups, if possible. These factors may include, for example, age, IQ, or ASD severity. Four questions were used to assess the strength of the study design:

1. Did the study employ a group design (have a comparison group)?
2. Were the groups randomly assigned?
3. If no, was there an appropriate comparison group?
4. If yes, was randomization done correctly?

Scoring: We expected studies to use a group design to get one point for this domain (+). Those that also received an affirmative response for either question 3 or 4 were given an additional point (++).

Diagnostic approach:

Clearly defined diagnostic techniques are essential for understanding the generalizability of study findings. In particular, it is important to know that the participants were diagnosed with autism using a validated tool. We developed the hierarchy of diagnostic approaches below to capture the method used; table 8 includes more information about each approach.

1. Was a valid diagnostic approach for ASD used within the study, or were referred participants diagnosed using a valid approach?

A. A clinical diagnosis based on the DSM-IV, in addition to the ADI-R and ADOS assessments.

B. A clinical diagnosis based on the DSM-IV, in addition to either the ADI-R or ADOS assessment.

C. A combination of a DSM-IV clinical diagnosis with one other assessment tool from Table 8; or the ADOS assessment in combination with one other assessment tool from Table 8.

D. Either a clinical DSM-IV-based diagnosis alone or the ADOS assessment alone.

E. Neither a clinical DSM-IV-based diagnosis nor the ADOS assessment

Scoring: We classified diagnostic approaches A and B as gold standard (++), C and D as adequate (+) and E as unacceptable (-).

Table 8. Overview of diagnostic tools used in quality scoring hierarchy

Diagnostic instrument	Overview
Autism Diagnostic Observation Schedule (ADOS)	Standardized, semi-structured observation-based review of social interaction, play, and communication for children and adults with suspected ASD; consists of 4 modules appropriate for various language and developmental levels (non-verbal to verbally fluent) and administered directly to the individual by an examiner. Modules provide social/communication situations/activities designed to engage individuals and elicit behaviors of interest. Does not currently provide scores related to restricted/repetitive behaviors so should be supplemented with additional diagnostic information.
Screening Tool for Autism in Two Year Olds (STAT)	Play and observation-based screening instrument designed to differentiate children with autism from children with other developmental disorders once abnormal development has been indicated with an initial screening tool such as the M-CHAT; designed to be used with children between the ages of 24 to 35 months via a play-like interaction between the examiner and child; assesses behaviors related to imitation, play, communication/interaction, and joint attention.
Autism Diagnostic Interview-Revised (ADI-R)	Standardized, semi-structured clinical review administered by clinicians to caregivers of children or adults with suspected ASD; focuses on behaviors in the domains/areas of social interaction, communication and language, and repetitive, restricted, and stereotyped behavior and interests. Scoring is based on the clinician's judgment related to the caregiver's responses regarding a subject's behavior; higher scores indicate problematic behavior in a given domain, and scores align with diagnostic criteria as outlined in the DSM-IV.
Clinical interview based on Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)	DSM-IV articulates criteria for diagnosis of ASD comprising impairments in the areas of social interaction; communication; restricted, repetitive, and stereotyped patterns of behavior, interests and activities; and delays in social interaction/communication and symbolic or imaginative play. Clinical judgment of autistic symptomatology based on DSM-IV criteria is considered the gold standard of ASD diagnosis.

Table 8. Overview of diagnostic tools used in quality scoring hierarchy (continued)

Diagnostic instrument	Overview
Childhood Autism Rating Scale (CARS)	Behavioral observation- or caregiver-report- based scale addressing over 10 domains typically affected in autism (e.g. socialization, communication, emotional responsivity) rated by the examiner on a 1 (age appropriate behavior) to 4 (severely abnormal behavior) scale. Total scores under 30 do not indicate autism, scores of 30-36 reflect mild to moderate autism, and scores between 37 and 60 indicate severe autism; intended to be used in concert with other instruments to diagnose ASD.
Modified Checklist for Autism in Toddlers (M-CHAT)	Caregiver-reported checklist designed to screen for autism in children between the ages of 16 and 30 months; includes items related to joint attention, social interests, imitation, responding to name.
Social Communication Questionnaire (SCQ)	Caregiver-reported screening questionnaire designed to evaluate communication and social skills/functioning in children with suspected ASD and determine the need for complete diagnostic evaluation; includes questions related to language and social behaviors--based on the ADI-R.
Social Responsiveness Scale (SRS)	Caregiver- or teacher- reported screening scale designed for use in children between the ages of 4 and 18; generates scores related to cognitive, expressive, receptive, and motivational aspects of social behavior in addition to autistic preoccupations; can be used to distinguish ASD from other childhood psychiatric disorders.
Autism Spectrum Screening Questionnaire (ASSQ)	Screening instrument designed to be used with children between the ages of 7 to 16 years; can be completed by teachers or caregivers. Addresses the domains of social interaction, communication, and restricted/repetitive behaviors considered to reflect behavioral characteristics of children with ASD, particularly higher functioning individuals.
Childhood Autism Spectrum Test (CAST)	Caregiver -reported screening tool designed for use in children between the ages of 4 and 11, used particularly with higher functioning children; includes questions related to social skills, language, and repetitive behaviors and interests.

Participant ascertainment:

The means by which participants enter the study cohort and are included in the analysis should be very clear, both so that the reader can gauge the applicability of the research to other populations, and to identify selection and attrition bias. In this literature, it is particularly important to understand the population in terms of characteristics commonly associated with outcomes such as IQ, language and cognitive ability. We used four questions to assess participant ascertainment, including who was included in the analysis:

1. Was the sample clearly characterized (e.g., information provided to characterize participants in terms of impairments associated with their ASD, such as cognitive or developmental level)?
2. Were inclusion and exclusion criteria clearly stated?
3. Do the authors report attrition?
4. Were characteristics of the drop-out group evaluated for differences with the participant group as a whole?

Scoring: Studies minimally had to have an affirmative answer for questions 1 and 2 of this domain to be adequate (+). Affirmative responses on 3 or 4 earned the study an additional point (++).

Intervention characteristics:

Sufficient detail should be provided on the intervention so that the reader can fully understand the treatment and so that the research is potentially reproducible. This includes provided information on dosage, formulation, timing, duration, intensity and other qualities of the intervention. Furthermore, for behavioral treatments there should be some assurance that the treatment providers stayed true to the treatment process (fidelity) and for medical treatment,

there should be some assurance that participants adhered to their medication or that adherence was accounted for. Furthermore, because other treatments occurring simultaneously with the treatment under study could have substantial impact on outcomes, it is important that authors gather data on treatments being obtained by their participants outside of the study. We used three questions to obtain quality information in this domain:

1. Was the intervention fully described?
2. Was treatment fidelity monitored in a systematic way? (for non-medical interventions)
3. Did the authors measure and report adherence to the intended treatment process? (for medical interventions)
4. Did the authors report differences in or hold steady all concomitant interventions?

Scoring: Authors needed to fully describe the intervention for the study to be awarded one point (+), and studies were given an additional point (++) if they also reported on or hold steady concomitant interventions and monitored either fidelity or adherence.

Outcomes measurement:

The ASD literature reviewed for this report included more than 100 outcome measures. To understand the meaning of the results at hand, readers need to be confident that the measure validly assessed the intended target behavior or symptom. It is also important that authors specify *a priori* what their outcome of primary interest is as the rest of the study, including sample size, should derive from the intent to measure this outcome. Finally, in measuring outcomes, the individual responsible for coding or measuring effect should be blinded to what intervention the participant received. We attempted to use three questions for this domain, but were forced to drop one regarding whether primary outcomes were pre-determined as it is uniformly impossible to tell whether authors had a "called shot" or *a priori* primary outcome, or whether they established these post hoc and wrote the paper as if a given outcome was the intended primary one. We were left with two questions:

1. Did outcome measures demonstrate adequate reliability and validity (including inter-observer reliability for behavior observation coding)?
2. Were outcomes coded and assessed by individuals blinded to the intervention status of the participants?

Scoring: To meet the requirement for an adequate score on outcomes measurement (+), studies were required to have an affirmative answer to both questions.

Statistical analysis:

For assessing the appropriateness of the statistical analysis, we considered the following methodologic issues:

1. For RCTs, was there an intent-to treat analysis?
2. For negative studies, was a power calculation provided?
3. For observational studies, were potential confounders and effect measure modifiers captured?
4. For observational studies, were potential confounders and effect measure modifiers handled appropriately?
5. Was the candidate variable selection discussed/noted?
6. Was the model-building approach described?

7. Were any variables unrelated to the studied variables that could have altered the outcome handled appropriately?
8. Were any variables not under study that affected the causal factors handled appropriately? Was the candidate variable selection discussed/noted?

Scoring: Studies needed a yes or NA on each of the analysis questions to receive a point (+) for analysis.

Scores were calculated first by domain and then summed and weighted as described in Table 9 to determine overall study quality (internal validity).

Table 9. Quality scoring algorithm

Definition and Scoring Algorithm	Rating
Score Algorithm for Internal Validity Quality Rating	
• 8/10 points, including a ++ on study design and ++ on diagnostic approach	Good internal validity
• 6/10 points, including at least a + on intervention	Fair internal validity
• 5/10 points or less	Poor internal validity

Applicability:

Finally, it is important to consider the ability of the outcomes observed to apply both to other populations and to other settings (especially for those therapies that take place within a clinical setting but are hoped to change behavior overall). Our assessment of applicability took place in three steps: 1) overview of PICOS in available literature for each intervention category and presented in Appendix I; 2) review of potential modifiers of effect of treatment to identify subgroups for which treatments may be effective and; 3) three questions on external validity on each study during quality assessment:

1. Were outcomes measured in at least one context outside of the treatment setting?
2. Were outcomes measured in natural environments to assess generalization? Considerations: Was an assessment conducted in the home, school, or community settings (i.e. a setting a child typically goes to in an ordinary week)?
3. Were follow-up measures of outcome conducted to assess maintenance of skills at least 3 months after the end of treatment?

Strength of Available Evidence

Strength of evidence is typically assigned to reviews of treatments after assessing four domains: risk of bias, consistency, directness and precision.[132] We assessed available evidence for each key question for each of these four domains; we then combined the domains to develop the strength of evidence for each key question.

We graded the body of literature for each key question and present those ratings as part of the discussion in Chapter 4. The possible grades were:

I. High: High confidence that the evidence reflects the true effect. Further research is unlikely to change estimates. At a minimum, a body of evidence needed at least 2 papers that were classified as good on our quality rating for a high SOE.

II. 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.

III. 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.

IV. Insufficient: Evidence is either unavailable or does not permit a conclusion.

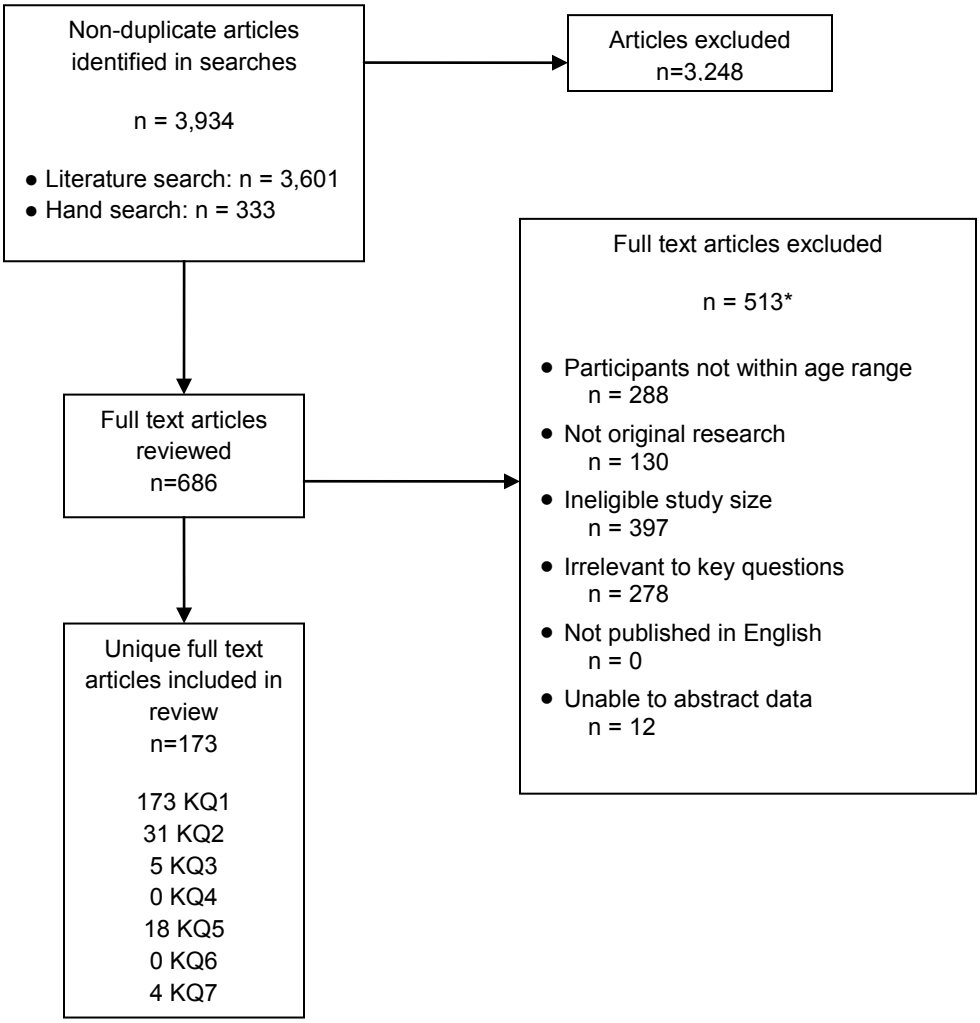
Chapter 3. Results

Chapter 3 presents the results of our systematic review. Each category of intervention includes first an overview of the content of the literature as a whole, including the range of study designs used, outcomes assessed and participants included. The summary of the literature provides further discussion and analysis, focusing primarily on those studies that received either a good or fair quality rating. Overview tables document the interventions included, availability of literature by study design, diagnostic approaches, timing of final outcome assessments, geographic location of study populations, and final numbers of participants with ASD for each intervention section (Tables 10, 15, 17, 24, 26). Studies that received a good or fair quality rating, and used a comparison group design (RCT, controlled trial or cohort study) also are described in more detailed summary tables in the relevant section of text. For information on studies not included in the summary tables, please see the evidence tables in Appendix C.

Article Selection

Of the entire group of 3,934 articles, 686 required full text review. For the full article review, two reviewers read each article and decided whether it met our inclusion criteria, using a Full Text Inclusion/Exclusion form. Reasons for article exclusion are listed in Appendix D.

Figure 2. Disposition of articles retrieved in literature searches



*The total number of articles in the exclusion categories exceeds the number of articles excluded because most of the articles fit into multiple exclusion categories.

Alternate text: This figure depicts the disposition of articles retrieved for the report. Of 3,934 articles located, 3,248 were excluded at the abstract review phase, leaving 686 articles for which the full text was reviewed. Of these, we included 173 articles in the review and excluded 513 .

KQ1. Effects of Treatment on Core and Commonly Associated Symptoms in Children with ASD: Behavioral Interventions

A wide range of interventions is typically classified as behavioral. For this review, we included studies of early intensive behavioral and developmental interventions; social skills interventions; focal play-based /interaction-based interventions; behavioral interventions focused

on associated behaviors; and a small group of other behavioral interventions assessing other interventions in core/associated areas (e.g., sleep workshops) (Table 10).

Table 10. Overview of behavioral studies

	RCTs	NRCTs	Prospective cohort studies	Retrospective cohort studies	Prospective case series	Retrospective case series	Total Literature
	(n=27)	(n=7)	(n=6)	(n=3)	(n=24)	(n=8)	(n=75)
Intervention							
Early intensive behavioral/ developmental	5	5	5	2	11	6	34
Social skills	7	0	0	1	7	0	15
Play-/interaction-based	7	0	0	0	3	2	12
Associated behaviors	7	1	1	0	2	0	11
Other	1	1	0	0	1	0	3
Diagnostic approach							
Clinical DSM-IV dx +ADI-R and/or ADOS	5	0	2	0	9	0	16
Combination approaches*	13	2	3	0	10	4	32
No DSM-IV or ADOS dx / unspecified	9	5	1	3	5	4	27
Last outcome assessment							
<1 month	3	0	0	0	2	0	5
>1 to ≤3 months	7	2	1	0	5	0	15
>3 to ≤6 months	9	0	0	0	1	1	11
>6 to ≤12 months	3	2	2	0	10	0	17
>12 months	4	2	3	3	5	5	22
Unknown/not reported	1	1	0	0	1	2	5
Study population							
U.S.	16	3	2	1	16	4	42
Europe	4	4	1	2	3	2	16
Asia	0	0	0	0	0	0	0
Other	7	0	3	0	5	2	17
Total N participants	1,081	215	254	157	829	529	3,065

ADI-R=Autism Diagnostic Interview-Revised; ADOS=Autism Diagnostic Observation Schedule; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition; dx=diagnosis; NRCT=non randomized controlled trial; RCT=randomized controlled trial

*Clinical DSM-IV dx +other diagnostic tool OR ADOS + other diagnostic tool OR only clinical DSM-IV dx OR only ADOS.

Early Intensive Behavioral and Developmental Interventions

Early intensive behavioral and developmental interventions include interventions based on:

- applied behavior analysis approaches (i.e., EIBI/ABA approaches including UCLA/Lovaas method and variants),
- family-based training (i.e., GIFT training, Pivotal Response Training, Hanen More Than Words, and social communication training), and
- naturalistic/developmental principles (i.e., Early Start Denver Model)

We adopted a similar approach to the operationalization of this category as Rogers and Vismara[46] in their review of "comprehensive" evidence-based treatments for early ASD. We included developmental and behavioral interventions that targeted primary and often several core or associated areas of ASD deficit (i.e., language, social, cognition, adaptive) with specified behavioral, developmental, or combined intervention approaches. Studies focusing on one specific targeted outcome area (e.g., social skills, maladaptive behavior, mental health comorbidities, play) and intervention studies delivered primarily via educational protocols or allied health providers are reviewed in other sections of this report.

Content of the literature. We identified 38 papers [4-8, 18-32, 133-150] from 34 unique study populations that addressed early intensive behavioral and developmental interventions. A majority of the reviewed literature examined specific EIBI approaches, with most using variants of the UCLA/Lovaas model or other ABA approaches.[4, 18-28, 30-32, 133-136, 138, 141, 143, 146, 148, 150] Additionally, two papers investigated the Early Start Denver Model (ESDM) of blended developmental-behavioral intervention,[29, 149] five papers evaluated various parent trainings aimed at social communication skills,[5-6, 8, 145, 147] two papers examined Pivotal Response Training (PRT),[7, 140] two studies examined and described eclectic approaches[137, 142, 144] and one study examined a parent training blending PRT and other behavioral approaches (GIFT training).[139] We have divided all papers into two primary categories: ABA Methodologies and Parent Training Approaches. Four studies[8, 29, 145, 149] examined approaches applicable to young children at risk for diagnosis of ASD; these studies examined the Early Denver Start Model, an approach blending ABA techniques with developmental and relational approaches; the Hanen More than Words program, focused on facilitating communication; and the Early Social Interaction (ESI) Project, which emphasizes a parent-implemented individualized curriculum in a natural environment. These studies are discussed in detail in the KQ7 section of the report focused on therapies for young children at risk for diagnosis of ASD. Table 10 summarizes additional study details.

Summary of the literature.. Of the 38 papers in this section[4-8, 18-25, 27-30, 32, 133-149] comprising 34 unique studies; one was good quality, 12 were fair, and 21 were poor. Outcomes of RCT and cohort studies rated good or fair in quality are summarized in Table 11.

Studies of ABA-based approaches. Of the two RCTs on the UCLA/Lovaas treatment that met inclusion criteria, one[18] was given a good quality score and the other was fair.[4] Both RCTs of the UCLA/Lovaas approach compared a clinic-based method to a parent program, and targeted children at about 36 months of age. The earlier study [4] was the first attempted replication of Lovaas' manualized intervention to use random assignment, a standardized assessment battery, and explicit accounting of intervention hours. It included 28 children with a mean IQ of 51 randomized to either an intensive treatment group (UCLA/Lovaas model with an average of 25 hours per week of individual treatment per year with reduced intervention over next 1 to2 years)

or a parent-training group (3-9 months of parent training). Gains in IQ were much more tempered than that of Lovaas' original non-controlled study.[48] Children in the treatment group gained a mean of 15 IQ points in comparison to the relatively stable cognitive functioning of the control group, and average IQ at outcome for the treatment group remained in the impaired range. Most of the children who demonstrated large gains in IQ were within the subgroup diagnosed with PDD-NOS, whereas children with classically defined Autistic Disorder demonstrated modest improvements. Only two children in the experimental group (vs. one in the control) achieved the "best outcome" or "recovery" status previously defined by Lovaas. No post-treatment group differences were seen in adaptive behavior or challenging behavior. Thus, while replicating improvements in cognitive ability for some children with ASD within the repeated discrete trial teaching inherent to UCLA/Lovaas method, the study in fact demonstrated a less dramatic impact for the population of children for whom this approach is often recommended (i.e., children with classically defined Autistic Disorder) compared with what was previously reported.

In the second RCT of the UCLA/Lovaas protocol, 23 children with a mean age of 35 to 37 months were randomized to two years in a clinic (n=13) or a parent directed program (n=10). In this study, the UCLA/Lovaas approach was modified to include components such as PECS language system and an emphasis on motivators and social play. Rather than measuring the impact of the UCLA/Lovaas approach per se, the authors intended to assess the effect of varying intensity levels. However, both clinic and parent groups received over 30 hours of intervention weekly and no group differences related to IQ, language, adaptive behavior, or other outcomes were seen. Children in both groups demonstrated substantial gains in a number of areas. Pretreatment imitation, early response to imitation, language (composite index), social responsiveness (composite index), and higher IQ at baseline predicted higher IQ at follow-up, as did initial IQ increase.

The study ultimately did not demonstrate beneficial effects of an expertly organized and delivered Lovaas guided ABA intervention over that of a parent-delivered and organized treatment based on the same principles, when implemented for comparable amounts of time. However, the results do provide further evidence of response to treatments anchored in the UCLA/Lovaas method, with some children demonstrating rapid acquisitions of new skills and change in IQ.

Seven prospective cohort studies and non-randomized trials were available on the ABA methodologies, but none made the same comparisons either in terms of interventions or populations. Hayward and colleagues[25-26] examined the progress of children receiving either intensive clinic directed UCLA/ABA intervention (n=23; mean age=36 months; 37 hours of weekly treatment) or an intensive parent-managed model (n=23; mean=34 months; 34 hours of weekly treatment) over the course of one year in the UK. Group assignment was based solely on geographic location. At follow up, both groups had improved significantly in IQ (16 point gain), non-verbal IQ (10 points), language use/understanding, and most areas of adaptive functioning with the exception of daily living skills but there were no differences between the groups.

Two studies compared intensive center-based treatment to community care. Howard and colleagues (2009)[27] studied preschool-aged children receiving intensive behavior analytic treatment (n=29, 1:1 for 25-40 hours per week), intensive "eclectic" intervention (n =16, higher teacher-student ratio intervention for approximately 30 hours per week), and children receiving general intervention in public early intervention programs (combined methods, small groups, 15

hours per week). Groups were assigned via educational placement teams that specifically included parent input. Controlling for age at diagnosis and combined parental education, children in the intensive behavior analytic group demonstrated significant improvements in all areas assessed at follow-up, including an average IQ of 89 (41-point improvement over baseline) and a 24-point difference from the combined mean of the other intervention groups. Significant differences between the eclectic and generic intervention groups were not present at follow-up. Findings do suggest substantial improvement via an intensive ABA-based approach for young children with autism; however, important differences in group assignment at baseline, difficulties with systematic measurement overtime, the lack of reported treatment fidelity or adherence characteristics, and the small number of children in the comparison group limits the interpretation of these findings.

These results were echoed in another study[32] of 42 children in which those receiving the Lovaas program had significantly higher IQs (mean=87, gain of 25; mean=73, 14 points) and adaptive behavior skills at outcome, compared with children in undefined community care. Receptive language improvements were observed but were not significant, and expressive language skills and socialization scores on the Vineland were not different for the two groups at year 3 outcome. Twelve of the 21 children in the behavioral group had IQs >85 compared with 7 of 21 in the eclectic treatment group at outcome. Likewise, more children in the Lovaas group were in typical schools subsequent to intervention (17 vs. 1); although this specific outcome is potentially attributable to a wide variety of factors including some that might correlate with differences in SES and family constellation evident between the groups.

One study[146] of two centers compared an eclectic approach (including DIR, TEACCH and ABA) to ABA-based intervention alone. Hours spent in the intervention were consistent at 8 hours per day, and children were assessed over one year. Significant group differences were noted in terms of both language/communication and reciprocal social interaction domain scores on the ADOS, with both groups showing decreases in symptom tallies but more substantial decreases with the ABA group. No significant differences in IQ change were reported. While demonstrating impact on certain ADOS symptom scores, these changes were small, and more recent approaches suggest that calculating an ASD severity score may be a more valuable and sensitive way for measuring changes in ASD symptoms in response to intervention.[151] In a subsequent study on diagnostic stability[21] with unclear sample overlap, most children receiving intervention continued to display scores in the ASD range on the ADOS (n=53) although some children's classification did shift.

Finally, one study tried to assess the role of intensity of the intervention on outcomes. Reed and colleagues[133] studied the effectiveness of varying intensity of home-based ABA programs offering primarily 1 to 1 teaching. High-intensity interventions (n=14) were defined as those provided for an average of 30 hours per week. Low intensity interventions (n=13) were provided for on average 13 hours per week. Assignment to the particular intervention modality was based on geographic location, and children in the high intensity group had higher ability and cognitive scores and lower autism severity scores at baseline. Children were assessed 9-10 months after initiation of intervention. Children receiving high-intensity intervention demonstrated statistically significant improvements in intellectual and educational functioning from baseline. Children receiving low-intensity intervention demonstrated statistically significant changes in educational functioning and non-significant improvement in cognitive functioning. The only significant difference between the groups was in improved educational functioning in associated

with high intensity interventions. No group differences were found in autism severity, cognitive functioning, or adaptive behavior functioning.

Three additional cohort studies[22, 134, 148] of ABA-based methodologies provided inconsistent data on the benefit of behavioral approaches, but all three had substantial risk of bias and were thereby rated as poor quality in this report. Nonetheless, they suggest that behavioral approaches may have promise for bolstering aspects of cognitive, language and adaptive functioning in preschool children with ASD.

Case series of early intervention approaches[19, 138, 141-142, 145, 150] had mixed results, likely in part due to the substantial heterogeneity of interventions examined even within individual studies, little or no control of concomitant interventions, and poor fidelity to any given approach. Outcomes in these studies were more likely to be parent-reported and not based on validated tools.

Several chart reviews and other retrospective analyses have been used to understand treatment patterns and effects.[20, 28, 136-137, 143-144] Interpretation of findings is most appropriately confined to noting that some children receiving intervention have displayed improvements during intervention in cognitive, adaptive, and autism-specific impairments, that characteristics of starting treatment and baseline abilities are correlated with improvement in some instances, and heterogeneity in terms of improvement is quite common. We do not describe these studies here, but details on all of them are available in the evidence tables in Appendix C. One chart review,[143] however, does provide some evidence for the feasibility of providing intensive behavioral interventions on a larger scale as it reviews data on 322 children served in a large service catchment area. Given the methodological limits including lack of a clearly defined intervention characteristics/protocol, lack of a comparison group, retrospective collection, and lack of key measures for certain children at certain times, the intervention results are limited. However, the study suggests the feasibility of providing intensive intervention to a large group of children.

*Parent training approaches***.** Of the 7 studies[5-8, 139-140, 147] on parent training, 4[5-8] included comparison groups and had fair[5-6, 8] or poor[7] quality. Two were RCTs,[5-6] but methods used and outcomes assessed were different. Drew et al.[6] compared the effects of a home-based, parent-delivered intervention aimed at improving social communication and managing challenging behavior for 12 children with ASD with a community-based control intervention group of 12 children (mean age 23 months at start of treatment). The social communication intervention components included developing joint attention, teaching routines, and play activities promoting interaction. The challenging behavior intervention components focused on reinforcement techniques, including reinforcing alternative behaviors. Training was conducted at home visits (3 hours weekly for 6 weeks), with parents asked to engage in intervention activities for a half to1 hour daily. One year after treatment initiation, the parent training group reported that their children used more words than the community group. There were no group differences on non-verbal IQ (NVIQ), autism symptom severity, or words/gestures observed during follow-up assessment. Unexpectedly, the treatment group lost IQ points during the study; whereas the control group demonstrated relatively stable cognitive abilities. This finding is further confounded by a significantly higher IQ present in the treatment group at initiation of the study.

Aldred et al.[5] compared a parent-based intervention focused on advancing social communication skills within interactions (n = 14, median age 51 months) to treatment as usual (n =14, median age 48 months). Parents participated in initial workshops, monthly intervention

sessions where videotaped interactions were reviewed, and 6 months of maintenance visits (approximately once every 2 months). Twelve months after baseline, blinded evaluations showed improvements on ADOS scores, with substantial improvement within the social domain, increased expressive vocabulary, as well as improved communication-related behaviors coded during interactions. Language gains were most prominent in younger, lower-functioning children. A lack of standardized measures of developmental performance, including baseline cognitive skills, as well as challenges in understanding and defining "treatment as usual" limit interpretation of the findings.

Stahmer and Gist[7] examined the effects of an explicit parent education support group with a parent education program focusing on Pivotal Response Training (PRT), a treatment program designed to enhance core skill areas in autism using naturalistic interactions. Parents met with the intervention provider weekly for 12 weeks and were taught techniques for presenting clear instructions, following and supplementing child choice, and providing direct/naturalistic reinforcement. Involvement in the 12-week intervention was successful in changing parenting techniques and perceived language gain. However, the lack of randomization, wide variation in children served, the lack of objectively assessed changes in child behavior, and the small number of participating limit the reported results.

Finally, one prospective cohort study focused on parent training in the Hanen More than Words program[8] and included preschool-aged children suspected of ASD (mean age, intervention group= 38 months, mean age, control group= 34 months); this study is discussed in detail in the KQ7 section of the report.

Table 11. Outcomes of early-developmentally based behavioral interventions

Author, Year Groups Study quality	Age,mean (months) ±SD Diagnostic category, N (%) Groups, N enrollment/N final	Key outcomes
ABA-Based Approaches		
Hayward et al.[25-26] 2009, UK **G1:** Intensive clinic-based tx **G2:** Intensive parent-managed tx Quality: Fair	**G1:** 35.7 ± 6.2 **G2:** 34.4 ± 5.7 NR **G1:** 23/20 **G2:** 21/19	• No significant group differences at follow-up • Improvements in both groups in IQ, non-verbal IQ, language use/understanding, and most areas of adaptive functioning, with the exception of daily living skills

Table 11. Outcomes of early-developmentally based behavioral interventions (continued)

Author, Year Groups Study quality	Age,mean (months) ±SD Diagnostic category, N (%) Groups, N enrollment/N final	Key outcomes
ABA-Based Approaches		
Reed et al.[133] 2007, UK **G1:** High-intensity intervention **G1a:** High-intensity with focus on Lovaas techniques **G1b:** High-intensity with focus on verbal behavior **G1c:** High-intensity with focus on CABAS methods **G2:** Low-intensity intervention in home-based direct teaching sessions Quality: Fair	**G1:** 42.9 (14.8) **G1a:** 47.5 (13.5) **G1b:** 38.0 (9.9) **G1c:** 44.2 (20.5) **G2**: 40.8 (5.6) NR **G1:** 14/14 **G1a:** 4/4 **G1b:** 5/5 **G1c:** 5/5 **G2:** 13/13	• Children in the high intensity group had higher ability and cognitive scores and lower autism severity scores at baseline • G1: statistically significant improvements in intellectual and educational functioning from baseline • G2: statistically significant changes in educational functioning • Group comparisons showed educational functioning improvements for G1 compared to G2 • No group differences were found in autism severity, cognitive functioning, or adaptive behavior functioning
Zachor et al.[146] 2007, Israel **G1:** ABA-based intervention **G2:** Eclectic approach Quality: Fair	**G1:** 25.1 ± 3.8 **G2:** 26.3 ± 4.6 Autism: 68 (100) **G1:** 53/53 **G2:** 15/15	• No baseline differences in terms of family characteristics or child functioning • Significant time by intervention effects noted in ADOS language/communication and reciprocal social interaction domain scores--more substantial decreases in the ABA group • Following intervention both groups showed improvements in cognitive and verbal scores and adaptive behavior skills
Cohen et al.[32] 2006, US **G1:** EIBI **G2:** Local services Quality: Fair	**G1:** 30.2 ± 5.8 **G2:** 33.2 ± 3.7 Autism : **G1:** 20 (95.2) **G2:** 15 (71.4) PDD-NOS: **G1:** 1 (4.8) **G2:** 6 (28.6) **G1:** 21/21 **G2:** 21/21	• Significantly higher IQs and adaptive behavior skills post-tx in G1 • Receptive language improvements noted at 3 years, but expressive language skills and socialization scores were not different for the two groups • Twelve of 21 in the behavioral group had IQs >85 compared with 7 of 21 in the eclectic tx group

Table 11. Outcomes of early-developmentally based behavioral interventions (continued)

Author, Year Groups Study quality	Age,mean (months) ±SD Diagnostic category, N (%) Groups, N enrollment/N final	Key outcomes
ABA-Based Approaches		
Sallows et al.[18] 2005, US **G1:** UCLA/Lovaas clinic-directed EIBI **G2:** Parent-directed, UCLA/Lovaas intensive tx Quality: Good	Intake: 33-34 Follow-up: 82-83 Autism: 23 (100) **G1:**13/13 **G2:**11/10	• No group differences at follow up • 48% receiving intervention achieved average post-tx scores and placement in regular education classrooms • Improvements in both groups in IQ, adaptive behavior, and ASD symptoms • Rapid learners showed significant increases in all areas of assessment • Moderate learners showed improvements in PIQ, Expressive Language, Adaptive Behavior
Howard et al.[27] 2005, US **G1:** EIBI **G2:** Intensive eclectic therapy **G3:** Non-intensive eclectic therapy Quality: Fair	At intake: **G1:** 30.86 ± 5.16 **G2:** 37.44 ± 5.68 **G3:** 34.56 ± 6.53 At follow-up: **G1:** 45.66 ± 6.24 **G2:** 50.69 ± 5.64 **G3:** 49.25 ± 6.81 **G1:** Autism: 24 (83) PDD-NOS: 5 (17) **G2:** Autism: 12 (75) PDD-NOS: 4 (25) **G3:** Autism: 9 (56) PDD-NOS: 7 (44) **G1:** 37/29 **G2+G3:** 41/32	• G1: significant improvements in all areas assessed at follow-up, including average IQ of 89 (representing a 41 pt improvement over baseline and a 24 pt improvement over the combined mean of the other intervention groups)
Eikeseth et al.[30-31] 2002, Norway **G1:** EIBI **G2:** Eclectic therapy, Quality: Fair	**G1:** 66.31 ± 11.31 **G2:** 65 ± 10.95 Autism: 25 (100) **G1:** 13/13 **G2:** 12/12	• Analysis of change scores demonstrated more improvement for G1 regarding IQ and language • G2 scores were higher at baseline across most areas of measurement compared with G1

Table 11. Outcomes of early-developmentally based behavioral interventions (continued)

Author, Year Groups Study quality	Age,mean (months) ±SD Diagnostic category, N (%) Groups, N enrollment/N final	Key outcomes
	• ABA-Based Approaches	
Smith et al.[4] 2000, US **G1:** EIBI **G2:** Parent training from Lovaas manual Quality: Fair	Intake: **G1:** 36.07 ± 6.00 **G2:** 35.77 ± 5.77 Follow-up: **G1:** 94.07 ± 13.07 **G2:** 92.23 ± 17.24 Autism: 14(50) PDD-NOS: 14(50) **G1:**15/15 **G2:** 13/13	• G1 gained mean of 15 IQ pts compared with relatively stable cognitive functioning of controls • Significant improvement for G1 in visual-spatial skills and expressive language • IQ scores averaged in impaired range at outcome for G1 and PDD-NOS children appeared to account for majority of change • No post-tx group differences seen for adaptive or challenging behavior
	Parent Training	
Aldred et al.[5] 2004 **G1:** Parent training in social communication intervention plus community intervention **G2:** Community intervention Quality: Fair	**G1:** median 48 mo **G2:** median 51 mo Autism: 28 (100) **G1:** 14 /14 **G2:** 14/14	• G1 showed improvements in ADOS scores, social interaction, expressive language, child communication acts during interaction • No adaptive behavior differences or differences in parenting stress between groups • Language gains particularly prominent in younger, lower functioning children
Drew et al.[6] 2002, UK **G1:** Parent training **G2:** Local/eclectic services Quality: Fair	Intake: **G1:** 21.4 ± 2.7 **G2:** 23.6 ± 3.8 Follow-up: **G1:** 33.5 ± 2.5 **G2:** 36.2 ± 4.5 Autism/PDD-NOS: 24 (100) **G1:** 12/12 **G2:** 12/12	• At 12 mo, G1 had more words and a trend toward understanding more words than G2 • No group differences on NVIQ, autism symptom severity, parental report of stress, or words or gestures produced during follow-up assessment

ABA=applied behavior analysis; ADI=Autism Diagnostic Interview; ADOS=Autism Diagnostic Observation Schedule; ASD=autism spectrum disorders; EIBI=early intensive behavioral intervention; ESDM=Early Start Denver Model; IQ=intelligence quotient; NVIQ=non-verbal intelligence quotient; PDD-NOS=Pervasive Development Disorder-Not Otherwise Specified; PIQ=Performance IQ; RBS=Repetitive Behavior Scale; VABS=Vineland Adaptive Behavior Scale

Social Skills Interventions

The social interventions reviewed in this section focus primarily on children at elementary-school ages and those functioning at higher cognitive/developmental levels. They employ a variety of approaches designed to address three primary dimensions of social competence:

specific behavioral skills (e.g., greetings, initiating game play, joint attention), affective understanding (e.g., recognizing emotions in self and others), and social cognition (e.g., theory of mind, problem-solving, self-regulation).

Content of the literature. We located 15 unique papers addressing social skills interventions. This number includes two sets of papers with possibly overlapping samples evaluating a Skillstreaming intervention[152-153] and a cognitive-behavioral-ecological social skills approach.[154-155] The ages of children studied ranged from 4-16 years old. Twelve studies focused exclusively on higher functioning children or included language and/or cognitive requirements among their eligibility criteria.[152-163] Three studies provided individual treatment to children,[154, 162, 164] three used a combination of individual and small group formats,[155, 163, 165] and nine employed a small group format only.[152-153, 156-161, 166] In addition, five interventions included some form of parent training or involvement as an adjunct to child treatment.[154, 156, 158, 161, 163] For the 14 studies with prospective designs, the total amount of training provided ranged from 6.7 hours to 180 hours. Table 10 summarizes additional details.

Among studies of social skills interventions, seven were fair quality and eight were poor.

Summary of the literature. Three RCTs [156, 158, 163] (Table 12) evaluated social skills interventions targeting high functioning children with ASD using a format that involved training for both children and their parents. The criteria for determining whether a child was high functioning and therefore eligible to participate varied by study, but at a minimum the child had to have a verbal IQ above 60. Different outcome measures were used across the samples, making direct comparisons difficult.

The Children's Friendship Training (CFT)[158] program involves children with and without ASD, and uses didactic instruction on rules of social behavior; modeling, coached behavioral rehearsal, and performance feedback during treatment sessions; rehearsal at home; homework assignments; and coaching by parents during play dates with a peer. Children were randomly assigned to receive CFT either immediately (CFT group) or 12 weeks later (delayed treatment control (DTC) group). Eligibility criteria required that participants were in second- to fifth-grade regular education classrooms (without a shadow), had a verbal IQ >60, were able to switch topics in a conversation, had knowledge of rules required for playing board and school yard games, and scored positively on the High Functioning Autism Spectrum Screening Questionnaire. Treatment was conducted in 60-minute small parallel group sessions for parents and children, and lasted 12 weeks.

Immediately following treatment, the CFT group showed significant improvements in social behavior and social cognition compared with the DTC group. Children in the treatment group also spent less time during the play date engaged in minimally socially interactive activities (such as watching TV) compared with the delayed treatment group ($p<0.001$), but did not spend significantly more time in socially interactive activities (e.g., talking). On the SSRS, parents of children in the CFT group reported that their children demonstrated increased self-control when provoked by others relative to the DTC group ($p<0.05$). Parent- and teacher-reported reductions in social withdrawal on the SSRS showed non-significant changes. Children in the treatment group self-reported decreased loneliness ($p<0.025$) and increased popularity ($p<0.025$) relative to the DTC group. Three months post-treatment significant improvements were maintained in the CFT group on parent reported hosting of play dates, conflict during play dates, time spent in minimally socially interactive activities, assertion, self-control, and social withdrawal compared with the baseline scores. After treatment, findings from the DTC group largely replicated those

of the CFT group.

Relative to CFT, the Social Adjustment Enhancement Curriculum (SAEC) has a more comprehensive curriculum targeting emotion and facial expression recognition; theory of mind, the ability to ascribe mental states to oneself and others to understand and forecast behavior; perspective taking; executive functioning, which allows for planning and abstract thinking; problem solving; and conversation skills. Eighteen boys between 8 and 12 years old met eligibility criteria (diagnosis of high functioning autism, AS, or PDD-NOS; an IQ above 75; and a passing score on a first-order theory of mind task (Smarties false belief task)) and participated in the study.[156] Participants were matched on age and IQ and randomly assigned to an immediate intervention condition or a wait list condition. Parents and children in the treatment condition received the Social Adjustment Enhancement Curriculum at a clinic for 20 weekly 1.5 hour sessions. Children and parents met separately. Child groups of four or five were structured with a high adult-to-child ratio and followed a consistent schedule each week, using a variety of instructional strategies including in vivo teaching, visual templates, games, and role playing.

Immediately following the intervention participants in SAEC had higher facial recognition scores post-treatment ($p<0.05$), while the scores of the participants in the wait list control group declined (although not significantly). There was significantly improved executive function skills (covarying Verbal IQ) post-treatment ($p<0.05$) in the intervention group, while the scores of those in the wait-list control declined. However, when the one child with a PDD-NOS diagnosis was excluded from the treatment group these results were no longer significant. Both the control and SAEC group demonstrated significant improvements on the Faux Pas Stories Task post-treatment ($p<0.001$) but not on the Strange Stories Task. Total social problems reported per time reporting dropped significantly from the first eight weeks of the intervention to the last eight weeks of the intervention ($p<0.05$).

Beaumont and Sofronoff[163] investigated a comprehensive social skills intervention that utilized a computer game as well as child and parent small therapy groups to teach emotion recognition and regulation, problem solving, and social interaction skills. Forty-nine children diagnosed with Asperger disorder between the ages of 7.5 and 11 years old were randomly assigned to the Junior Detective Training Program (JDTP) or a wait list control. Data suggests that this computerized intervention was beneficial for improving knowledge of emotion management strategies and parent-reported social skills, but not emotion recognition, immediately after treatment over a the waitlist control. Some of these results were also replicated when the wait-list group underwent treatment in pre-post analyses. Pre- Post scores were significantly different on the parent-reported measures of social skills for the intervention group immediately, 6 weeks, and 5 months following the intervention, suggesting maintenance of these treatment effects. However this study had substantial risk of bias and was rated as poor quality in this report. Additional details on this and other studies not fully described in this section are available in the evidence tables in Appendix C.

One study attempted to ascertain whether the type of feedback that children received during a social skills intervention affected the outcomes.[152] Skillstreaming[52] is a comprehensive, structured social skills curriculum that employs systematic procedures for teaching specific social behaviors (e.g., listening, sharing, having a conversation, accepting a compliment, responding to teasing), as well as social cognition (using self-control), and affect (e.g., recognizing and expressing feelings, responding to anger). The Skillstreaming curriculum used in the study was adapted to focus on social skills particularly important for children with autism.

Unlike in the previous RCTs reviewed in this section, this intervention did not include a parent training component. Fifty-four children between the ages of 6 and 13 years with high functioning ASD were randomly assigned to small-group Skillstreaming intervention that used either a response-cost (RC) condition (involving immediate performance feedback and rewards based on specific social skills and behaviors) or a non-categorical (NC) feedback condition (involving more general feedback and non-contingent rewards). The only difference found between the RC and NC intervention conditions post-treatment was that interventionists reported significant improvements on the Behavioral Assessment System for Children (BASC) Atypicality, Withdrawal, and Behavior Symptoms Index (BSI) subscales in the RC group relative to the NC group ($p<0.05$). However, both groups combined made significant improvements after treatment on both parent and interventionist report of BASC social skills ($p<0.01$) and Skillstreaming Survey (Ss) social skills ($p<0.001$). The two groups combined also made significant improvements on parent and staff reported BASC Withdrawal ($p<0.05$), Adaptive Skills ($p<0.05$), and BSI ($p<0.05$). As for facial recognition, participants in neither group made significant improvements on the Diagnostic Analysis of Non-Verbal Accuracy (DANVA). A previous case series to assess Skillstreaming[153] for 21 children between 6 and 13 years old diagnosed with Asperger disorder, which only used the BASC as an outcome measure, found similar results: significant improvements on all of the parent reported subscales (Social Skills, Adaptability, and Atypicality) and on staff reported social skills.

Three RCTs[160, 162, 166] and a related retrospective cohort study[165] evaluated social skills interventions focused on improving children's ability to socially interact with others while playing. The Quirmbach et al.[162] study evaluated the effectiveness of using Social Stories to teach seven to 14 year old children with ASD social skills when playing board games. Social Stories[53] are descriptive brief vignettes constructed according to a specific formula that are read to or by individuals with ASD to convey appropriate behavior expected for a specific situation. Children in one of two social stories groups (standard or directive) showed significant game play skill improvements across the four trials ($p<0.001$) while the children who received the control story did not. Children in the two experimental conditions maintained the results of the intervention a week later. These results provide preliminary support for the effectiveness of a short, focused intervention on improving the specific targeted skills. However, further research is needed to ascertain whether these results generalize to other people (such as peers) and other settings, whether these results are maintained when the intervention is discontinued (i.e. the child stops reading the Social Story), and whether other Social Stories are successful at improving the skills that they target. Despite authors' predictions that the children who read the directive story would improve their game play skills at a faster rate than the children who read the standard story (because the directive story does not include additional information), there were no significant differences in results between participants receiving the standard vs. directive social stories (both groups showed significant improvements across trials).

In the other studies, direct teaching was associated with greater gains in initiating, responding, and interacting behaviors than an unstructured play group,.[166] in 4 to 6 year olds. Results on LEGO therapy were conflicting, with one a retrospective cohort study [165] showing benefit for LEGO therapy over an unspecified "other" intervention on socialization measures, while one RCT [160] had inconsistent results on the benefit of LEGO therapy over a Social Use of Language Program (SULP) and no intervention. The Lego group improved on measures of social skills when compared to the SULP and control groups; and pre-post scores did not significantly

differ on these measures for the Lego group. Both the Lego and SULP groups improved on measures of maladaptive behavior over the no intervention group. The Lego group improved in the duration of social interaction on the playground from pre to post treatment.

Six additional studies used prospective case series designs to evaluate the effectiveness of social skills interventions.[154-155, 157, 159, 161, 164] All studies noted improvements in some social behaviors that, depending on the study, included eye contact, emotion recognition, and interaction with peers; outcome measures were generally parent-reported. The studies also lacked control groups so it is difficult to determine whether improvements are treatment-specific.

Table 12. Outcomes of RCTs of social skills behavioral interventions

Author, Year Groups Study quality	N enrollment /N final	Age, mean years ± SD IQ, mean ± SD	Key social outcomes
Quirmbach et al.[162] 2009, US **G1:** Social Stories, standard condition **G2:** Social stories, directive condition **G3:** Control story unrelated to social skills Quality: Fair	**G1:** 15/15 **G2:** 15/15 **G3:** 15/15	**G1:** 9.49 ± 2.09 **G2:** 10.33 ± 2.53 **G3:** 8.85 ± 1.59 **G1:** 86.2 ± 22.8 **G2:**81.00 ± 20.26 **G3:** 79.47 ± 22.68	• G1 & G2 showed significant game play skill improvements across four trials while G3 did not (p<0.001) • Game play skills for G1 & G2 maintained a week later
Lopata et al.[152] 2008, US **G1:** Response-cost; receive feedback based on operationally defined behaviors) **G2:** Non-categorical; receive feedback based on no predetermined categories Quality: Fair	**G1:** 29/29 **G2:** 25/25	**G1:** 9.60 ± 2.12 **G2:** 9.41 ± 2.31 **G1:** 100.87 ± 17.92 **G2:** 97.56 ± 13.62	• Both groups (as a whole) demonstrated significant improvements on parent and interventionist reported social skills post-tx (p<0.01). Group differences were not significant on any of parent reported measures. • Interventionists reported significant improvements on BASC Atypicality and Withdrawal subscales in G1 compared with G2 (p<0.05) • Neither group improved significantly on facial expression recognition.

Table 12. Outcomes of RCTs of social skills behavioral interventions (continued)

Author, Year Groups Study quality	N enrollment /N final	Age, mean years ± SD IQ, mean ± SD	Key social outcomes
Solomon et al.[156] 2004, US **G1:**Social Adjustment Enhancement Intervention **G2:** Waitlist group **Ga:** Younger participants with higher mean FSIQ **Gb:** Older participants with lower mean FSIQ Quality: Fair	**G1:** 9/9 **G2:** 9/9	**G1a:** 8.58 **G1b:** 10.83 **G2a:** 8.33 **G2b:** 10.17 **G1a:** 115 **G1b:** 86 **G2a:** 119 **G2b:** 95	• Fewer social problems reported by parents of G1 (p<0.05) • G1 recognized more facial expressions post-intervention than G2 (p=0.003) (but not more than before tx) • No group differences evident on theory of mind measures post-intervention • G1 demonstrated improved executive function skills post-intervention, compared with G2, (p<0.05).
Frankel et al.[158] 2010, US **G1:** Children's Friendship Training **G2:** CFT after 12-week delay Quality: Fair	**G1:** 35/26 **G2:** 33/31	**G1:** 8.6 ± 1.27 **G2:** 8.46 ± 1.25 **G1:** 106.9 ± 19.1 **G2:** 100.5 ± 15.7	• Parents of G1 reported that their children hosted significantly more play dates after tx relative to G2 (p<0.0001), but were not invited to significantly more play dates. • Parents reported that G1 spent less time engaged in minimally socially interactive activities during play dates compared with G2 (p<0.001), but did not spend significantly more time in socially interactive activities (such as talking). • Parents of G1 reported increased self-control in children (p<0.05) when provoked by others. • No changes reported by teachers • G1 showed significant decreases in loneliness (p<0.025) and increases in popularity (p<0.025) following tx relative to G2

BASC=Behavior Assessment System for Children; CFT=Children's Friendship Training; DTC=delayed treatment control group; FSIQ=full scale intelligence quotient; NR=not reported; tx=treatment; GARS-SI=Gilliam Autism Rating Scale-Social Interaction subscale; SULP=Social Use of Language Program; tx=treatment; VABS=Vineland Adaptive Behavior Scale

Play-/Interaction-based interventions

These interventions focused on children's interactions with either their parents or experimenters and targeted a variety of skills including joint attention and play abilities. Most studies were conducted in the context of a play situation, and included children across broad age and developmental ranges.

Content of the literature. We included 14 papers addressing play- or interaction-based interventions[167-180] comprising 12 unique populations. Seven studies were randomized controlled trials,[167-171, 175, 177-179] including a trial of the Stepping Stones Triple P program with two publications,[167-168] and a trial comparing joint attention and symbolic play interventions with two

publications.[169-170] Two additional studies assessed joint attention and symbolic play and likely share overlapping participants with this trial.[171-172] Three RCTs assessed comparable interventions (imitation compared with contingent responsiveness) using similar procedures;[177-179] two of these [177, 179] may share participants. Multiple interventions involved parent training or parent interaction components, including Parent-Child Interaction Therapy (PCIT),[175] responsive teaching,[180] play-based approaches based on the DIR/Floortime model,[174] the Mifne model,[176] the Stepping Stones Triple P program,[167-168] and the Relationship Development Intervention program.[173] Participants ranged in age from 12 months[180] to 12 years[175] across all studies. Duration of therapy in prospective studies ranged from five weeks[170-171] to 12 months.[174, 180] Table 10 includes additional study details. Among the 12 unique studies, one was fair quality and 11 were poor.

Summary of the literature. The one study that did not receive a poor quality assessment was an RCT evaluating Parent-Child Interaction Therapy (PCIT),[175] in which parents of children with an ASD were trained to interact with their children using behavior management strategies (Table 13). The PCIT intervention group consisted of ten children and the wait-list control group included nine; children in both groups were on average 8 years old. Improvements were greater in the intervention group in challenging behavior, behavioral flexibility and atypical behaviors, and hyperactivity, inattention, challenging behaviors, and depression ratings. However changes on each scale fell short of statistical significance in comparison with the control group. A second parent-focused RCT addressed the Stepping Stones Triple P Parenting Program[167-168], which focuses on managing children's behavior by considering the function of the behavior and uses procedures such as descriptive praise, planned ignoring, skill acquisition, and communication. Parents of the children in the treatment group reported statistically significant decreases in child challenging behavior on the ECBI Intensity and Problem Scales. Wait-list controls eventually received the same treatment, and parents of children in this group also reported statistically significant decreases in child challenging behavior on both ECBI scales. At six-month follow up, the treatment group maintained gains on both the ECBI scales.

The additional studies in this section included three RCTs that compared the effects of imitation and contingent responsiveness.[177-179] Contingently responsive behavior refers to the adult responding to the child's initiations by either commenting back or gesturing within the play context. In the first phase, the child entered the room with an adult present holding a neutral facial expression. During Phase 2, the adult interacted with the child by using either imitation or contingently responsive behavior in response to the child's behavior. The third phase mimicked Phase 1, and the fourth and final phase included a spontaneous play interaction. Each of these four phases was three minutes in duration. Each of the three RCTs included 20 children randomly assigned to either the imitation group or the contingently responsive group,[177-179] Significantly greater effects were seen in the imitation group compared with the contingent responsiveness groups in all three studies. Improvements included spending more time engaged with both objects and adults [177], a greater reduction in motor activity[179], and more social interest.[178]

Two RCTs[169-171] and a case series[172]focused on the potential for interventions based on joint attention (JA) or symbolic play (SP). Generally speaking, interventions with a joint attention focus did result in improvements in tasks based on joint attention. In the first RCT, all groups improved in coordinated joint looks over time. No differences were found in pointing to a toy or giving a toy to an adult to share in any group. Both joint attention and symbolic play groups

improved in the following areas compared to controls: showing toys to an adult, shared looks between a toy and the child's mother, and symbolic play skills. Compared with other groups, the joint attention group showed more improvement in responding to joint attention over time. With respect to mother-child interactions (generalization) assessing the same outcome areas, the JA group had significantly greater improvement than the SP group in giving and showing a toy. Children in the JA group engaged in more child-initiated joint engagement than those in the control group. The symbolic play group showed significantly greater improvement on the Structured Play Assessment than did the control group for overall mastered level of play. No differences were reported between SP and JA groups or JA and controls. In the second RCT,[171] significantly more children in the JA group engaged in coordinated looks during the final stimulus presentation (76.5 percent) than in the SP group (38.9 percent). Children in the JA group engaged in significantly longer periods of coordinated looks between the person in the room and the stimulus presentations across the three time periods.

None of the four additional case series that met criteria for inclusion in this section described the same intervention. They described a relationship-focused intervention teaching parents to use responsive teaching strategies to assist their children with acquiring pivotal behaviors,[180] the DIR/Floortime model,[174] the Relationship Development Intervention,[173] and the Mifne treatment model.[176]All four report positive outcomes that are difficult to interpret absent a comparison group.

Table 13. Outcomes of RCTs assessing play/interaction-based interventions

Author, Year, Country Intervention	Groups, N enrollment/ N final Age, mean ± SD (range)	Key Outcomes
Parent-focused Interventions		
Solomon et al.[175] 2008, US **G1:** Parent training focused on behavior management and requesting (PCIT) **G2:** Wait list Quality: Fair	**G1:** 10/10 **G2:** (waiting list), 9/9 **G1:** 8.2 yrs ± 1.7 **G2:** 8.1 yrs ± 2.2	• Challenging behaviors decreased in both groups • Scores declined on BASC Hyperactivity Scale for G1 but not G2 • Score on BASC Adaptability Scale increased significantly for G1 • Parents of G1 children reported significantly less atypicality on the BASC scale

BASC=Behavior Assessment for Children; PCIT=Parent-Child Interaction Therapy

Behavioral Interventions Focused on Associated Behaviors

Several behavioral interventions target symptoms commonly associated with autism, such as anxiety and anger management. Cognitive behavioral therapy-based (CBT) interventions are particularly common and involve teaching cognitive skills and relaxation strategies, promoting recognition of anxious feelings, and providing children with behavioral exposures in which to utilize their new coping skills in the face of anxiety-provoking stimuli, with an ultimate goal of reducing anxiety symptoms over time.[60]

Parent training protocols, often implemented to help parents deal with challenging behaviors, such as non-compliance, tantrums, self-injury, and aggression, attempt to teach parents strategies to curb negative behaviors. Once trained, parents can act as "co-therapists," shaping behavior

toward the goal of reducing challenging behaviors in daily life, where parents by necessity must act as the primary interventionist. Parent training interventions also often have secondary targets of improving parental feelings of self-efficacy and decreasing parental stress.

Content of the literature. We identified 11 studies reported in 12 papers [36, 56-57, 181-189] that addressed behavioral interventions focused on symptoms commonly associated with ASD including anxiety and anger management. Six studies reported on cognitive behavioral therapy (CBT) interventions,[56-57, 181-184, 189] four used parent training techniques,[36, 185, 187-188]and one used teacher training methods.[186] While the overlap among studies is somewhat unclear, sets of studies from the same authors and using the same methodology appear to include the same or overlapping samples.[182, 189];[183-184];[187-188] Accounting for this potential overlap, it appears that there are at least four independent studies of CBT interventions and three independent studies of parent training to address anxiety and anger in children with ASD. All studies examining CBT treatments included children ages seven and older, with means ranging from nine to eleven years of age. In two studies examining CBT treatments, only children with an Asperger diagnosis were included,[182, 189] while the Wood et al. RCT enrolled children with an ASD and a comorbid anxiety disorder.[183-184] Parent training studies included parents of children ranging from age four to twelve with mean ages spanning seven to nine years.[149, 185, 187-188] In three of four parent training studies, only parents of children with Asperger Syndrome were included.[149, 187-188] In the teacher training study, children ranged in age from two to fifteen and all had diagnoses of autistic disorder.[186] Table 10 summarizes additional study details. Among all studies, six were fair quality and five were poor.

Summary of the literature. Among the studies assessing cognitive-behavioral therapy approaches, one RCT examined the efficacy of a modified version of the Building Confidence CBT program for treating comorbid anxiety disorders (i.e., separation anxiety disorder, social phobia, or obsessive compulsive disorder) in seven to eleven year-old children with ASD.[183-184] This was the only RCT where CBT occurred at the individual level. The intervention program consisted of sixteen 90-minute weekly sessions conducted by clinical or educational psychologists or trainees in these programs. In the first report from the study,[183-184] anxiety symptoms were assessed by evaluators blind to treatment condition using the Anxiety Disorders Interview Schedule (ADIS), Clinical Global Impression (CGI) – Improvement Scale, and both parent and child versions of the Multidimensional Anxiety Scale for Children (MASC). On the CGI, 92.9 percent of children in the intervention condition met criteria for positive treatment response, while only 9.1 percent of children in the waitlist control group met the same criteria; on the ADIS, 64.3 percent of children in the intervention group no longer met criteria for any anxiety disorder, whereas only 9.1 percent of children in the waitlist control group lost their anxiety disorder diagnosis at post-test.

Eight of ten children from the intervention group who returned for a three-month follow-up did not meet criteria for any anxiety disorder at follow-up. Maintenance of treatment response was also indicated by CGI and MASC scores at follow-up. The second report from the study[184] included 58 percent of participants from the initial report (42 percent new participants), and measured effects of the intervention on autism symptoms using the Social Responsiveness Scale (SRS). Significant group differences were observed at outcome in the SRS total score as well as the social communication, social motivation, and social awareness subscales, with children in the intervention group showing fewer autism symptoms post-treatment than children in the waitlist control group.

The remainder of CBT-based interventions (Table 14) were conducted in group settings or directed toward parents. Reaven et al.[57] conducted a non-randomized trial of a 12-week CBT-based group intervention for high-functioning (i.e., IQ above 70) children ages eight to fourteen years (mean = 11.83) with ASD and comorbid anxiety disorders (as rated on the Kiddie-Schedule for Affective Disorders and Schizophrenia or on the Screen for Child Anxiety and Related Emotional Disorders [SCARED]). The authors created an original protocol,[58] and treatment involved both children and their parents. Ten children received active treatment in this pilot study, while 23 served as a wait-list control. Anxiety symptoms in children participating in the treatment group decreased over time, while symptoms in the control group did not on the parent (but not child) version of the SCARED.

Chalfant et al.[56] examined children ages eight to thirteen years (mean= 10.8) with ASD and one or more comorbid anxiety disorder diagnoses including separation anxiety, generalized anxiety, social phobia, specific phobia, and panic disorder confirmed by structured clinical interview using the ADIS. Children were randomly assigned to treatment and waitlist conditions. Treatment involved a 12-session CBT-based group therapy protocol, led by licensed clinical psychologists, with nine weekly two-hour sessions followed by three monthly booster sessions. The protocol for the study was based on a manualized CBT-based anxiety intervention for children (Cool Kids) with adaptations made to account for the learning style of children with ASD (e.g., more visual aids and structured worksheets, increased focus on relaxation and exposure, simplification and decreased emphasis on cognitive components of the treatment). Parents of children in the intervention group participated in concurrent parent groups with a manual also adapted from the Cool Kids program. Self-report of anxiety was obtained using the Revised Children's Manifest Anxiety Scale (RCMAS), the Spence Children's Anxiety Scale (SCAS), and the Children's Automatic Thoughts Scale (CATS); parent report was obtained using the parent report version of the SCAS and the Strengths and Difficulties Questionnaire – Parent Report (SDQ-Parent). Finally, teacher report was collected on the SDQ Teacher Report. Measures were collected at baseline and at the completion of intervention (approximately five and a half months later); clinicians administering the pre- and post-intervention measures were the same clinicians who led treatment groups. No group differences were observed on any measure at baseline. However, children in the treatment group improved significantly over time while children on the waitlist did not in the number of anxiety disorder diagnoses present, as well as in the number of anxiety symptoms reported by children on the CATS Internalising Scales, RCMAS, and SCAS, by parents in their report on the SCAS -Parent and the SDQ Emotional and Externalizing Scales, and by teachers using the SDQ Emotional and Externalizing Scales.

Table 14. Studies assessing interventions targeting conditions commonly associated with ASD

Author, Year, Country Study Design Groups Study quality	Groups, N enrollment/ N final	Age, mean/yrs ± SD IQ, mean ± SD	Key Outcomes
		CBT	
Reaven et al.[57] 2009, US Non-randomized controlled trial **G1:** Active CBT **G2:** Wait list Note: for children with comorbid anxiety Quality: Fair	**G1:** 10/10 **G2:** 23/21	**G1+G2:** 11.02 ± 1.9 **G1+G2:** 102.65 ± 16.22	• Anxiety symptoms in G1 decreased over time, while symptoms in G2 did not (p=0.01)
Wood et al.[183-184] 2009, US RCT **G1:** Building confidence CBT program **G2:** Wait list Quality: Fair	**G1:**17/17, **G2:** 23/23,	**G1:** 9.18 ±1.42 **G2**: 9.22 ±1.57 NR	• 92.9% of children in the intervention condition met criteria for positive tx response • 64.3% of children in G1 no longer met criteria for any anxiety disorder on the ADIS • MASC scores were significantly lower (i.e. reduction in anxiety) in G1 than in G2 post-test (p<0.0001) • Maintenance of tx response was indicated by diagnosis and CGI and MASC scores at follow-up • Children in the autism group had lower scores than control group children at outcome on the SRS total score as well as the social communication, social motivation, and social awareness subscales

Table 14. Studies assessing interventions targeting conditions commonly associated with ASD (continued)

Author, Year, Country Study Design Groups Study quality	Groups, N enrollment/ N final	Age, mean/yrs ± SD IQ, mean ± SD	Key Outcomes
		CBT	
Sofronoff et al.[181] 2007, Australia RCT **G1:** CBT **G2:** Wait list Note: for children with Asperger Disorder and anger management difficulties Quality: Fair	**G1:** 24/24 **G2:** 21/21	**G1:** 10.79 ± 1.12 **G2:** 10.77 ± 0.87 **G1:** 105.24 ± 22.3 **G2:** 108.7 ± 21.6	• G1 had significant improvement on parent-reported anger inventory between pre- and post-intervention (p<0.0001) and between pre-intervention and.6-wk follow-up (p<0.001) • Significant improvement on frustration and relationships with authority subscales in G1 • Parents of children in G1 reported fewer instances of anger post-intervention (and at six-wk follow up) than pre-intervention • Significant between-group differences in reports of anger incidents post-intervention (p<0.02) and at follow-up (p=0.005) • G1 generated significantly more anger management strategies post-intervention and at six-wk follow up (p<0.01 and p<0.05, respectively) relative to baseline and relative to children in G2 at post-intervention (p<0.01)
Sofronoff et al.[182] 2005, Australia RCT **G1:** Child only CBT **G2:** Wait list **G3:** Child and Parent CBT Note: Children with Asperger Disorder and anxiety symptoms Quality: Fair	**G1:** 23/22, Child-only **G2:** 23/20, Wait-list **G3:** 25/24, Child + parents	**G1:** 10.56 ± 0.99 **G2:** 10.75 ± 1.04 **G3:** 10.54 ± 1.26 **G1:** 107.5 ± 27.3 **G2:** 101 ± 27.2 **G3:** 105.6 ± 21.2	• Significant differences on the SCAS-P total score observed between the two intervention groups, G3 (p<0.03) • Significant time by group interaction (SWQ) observed (p<0.0001), with significant improvement in scores between baseline and six-wk follow-up observed for both G1 and G3 (p<0.001) • G1 and G3 scored better than G2 at follow-up on the James and the Maths test, and G3 scored better than G1 at follow-up (p<0.0001)

Table 14. Studies assessing interventions targeting conditions commonly associated with ASD (continued)

Author, Year, Country Study Design Groups Study quality	Groups, N enrollment/N final	Age, mean/yrs ± SD IQ, mean ± SD	Key Outcomes
Parent/teacher Training			
Aman et al.[36] 2009, US RCT **G1:** Risperidone **G2:** Risperidone + parent training Quality: Fair	**G1:** 49/40 **G2:** 75/55	**G1:** 7.5 ± 2.80 **G2:** 7.38 ± 2.21 NR	• Significant group by time interaction on the HSQ (p<0.006); HSQ scores declined (i.e., decreased severity) in more children in G2. • ABC irritability, stereotypic behaviors, hyperactivity subscales all showed significant group differences over time with less severe symptoms in each of the domains in G2.

ABC=Aberrant Behavior Checklist; ADIS=Anxiety Disorders Interview Schedule; CBT=cognitive behavioral therapy; CGI=Clinical Global impression; CHiAP=Children's Inventory of Anger-Parent report; ECBI=Eyberg Child Behavior Inventory; HSQ=Home Situations Questionnaire; MASC=Multidimensional Anxiety Scale for Children; NR=not reported; SCAS-P=Spence Child Anxiety Scale-Parent version; SRS=Social Responsiveness Scale; SWQ=Social Worries Questionnaire; tx=treatment;

A series of papers examined CBT approaches delivered directly to children and via parent training. CBT provided by graduate students in psychology was assessed in high functioning children with Asperger Disorder with comparisons made across two intervention conditions (child-only and parent-plus-child) and waitlist controls.[182, 189] Significant improvements in SCAS-P scores were observed for both intervention groups on the total score and separation anxiety, OCD, social phobia, panic, and generalized anxiety scales; significant improvement on the personal injury scale was observed for the parent-plus-child intervention group. No significant differences were observed from baseline to six-week follow-up in the waitlist control group. On the SWQ, there were significant improvement in scores between baseline and six-week follow-up observed for both intervention groups, but not for the waitlist control group. Similarly, children in both intervention groups generated more strategies to cope with anxiety at six-week follow-up than at baseline, while children in the waitlist control group did not. Both intervention groups scored better than the wait-list control group at follow-up, and children in the parent-plus-child condition scored better than children from the child-only groups at follow-up. A separate study of the same intervention [181] to examine the impact of CBT-based treatment on anger management difficulties in high-functioning (i.e., average IQ above 100) children ages ten to fourteen years with Asperger Syndrome found similarly positive results.

Parent training in using CBT approaches [187-188]for parents of children ages six to twelve years with Asperger Syndrome diagnoses includes psychoeducation, comic strip conversations and social stories introduction, and management techniques for externalizing behaviors, rigid behaviors, and anxiety. In studies of this approach, parents who attended a one-day workshop or who participated in six weekly one-hour individual sessions reported fewer challenging behaviors at both one-month post-treatment and three-month follow-up relative to baseline, while there were no significant differences over time for the waiting list control group. Parents

from both intervention groups also reported significantly fewer challenging behaviors in their children, decreased challenging behavior intensity and improved social skills at both time points. At three-month follow-up, individual session participants reported significantly lower intensity of challenging behaviors relative to both the waiting list control group and workshop intervention group; the workshop group no longer showed differences from the control group by three-month follow-up in terms of parental report of child challenging behavior intensity.

The RUPP Autism Network first reported on the feasibility of a parent-training program for parents of children with autism spectrum disorders ages four to thirteen years who were on stable medications for behavior problems.[185] The parent training protocol consisted of 11 required sessions covering topics including prevention strategies, schedules, reinforcement, planned ignoring, compliance training, functional communication training, teaching techniques, and generalization. Two home visits were always conducted, four optional sessions were available, and booster sessions were provided to parents in later weeks; parent training was administered according to a structured curriculum. Outcome measures related to child functioning included the Home Situations Questionnaire (HSQ), the Aberrant Behavior Checklist (ABC), the Clinical Global Impressions – Improvement Scale (CGI-I), the Vineland Adaptive Behavior Scales – Survey Form (VABS-Survey), and the Assessment of Basic Language and Learning Skills (ABLLS). Results indicated significant decrease in noncompliance on the HSQ over the course of parent training intervention. Irritability and Hyperactivity/Noncompliance measured on the ABC showed improvement over time. Fifty-three percent of children were reported as very much improved on the CGI-I, and thirty percent were reported to show minimal improvement. Finally, with regard to adaptive behavior, improvement in daily living skills (VABS-Survey) and increase in adaptive skills were also shown over the course of treatment. The correlation between improved compliance and improved adaptive behavior also strengthened over the course of treatment.

Following the initial feasibility study,[185] Aman et al.[36] conducted an RCT assessing whether risperidone treatment combined with parent training in behavior management was superior to risperidone treatment alone; this study was conducted as part of the RUPP Autism Network. Parents of children ages four to thirteen years with ASD and significant tantrums, self-injury, and aggression who were randomly assigned to the combined treatment group received parent training with a behavior therapist according to a RUPP manual. As noted, the manual specified 11 core treatment sessions, three optional sessions, and up to three booster sessions of 60-90 minutes in length. On average, parents in the combined condition participated in 10.82 sessions. As in the feasibility study, outcome was assessed on the HSQ and ABC; the Children's Yale-Brown Obsessive Compulsive Scale – PDD version (CYBOCS) was also administered both pre- and post-intervention. After 24 weeks of treatment, HSQ scores for 71 percent of children assigned to the combined treatment group and 60 percent of children assigned to the medication-only treatment group declined (i.e., decreased severity), which represents a significant difference between groups over time. In addition, the ABC irritability, stereotypic behaviors, and hyperactivity/noncompliance subscales all showed significant group differences over time, with children of parents who received the parent training showing less severe symptoms in each of the domains.

One case series of a teacher training procedure in reducing challenging behaviors (e.g., aggression, non-compliance, off-task behavior)[186] reported a significant reduction in the rate of the target behavior following classroom instruction (45 hours) and practical application, training,

and supervision (45 hours) in applied behavior analysis (ABA).

Other Behavioral Interventions

Additional behavioral interventions include techniques such as neurofeedback and sleep hygiene education. Neurofeedback, or EEG biofeedback, aims to remediate abnormal brainwave activity associated with disorders such as anxiety, ADHD, and ASD through training individuals to control brain activity patterns. Neurofeedback involves the placement of electrodes to monitor brain activity while participants interact with specially designed computer games or other modalities designed to promote attention or other skills.[190] Behavioral treatments for sleep problems may attempt to affect the timing of sleep, sleep-wake cycle disorders, or promote efficacious sleep behaviors like bedtime routines and positive reinforcement.[191]

Content of the literature. Three studies[192-194] of additional behavioral interventions met our inclusion criteria. Participant ages ranged from three to fourteen years across the studies, and all three occurred in a clinic setting. Jarusiewicz[192] and Coben et al.[193] used neurofeedback with children directly while the Reed et al. sleep workshops were aimed at parents using a group approach.[194] Table 10 includes additional study details. All three studies in this section were considered poor quality.

Summary of the literature. Jarusiewicz's RCT examined the efficacy of neurofeedback on autistic symptoms as assessed using the parent-rated Autism Treatment Evaluation Checklist (ATEC) as the primary outcome measure.[192] Participants included 40 children ages four to 13 (mean=seven) with a previous diagnosis of autism; participants were matched on gender, age, and autism severity, and individuals in each pair were randomly assigned to either neurofeedback or a wait list. Diagnostic and randomization procedures were not described. Neurofeedback protocols varied depending on a child's autism severity as assessed by the ATEC and parental report of troubling symptoms; children typically received one to three sessions per week. Eight children in the neurofeedback group dropped out of the study due to family considerations or non-ASD-related illness; the twelve remaining participants completed 20 to 69 neurofeedback sessions (mean=36). Scores on the ATEC improved from eight percent to 56 percent post-neurofeedback training, with an overall average reduction of 26 percent ($p < 0.001$). Scores for control participants improved by three percent overall (ns).

Coben et al.[193] sought to extend Jarusiewicz's findings in a non-randomized controlled trial of 49 children diagnosed with ASD; diagnostic techniques were not described. Children in the experimental (n=37) and control (n=12) groups were matched on age, gender, handedness, ASD severity as assessed by the ATEC, and other treatments received. Participants' ages across groups ranged from 3-14 years; the majority (75 percent) of participants in the neurofeedback group were diagnosed with PDD-NOS or autism. Four children in this group had Childhood Disintegrative Disorder (CDD). Outcome measures included the ATEC, Gilliam Autism Rating Scale (GARS), Gilliam Asperger Disorder Scale (GADS), the Personality Inventory for Children (PIC-2), Behavior Rating Inventory of Executive Function (BRIEF) as well as parental ratings of the effectiveness of the treatment and a battery of neuropsychological tests to assess attention, visual-perceptual, executive function, and language skills.

Neurofeedback protocols were individualized for each child based on assessment information and initial quantitative electroencephalogram (qEEG) results; treatment consisted of 20 sessions, with sessions occurring twice weekly for an unspecified duration. Eighty-nine percent of parents reported improvement in the neurofeedback group; 83 percent of control group parents reported

no change (z=2.167, p=0.000). Scores on the ATEC, GADS, BRIEF, PIC-2, and neuropsychological tests improved significantly in the treatment group (p=0.000 to 0.006). The authors did not correct for multiple testing, however.

Reed at al.[194] employed sleep hygiene workshops targeted at parents and taught by a neurology sleep specialist, pediatrician with an ASD treatment background, educational psychologist, and nurse educator. Twenty families participated and completed both baseline and follow-up assessments; the mean age of children in the study was 5.8±2.7 years, and the majority (n=15) had ADOS scores in the autism range. Workshops addressed establishing effective daytime/nighttime routines, minimizing night and early waking, and discussion of techniques to handle individual sleep concerns. Assessments, conducted prior to the initial workshop and approximately one month after the final session, included the Children's Sleep Habits Questionnaire (CSHQ), Family Inventory of Sleep Habits, Parental Concerns Questionnaire, Repetitive Behavior Scale-Revised (RBS), Parenting Stress Index-Short Form, and a week of actigraphy measurement of sleep-wake patterns coupled with a parent-maintained sleep diary.

Significant improvements (P<0.05) over baseline scores were seen in the hyperactivity, sleep disturbance, and self-stimulatory subscales of the Parental Concerns Questionnaire; the bedtime resistance, sleep onset delay, and sleep duration subscales of the CHSQ as well as the total CHSQ score; and the restricted behavior scale of the RBS. Items related to reduction of stimulating activities before bedtime and the use of bedtime routines improved on the Family Inventory of Sleep Habits. Actigraphy data, available for 12 children, illustrated a decrease in sleep latency in nine children with difficulty initiating sleep (p=0.039); among all 12 children, time in bed also significantly improved (p=0.039). Parental stress did not change significantly with the workshops.

KQ1. Effects of Treatment on Core and Commonly Associated Symptoms in Children with ASD: Educational Interventions

Education through schools and other community settings (e.g., centers) has been and remains the primary treatment for children with ASD. Educational interventions have focused both on traditional areas of academic progression/achievement, but are also often utilized to address core areas of social, cognitive, and behavioral vulnerability via classroom or specialized instruction. Educational approaches vary in scope from specific intervention techniques attempting to impart change in short periods of time to comprehensive intervention programs aimed at improving many areas of development. Within the context of this review we examine the available literature focusing on applications of the Treatment and Education of Autistic and Communication-related Handicapped Children (TEACCH) program, broad-based early intervention center- or classroom-based instruction, and computer-based approaches to educational intervention. Table 15 summarizes information about the studies included, and Table 17 summarizes key outcomes of studies of good or fair quality.

Table 15. Overview of educational studies

	RCTs	NRCTs	Prospective cohort studies	Retrospective cohort studies	Prospective case series	Retrospective case series	Total Literature
	(n=2)	(n=1)	(n=5)	(n=0)	(n=3)	(n=2)	(n=13)
Intervention							
TEACCH	0	0	2	0	2	0	4
Broad-based approaches	1	1	3	0	1	1	7
Computer-aided approaches	1	0	0	0	0	1	2
Diagnostic approach							
Clinical DSM-IV dx +ADI-R and/or ADOS	1	0	1	0	0	0	2
Combination approaches*	0	0	1	0	3	0	4
No DSM-IV or ADOS dx/ unspecified	1	1	3	0	0	2	7
Last outcome assessment							
≤1 month	1	0	0	0	0	0	1
>1 to ≤3 months	0	0	1	0	1	0	2
>3 to ≤6 months	0	0	0	0	0	1	1
>6 to ≤12 months	0	1	2	0	1	1	5
>12 months	1	0	2	0	1	0	4
Study population							
U.S.	1	0	0	0	1	1	3
Europe	0	1	4	0	2	1	8
Asia	0	0	1	0	0	0	1
Other	1	0	0	0	0	0	1
Total N participants	53	17	209	0	40	44	363

ADI-R=Autism Diagnostic Interview-Revised; ADOS=Autism Diagnostic Observation Schedule; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition; dx=diagnosis; NRCT=non randomized controlled trial; RCT=randomized controlled trial; TEACCH= Treatment and Education of Autistic and Communication-Related Handicapped Children

*Clinical DSM-IV dx +other diagnostic tool OR ADOS + other diagnostic tool OR only clinical DSM-IV dx OR only ADOS.

TEACCH

Originally founded in the 1970s at the University of North Carolina at Chapel Hill, TEACCH involves primarily "structured teaching." Structured teaching refers to applying 'structure' to the organization of time, space, and sequences of events within the educational environment to promote learning by making activities clearer and easier to perform. Instruction is based on the idea that individuals on the autism spectrum have specific neuropsychological profiles described

by strengths regarding processing visual information (compared with language use/understanding), heighted attention to details, significant variability regarding attention, communication difficulties, difficulties with time, attachment to routines, intense interests and impulses, and marked sensory preferences and aversions.[195] By applying physical structure, indicating sequences of events, organizing individual tasks, and work/systems within a classroom environment children with autism are thought to engage in more developmentally appropriate behaviors that ultimately promote learning. TEACCH approaches often include a heavy reliance on visual supports (e.g., picture schedule) and arranging the physical environment to support individual learning.

Content of the literature. We identified 13 studies evaluating educational interventions overall (Table 15).[9-10, 196-206] Four of those studies[196-199] evaluated implementation of iterations of the TEACCH program. Among studies assessing TEACCH, one was good quality, one was fair, and two were poor.

Summary of the literature. Four studies assessed various outcomes associated with implementation of components of the TEACCH curriculum (Table 16). One prospective cohort study[198] evaluated the TEACCH program over 12 months for 18 children involved in a TEACCH classroom, with 16 receiving other types of individualized training (age range, 3-5 years). Evaluations of cognitive/developmental level, nonverbal intelligence, and adaptive behavior, were assessed using the Chinese version of the PEP-R (CPEP-R), The Merrill-Palmer Scale of Mental Tests, and the Hong Kong Based Adaptive Behavioral Scales (HKBABS) respectively at baseline, six months after initiation of treatment (Posttest 1), and again at 12 months (Posttest 2). The Merill-Palmer Scale of Mental Tests assessed cognitive functioning and the HKBABS assessed social adaptive functioning.

The intervention group demonstrated statistically significant improvement compared with the control group on the CPEP-R Developmental Scale in perception, fine motor skills and gross motor skills ($p \leq 0.05$) after controlling for age, IQ, and pretest scores at Posttest 1. However, the control group showed more progress than the intervention group in the daily-living domain and the HKBABS sum of domains standard score ($p \leq 0.05$). Although significant improvements were see in the intervention group at 12 months for all scales and subscales in CPEP-R, Merrill-Palmer Scale of Mental Test (total raw scores and mental age), and the HKBABS the 12 month data are not provided for the control group.

The second prospective cohort study compared the effects of TEACCH in a residential center (R-TEACCH; N=11, mean age = 9.66 years), a specific school setting (NS-TEACCH; N=13, mean age = 8.66 years), and included a comparison group in an inclusive mainstream classroom (INSP; N=10, mean age 9.09 years)[196] The main components of the TEACCH intervention groups included arranging the environment with visual aids, individualized communication systems, self-care skills training, and daily living skills related intervention.

Cognitive/developmental level and adaptive behavior were evaluated for each participant twice with a three-year interval between evaluations, using the PEP-R and the VABS respectively. Both TEACCH groups showed significant improvement on adaptive measures, but the INSP group did not. The INSP group improved significantly on the PEP-R perception measure only, which both TEACCH groups demonstrated cognitive improvements on the PEP-R on a variety of additional subscales.

Two case series of TEACCH were identified, one focused on a psycho-educational training program for parents[199] and the other on teachers.[197] Both had poor quality scores on our

assessment. Each included 10 children with ASD. After the parent training, children improved on the Ankara Developmental Screening Inventory (ADSI) in total development score, language-cognitive subscale, social and self-care subscale, fine motor subscale, and gross motor subscale. The teacher training program was targeted to slightly older children (mean age 10 years), and evaluated effectiveness with a study-designed tool called Classroom Child Behavioral Symptoms questionnaire (CCBSQ), which was completed by their teachers at baseline and post-treatment (nine months later). CCBSQ scores decreased from a mean pretest score of 106.4 to a post-test score of 100.8, representing a medium range effect size of d = 0.66.

Broad-Based Educational Approaches

Classroom and center-based approaches include a blend of teaching strategies that rely on the principles and techniques of applied behavior analysis (ABA) including reinforcement-based procedures such incidental teaching, discrete trial training, and pivotal response training. Other interventions, such as TEACCH and language development interventions may also be incorporated in center-based treatment.

Content of the literature. Seven papers evaluated a variety of broad-based educational strategies.[9-10, 202-206] One study in this category was good, three were fair quality, and three were poor.

Summary of the literature. Several studies have investigated outcomes of children receiving specific or general instruction within early intervention centers or other classroom environment either within a specific curriculum or across multiple types of interventions (e.g., speech therapy, parent education, ABA instruction) (Table 16). A non-randomized controlled trial[206] compared a developmentally based early intervention (N=12, mean age = 42.6 months) to no treatment (N=5, mean age = 37.7 months). The Scottish Centre for Autism (SCA) developed an individualized treatment program for preschool aged children with ASD focusing on social, communicative, play, and adaptive behaviors and included a parent training component focusing on behavior management and teaching new skills. After approximately 11 months of treatment, adaptive behavior scores (Vineland Adaptive Behavior Scales for socialization, daily living skills, motor, and composite) improved significantly for the intervention group compared with controls. The intervention group also showed a statistically significant improvement in imitation scores on the Pre-Verbal Communication Schedule (PVCS), as well as joint attention scores, and social interaction skills measured on the Early Social Communication Scales.

One prospective cohort study compared an EIBI, home-based intervention using discrete trial techniques (and Verbal Behavior) (N=28) to a nursery school-based eclectic intervention (based in autism-specific classrooms) (N=16), which included components of TEACCH, PECS, and other developmental and behavioral teaching strategies.[9] The EIBI home-based intervention group and the nursery school-based intervention group had a mean age of 38 and 42.5 months, respectively. Nonverbal intelligence, cognitive ability, language skills, academic achievement/aptitude, and adaptive behavior were evaluated twice, with a 23-27 month interval between assessments. No statistically significant differences were identified between the groups post-intervention on any of the measures, although both groups demonstrated improvement across measurements on average. A majority of the children demonstrating improvement had initial IQs above 70 and all but one were verbal at pre-treatment. Initial IQ and receptive language scores were correlated with progress over time.

Another prospective cohort study described outcomes for 65 children (ages 2.5 – 4 years) at

start of treatment involved in broad-based eclectic teaching interventions and programs, often including reinforcement–based interventions, special nursery placements, speech and language therapy, and parent education programs. The authors compared groups (based on median split) of children receiving either[205] high/low intensity (less than 15.6 hours per week of intervention) intervention whose parents either reported high or low levels of stress (median split on PSEI). Children were assessed at baseline and then after 9-10 months, including assessments of developmental/cognitive and adaptive behavior. Children receiving more intervention time (high intensity) had greater improvements across all three measures compared with those with less intervention time. Parenting stress did not affect gains with low intensity interventions but reduced the gains made by those in higher time interventions.

A prospective cohort study[10] compared home-based tutor-led ABA teaching interventions (N=12) to two other teaching interventions, one of which was a school-based teaching program borrowing components from TEACCH with 6-8 children in each class (Special Nursery Placement) (N=20), and one (Portage) of which was a home-based, tutor-led program (N=16). The ABA intervention group received 1:1 interaction for two to three hours (including Lovaas, verbal behavior, and CABAS interventions). In the Special Nursery group, the children had several two to three hour sessions per week in a structured classroom (outlined by TEACCH methodology) with 6-8 other student and a teacher. In the portage group, a supervisor visited parents once every one to two weeks to demonstrate how to apply a system developed by a portage supervisor. Sessions were 40 to 60 minutes per day and scheduled when the parent believed the child would be at his or her most receptive. Children were taught new skills through the use of questions and tasks, prompts, and rewards.

The children were evaluated using the Gillian Autism Rating Scale (GARS), the Psychoeducational Profile-Revised (PEP-R), the British Abilities Scales II (BAS-II), the Vineland Adaptive Behavior Scales (VABS), and the Conners' Rating Scale – Revised (CRS-R). For PEP-R (intellectual functioning), the ABA intervention group produced an overall gain of approximately 14 points, the nursery, approximately 10 points, and little gain was shown in the portage group (~2 points). Authors documented cognitive, behavioral and adaptive behavioral skill improvements within each intervention group, but did not conduct direct comparisons between groups.

Rickards et al.[204] investigated the addition of home-based intervention to a center-based educational program. The center-based program used training techniques like chaining, variety, repetition, sequencing, and a reward system to encourage learning through play, and used communication systems and behavior reinforcement. The home-based program included one of two specialist preschool teachers who visited each family weekly for one to one and a half hours for 12 months to discuss protocols developed at the centers, and develop new goals and strategies. The home-based program also included parent training and adapting the home environment for the needs of the child. Outcome measures included the Bayley Scales of Infant Development – Second Edition, the Weschler Preschool and Primary School Intelligence scales – Revised, Vineland Adaptive Behavior Scales, the Bayley Behavior Rating Scale (BRS), the Behavior Screening Questionnaire (BSQ), and the Preschool Behavior Checklist (PBCL). IQ improved by 1.6 points between T1 and T2 for the home plus center group and decreased by 4.3 for the center only group ($p = .09$). PBCL scores decreased by 8.4 for the intervention group and decreased by 1.8 for the control group ($p=0.054$).

Case series[202-203] evaluating the effects of a variety of ABA methods used within a teaching

context in center-based classrooms were consistent with group design studies, measuring improvements in social and communication behaviors.

Computer-Based Educational Approaches

Computer-based programs use technology to deliver behaviorally-based teaching in areas such as language acquisition and reading skills.

Content of the literature. We also identified two papers evaluating computer-based intervention programs delivered in school settings.[200-201] Both studies in this section were poor quality.

Summary of the literature. One randomized controlled trial[200] and one prospective case series[201] of computer-based academic interventions were included in this review. The randomized controlled trial compared a computer and teacher-led vocabulary acquisition program using behaviorally-based teaching strategies like positive reinforcement,[200] with seven children ages 3 to 6 years in each group. The computer program paralleled the teacher led approach with the addition of features such as color, animation and music. Children recalled more nouns after exposure to the computer, program, (mean=4.43, 74 percent) compared with teacher presentation (mean= 2.43, 41 percent), ($p < .01$) and were more attentive to the computer than to the teacher (mean= 97 percent vs. 67 percent), $p<0.01$. In the case series on the use of multimedia computer program using voice, animation, video and sign language for increasing literacy and language,[201] children also increased in verbal expressions ($p=0.02$), seeking help ($p<0.05$) and enjoyment ($p<0.05$) from pre to post intervention.

Table 16. Outcomes of studies assessing educational interventions

Author year Study design Groups Study quality	Groups, N Age, mean/yrs ± SD (range)	Key Outcomes
TEACCH		
Panerai et al.[196] 2009 Prospective Cohort **G1:** TEACCH in a residential center **G2:** TEACCH at home and at mainstream schools **G3:** Inclusive education in mainstream schools Quality: Good	**G1:** 11 **G2:** 13 **G3:** 10 **G1:** 9.66 (2.31) **G2:** 8.66 (2.01) **G3:** 9.09 (2.07)	• Significant difference in PEP-R analysis from baseline to post-intervention (G1, p=0.02, G2, p=0.022, G3: p=ns) and between-groups (G3 vs. G1 vs. G2: p=0.009, G3 vs. G2: p=0.001, G3 vs. G1: p=ns, G2 vs. G1: p=ns) • Significant difference in VABS analysis between outcome vs. baseline (G1: p=0.02, G2: p=0.02, G3: p=ns) but not between-groups (G3 vs. G1 vs. G2: p=n.s, G3 vs. G2: p=n.s, G3 vs. G1: p=ns, G2 vs. G1: p=n.s)

Table 16. Outcomes of studies assessing educational interventions (continued)

Author year Study design Groups Study quality	Groups, N Age, mean/yrs ± SD (range)	Key Outcomes
TEACCH		
Tsang [198] 2007 Prospective cohort **G1:** TEACCH curriculum (Chinese version) **G2**: Non-TEACCH classroom setup and teaching Quality: Fair	**G1:** 18 **G2:** 16 **G1:** 4.063 ± 0.529 (3-5) **G2:** 4.050 ± 0.734 (3-5)	• G1 statistically significant improvement compared with G2 for CPEP-R Developmental Scale in perception (p≤0.05), Fine Motor (p≤0.01), and Gross Motor (p≤0.05) subsets (means adjusted after controlling for age, IQ, and pretest scores) • G2 showed more progress than G1 in the Daily-living domain (p≤0.001) and the HKBABS sum of domains standard score (p≤0.05) (means adjusted after controlling for age, IQ, and pretest scores) Improvement differences over time in G1 were significant over 12 mo (pre-test, post-test 1, and post-test 2) for all scales and subscales in CPEP-R, Merrill-Palmer Scale of Mental Test (total raw scores and mental age), and the HKBABS (all indicators except overall sum of domain standard score) (range: p<0.05 to p<0.001)
Broad-Based Educational Approaches		
Rickards et al.[204] 2007 RCT **G1:** Combined center-based and home based program **G2:** Center based program only Quality: Good	**G1:** 18 **G2:** 21 **G1:** 44.6 (6.1) **G2:** 43.1 (6.5)	• IQ improved by 1.6 points between T1 and T2 for G1 and decreased by 4.3 for G2 (p= 0.09) • PBCL scores decreased by 8.4 for G1 and decreased by 1.8 for G2 (p=0.054) • NOTE: also includes children diagnosed with developmental and language delays

Table 16. Outcomes of studies assessing educational interventions (continued)

Author year Study design Groups Study quality	Groups, N Age, mean/yrs ± SD (range)	Key Outcomes
Broad-Based Educational Approaches		
Reed et al.[10] 2007, UK Prospective cohort **G1:** ABA **G2:** Special Nursery based on TEACCH **G3**: Portage (visits to parents) Quality:Fair	**G1:** 40 (32-47) **G2:** 43 (41-48) **G3:** 38 (30-45)	• Gains in intellectual functioning: G1-overall gain of approximately 14 points, G2-approximately 10 points; little gain for G3 (~2 points). • Statistically significant gains in the sub-domains of the PEP-R for G1 in imitation (p<0.01), perception (p<0.01), gross motor (p<0.01), hand-eye (p<0.05), cognitive (p<0.01), and verbal (p<0.05) • Statistically significant gains in the sub-domains of the PEP-R for G2 in gross motor (p<0.01), cognitive (p<0.01), and verbal (p<0.01) • Statistically significant gains in the sub-domains of the BAS II for G1 in verbal comprehension (p<0.05), picture matching (p<0.01), naming (p<0.01), and early number skills (p<0.01) • Statistically significant gains in the sub-domains of the BAS II for G2 picture matching (p<0.01), naming (p<0.01), and early number skills (p<0.05) • Statistically significant gains in the sub-domains of the BAS II for G3 in picture matching (p<0.01) • In the sub-domains of the VABS for G2 in communication and socialization (p<0.05) • Statistically significant gains in the sub-domains of the VABS for G3 in communication (p<0.05)
Magiati et al.[9] 2007 Prospective cohort **G1:** Home based family intervention with EIBI **G2:** Autism nursery with eclectic approach Quality: Fair	**G1:** 28 **G2:** 16 **G1:** 38 (7.2) **G2:** 42.5 (7.8)	• No statistically significant differences between the groups post-intervention

ABA=applied behavior analysis; BASII=British Abilities Scale-2nd edition; BCBA=Board Certified Behavior Analyst; CABAS= Comprehensive Application of Behavior Analysis to Schooling; C-PEPR=Chinese version of the PsychoEducational Profile-Revised; EIBI=early intensive behavioral intervention; HKBABS=Hong Kong Based Adaptive Behavior Scales; IQ=intelligence quotient; M=mean; PEP-R=PsychoEducational Profile-Revised; TEACCH= Treatment and Education of Autistic and related Communication-handicapped Children

KQ1. Effects of Treatment on Core and Commonly Associated Symptoms in Children with ASD: Medical Interventions

Medical treatments for symptoms of ASD comprise a variety of pharmacologic agents including antipsychotics, psychostimulants, and serotonin reuptake inhibitors (SRIs). Modalities such as therapeutic diets, supplements, hormonal supplements, immunoglobulin, hyperbaric oxygen, and chelating agents have been employed to treat ASD symptoms. A total of 39 studies were identified in the medical literature, of which 25 were RCTs (Table 17).

Table 17. Overview of studies of medical interventions

	RCTs	NRCTs	Prospective cohort studies	Retrospective cohort studies	Prospective case series	Retrospective case series	Total Literature
	(n=25)	(n=0)	(n=0)	(n=0)	(n=8)	(n=6)	(n=39)
Intervention							
Antipsychotics	7	0	0	0	1	0	8
Serotonin Reuptake Inhibitors	2	0	0	0	1	2	5
Stimulants and other medications for hyperactivity	1	0	0	0	0	3	4
Secretin	7	0	0	0	1	0	8
Dietary and other	8	0	0	0	5	1	14
Diagnostic approach							
Clinical DSM-IV dx +ADI-R and/or ADOS	13	0	0	0	1	0	14
Combination approaches*	10	0	0	0	6	6	22
No DSM-IV or ADOS dx/ unspecified	2	0	0	0	1	0	3
Last outcome assessment							
≤1 month	5	0	0	0	0	0	5
>1 to ≤3 months	16	0	0	0	5	0	21
>3 to ≤6 months	3	0	0	0	0	0	3
>6 to ≤12 months	1	0	0	0	1	0	2
>12 months	0	0	0	0	2	4	6
Unknown	0	0	0	0	0	2	2

Table 17. Overview of studies of medical interventions (continued)

	RCTs	NRCTs	Prospective cohort studies	Retrospective cohort studies	Prospective case series	Retrospective case series	Total Literature
Study population							
U.S.	19	0	0	0	3	6	28
Europe	0	0	0	0	3	0	3
Asia	1	0	0	0	0	0	1
Other	5	0	0	0	2	0	7
Total N participants	1,556	0	0	0	294	655	1,850

ADI-R=Autism Diagnostic Interview-Revised; ADOS=Autism Diagnostic Observation Schedule; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition; dx=diagnosis; NRCT=non randomized controlled trial; RCT=randomized controlled trial
*Clinical DSM-IV dx +other diagnostic tool OR ADOS + other diagnostic tool OR only clinical DSM-IV dx OR only ADOS.

Antipsychotics

Recent clinical trials in children with ASD have focused on the efficacy of a number of atypical antipsychotic medications for treating challenging behavior as well as other distressing symptoms. Risperidone was the first medication to receive FDA approval for the treatment of irritability in children ASD. Aripiprazole also recently received FDA approval for irritability in children with ASD.

Content of the literature. We identified 17 papers from eight studies that addressed the use of antipsychotic medications in children with autism spectrum disorders. Five of these studies evaluated the effects of risperidone,[33-35, 37, 207-210, 211 , 212-215] two of aripiprazole,[216-217] and one of the addition of cyproheptadine to haloperidol.[218] Most participants were recruited from non-primary care populations; table 17 summarizes additional information about these studies. The risperidone literature base includes four RCTs,[33-34, 213-215]all comparing risperidone to placebo. Three of these RCTs were conducted in academic clinic settings using institutional and grant funding.[33-34, 215] The pharmaceutical company that owned the patent for risperidone sponsored another RCT.[213-214]

The literature base on the effects of aripiprazole in children with ASD includes two RCTs,[216-217] both conducted by the pharmaceutical company that owned the patent for aripiprazole. Each RCT compared aripiprazole to placebo in multiple study centers including both academic clinics and independent research centers.[216-217]

The literature base on the effects of cyproheptadine added to haloperidol includes one RCT.[218] This study compared haloperidol alone to haloperidol plus cyptoheptadine in an academic clinic setting.

A variety of outcomes are reported in the literature on antipsychotic effects in children with ASD, but the literature converges on the Aberrant Behavior Checklist-Community Version (ABC-C), a rating scale completed by caregivers of individuals with ASD. For the purposes of this review, we will emphasize specific domains of behavioral change because most studies with

significant differences in overall ratings also showed significant improvements on more specific measures.

Potential side effects or harms, including assessment of weight gain, somnolence, and GI symptoms, were also assessed by most of these studies.

The RCTs included a total of 322 participants in treatment arms, and 214 participants in comparison arms. Participants had an average age of 9.0 and 8.7 years, in the treatment and comparison groups, respectively, when excluding one study that did not provide average ages in each arm.[33] Both treatment and comparison groups had more male subjects (83.9 percent and 83.2 percent, respectively). Five of the studies included only participants with a DSM-IV diagnosis of Autistic Disorder;[33-34, 216-218] whereas one included subjects with any PDD (Autistic Disorder, PDD-NOS or Asperger Disorder).[214] Four of the studies used the Autism Diagnostic Interview Revised (ADI-R) to corroborate diagnosis;[33-34, 216-217] whereas one study used the CARS[214]and another study used DSM-IV criteria only.[218] Only three RCTs provided IQ data on subjects, with the majority of subjects with IQs in the intellectual disability range.[33-34, 214]

Among the studies of antipsychotics, three were good quality, four were fair, and one was poor.

Summary of the literature.

Risperidone. Of the four RCTs of risperidone, two targeted challenging behavior as the primary outcome (Table 18).[33, 214] The first study[33, 35, 207-212] 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.[214] These studies included a total of 89 subjects in risperidone arms and 91 subjects in placebo arms. Both studies used a graduated dose titration design over eight weeks, with an average risperidone dose ranging from 1.5-1.8 mg per day, with one study using primarily once daily dosing[214] and the other using twice daily dosing.[33, 35, 207-212] In these two studies, baseline ratings of irritability were similar across risperidone (ABC-C-I 18.9-26.2) and placebo (ABC-C-I 21.2-25.5) arms. Decreases in ABC-C Irritability were significantly greater for the risperidone arms in both studies, which saw improvements of 12.1-14.9, compared with the placebo arms, which saw improvements of 3.6-6.5.

Similar improvements for a second measure of challenging behavior, the ABC-C Hyperactivity subscale (ABC-C-H), which indexes non-compliance as well as hyperactivity, were also seen in both trials. Baseline ratings of hyperactivity were similar, with decreases in significantly greater for risperidone compared with placebo (14.8-14.9, in comparison to 4.7-7.4). The RUPP study also reported a number of other outcomes that may correlate with challenging behavior, including the Ritvo-Freeman Real Life Rating Scale Affectual Reactions subscale, which includes abrupt changes in mood, temper tantrums, and crying, the Vineland Adaptive Behavior Scale Maladaptive Behavior Domain, and quantitative ratings of parent-rated target symptoms, each of which showed significant improvements in the risperidone group.[35, 210]

Secondary outcomes in the two RCTs of risperidone included measures of repetitive behavior. Both studies included the ABC-C Stereotypy Subscale (ABC-C-S), which showed greater response in the risperidone arm. Baseline ratings of stereotypy were similar across risperidone and placebo arms. Decreases in ABC-C-S were significantly greater for risperidone in one RCT (4.8 vs. 1.7)[33] but would not have been significant after correction for multiple testing in the other RCT (4.3 vs. 2.4).[214] One study[33, 35] also used the CYBOCS-PDD to assess repetitive behavior, finding no baseline differences between the groups but a significantly greater

decrease in the risperidone compared with placebo arms (3.9 vs. 1.0). A number of other outcomes were measured in these studies, but none outside of challenging behavior and repetitive behavior would have yielded statistically significant findings once corrected for multiple comparisons.

Two additional RCTs were identified that did not provide specific numerical ratings on either challenging behavior or repetitive behavior.[34, 215] One of these was an eight-week drug discontinuation RCT with risperidone and placebo arms[34] after positive response during four months of open label risperidone treatment following the RUPP risperidone RCT.[33] This publication did not provide quantitative outcome data but instead indexed 'relapse' using a composite measure of ABC-C-I and clinician ratings of CGI-I,[34] finding significantly less 'relapse' in the risperidone arm (2 of 16 subjects) in comparison to the placebo arm (10 of 16 subjects).

The last RCT was a six-month RCT with risperidone and placebo arms that used a variety of general rating scales to assess response and provided quantitative outcome data on only some of these scales,[215] with the primary outcome measures being parent ratings on the Childhood Autism Rating Scale (CARS) and clinician ratings on the Children's Global Assessment Scale (CGAS). The study only reports CARS median ratings for those participants with at least a 20 percent response.[215] Average ratings on the CGAS were similar in the risperidone (29.8) and placebo (32.7) arms with more improvement in the risperidone (11.1) than placebo (2.5) arms.

All of the risperidone RCTs also provided data on adverse events or side effects (Table 20). All studies reported on weight gain,[33-34, 208, 213-215] which was greater in the risperidone arms (2.7-2.8 kg) than in the placebo arms (0.8-1.7 kg), with a statistically significant difference reported in two of the studies.[33, 208, 213-214] Three of the RCTs[33-34, 208, 213-214] provided data on other adverse events in both the risperidone and placebo arms. Somnolence or drowsiness was the most common adverse event in two of these studies, occurring in 53 of 89 subjects in risperidone arms and nine of 91 subjects in placebo arms.[33, 208, 213-214] These studies also reported that this somnolence improved over time.[33, 208, 213-214] Both these studies also reported more extrapyramidal symptoms, including tremor, dyskinesia, and rigidity, in the risperidone arm in comparison with the placebo arm, but these events were categorized and summed differently between the two studies and did not clearly show a statistically significant difference between treatment arms.[33, 208, 213-214] The RUPP study[33] also reported a greater rise in prolactin levels in the risperidone arm (27.7 ng/mL) compared with the placebo arm (0.8 ng/mL);[212] although it did not report clinical events such as gynecomastia or galactorhea that could be related to elevated prolactin levels.[33-34] 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.[33, 207]

Table 18. Outcomes of RCTs of antipsychotic medications for challenging and repetitive behaviors

Author Year Study quality	Groups, N enrollment/N final	Mean age, years ± SD	Mean IQ ±SD	Outcome measure/Baseline scores, mean ±SD	Outcome measure/Post-treatment scores*, mean ± SD
RUPP[34] 2005 Quality: Fair	**G1**:risperidone, 16/16 **G2**:placebo, 16/16	NR, subset of subjects from RUPP 2002	NR, subset of subjects from RUPP 2002	Overall, ABC-C-Irritability: 27.6 ± 6.1 Overall, ABC-C-Hyperactivity/ Noncompliance: 34.4 ± 8.7 Relapse: 2 consecutive weeks of 25% increase on ABC-C-Irritability and CGI-I of 'much worse' or 'very much worse'	Relapse: **G1:** 2/16 (12.5%) **G2:** 10/16 (62.5%) p=0.01
Shea, et al.[213-214] 2004 Quality: Fair	**G1:** risperidone, 41/39 **G2:** placebo, 39/38	**G1:** 7.6 ± 2.3 **G2:** 7.3 ± 2.3	**G1:** ≥85:3 71-84:6 50-70:12 35-49:10 **G2:** ≥85:11 71-84:4 50-70:8 35-49:12	ABC-C-Irritability: **G1:** 18.9 ± 8.8 **G2:** 21.2 ± 9.7 ABC-C-Hyperactivity/ Noncompliance: **G1:** 27.3±9.7 **G2:** 30.9±8.8 ABC-Stereotypic behavior: **G1:** 7.9±5.0 **G2:** 8.1± 5.6	Change in: ABC-C-Irritability: **G1:** -12.1 ± 5.8 **G2:** -6.5 ± 8.4 p ≤ 0.001 ABC-C-Hyperactivity/ Noncompliance: **G1:** -14.9±6.7 **G2:** 7.4±9.7 p ≤ 0.001 ABC-Stereotypic behavior: **G1:** -4.3± 3.8 **G2:** -2.4±4.0 p ≤ 0.05

Table 18. Outcomes of RCTs of antipsychotic medications for challenging and repetitive behaviors (continued)

Author Year Study quality	Groups, N enrollment/N final	Mean age, years ± SD	Mean IQ ±SD	Outcome measure/Baseline scores, mean ±SD	Outcome measure/Post-treatment scores*, mean ± SD
RUPP[33, 35, 207-212] 2002 Quality: Good	**G1**:risperidone, 49/49 **G2**:placebo, 52/52	Overall 8.8 ± 2.7	Overall, N(%) ≥Avg: 3(7) Borderline: 8(17) Mild or moderate retard-ation: 20(43) Severe retard-ation: 15(33)	ABC-C-Irritability: **G1:** 26.2±7.9 **G2:** 25.5±6.6 ABC-C-Hyperactivity/ Noncompliance: **G1:** 31.8±9.6 **G2:** 32.3±8.5 ABC-Stereotypic behavior: **G1:**10.6±4.9 **G2:** 9.0±4.4 CYBOCS: **G1:** 15.51 ± 2.73 **G2:** 15.18±3.88	ABC-C-Irritability: **G1:** 11.3 ± 7.4 **G2:** 21.9 ± 9.5 p<0.001 ABC-C-Hyperactivity/ Noncompliance: **G1:** 17.0 ± 9.7 **G2:** 27.6 ± 10.6 p<0.001 ABC-Stereotypic behavior: **G1:** 5.8 ± 4.6 **G2**: 7.3 ± 4.8 p<0.001 CYBOCS: **G1:** 11.65 ± 4.02 **G2:** 14.21 ± 4.81 p<0.005

Table 18. Outcomes of RCTs of antipsychotic medications for challenging and repetitive behaviors (continued)

Author Year Study quality	Groups, N enrollment/N final	Mean age, years ± SD	Mean IQ ±SD	Outcome measure/Baseline scores, mean ±SD	Outcome measure/Post-treatment scores*, mean ± SD
Marcus et al.[216] 2009 Quality: Good	**G1**: aripiprazole 5 mg, 53/44 **G2**:aripiprazole 10 mg, 59/49 **G3**:aripiprazole 15, 54/47 **G4**:placebo, 52/38	**G1:** 9 ± 2.8 **G2:** 10±3.2 **G3:** 9.5±3.1 **G4:** 10.2±3.1	NR	ABC-C-Irritability: **G1:** 28.6 ± 7.6 **G2:** 28.2 ± 7.4 **G3**: 28.9 ± 6.4 **G4:** 28 ± 6.9 ABC-C-Hyperactivity/ Noncompliance: **G1:** 33.1 ± 1.4 **G2:** 33.7 ± 1.3 **G3:** 32.2 ± 1.4 **G4:** 31.0 ± 1.4 ABC-C-Stereotypic: **G1:** 11.4 ± 0.8 **G2:** 11.6 ± 0.8 **G3:** 11.6 ± 0.8 **G4:** 10.7 ± 0.8 CYBOCS: **G1:** 13.9 ± 0.6 **G2**: 13.5 ± 0.5 **G3:** 14.1 ± 0.5 **G4:** 13.7 ± 0.6	Change in: ABC-Irritability **G1**:-12.4 **G2:** -13.2 **G3:** -14.4**G4:** -8.4 **G1 v G4:** p=0.032 **G2 v G4:** p=0.008 **G3 v G4:** p=0.001 ABC-C-Hyperactivity/ Noncompliance: **G1:** -14.0 ± 1.6 **G2:** -13.3 ± 1.5 **G3:** -16.3 ± 1.6 **G4:** -7.7 ± 1.7 **G1 v G4:** p≤0.005 **G2 v G4:** p≤0.05 **G3 v G4:** p≤0.001 ABC-C-Stereotypic **G1:** -4.5±0.68 **G2:** -4.2±0.63 **G3:** -4.5±0.66 **G4:** -1.8±0.69 **G1 v G4:** p≤0.005 **G2 v G4:** p≤0.05 **G3 v G4:** p≤0.005 CYBOCS: **G1:** -2.6±0.5 **G2:** -2.4±0.4 **G3:** -3.2±0.5 **G4:** -1.7±0.5 G1 v G4:p NS G2 v G4: p NS G3 v G4:p≤ 0.05

Table 18. Outcomes of RCTs of antipsychotic medications for challenging and repetitive behaviors (continued)

Author Year Study quality	Groups, N enrollment/N final	Mean age, years ± SD	Mean IQ ±SD	Outcome measure/Baseline scores, mean ±SD	Outcome measure/Post-treatment scores*, mean ± SD
Owen et al.[217] 2009 Quality: Good	**G1**:aripi-prazole, 47/39 **G2**: placebo, 51/36	**G1:** 9.7 ± 3.2 **G2:** 8.8 ± 2.6	NR	ABC-C-Irritability: **G1:** 29.6 ± 6.4 **G2:** 30.2 ± 6.5 ABC-C-Hyperactivity/ Noncompliance: **G1:** 34.1 **G2:** 34.7 ABC-C-Stereotypic: **G1:** 11.9 **G2:** 10.7 CYBOCS: **G1:** 12.8 **G2:** 13.7	Change in: ABC-Irritability (change): **G1:** -12.9 **G2:** -5.0 P< 0.001 ABC-C-Hyperactivity/ Noncompliance (change): **G1:** -12.7 **G2:** -2.8 P< 0.001 ABC-C-Stereotypic (change): **G1:** -4.8 **G2:** -2.0 p< 0.001 CYBOCS (change): **G1:** -3.8 **G2:** -0.8 p< 0.001 CYBOCS (change): **G1:** -3.8 **G2:** -0.8 p< 0.001

*Decrease in scores on outcome measures indicates improvement in behavior assessed. ABC-C=Aberrant Behavior Checklist-Community Version; CGI-I=Clinical Global Impression-Irritability; CYBOCS=Children's Yale-Brown Obsessive Compulsive Scale; NR=not reported; RUPP=Research Units on Pediatric Psychopharmacology

Case series data, including that from the risperidone arm and open label extension of the RUPP RCT,[34] indicated results consistent with the risperidone arms of the RCTs.[33, 34, 36, 211].

Aripiprazole. We identified two eight-week randomized, controlled trials of aripiprazole in children with ASD.[216-217] The manufacturer of aripiprazole sponsored both studies. The primary outcome for these studies was challenging behavior indexed by the Autism Behavior Checklist-Community Version Irritability (ABC-C-I) subscale. These studies included a total of 213 subjects in aripiprazole arms and 103 subjects in placebo arms within the intent to treat analyses. One study used a fixed dose design with one placebo arm and three arms corresponding to 5, 10, and 15 mg per day of aripiprazole,[216] with all subjects beginning at two mg per day with forced titration weekly to the next dose until they reached their goal dose. The other study used a dose

titration schedule with weekly progression from 2 mg to 5 mg, 10 mg, and 15 mg per day following clinical judgment.[217] In these two studies, baseline ratings of irritability were similar across aripiprazole (ABC-C-I 28.2-29.6) and placebo (ABC-C-I 28.0-30.8) arms. Decreases in ABC-C Irritability were significantly greater for the aripiprazole arms in both studies, with improvements of 12.4-14.4, in comparison to the placebo arms, with improvements of 5.0-8.4. The trial with differing set doses of aripiprazole demonstrated increasing response with increasing dose.[216] Overall, the results of the trial that used titration following clinical judgment were more pronounced.[217]

Additional assessments of challenging behavior were also performed in these two aripripazole RCTs. Similar improvements for a second measure of challenging behavior, the ABC-C Hyperactivity subscale (ABC-C-H), which indexes non-compliance as well as hyperactivity, were also seen across both trials. Baseline ratings of hyperactivity were similar across aripiprazole and placebo arms. Decreases in ABC-C-H were significantly greater for aripiprazole in which improvements of 12.7-16.3 were seen, in comparison to the placebo arms, with improvements of 2.8-7.7. The ABC-C Inappropriate Speech subscale (ABC-C-IS) also showed significant improvement in one study[217] with a supportive trend in the other.[216]

Secondary outcomes in the two major RCTs of aripiprazole included measures of repetitive behavior.[219] Both studies included the ABC-C Stereotypy Subscale (ABC-C-S), which showed significantly greater response in the aripiprazole arms. Baseline ratings of stereotypy were similar across aripiprazole and placebo arms. Decreases in ABC-C-S were greater for aripiprazole, with improvements of 4.2-4.8, in comparison to placebo arms, with improvements of 1.8-2.0. Both studies also used the CYBOCS-PDD to assess repetitive behavior, finding no baseline differences between the groups but a greater decrease in the aripiprazole compared with placebo arms (2.4-3.8 vs. 0.8-1.7). A number of other outcomes were measured in these two studies, but none outside of challenging behavior and repetitive behavior yielded statistically significant findings once corrected for multiple comparisons.

The two aripiprazole RCTs also provided data on harms (Table 20). Both studies reported on weight gain,[216-217] which was greater in the aripiprazole arms (1.3-2.0 kg) than in the placebo arms (0.3-0.8 kg), with a statistically significant difference reported in both of the studies.[216-217] Somnolence and sedation were the most common adverse events in both of these studies, occurring in 66 of 210 subjects in aripiprazole arms and eight of 101 subjects in placebo arms.[216-217] Both studies also reported more extrapyramidal symptoms, including tremor, dyskinesia, and rigidity, occurring in 44 of 210 subjects in the aripiprazole arms in comparison with ten of 210 subjects in the placebo arms.[216-217] Both studies found a statistically significant decrease in prolactin levels in the aripiprazole arms in contrast with the placebo arms.[216-217]

Cyproheptadine plus haloperidol. One eight-week RCT compared addition of cyproheptadine versus placebo to haloperidol.[218] Each arm contained 20 subjects.[218] The medication doses were titrated up from some starting point to cyproheptadine 0.05 mg/kg/day and haloperidol 0.2 mg/kg/day, but no details are provided. Two general outcome measures were used, the ABC-C and the CARS, each of which was apparently translated into Farsi; although no details were provided on validation of the translated versions, nor is it clear whether parents completed paper and pencil versions of these measures or were interviewed. Baseline scores of the ABC-C and CARS measures were only presented in graphs. The ABC-C scores shown are markedly lower than the total ABC-C scores obtained at baseline in other medication trials,[33, 214, 216-217] suggesting that a subscale may have been administered; although this is not stated.[218] The

response to placebo plus haloperidol was smaller[218] than the response found in previous haloperidol trials.[70, 220] The improvement in ABC-C score in the cyproheptadine plus haloperidol arm was larger (10.9) than the improvement in the placebo plus haloperidol arm (3.7).[218] Similarly, the improvement in CARS score was greater in the cyproheptadine plus haloperidol arm (1.85) than in the placebo plus haloperidol arm (0.37).

Serotonin Reuptake Inhibitors

Serotonin reuptake inhibitors (SRIs) have come into wide use for the treatment of depression and anxiety and are some of the most commonly prescribed medications for children with ASD.[72-74] Most recent clinical trials in children with ASD have focused on their potential to decrease repetitive behaviors.[80]

Content of the literature. We identified five studies that addressed the use of serotonin reuptake inhibitor medications in children with autism spectrum disorders; table 17 includes additional details. Two of these studies evaluate the effects of fluoxetine,[221-222] one of citalopram,[223] one of escitalopram,[12] and one of a variety of SRIs.[11]The literature base on the effects of fluoxetine in children with ASD included one retrospective case series[222] and one randomized, controlled, cross-over trial of fluoxetine compared with placebo. Both of these studies were conducted in academic clinic settings using institutional or grant funding.[221] The single study on the effects of citalopram in children with ASD was a randomized, controlled trial conducted in multiple academic centers using institutional and grant funding.[223] The single study on the effects of escitalopram in children with ASD was a prospective case series[12] that analyzed outcome by serotonin transporter genotype, and is therefore discussed in detail in the Modifiers of Treatment Effectiveness (Key Question 2) section of the report. One retrospective case series[11] reported on a number of SRIs.

The two RCTs included a total of 112 participants in treatment arms, and 115 participants in comparison arms. Participants had an average age of 8.8 and 9.1, in the treatment and comparison groups, respectively.[221, 223] Both treatment and comparison groups had more male subjects (83.7 percent and 81.7 percent, respectively). Both of the studies included subjects with any PDD (Autistic Disorder, PDD-NOS, or Asperger Disorder and used either the ADI-R[223] or the ADI-R and the ADOS for corroboration.[221] One of the RCTs had a minority of subjects with intellectual disability,[223] and the other had an average IQ in the intellectual disability range.[221] The three case series included 276 subjects with any diagnosis of PDD.[11-12, 222] One study used ADI-R to corroborate DSM-IV diagnosis,[12] one used CARS plus ADOS,[222] and one used DSM-IV only.[11] Among the case series subjects, the average age was 6.9 years old and 87.1 percent were male. Only one case series provided IQ measures on subjects[12] and had average verbal and nonverbal IQ in the borderline to low average range (76 and 86, respectively). Among all studies of SRIs, one was good quality, two were fair, and two were poor.

Summary of the literature. We review citalopram and escitalopram together because escitalopram is the active component (enantiomer) of citalopram. One 12-week randomized, controlled trial of citalopram was identified.[223] This trial focused on repetitive behavior outcomes with a number of secondary outcomes also measured. The entry criteria for the study were a PDD diagnosis corroborated by both ADI-R and ADOS, moderate illness severity on the CGI-S and significant repetitive behavior on the CYBOCS-PDD.[223] It had 73 subjects in the citalopram arm and 76 in the placebo arm.[223] Subjects were begun on 2.5 mg of citalopram daily with weekly increases of 2.5 mg per day for the first five to six weeks as clinically indicated,

followed by weekly increases of up to five mg per day thereafter, up to a maximum dose of 20 mg per day.[223] This dose is lower than the equivalent daily dose of SRIs used in obsessive compulsive disorder in previous studies,[224-225] but it is similar to dosing used in an earlier case series in autism.[226]

No significant difference between citalopram and placebo arms was seen in measures of repetitive behavior, with similar baseline scores on the CYBOCS-PDD (15.1 vs. 15.0) and similar improvements (2.0 vs. 1.9) in each arm. The other measures of repetitive behavior, including the Repetitive Behavior Scale Revised, also showed similar baseline scores and similar improvements in each arm with no evidence for an effect of citalopram (Table 19).[223] The CGI-I similarly showed no significant difference between the citalopram and the placebo arm. On the other hand, the primary measure of challenging behavior reported in this trial, the ABC-C Irritability (ABC-C-I) subscale, showed an advantage for citalopram. The baseline ratings were not statistically different between the citalopram and placebo arms (13.2 and 11.2, respectively), but more improvement was seen for citalopram (3.2) than for placebo (0.9).[223] Adverse effects in this study included a marked increase in what were termed 'activation' symptoms, including increased energy, hyperactivity, inattention, disinhibition, and decreased sleep in the citalopram arm in comparison to the placebo arm.[223] Diarrhea and dry or itchy skin were also more common in the citalopram arm.[223]

Table 19. Outcomes of studies of SRIs for the treatment of repetitive & challenging behaviors in ASD

Author, Year, Country Study quality	Groups, N enrollment/N final	Mean age, years ±SD	Mean IQ ±SD	Outcome measure/Baseline scores, mean ±SD	Outcome measure/Post-treatment scores*, mean ±SD
King et al.[223] 2009, US Quality: Good	**G1**:citalopram hydrobromide, 73/60 **G2**:placebo, 76/63	**G1**: 9.1 ± 3.2 **G2**: 9.6 ± 3.1	**G1**: >70, N (%): 43(61.4) **G2**: >70, N (%): 43(60.6)	CYBOCS-PDD: **G1**:15.1 ± 1.8 **G2**: 15 ± 2.1	CYBOCS-PDD: **G1**: 13.1 ± 3.7 **G2**: 13.1 ± 3.2

Table 19. Outcomes of studies of SRIs for the treatment of repetitive & challenging behaviors in ASD (continued)

Author, Year, Country Study quality	Groups, N enrollment/N final	Mean age, years ±SD	Mean IQ ±SD	Outcome measure/Baseline scores, mean ±SD	Outcome measure/Post-treatment scores*, mean ±SD
Hollander et al.[221] 2005, US Quality: Fair	**G1**a:placebo /fluoxetine, placebo segment 45(total)/20	7.35 SD - NR	68.1 ± 26.7	CYBOCS: Wk 0: 13.5±2.9	CYBOCS: Wk 8: 13.0 ± 3.2
	G1b:placebo/ fluoxetine, fluoxetine segment 45(total)/20	7.35	68.1 ± 26.7	CYBOCS: Wk 12: 12.9 ± 3.5	CYBOCS: Wk 20: 11.8 ± 3.2 P<0.05 for repeated measures cross-over comparison of G1b to G1a and G2a to G2b
	G2a:fluoxetine /placebo, fluoxetine segment 45(total)/19	9.1±3.7	59.2 ± 29.1	CYBOCS: Wk 0: 12.8 ± 2.6	CYBOCS: Wk 8: 11.6 ± 3.8 P>0.05 for parallel group comparison of G2a to G1a
	G2a:fluoxetine /placebo, placebo segment 45(total)/19	9.1±3.7	59.2 ± 29.1	CYBOCS: Wk 12: 12.2 ± 3.5	CYBOCS: Wk 20: 12.4 ± 2.4

* Decrease in scores on outcome measure indicates improvement in behavior assessed. ABC-C=Aberrant Behavior Checklist-Community Version; CYBOCS=Children's Yale-Brown Obsessive Compulsive Scale; CYBOCS-PDD=Childrens Yale-Brown Obsessive Compulsive Scale-Pervasive Development Disorders

One prospective case series of escitalopram was identified.[12] This ten-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 with a PDD corroborated by ADI-R and a minimum ABC-C-I score of 12 underwent a forced dose titration of escitalopram from 2.5 mg daily increasing weekly to 5 mg, 10 mg, 15 mg, and 20 mg, essentially twice the dose equivalent of citalopram given that escitalopram is the active component of racemic citalopram. Pre-designated dose-limiting side effects included sleep disruption and an increase in ABC-C Irritability or Hyperactivity subscales of ten points over the previous week. Average daily doses of escitalopram were 10.8-12.4 mg and did not differ across genotype groups, which reflects the fact that most subjects in all genotype groups could not tolerate the maximum dose. Unfortunately, the data are presented in figures only, and raw values cannot be inferred. It is evident, however, that the ABC-C-I for all subjects was 20 or greater at baseline and that

improvements were about ten points for three of the four genotype groups.[12] Adverse effects were not directly assessed in this study.

One randomized, controlled cross-over trial of fluoxetine was identified with two eight-week treatment periods separated by a four-week washout period.[221] Thirty-nine subjects with a PDD corroborated with ADI-R and ADOS were included in the final analysis with no minimum required score on a repetitive behavior scale. Five additional subjects were randomized but not included in the analysis for various reasons. Of the randomized subjects, 19 received fluoxetine followed by placebo and 20 received placebo followed by fluoxetine. During each phase of the study, subjects began the first week at 2.5 mg per day of fluoxetine or placebo, followed as clinically indicated by weekly upward titration to 0.3 mg/kg for week 2, 0.5 mg/kg/day for week 3, and 0.8 mg/kg/day for weeks four to eight. During the first eight-week treatment period of the study, subjects randomized to fluoxetine first had baseline CYBOCS scores of 12.8 and those to placebo first had baseline scores of 13.5. Subjects in the first fluoxetine group showed an improvement of 1.2, and those in the first placebo arm showed an improvement of 0.5. These differences were not statistically significant when considered alone. In the second eight-week treatment period, subjects randomized to fluoxetine second had baseline CYBOCS scores of 12.8 and those to placebo second had baseline scores of 12.2. 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 CYBOCS change in the fluoxetine arms was significantly greater than the CYBOCS change in the placebo arms. No adverse events were significantly more frequent in the fluoxetine group; although more subjects on fluoxetine had their dose reduced due to agitation.[221] The two chart reviews of SRIs [11, 222] reported in the literature were of poor quality and included general outcome measures that are difficult to compare with the RCT data.

Table 20. Harms frequently reported in studies of medical interventions*

Range % subjects with adverse event (number of studies)	Placebo	Risperidone	Aripiprazole	SRIs	Psycho-stimulants
Abdominal pain	1.5-18 (5)	1.6-20 (4)	4.2 (1)	1.1-17.8 (2)	12.0 (1)
Constipation	2.6-12 (2)	3.2-31.5 (5)	NR	3.4 (1)	NR
Diarrhea	6.1-22 (5)	1.6-33.1 (3)	8.5 (1)	4.5-26.0 (3)	4.6 (1)
Appetite changes/weight gain	3.0-25 (6)	7.9-89.5 (7)	12.1-14.9 (2)	3.4-24.7 (3)	24.2 (1)
Nausea/vomiting	3.0- 24 (6)	4.8-42.7 (4)	13.3-14.9 (2)	19.2 (1)	NR

Table 20. Harms frequently reported in studies of medical interventions (continued)

Range % subjects with adverse event (number of studies)	Placebo	Risperidone	Aripiprazole	SRIs	Psycho-stimulants
Fatigue	0-27 (6)	1.6-75 (4)	15.2-21.3 (2)	13.7-17.9 (2)	6.1 (1)
Insomnia	1.5-47.2 (5)	4.8-37.9 (4)	6.4 (1)	12.4-38.4 (3)	18.2 (1)
Somnolence/sedation/ drowsiness	3.9-12 (4)	3.2-72.5 (7)	17.0-23.6 (2)	NR	NR
Urinary symptoms	2.0-29 (4)	3.2-38.7 (4)	2.4-6.4 (2)	10.3 (1)	NR
Rash or other skin changes	2.0-14 (3)	4.8-29.0 (3)	2.4 (1)	28.7 (1)	NR
Headache	0-16.0 (6)	3.2-34.7 (4)	6.4-7.9 (2)	1.1-20.5 (2)	6.0 (1)
Fever/pyrexia	0-17.9 (3)	4.8-21.0 (3)	8.5-9.1 (2)	NR	NR
Cold/flu/respiratory infection/cough/nasal congestion	3.9-39 (5)	6.3-79.8 (5)	6.4-9.7 (2)	42.5 (1)	NR
Cardiac changes	0-6.1 (3)	12-14.5 (3)	NR	NR	4.6 (1)
Extra pyramidal symptoms	0-12.8 (5)	1.6-27.5 (6)	10.3-14.9 (2)	1.1 (1)	NR
Mood changes (irritability, outbursts, agitation)	3.0-44.0 (4)	1.6 (1)	NR	24.7-46.2 (3)	13.6 (1)
Anxiety/nervousness	3.0-33.3 (4)	4.8-29.0 (4)	NR	1.1-15.9 (3)	8.0 (1)
Self injury or suicide ideation	2.8-6.0 (2)	NR	2.1 (1)	NR	6.0 (1)
Withdrawal from study due to adverse event	2.5-9.2 (4)	1.6-22.6 (4)	10.2-10.6 (2)	12.3-19.0 (2)	18.1 (1)

*Includes interventions for which there was more than one study; NR=not reported, SRI=serotonin reuptake inhibitor

Stimulants and Other Medications to Treat Hyperactivity

Psychostimulants treat hyperactivity and inattention in patients diagnosed with attention deficit hyperactivity disorder (ADHD) and include agents such as methylphenidate (MPH), amphetamine, and dextroamphetamine. Other medications studied for the treatment of ADHD have also been studied for the treatment of hyperactivity in ASD.[81-85]

Content of the literature. We identified six publications[13-17, 227] from four studies that addressed stimulant and other medications to treat hyperactivity; table 17 summarizes study information. Most participants were recruited from centers in the Research Units on Pediatric Psychopharmacology (RUPP) network.[13-15] Studies assessed the use of methylphenidate hydrochloride (MPH) in children with PDD-NOS and hyperactivity;[13-15] psychostimulants[16, 227] ; and guanfacine to target hyperactivity, inattention, and impulsivity in children with PDD.[17] Among all studies of these medications, one was good quality and three were poor.

Summary of the literature. The RUPP Autism Network's double-blind cross-over trial[13-15] of MPH included 72 children with autism, PDD-NOS or Asperger disorder who received a one-day placebo followed by two days at each of three (low, medium, high) test doses of MPH; doses ranged from 7.5 mg/day to 50.0 mg/day. Subjects tolerating MPH (n=66) moved on to a four week, double-blind crossover phase. Subjects with a positive response in the double blind phase (n=34) completed an eight week open label continuation phase at their best dose. The primary outcome measure was hyperactivity as assessed by the Aberrant Behavior Checklist (ABC) teacher-rated hyperactivity subscale; secondary measures included the ABC parent-rated hyperactivity subscale. Blinded clinicians also assessed participants using the CGI-Irritability (CGI-I) scale; this subscale and the ABC parent and teacher rated hyperactivity subscales were combined to assess response.

In the double-blind crossover phase, all MPH doses demonstrated effects that were statistically superior to placebo, and effect sizes favored the medium dose for parent ratings and high dose for teacher ratings. Parent-rated lethargy/ social withdrawal significantly worsened during the high dose of MPH compared with placebo. Significant improvement in parent-rated stereotypy and inappropriate speech were seen at the medium dose of MPH compared with placebo. Hyperactivity/impulsivity also improved more with the medium and high MPH doses than at the low dose (Table 21).

Significantly more joint attention behaviors as measured on the Joint Attention from the Early Social Communication Scales (JAMES) in the intervention group were reported both with the best MPH dose and with the low dose compared with placebo. There was improved self-regulation, as assessed in a "competing demands" task in low dose as well as in medium dose MPH compared with placebo. A significant increase in neutral affect was also found for the medium and high dose, which could be either beneficial, in the case of children with a labile mood, or damaging, in the case of children with flattened affect due to a medication side effect. Irritability was the most frequent reason for discontinuation (18 percent) of treatment.

Table 21.Outcomes of studies of stimulants for the treatment of hyperactivity in ASD

Author, Year, Country Study quality	Groups, N enrollment/N final	Mean age, years ±SD; Mean IQ ±SD	Outcome measure/ Baseline scores, mean ±SD	Outcome measure/Post-tx scores*, mean ±SD
RUPP,[13] Posey et al.[14]& Jahromi et al.[15] 2005, 2007, & 2009, US Quality:Good	Total N=66 **G1:** low dose MPH (n=45) **G2:** medium dose MPH (n=52) **G3**: high dose MPH (n=33) **G4**: optimal dose MPH (n=58) **G5:** placebo (n=46)	7.5 ± 2.2 Slosson IQ: 62.6 ± (32.9)	Teacher ABC-Hyperactivity: 30.9 ± 7.9	**G1:** 22.9 ± 12.8, p=0.03 **G2:** 23.6 ± 12.5, p=0.008 **G3:** 20.3 ± 11.9, p=0.002 **G4:** 20.1 ± 12.4, p<0.001 **G5:** 26.0 ± 11.7

*Decrease in scores indicates improvement in outcome assessed. ABC=Aberrant Behavior Checklist; IQ=intelligence quotient; MPH=methylphenidate; RUPP=Research Units on Pediatric Psychopharmacology

Three chart reviews assessed guanfacine and psychostimulant use in children with ASDs, all of which were poor in quality and provided conflicting results on the effectiveness of stimulants for hyperactivity in children with ASD.[16-17, 227]. The three chart reviews had a longer duration of follow-up visits: 7-1,776 days,[17] 1-3650 days,[16] 4 ± 3.9 years,[227] while the RCT followed their patients only for 8 weeks.[13-15]

Secretin

Interest in secretin for the treatment of ASD symptoms stemmed from a non-blinded, uncontrolled cases series of three children that reported social, cognitive and communicative gains in recipients after the first infusion and after a second infusion given weeks later.[90] Multiple studies conducted after the initial case series have evaluated secretin's utility in treating autistic symptoms, employing single or multiple doses of synthetic human or porcine secretin.

Content of the literature. We identified eight publications[228-235] addressing secretin use in eight unique populations; table 17 summarizes additional study information. Among studies of secretin, two were good quality, five were fair, and one was poor.

Summary of the literature. Of the eight studies evaluating the impact of secretin in the treatment of ASD, one[232] was a repeated dose intervention study. Two studies used synthetic human secretin,[228-229] three used porcine secretin,[231, 233-234] and one biologic secretin.[230] All were randomized controlled trials except one open label trial of secretin (type unknown) with a prospective case series study design;[235] all of the studies evaluated only short term outcomes with follow-up periods ranging from 3 to 12 weeks.

No studies showed significantly greater improvements in measures of language, cognition or autistic symptoms when compared with placebo; in those studies that demonstrated improvement

over time, they did so equally in both intervention and placebo groups. There also was no benefit by type of secretin (porcine or synthetic).

Dietary and Other Medical Interventions

Additional studies in the medical literature addressed the use of dietary interventions (including special diets) as well as medical therapies for sleep and gastrointestinal dysfunction, hyperbaric oxygen, and other agents.

Content of the literature-dietary interventions*:* We identified seven studies conducted in the clinic setting that addressed the use of various oral dietary supplements to treat ASD in children, including ages ranging from one to 18 years; interventions included iron,[236] magnesium-vitamin B6,[237] melatonin,[238] ketogenic diet,[239] and fish oil and evening primrose oil.[240] Two studies focused on amino acid derivatives, including L-carnosine[241] and N,N dimethylglycine.[242] Studies measured a wide range of outcomes, with little overlap in instruments utilized among the studies. Most studies analyzed outcomes after 18 days to three months;[236, 240-242]one study assessed outcomes after six months,[239] one study after a mean of eight months,[237]and one examined data at a mean of 1.8 years of follow-up.[238] Four studies reported adverse events.[236, 239, 242-243] Table 17 includes additional study information.

Summary of the literature-dietary interventions. Two RCTs explored dietary supplementation with amino acid derivatives in ASD. The eight-week RCT of daily L-carnosine supplementation was conducted at a specialty clinic in Illinois and included 31 children ages three to twelve years with ASD.[241] Significant changes in CGI at two weeks compared with six weeks were observed in the L-carnosine group; significant effects on receptive vocabulary and Gilliam Scale scores were also observed before vs. after treatment in this group. However, no significant changes were observed between groups in the Gilliam Autism Rating Scale measure of ASD severity, Receptive and Expressive Picture Vocabulary scores, or parent-rated CGI measure of overall improvement. Adverse effects in the L-carnosine group included sporadic hyperactivity and were alleviated by dose reduction.

The four-week randomized controlled trial of daily N,N-dimethylglycine treatment was conducted at an academic clinic in Texas and included 37 children with ASD ages three to eleven years.[242] The dimethylglycine group did not improve more than the placebo group on any behavioral measure (Vineland, ABC-C). There was no significant effect on neurologic examination of motor skills, muscle tone, or coordination. Adverse effects in the dimethylglycine group were similar to placebo.

Table 22. Outcomes of RCTs of dietary supplements for the treatment of ASD

Author, Year, Country Study quality	Groups, N enrollment/N final	Mean age, years ± SD Mean IQ ± SD	Key Outcomes
Chez et al.[241] 2002 US Quality: Fair	**G1**: L-carnosine, 14/14 **G2:** placebo, 17/17	**G1**: 7.71 ± 2.41 NR **G2:** 7.14 ± 2.05 NR	• Significant difference at baseline in communication subscale of the Gilliam Autism Rating Scale, with worse scores in G1 (p=0.02) • Pre-post changes on some measures present in the intervention group only, but the authors did not compare the differences across groups

Table 22. Outcomes of RCTs of dietary supplements for the treatment of ASD (continued)

Author, Year, Country Study quality	Groups, N enrollment/N final	Mean age, years ± SD Mean IQ ± SD	Key Outcomes
Kern et al.[242] 2001 US Quality: Fair	**G1:**dimethylglycine, 39(total)/18 **G2**:placebo, 39(total)/19	Overall 3-11 (mean & SD NR) NR	• No significant differences on any outcomes assessed were observed between N,N-dimethylglycine and placebo arms.

The remainder of the studies were case series of poor quality, in which modest effects were observed in improving sleep with iron supplementation[236] and melatonin[238], and for affecting general autism symptoms with magnesium and vitamin B6 [237] and a combination of fish oil and evening primrose oil[240] . Modest improvements were seen in some children with a ketogenic diet, but drop out was high.[239]

Content of the literature-other interventions*:* We identified eight papers from seven studies conducted in the clinic setting that examined various other medical therapies for treatment of ASD in children, including ages ranging from two to 19 years; interventions included amantadine,[244] piracetam added to a risperidone regimen,[245] hyperbaric therapy,[246] oral human immunoglobulin,[98] and dimercapto succinic acid (DMSA).[243, 247] Two studies focused on cholinesterase antagonists, including rivastigmine tartrate[248] and donezepil hydrochloride (DH).[249] These studies typically examined outcomes after three to 12 weeks of therapy.[98, 244-246, 248-249] Six studies reported on adverse events.[98, 244-247, 249] Table 17 summarizes additional study details. Among all studies of dietary and other interventions, two were good quality, five were fair, and seven were poor.

Summary of the literature-other interventions. The RCT of amantadine,[244] conducted at six academic clinics in the US and UK and including 39 children, showed no effect of daily amantadine over four weeks on parent-rated Aberrant Behavior Checklist-Community (ABC-C) behavior scores and clinician-rated CGI rating of overall improvement (Table 23). However, children in the amantadine arm improved significantly more than those receiving placebo in clinician-rated ABC-C subscales for hyperactivity and inappropriate speech. There were no differences in harms, and no serious complications.

Table 23. Outcomes of RCTs of other medical interventions for the treatment of ASD

Author, Year, Country Study quality	Groups, N enrollment/N final	Mean age, years ±SD Mean IQ ±SD	Key Outcomes
King et al.[244] 2001 US Quality: Fair	**G1:** amantadine, 43(total)/19 **G2:** placebo, 43(total)/20	**G1:** 7 (5-11 range) >35 **G2:** 7 (5-15 range) >35	• Proportion of responders (reduction of at least 25% in subscale scores for ABC-C-irritability &/or hyperactivity) in tx group (9, 47%) was higher than in the placebo group (7, 37%), but was not statistically significant (p=0.511)

Table 23. Outcomes of RCTs of other medical interventions for the treatment of ASD (continued)

Author, Year, Country Study quality	Groups, N enrollment/N final	Mean age, years ±SD Mean IQ ±SD	Key Outcomes
Handen et al.[98] 2009 US Quality: Good	**G1a**: IGOH(140 mg/day), 32/27 **G1b:** IGOH(420 mg/day), 31/23 **G1c:** IGOH(840 mg/day), 31/24 **G2:** placebo, 31/26	**G1a:**7.4±3.1 NR **G1b:** 8±4.1 NR **G1c:**7.6±3.5 NR **G1d:**6.2±3.3 NR	• No significant difference between groups in the primary endpoint, overall clinical response to tx based on MGIS (140 mg/day, p=0.39; 420 mg/day, p=0.19; 840 mg/day, p=0.44) • No significant benefit of all active txs combined compared with placebo (p=0.22)
Rossignol et al.[246] 2009 US Quality: Good	**G1:** hyperbaric oxygen, 33/30 **G2:** pressurized room air, 29/26	**G1:** 4.97 ± 1.29 **G2:** 4.86 ± 1.13 Mean IQ NR	• Significant improvements on ABC total score (p=0.0118); in the treatment group only, indicating improvements in challenging behaviors • Significant improvements on the ATEC sensory/cognitive awareness subscale in the treatment group compared with the control group
Chez et al.[249] 2003 US Quality: Fair	**G1:** DH, 23/17 **G2:** placebo, 20/17	**G1:** 6.8 NR **G2:** 6.9 NR	• Speech and language (EOWPVT & ROWPVT) improved in the tx group relative to baseline scores but not when compared to the placebo group

ABC=Aberrant Behavior Checklist; ATEC=Autism Treatment Evaluation Checklist; DH=donepezil hydrochloride; EOWPVT=Gardner's Expressive One Word Picture Vocabulary Test; IGOH=oral human immunoglobulin; ROWPVT=Gardner's Receptive One Word Picture Vocabulary Test; tx=treatment

Risperidone plus piracetem was associated with more improvement on the ABC-C than risperidone alone in one RCT of 40 children ages 3 - 11, with similar incidence of extrapyramidal symptoms, and other adverse events.[245]

In one RCT at 12 US centers, oral human immunoglobulin showed no effect on GI symptoms, ABC-C scores or clinical rated global impression scores, and there was a significant effect in favor of placebo on the parent-rated global impression scores.[98]

Hyperbaric therapy was also studied in one RCT and showed some benefit. The study was conducted at six US clinics and included 62 children ages 2-7 years with ASD.[246] Participants were randomized to 40 hourly sessions over four weeks of either hyperbaric therapy (room pressure 1.3 atmospheres (atm); 24 percent oxygen) or slightly pressurized room air (1.03 atm; 21percent oxygen). Both groups had significant improvement in clinician-rated CGI after treatment as compared with baseline; however, while eighty percent of children in the hyperbaric group improved on this outcome, only 38 percent of control participants improved. There was no significant difference in ABC-C or parent-rated CGI between groups at outcome. There were significant changes in ATEC total scores and some subscales for both groups compared with baseline; significant between-group differences in the amount of change were observed on the sensory/cognitive awareness subscale only. No episodes of seizure or barotrauma occurred during the sessions; other adverse events were rare and included two skin-related events,

worsening of asthma, and GI symptoms.

Two studies explored the use of cholinesterase inhibitors in ASD, both conducted at a specialty clinic in Illinois. The study of donepezil hydrochloride (DH) included 43 children ages 2-10 years with ASD.[249] Children were randomized to six weeks of donepezil or placebo, followed by a six-week open label continuation. Both groups showed significant improvements on the CARS measure, but there were no between group differences. Nine children withdrew after the first six weeks; six of these children were in the donepezil group when blinding was broken and two of these discontinued due to gastrointestinal problems, while six discontinued due to increased irritability and associated behavioral issues.

One poor study each was identified for rivastigmine tartrate therapy [248] and daily oral DMSA.[243, 247] In a 2-week open label study of rivastigmine tartrate therapy scores at 12 weeks were significantly improved for CARS, expressive picture vocabulary, and the 48-item Conners' Parent Rating Scale measure of oppositional, hyperactive, and inattention-related behaviors; no significant effects were observed on receptive picture vocabulary at 12 weeks. . The randomized controlled trial of DMSA demonstrated no advantage of DMSA over placebo.

KQ1. Effects of Treatment on Core and Commonly Associated Symptoms in Children with ASD: Allied Health Interventions

Among allied health disciplines, several intervention approaches have been developed to address core symptoms of autism, as well as associated difficulties and deficits. We broadly divided allied health studies meeting our inclusion criteria into those focused on language, those employing sensory or auditory integration techniques including music therapy, and those addressing techniques such as horseback riding and occupational therapy (Table 24).

Table 24. Overview of allied health studies

	RCTs	NRCTs	Prospective cohort studies	Retrospective cohort studies	Prospective case series	Retrospective case series	Total Literature
Intervention	(n=6)	(n=2)	(n=0)	(n=0)	(n=8)	(n=0)	(n=16)
Language therapy	2	1	0	0	1	0	4
Sensory	1	0	0	0	1	0	2
Auditory/music therapy	2	0	0	0	1	0	3
Other	1	1	0	0	5	0	7
Diagnostic approach							
Clinical DSM-IV dx +ADI-R and/or ADOS	2	0	0	0	0	0	2
Combination approaches*	4	0	0	0	2	0	6
No DSM-IV or ADOS dx/ unspecified	0	2	0	0	6	0	8

Table 24. Overview of allied health studies (continued)

	RCTs	NRCTs	Prospective cohort studies	Retrospective cohort studies	Prospective case series	Retrospective case series	Total Literature
Last outcome assessment							
≤1 month	0	0	0	0	1	0	1
>1 to ≤3 months	2	1	0	0	0	0	3
>3 to ≤6 months	2	0	0	0	2	0	4
>6 to ≤12 months	1	0	0	0	1	0	2
>12 months	1	0	0	0	1	0	2
Unknown/not reported	0	1	0	0	3	0	4
Study population							
U.S.	3	1	0	0	2	0	6
Europe	3	1	0	0	3	0	7
Asia	0	0	0	0	3	0	3
Other	0	0	0	0	0	0	0
Total N participants	201	105	0	0	196	0	502

ADI-R=Autism Diagnostic Interview-Revised; ADOS=Autism Diagnostic Observation Schedule; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition; dx=diagnosis; NRCT=non randomized controlled trial; RCT=randomized controlled trial
*Clinical DSM-IV dx +other diagnostic tool OR ADOS + other diagnostic tool OR only clinical DSM-IV dx OR only ADOS.

Language Interventions

Two approaches to increasing speech and language were identified in the included studies: the Picture Exchange Communication System (PECS) and Responsive Education and Prelinguistic Milieu Teaching (RPMT). We have clustered these two approaches for the purposes of the report, and because in the one study that compared different approaches, these were the two comparative conditions.

Content of the literature. Our search identified eight publications focused on speech and language interventions,[250-257] representing four distinct study populations. Two of the studies were RCTs; one was described in four papers,[250-253] and one in a single study.[255] Three of the four studies referred to a protocol, and one measured treatment fidelity. No two studies used exactly the same outcome measure, making it difficult to summarize across studies. Each is therefore described separately below, and Table 24 provides an overview of study information. Among the four studies, one was good quality and three were poor.

Summary of the literature. Four analyses from one randomized trial[250-253] comparing RPMT to PECS in the United States met our criteria and were included. The 36 preschoolers included in the study had a confirmed diagnosis of Autistic Disorder or PDD-NOS, were between 18 and 60 months of age, and were nonverbal or had low verbal status (fewer than 20

different words used cumulatively during three communication samples). Most (86 percent) of the participants were male, and most (69 percent) were white. Although the mean chronologic age of the children was 33.6 months (range from 21 to 54 months), the mean mental age in the nonverbal children was 18.6 months and in the verbal children was 11.9 months, based on Mullen Scales of Early Learning. Diagnosis of autism was confirmed with the ADOS for all children. Nineteen children were randomized to receive PECS and 17 to receive RPMT.

During the six-month treatment phase, children attended three 20-minute therapy sessions per week, with parents offered up to 15 hours of training. Outcomes were measured at the end of treatment and six months after treatment completion in the context of a 15-minute free play session in which the interaction style, toys, examiner and location were all different from those in which the intervention was done. Treatment fidelity was assessed monthly, interrater reliability was assessed on at least 20 percent of data points, and coded data were double entered to ensure accuracy.

At Time 2, the PECS group had significantly higher frequency of nonimitative spoken communication at Time 2 than the RPMT group, and higher numbers of different non-imitative words. No overall significant between group differences were observed at Time 3, indicating that the treatment effects did not maintain at six months after the end of treatment. This study included an analysis of initial characteristics of the children, demonstrating that children who were low in initial object exploration benefitted more from RPMT, which explicitly teaches play with objects; while children who were relatively high in initial object exploration demonstrated more benefit from PECS. These results were maintained at six months. An additional analysis based on this study[252] showed greater increases in generalized turn-taking and initiating joint attention in the RPMT group than in PECS. The increased benefit for RPMT in join attention was only seen, however, in children who began the study with at least some initiation of joint attention. Specifically, children most likely to benefit from RPMT in increasing joint attention had demonstrated at least 7 acts of joint attention in the pre-intervention assessment. RPMT was also superior in this analysis in increasing object exchange turns.

The second RCT[255] in this literature was a pragmatic trial focused on the effect of providing expert training in PECS to teachers in specialist schools, under the assumption that although more than half of autism-specific schools in the UK claim to use PECS system, few teachers have been adequately trained to provide it. This study aimed to explore the potential effects of intensive training of teachers on child outcomes in spontaneous communication and speech; thus randomization occurred at the classroom level in three groups – immediate treatment group (ITG), delayed treatment group (DTG) and no treatment group (NTG). Teachers in the delayed treatment group received intensive training 2 terms after the immediate treatment group.

The 83 children included in the study were between the ages of 4 and 11 and had little or no functional language; most (75) met ADOS-G criteria for Autistic Disorder, and 9 met criteria for an ASD. Treatment and assessment of language and non-verbal developmental quotient (NVDQ=nonverbal mental age equivalent/chronological age X 100) took place in schools with children videotaped and language outcomes codes by nonblinded assessors. Videotaping took place during snack sessions, selected because they are time limited and structured to include requesting and other social communication.

The use of PECS in treatment classrooms was substantially increased immediately after training, with children in the PECS training classrooms having 3.90 times (95 percent CI: 1.75 – 8.68) the odds of being in a higher PECS use category than those whose teachers received no

PECS training. The effect, however, was not maintained, and by Time 3, the ITG children were no more likely to be in a higher PECS rate category than untreated children (OR 1.10; 95 percent CI: 0.46 – 2.62).

The third trial available on language intervention was also on PECS and was a non-randomized controlled trial, with selection into or out of treatment based on a geographical limit. This study was reported in two papers.[254, 257] Intervention was provided to 24 children whose special education classrooms were within 50 miles of the researchers; while a comparison group was selected from special education classrooms outside the 50-mile limit. Children were between 3 and 7 years old, with a diagnosis of Autistic Disorder. Diagnosis was clinically based, and not independently confirmed by the investigators. Children in the study were to have received no PECS training prior to the research.

Children in the intervention group received a total of 15 hours of PECS teaching during various classroom activities over 4 to 5 weeks. The research team designed the instrument by which they assessed communicative interactions. They did not validate the instrument. The investigators followed the Bondy and Frost guidance[115] for using PECS in the classroom, but at Phase III randomly assigned children to either the approach specified in the PECS manual, or a modified discriminations-based teaching procedure.[257]

Observation occurred 6 weeks prior to commencement of PECS intervention, 1 week prior to intervention and during the week immediately following completion of the 15 hours of PECS. The authors contended that the differences observed between the first and second observation periods (during which no intervention took place) would provide a measure of rate of maturation that could be used to differentiate maturation from treatment effects after the intervention phase; however, no evidence that this approach is valid was provided in the paper.

No differences were observed on child-initiated communication either between the two pre-intervention measurement periods or between the two groups immediately prior to intervention. After intervention, however, the children in the PECS group had a significant increase in initiations, while the children in the control group had no increase, and the frequency of child to adult initiations was higher overall in the PECS group. Total adult-to-child initiations with the opportunity for child response showed an opposite response, with no significant increase in the PECS group, but a significant increase in the control group.

Because the study only measured outcomes immediately after intervention in the classroom setting (at 6 weeks) it is impossible to determine whether the outcomes have any durability, or to assess the effects outside of the classroom. Furthermore, although reliability of the observations was reported to be high (89.78 percent agreement), it was measured in only 56 percent of observation sessions, and the observers were not blinded to intervention status.

Sensory- and Auditory-Focused Interventions

Sensory integration, a specialized occupational therapy model based on the premise that the brain's response to basic sensory input must be normalized before higher-order processes can be addressed,[118] typically involves one-on-one, child-directed treatment with a trained occupational therapist and a focus on somatosensory and vestibular systems. Ultimately, it is hypothesized that if a child is better able to process, modulate, and integrate sensory information, he will then be better able to acquire higher-order skills.[119] Auditory integration training (AIT) relates more specifically to sensory differences in the auditory realm. AIT involves repeatedly presenting children with modulated music according to specific protocols with a therapeutic goal of

improving auditory processing, lessening auditory hypersensitivities, and increasing concentration.[121] Finally, music therapy is at times employed with children with ASD, hinging on speculation that children engage more with music. This treatment method is improvisational and unstructured in nature, and practitioners purport that it can improve both verbal and non-verbal communication skills including joint attention abilities, thereby improving core symptoms of autism.[122-123]

Content of the literature. We identified two studies[258-260] that addressed sensory integration interventions, including a prospective case series with two publications presenting nearly identical results[259-260] conducted in South Korea. Both were completed in a clinic setting and included children ages six years[259-260] and older.[258] All children in both studies met criteria for autism (i.e., none had diagnoses of PDD-NOS or Asperger Disorder). Both studies used outcome assessments developed within the project and focused on sensory and motor functioning. Both sensory studies were poor quality.

Two papers assessed auditory integration interventions[261-262] and targeted children aged three to seven[262] and seven to thirteen.[261] Both studies were conducted through a clinic associated with an academic institution and enrolled children with diagnoses of autism across a broad range of cognitive functioning levels. Table 24 provides additional study details.

We identified two papers from a single study that compared music and play therapy interventions.[123, 263] The study included children ages three to five years meeting DSM-IV criteria for autism and meeting criteria on the Childhood Autism Rating Scale (CARS); some were also administered the ADOS to confirm diagnosis. Among studies of auditory integration and music therapy, two were fair quality and one was poor.

Summary of the literature. Two studies examining sensory integration training met our inclusion criteria (Table 25).[258-260] An RCT from Fazlioglu and colleagues[258] examined the effects of a sensory integration protocol on low-functioning children with autism ages seven to eleven years who had not previously received sensory integration therapy. The intervention program used in this study was based on "The Sensory Diet" and included a prescribed schedule of somatosensory stimulation activities targeting 13 behaviors across sensory modalities and motor skills development and conducted in a specially arranged sensory room. Results indicated that the difference between treatment and control groups was significant at outcome, but not at baseline, with children receiving sensory integration intervention showing significantly fewer sensory problems at follow-up than children in the control group.

In contrast to Fazlioglu's more traditional play-based, child-directed sensory integration intervention, Jung et al.[259-260] used a virtual reality – tangible interaction system (VR-TIS) sensory integration training protocol in 12 five- and six-year-old children with autism The sensory integration components comprised less than a third of the intervention described, and no outcome measures were reported related to sensory integration activities.

To study auditory integration intervention (Table 25), Corbett et al.[262] used a double-blind, placebo-controlled crossover design on the effects of Tomatis Sound Therapy on language skills in children with autistic disorder, ages three to seven years who had not previously had auditory stimulation treatments. In the treatment condition, children listened to music passed through an electronic ear for attenuation and modulation for two hours per day in accordance with the Tomatis Method protocol. The protocol was divided into four blocks, each lasting three weeks. In the placebo condition, children listened to commercially produced music in the same blocked schedule. No improvements in receptive or expressive language were related to treatment

conditions, as the increase in scores over time (i.e., pre-first condition, midpoint, post-second condition) was not different between groups (i.e., Treatment/Placebo and Placebo/Treatment).

Mudford and colleagues studied auditory integration training in children with autism ages 5 to 13 years (mean = 9.4);[261] all children had significant language delays and low adaptive behavior levels. No significant benefit of auditory integration training was found.

Table 25. Outcomes of RCTs of auditory/music interventions for the treatment of ASD

Author, Year, Country Intervention, duration/intensity Study quality	Groups, N enrollment/ N final	Age, mean years ±SD IQ, mean ±SD	Key Outcomes
Corbett et al.[262] 2008, US **G1:** Tomatis Sound Therapy followed by placebo in four three-wk blocks. **G2:** placebo followed by Tomatis Sound Therapy in four three-wk blocks Quality: Fair	**G1:** 6/6 **G2:** 5/5	**G1:** 5.25 (range: 3.5-7.42) **G2:** 5.93 (range: 4-7.17) 66.8 (combined)	• Results indicated no improvements in receptive or expressive language related to tx
Mudford et al.[261] 2000, UK **G1:** auditory integration followed by control **G2:** control followed by auditory integration AIT/control received two thirty-min sessions/day across 10 consecutive school days; 4-mo break between conditions Quality:Fair	Total N at enrollment: 21 Final N: **G1**: 7 **G2**: 9	9.42 yrs ± 29 mo 6/21 untestable; 15/21 mean=56	• No significant benefit of auditory integration found; greater reduction in challenging behavior and hyperactivity following control relative to tx condition

AIT=auditory integration therapy; NR=not reported; SI=sensory integration; tx=treatment

One study investigated the effects of music therapy in children ages 3 to 5 years (mean = 51.2 months) with autism in comparison to the effects of play-based sessions on joint attention behaviors with results reported in two papers.[123, 263] A crossover design was used such that all children completed both music and play interventions, with treatment order randomly assigned. Sessions in both conditions were divided into 15 minutes of undirected child-led activities, followed by 15 minutes of directed activities according to a semi-flexible treatment manual developed for the study. There were no significant between group differences on the PDDBI, though both groups improved with time. Results from the ESCS, reflecting growth in joint attention skills, suggested that music therapy was significantly more effective than play sessions. Change scores pre- to post- music therapy were significantly greater than change scores pre- to post- play sessions.

In the second paper,[123] treatment sessions were coded for emotional and motivational responsiveness (i.e., joy, emotional synchronicity, initiation of engagement) toward attunement

promoted by the therapist and for responsiveness (i.e., social invitation and interpersonal demands) toward the therapist's initiation of interaction during joint attention episodes within selected four-minute segments of four treatment sessions. More joy, emotional synchronicity, and initiation of engagement were observed during music therapy than play sessions. In addition, children had significantly more compliant behavior and significantly fewer episodes of no response behaviors in the music therapy condition.

Additional Allied Health Interventions

A number of studies addressing interventions such as animal-assisted therapies and assistive tools met our review criteria.

Content of the literature. We found seven studies[264-270] addressing additional allied health interventions. Two papers report similar interventions and participants recruited from similar locations and may include overlapping participants.[267, 269]

Treatment duration ranged from 47 days[270] to fifteen weeks,[264] and participants ages ranged from three to eighteen years.[265] Table 24 provides additional study details.

All studies in this section were considered poor.

Summary of the literature. Bass and colleagues conducted a randomized controlled trial investigating the potential benefits of therapeutic horseback riding sessions in 34 children with ASD assigned to either a horseback riding group (19, mean age 6.95 yrs ±1.67) or wait-listed group (15, mean age 7.73 yrs±1.65).[268] Children in the riding group attended sessions of one hour per week over twelve weeks. Activities included mounting and dismounting instructional sessions, riding skills, mounted games, and horsemanship and grooming activities. Scores on four of the five Sensory Profile (SP) subscales (sensory seeking, inattention/distractibility, sensory sensitivity, and sedentary), along with the overall SP mean score, showed a significant between-group difference. The overall Social Responsiveness Scale score and social motivation subscale also showed a significant between-group difference.

A non-randomized controlled trial investigated the effect of movement therapy on behavior among children with ASD.[266] Children were recruited from specialized schools and underwent 30-minute movement training sessions twice a week for two months. Behavior was recorded during the first and last meetings for six one-minute periods, in 10-second sample units. Eight behaviors were reported on: stereotypical behaviors, wandering, responding to touch negatively, on-task passive, on-task active, eye contact, social relatedness towards the teacher, and resisting the teacher. Of these, four exhibited significant changes: a decrease in wandering, responding to touch negatively, resisting the teacher, and an increase in on-task passive behavior

Two prospective case series focused on the effect of incorporating colored overlays to assess effects on reading in children with ASD.[267, 269] In the initial study,[269] participants attended one session with researchers and performed reads of thirty seconds and one minute. Children with autism read significantly more words per minute with than without colored overlays. Seventy-nine percent of children with ASD showed improvement in reading with colored overlays.[269] In a later study,[267] Ludlow and colleagues conducted three individual tests to assess the therapeutic benefits of colored overlays when reading; results showed more words read using overlays and slightly better performance on a picture matching task using overlays

One prospective case series aimed at identifying the effect of therapeutic sessions incorporating animal interaction among children with ASD.[264] Therapy sessions focused on facilitating sensory integration, language use, sensory skills, and motor skills, with each

participant attending at least two sessions of each type over a duration of fifteen weeks. Results indicated that participants engaged in significantly greater use of language and social interaction in the therapy sessions incorporating animal interaction than in the standard occupational therapy sessions. In another series, Carmody and colleagues examined the effect of eyeglasses with specialized prism lenses.[265] Children were recruited from a child development center, and each child was assessed for 20 to 30 minutes by a single interviewer, with trials of 60 to 90 seconds without glasses and with each of the lens orientations. Participants showed a significant improvement in a ball catching when wearing lenses (64 percent compared with 20 percent without lenses).

Finally, Laud and colleagues conducted a prospective case series that included a systematic feeding program and oral motor therapy aimed at improving feeding behaviors among children with ASD.[270] Participants underwent three hours of behavioral training and one hour of oral therapy at least five days per week. Behavioral training consisted of systematic meal sessions with individualized behavior protocols while the oral training was conducted by an occupational therapist or speech pathologist to determine skill and safety while eating. Significant changes from admission to discharge were found in the following areas: increases in acceptance and grams consumed, increase in refusal behavior, and a decrease in negative vocalizations.

KQ1. Effects of Treatment on Core and Commonly Associated Symptoms in Children with ASD: CAM

CAM Interventions

As noted, studies of complementary and alternative medicine (CAM) interventions meeting our criteria addressed acupuncture and massage, including qigong massage.

Content of the literature. We found six studies[271-276] of CAM interventions meeting our inclusion criteria (Table 26); two studies[273-274] likely contain overlapping participants. Interventions occurred in the clinic[271, 273-274] and home,[273-275] and studies addressed massage,[275-276] qigong massage,[273-274] and acupuncture.[271-272] Treatment duration ranged from one[275] to nine months,[271] and participants' ages ranged from three to seven years. Among the six CAM studies, two were fair quality and four were poor.

Table 26. Overview of CAM studies

	RCT	NRCT	Prospective cohort studies	Retrospective cohort studies	Prospective case series	Retrospective case series	Total Literature
Intervention	(n=5)	(n=0)	(n=0)	(n=0)	(n=1)	(n=0)	(n=6)
Massage	3	0	0	0	1	0	4
Acupuncture	2	0	0	0	0	0	2
Diagnostic approach							
Clinical DSM-IV dx +ADI-R and/or ADOS	1	0	0	0	0	0	1

Table 26. Overview of CAM studies (continued)

	RCT	NRCT	Prospective cohort studies	Retrospective cohort studies	Prospective case series	Retrospective case series	Total Literature
Combination approaches*	1	0	0	0	0	0	1
No DSM-IV or ADOS dx/ unspecified	3	0	0	0	1	0	4
Last outcome assessment							
≤1 month	1	0	0	0	0	0	1
>1 to ≤3 months	1	0	0	0	0	0	1
>3 to ≤6 months	0	0	0	0	0	0	0
>6 to ≤12 months	3	0	0	0	1	0	4
>12 months	0	0	0	0	0	0	0
Study population	5	0	0	0	1	0	6
U.S.	3	0	0	0	1	0	4
Other	2	0	0	0	0	0	2
Total N participants	104	0	0	0	26	0	130

ADI-R=Autism Diagnostic Interview-Revised; ADOS=Autism Diagnostic Observation Schedule; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition; dx=diagnosis; CAM=complementary and alternative medicine; NRCT=non randomized controlled trial; RCT=randomized controlled trial
*Clinical DSM-IV dx +other diagnostic tool OR ADOS + other diagnostic tool OR only clinical DSM-IV dx OR only ADOS.

Summary of the literature. Studies assessing massage focused primarily on sensory impairments; a series of studies from Silva et al. assessed qigong massage using similar approaches and potentially including overlapping participants, though the exact overlap is unclear. A 2007 RCT[274] extended a 2005 case series (not included in the present review) of eight children with ASD; the RCT[274] included 15 participants with autism diagnosed according to DSM-IV criteria (mean age at first assessment=4 years, 10 months). Children were stratified into three cognitive groups according to Batelle Development Inventory scores and randomly assigned to treatment or control within each group. Massage treatment for the eight intervention group participants consisted of 11 different qigong massage movements. A trained practitioner delivered massage twice a week in the clinic for two five-week periods separated by five weeks of no practitioner-delivered therapy. Parents were trained to provide massage at least once daily during the five week practitioner-delivered and interval periods; parents were also tested to ensure accurate administration of massage. The seven control children received special education, and four were concurrently receiving speech therapy.

Total Sensory Profile scores improved in the massage group by an average of 5.4 points, with an average worsening in control group of 2.7 points ($p<0.01$); average improvement in daily living skills as assessed by the VABS was 9.8 months compared with 0.9 months in the untreated group ($p<0.02$) and 10.0 months compared with 4.7 months in control participants ($p<0.04$). No significant differences between groups were seen in VABS language and motor development scores or on the Autism Behavior Checklist. Children with bowel or sleep difficulties in the

treatment group improved according to parent report.

A 2008 case series assessed whether individuals completing an 80 hour training program could deliver qigong massage yielding positive adaptive behavior and sensory outcomes.[273] The qigong sensory training (QST) curriculum for trainers included didactic and experiential instruction; during the five month intervention, each of the 18 trainers worked with two families with a supervisor present for several sessions to assess treatment fidelity; several treatment sessions were also videotaped to inform training efforts. Participants showed gains in sensory and adaptive behavior, and most trainers were considered to have mastered the training program.

A later multi-site RCT assessing a similar qigong methodology modified for application in early intervention programs[276] included 46 children between the ages of three and six and evaluated participants in both the home and preschool settings. Children were randomized to either QST, comprising ten hours of practitioner-delivered therapy in addition to daily parent-delivered massage. Practitioners, including some early intervention personnel, received training and weekly supervision during the intervention period. Six therapy sessions were also videotaped over the course of the project to assess treatment fidelity. Assessments were conducted prior to the intervention, after the final massage session, and five months after the final session (parent-report) to evaluate maintenance of effects.

The QST group (n=25, mean age=65.2 ± 20.7months) and wait list control group (n=21, mean age=53.3 ± 18.7 months) differed significantly in parent-rated PDDBI Social/Communication and PDDBI Autism composite scores ($p<0.05$) as well as teacher-rated PDDBI Sensory scores ($p<0.01$) at baseline. Scores from pre- to post-treatment for the QST group improved significantly on all measures ($p<0.00$); only change scores on the teacher-rated PDDBI maladaptive behavior subscale reached significance for the control group ($p<0.01$). Parent-rated data illustrated a significant overall treatment effect on outcomes and in adjusted comparisons on the Sense and Systems Checklist, PDDBI sensory, maladaptive behavior, social/communication, and autism domains; effect sizes (partial η^2) were considered to be large. Treatment effect for teacher rated data was also significant overall, and adjusted comparisons found significant effects (moderate effect size) for the PDDBI social/communication composite and the Autism Behavior Checklist. Descriptive data collected five months after the final massage session in 19 participants available for follow-up showed significant differences in all scores on parent-rated measures at all three assessment times.

In a one-month study of pre-bedtime, parent-delivered massage,[275] twenty children with autism (mean age ± SD=5.2 ± 1.8, range 3-6 years) as diagnosed according to the DSM III-R criteria were randomly assigned to nightly massage or reading attention control groups. Assessments, conducted on the first and last days of the study, included subscales of the Conners Teacher and Parent Scales, behavioral observations in the classroom and playground by blinded research associates, and parent-maintained sleep diaries. Teachers' blinded ratings on the Conners Scale showed greater improvement for children in the massage group on the Emotional Index and the DSM-IV criteria for inattentiveness ($p<0.05$). Parent ratings were significant for these subscales as well as the ADHD and restless-impulsive behavior indices ($p<0.05$). Observation ratings across the playground and classroom illustrated a decrease in stereotypical behaviors and increase in on-task behaviors in the massage group. Poor sleep behaviors also exhibited greater declines among the massage group according to parent report.

Two studies meeting our criteria addressed acupuncture. An RCT conducted in Egypt[271] assessed the effects of scalp acupuncture and language therapy compared with language therapy

alone on elements of attention, receptive and expressive semantics and syntax, phonology, and pragmatics. Children included in the nine month study were between the ages of 4 and 7, were diagnosed with autism and delayed language development, and had CARS scores ≥30. Children randomized to language therapy plus acupuncture (n=10) received language therapy twice a week and scalp acupuncture twice a week for two months, followed by a two week rest period for the nine months of the study. Children randomized to language therapy alone (n=10) received treatment twice a week for the nine month study; further detail on the content of language sessions was not reported. The Arabic Language Test was used to measure outcomes. The acupuncture and language therapy group showed significant pre-post gains in attention (p=0.001) and receptive (p=0.001) and expressive semantics (p=0.021). Children receiving language therapy only improved in attention, cognition, and receptive semantics from pre- to post-treatment, but the magnitude of improvement is not reported. Outcomes between groups were significant for attention (p=0.008) and receptive semantics (p=0.034).

A six week RCT of the seven star needle acupuncture technique[272] similarly assessed changes in language function as well as social and stereotyped behaviors. The acupuncture technique uses a specially designed dermatoneural hammer housing seven needles in the shape of a star. Thirty-two children with ASD (diagnosis not specified) included in the study were randomized to treatment (five 5-10 minute daily sessions per week for 6 weeks) or a wait list control group. Assessments were conducted before and after the six week study period and included a Parent Rating Questionnaire designed for the study and evaluating language, social, and motor functioning and stereotyped behaviors. qEEG data, assessed by a rater blinded to treatment status, measured changes in neural processing. Children in the treatment (n=16, mean age=6.85±1.76, mean IQ=84.06 ± 15.75) and control (n=16, mean age=6.89 ± 1.77, mean IQ=86.82 ± 19.91) groups were matched in age and IQ as measured by the Test of Nonverbal Intelligence. Parents of children in the treatment group reported significantly greater overall improvement than parents of control group children as well as greater improvement in language, especially related to sentence length and speech clarity and frequency. Social interaction, including gains in eye contact and facial expression, was also significantly improved for the treatment as compared with the control group. Changes in qEEG data, which was available for 9 control and 7 treatment group children, suggested that the brain's information processing functions were affected by the seven star treatment.

KQ2. Modifiers of Treatment Outcomes

Identifying subgroups of children for whom treatments are more or less effective, as well as factors that increase or decrease effectiveness, may help to understand which treatments are applicable under what circumstances. We searched all of the included studies in this review for information about modifiers of effectiveness, with particular focus on child and family characteristics, the effect of setting of care, including training of the care provider, and the intensity of treatment provided, including frequency and duration.

Behavioral Interventions

Frequency, duration, and intensity. The characteristics most commonly noted as potential modifiers in the study of behavioral interventions are treatment intensity and approach (e.g. parent-led versus clinician-led) as well as baseline measures of child characteristics, including

IQ, language and verbal skills and severity of the autistic disorder. No studies were available to explicitly examine the impact of training or experience of the individual providing the intervention.

Characteristics of treatment such as providers/training, supervision, and amount have been examined. A majority of the reviewed work has examined different aspects of treatment across approaches (e.g., comparing EIBI/ABA to an eclectic treatment of a different focus, intensity, and duration), which presents challenges to interpretation of true modification of treatment. Of studies examining such variation within a specific modality, type of provider, type of training, level of supervision, and treatment amount have been noted to modify treatment.

Regarding provider type/training, intensive parent-based and clinic-based UCLA/Lovaas treatment programs have been demonstrated to result in equivalent group change when delivered in the same intensity.[18, 25-26, 277] Vismara and colleagues[149] demonstrated equivalent results across training (distance vs. in person) modalities for providers of Early Start Denver Model Treatment. When examining characteristics of UCLA/Lovaas-based intervention, Luiselli et al. found that months of treatment was significantly related to language gain, but numbers of hours per week and total hours of treatment were not.[28] Intensity of supervision within UCLA/Lovaas-based treatment has also been demonstrated to be positively correlated with change in cognitive in cognitive abilities, although not other skills domains, within one treatment study.[25-26]

Because of the potentially increased efficiency and desirability of having parents provide intervention to their children in their own homes, several studies have examined varying approaches to preparing parents to provide behavioral therapies. Sofronoff et al.[187-188] conducted a parent training intervention with parents of children ages six to twelve years with Asperger Syndrome diagnoses. Parents either a) participated in a one-day workshop, b) attended six weekly one-hour individual sessions conducted by master's or doctoral students in psychology, or c) were placed in a waitlist control group. Components of the intervention were the same in both treatment groups and involved psychoeducation, comic strip conversations and social stories introduction, and management techniques for externalizing behaviors, rigid behaviors, and anxiety. Parents from both intervention groups reported significantly better social skills in their children than did parents in the waitlist control group at both one month post-treatment and three-month follow-up; at three-month follow-up, parents from the individual session group reported marginally better social skills for their children than did parents from the workshop group, suggesting little modification of effect by intensity (one day vs. weekly training).

Finally, in a trial intended to improve either joint attention or symbolic play skills, a teacher-led approach was compared with one in which the child took the lead and found positive effects associated with the teacher leadership.[172]

Child characteristics. Several characteristics of the child have been assessed to determine whether there were identifiable predictors of success associated with intensive behavioral interventions.

Cognitive abilities/IQ: The most commonly reported characteristic investigated relates to pretreatment cognitive abilities/IQ. Several investigations have noted that pretreatment IQ and language predicts IQ at follow-up within the context of EIBI/ABA methodologies.[18-22] However, other studies have suggested having a lower IQ at initiation of treatment is related to increased change in IQ over time[23] or and change in response to intervention[24-26] within this same methodology. In contrast to EIBI/ABA methodologies there is evidence within parent training methodologies for teaching early social communication skills, that children with lower language

levels and/or lower IQ at baseline may actually benefit more from this intervention.[5-6] Within PRT interventions there is some data suggesting more less impaired children do better in response to offered parent training.[140]

Language/communication skills: Baseline language/communication skills may also correlate with treatment success, with studies generally suggesting a benefit for communication skills, including changes in ASD classification associated with baseline language skills in an ABA approach.[21, 24] In one RCT[169-170] comparing the use of targeted joint attention (JA) intervention to development of symbolic play skills (SP), children with initially higher levels of expressive language showed greater growth in expressive language from pre-intervention to 12 months post-intervention. Among children with lower expressive language initially, those in the JA group showed significantly greater improvements in expressive language. In addition, JA initiations, responding to JA, the duration of child-initiated JA, average highest level of play, total number of SP types, and initial receptive language age all predicted greater gains at 6 and 12 months post intervention.

Similarly, social skills studies have found verbal skills, either verbal comprehension (using the Verbal Comprehension Index) or expressive communication skills to be associated with social skills at outcome. Children with higher verbal comprehension scores who participated in the Social Story intervention[162] made larger gains in the evaluated game play skills, while children with extremely low verbal comprehension scores did not. Social Stories, an intervention program that relies heavily on the child understanding information presented in a written format, may not be as effective for children with low verbal comprehension abilities. In another study [156] pre-treatment communication skills, as measured by VABS Communication domain and Verbal IQ, were associated with social skills at outcome (VABS Socialization) in both a Lego treatment group and the treatment as usual control group (but more so in the Lego group).

Autism symptom severity: There is some evidence that specific constellations of symptoms related to ASD may be important in understanding response to treatment. Social responsiveness and imitation skills have been suggested as skills that may predict improved treatment response in EIBI/ABA treatment,[18] whereas 'aloof' subtypes of ASD have been suggested to be associated with less robust changes in IQ,[135] and lower baseline symptom tallies have also been demonstrated to be related to specific gains.[19] Other studies have seen specific improvement in EIBI/ABA for children with PDD-NOS vs. Autistic Disorder diagnoses,[4] which may be indicative of baseline symptom differences. However, many other studies have failed to find a relationship between autism symptoms and treatment response. Two social skills studies[156, 165] looked at the diagnosis of participants (PDD-NOS vs. High functioning autism vs. Asperger Syndrome for one study, AD vs. Asperger/PDD-NOS for the other) as a potential modifier of treatment effects and failed to find any significant direct effects. However in the study evaluating the social adjustment enhancement curriculum,[156] the results on a measure of theory of mind were no longer significant when the one participant with PDD-NOS was excluded.

Age at identification/initiation of treatment: There is some indication that children initiating treatment at earlier ages may benefit more from EIBI intervention;[20, 27] however, other explicit comparisons have not found this same relationship for EIBI/ABA intervention[28] and age at initiation of treatment may in fact be confounded by type of treatment initiated.[27]

Neurobiological and genetic variation: Only one of the included and reviewed studies examined the relations between potential underlying neurobiological markers/variation and this

study simply indexed head circumference as a measurement within design[24] and this did not appear to be related to outcome.

Family characteristics. Although family characteristics were rarely reported in the behavioral literature, in one study of a parent-directed play interaction, change in child behavior measured on the Eyberg Child Behavior Inventory (ECBI) was not significantly predicted by whether parents perceived their child having a causal role in their own behavior or the parent having a causal role in their child's behavior,[168, 175] but parent positive affect, measured through behavioral coding was positively related to parental reports of child adaptive behavior and negatively related to parental reports of child challenging behaviors.

Educational Interventions

Child characteristics. In educational interventions, baseline IQ and receptive language predicted rate of progress in one study.[9] In a comparison of a home-based intervention plus center-based (intervention) to a center-based only (control) educational intervention,[204] no girls in the intervention group improved in IQ or on the Preschool Behavior Checklist (PBCL). In the control group, one girl improved in IQ, and 2 improved on PBCL. Improvement in IQ in the intervention group was higher with low socioeconomic status, younger age, and high family stress. Improvement in PBCL was associated with younger age in the intervention group. This study also considered the potential effect of family stress and non-English speaking in the home and found no effect on outcomes.

Family characteristics. One study measured parental stress and its association with outcomes in four different teaching interventions (reinforcement–based interventions, special nursery, speech and language therapy, and parent education programs),[205] and found that parenting stress did not affect gains with interventions that required less total time but reduced the gains made by those interventions that required more total time. Moreover, there is evidence that at lower levels of parenting stress, higher time intensity interventions are more effective than lower time intensity interventions. For the lower parenting stress group, higher time intensity interventions significantly improved intellectual functioning and educational functioning but not adaptive functioning as measured by the Vineland Adaptive Behavior Scale.

Medical Interventions

No modifiers of treatment outcome were identified in studies of antipsychotic medications in ASD, though one case series of risperidone use[209] reported a correlation between weight gain in the first month and final weight gain. We were, however, able to identify papers that included modifier data for stimulants and SRIs. None assessed measures of frequency, duration or intensity of treatment specifically; nor did they assess training experience of the investigator or clinician providing care.

Child and family characteristics. Some characteristics of the family and child were found to be useful in predicting treatment success, including a history of psychiatric diagnoses in the family, early verbal skills in the child,[11] and, potentially, genotype for predicting lack of treatment response.[12] Several studies of stimulant use highlighted differences in effectiveness by diagnosis type[13-17] finding that children with Asperger syndrome were typically more responsive to psychostimulant treatment than those with autistic disorder. The presence of co-morbid intellectual disability was associated with lower treatment response in one study.[17]Two studies

sought to examine differences in treatment response by gender and found none.[17, 227] Details are provided below.

One open-ended study of fluoxetine treatment in 129 children assessed response qualitatively. Subjects with an average age of 4.5 years were diagnosed with a PDD by DSM-IV criteria corroborated by CARS and ADOS and were then treated with fluoxetine as felt to be clinically indicated, with up to 72 months of treatment. They analyzed potential predictors of good/excellent response, including family history and subject characteristics. When comparing to subjects with fair/poor response, they found an increased rate of family history of affective disorder (major depressive disorder and bipolar disorder) and 'unusual intellectual achievement' in those subjects with a good/excellent response. Subjects with good/excellent response also showed an increased rate of verbal language before starting fluoxetine. Finally, subjects with a good/excellent response were more likely to have 'hyperlexia,' an early or precocious interest in letters or numbers. They did not find a significant relationship between history of regression and response to fluoxetine. They also did not find a relationship between dose of fluoxetine and likelihood of response.

One additional retrospective case series described response to various serotonin reuptake inhibitors, primarily sertraline, citalopram, paroxetine, and fluvoxamine in 89 children and adolescents with ASD by DSM-IV criteria.[11] The CGI-I was used to gauge medication response, with 40 subjects rated as at least 'much improved'. Family history of ASD was significantly associated with positive treatment response. Other possible moderators showed no association with response, including family history of depression or anxiety, subject diagnosis, concurrent medications, specific SRI prescribed, and indication for SRI initiation, whether for anxiety, repetitive behavior, aggression, or depression.

In the double-blind cross-over trial of MPH in 66 children with PDDs,[13-15] authors found no effect of age, IQ, weight, or diagnosis on teacher- or parent-rated hyperactivity subscale scores / SNAP-IV / CYPBOCS-PDD scores. Children with Asperger Syndrome /PDD-NOS (n=19) showed a trend of being more likely to be classified as responders to both placebo and MPH than those with autism. Response to each dose of MPH was significantly superior to placebo in the autism subgroup but not for the Asperger / PDD—NOS subgroup. Similarly, Posey et al., in their retrospective review of 80 children with PDDs treated with guanfacine,[17] found that subjects with PDD-NOS and Asperger syndrome showed a greater rate of global response than those with autistic disorder. Those without intellectual disability (ID) showed a higher rate of global response to guanfacine (37.5 percent) than those with co-morbid ID (17.9 percent). They also identified that the responders were less aggressive at baseline by the CGI severity item. Finally, Stigler et al., in their study on the effectiveness of psychostimulants in 195 children with PDDs, found that children with Asperger disorder were found to be more likely to respond to treatment than those with autistic disorder or PDD-NOS. Those children on concomitant medication were also found to be more likely to respond to treatment; the study did not find any association between stimulant type, gender or IQ and response to treatment.[16]

Of particular interest currently in the study of medical treatment of autism is the possibility of genetic modifiers that might be used to target treatment choices. One prospective ten-week case series of escitalopram sought to identify pharmacogenetic modifiers of treatment response in the challenging behavior domain as measured by the ABC-C-I.[12] Fifty-eight subjects with ASD corroborated by ADI-R and a minimum ABC-C-I score of 12 underwent a forced dose titration of escitalopram from 2.5 mg daily increasing weekly to five mg, ten mg, 15 mg, and 20

mg, essentially twice the dose equivalent of citalopram given that escitalopram is the active component of racemic citalopram. Pre-designated dose-limiting side effects included sleep disruption and an increase in ABC-C Irritability or Hyperactivity subscales of ten points over the previous week. Subjects were also genotyped at several polymorphisms in the serotonin transporter gene. Average daily doses of escitalopram were 10.8-12.4 mg and did not differ across genotype groups, which reflects the fact that most subjects in all genotype groups could not tolerate the maximum dose. One genotype group, designated *a priori* as the low-expression genotype group, showed diminished response to escitalopram,[12] with a particularly striking difference in a subgroup of the low-expression genotype based upon previous association with platelet serotonin uptake measures.[278] The low-expression genotype group also had verbal and non-verbal IQ scores that were 25 to 26 points lower than the other subjects; although this was not described as a statistically significant difference. Genotype groups also differed with respect to percentage of Caucasian subjects, with the high-expression genotype group only containing Caucasian subjects; although the pattern of results was reported to be the same in a Caucasian-only analysis.

In other medical studies, children treated with DMSA[243, 247] had greater improvement in core and associated ASD symptoms if they were older than age 5. Children with lower initial ADOS scores (below the 50th percentile) also had greater improvements than were seen among children with initially higher scores. It is unclear whether either of these modifiers is significant in the context of a trial with no overall difference in response between DMSA and placebo. In one study of a ketogenic diet,[239] the two patients with the greatest improvement were those whose baseline condition was classified as mild using CARS scores, and those with severe autistic behavior showed substantially less improvement. In a study assessing omega 3 fatty acid use, a negative correlation between docosahexaenoic acid (DHA) level and CARS before treatment was observed in nonresponders. Finally, attempts to identify subgroups of children for whom oral immunoglobulin was successful in treating GI symptoms and associated autism symptoms found no effect of age, regression onset of symptoms, or predominant bowel type.[98]The treatment was uniformly ineffective.

Allied Health Interventions

Two analyses of modifiers within a single study were available in the Allied Health portion of the review, specifically in relation to the comparisons of PECS and RPMT for language development. This study[251] included an analysis of initial characteristics of the children demonstrating that children who were low in initial object exploration benefitted more from RPMT, which explicitly teaches play with objects, while children who were relatively high in initial object exploration demonstrated more benefit from PECS. These results were maintained at six months. An additional analysis based on this study[252] showed greater increases in generalized turn taking and initiating joint attention in the RPMT group than in PECS. The increased benefit for RPMT in join attention was only seen, however, in children who began the study with at least some initiation of joint attention. Specifically, children most likely to benefit from RPMT in increasing joint attention had demonstrated at least 7 acts of joint attention in the pre-intervention assessment. RPMT was also superior in this analysis in increasing object exchange turns.

CAM Interventions

One CAM study[276] assessed potential modifiers and noted correlations between changes in scores on sensory measures (PDDBI sensory, Sense and Systems Checklist) after qigong massage therapy and positive behavioral changes.

KQ3. Early Results in the Treatment Phase That Predict Outcomes

Early Identifiable Changes Predicting Response/Outcome

Information about early response to treatment, or lack thereof, can be essential to guiding treatment selection, implementation, and modification. The reviewed literature offers almost no information about what specific changes predict long-terms outcome and response. There is some evidence that early response to both EIBI/ABA and ESDM intervention in terms of changes in IQ over the first year of treatment predicts, or accounts for, longer-term change in IQ.[18, 29] However, findings also suggest that while gains in the cognitive domain might be accounted for primarily within the first year of treatment, changes in adaptive behavior in response to these same interventions may occur over a longer time frame[18, 29-31] if they occur at all.[32]

KQ4. End of Treatment Effects That Predict Outcomes

We were unable to identify any studies that described early treatment effects that could predict later outcomes, either positive or negative. Therefore, this key question is addressed mostly in future research.

KQ5. Generalization of Treatment Effects

We abstracted data on generalization from studies that collected outcomes data in multiple settings, including those naturalistic settings such as home and school, but found such data to be rarely collected.

The majority of studies of behavioral interventions targeting associated conditions did not measure outcomes in the treatment context (i.e., within therapy sessions or groups). Outcome was primarily assessed using parent, self, and/or teacher report of targeted symptoms (e.g., anxiety, externalizing behaviors) at home, at school, and in the community, thus suggesting that those interventions conducted in a clinical setting for which measured outcomes were positive are generalizable in the sense that they achieve outcomes in the "natural setting" of the child. On the other hand, in most cases, these outcomes are parent report and not confirmed with direct observation. Behavioral intervention studies uniformly failed to measure outcomes beyond the intervention period, and therefore, we cannot assume that effects are maintained over time.

In the category of social skills interventions, participants in two interventions, Cognitive-behavioral-ecological[154-155] and Lego therapy[160] demonstrated improvements in social skills in non-intervention settings when evaluated using direct observation measures (as opposed to, for example, parent report). Other studies generated parent reports of improvements as well,[152-153, 160-161, 165] but the parents in these studies were not blind to the intervention status of their children

and in some cases were involved in the treatment themselves. Furthermore, improvements reported in the home did not necessarily translate to all naturalistic environments. Although the parents of children involved in Children's Friendship Training[158] reported significant changes in child social behavior at home immediately following the intervention (as well as 3 months later), teachers did not report any changes in the children's behavior at school. On the other hand, teachers of children involved in Social competency and Social Skills training program,[157] reported improvements in student behavior at school.

One study attempted to assess the ability of children to apply new skills across changing intervention conditions in that participants in Social Stories[162] were able to generalize the social skills they learned while interacting with one set of board games to a different set of board games. However these "generalization" trials were conducted by the same experimenter in the same room as the other assessments, so it is not clear whether the targeted social skills would generalize to more naturalistic settings with peers.

For medical studies, data across classes of medications are likely to be generalizable outside of the clinic setting, primarily because the outcome measures used in these studies rely on parent report of the subjects' behavior in the home and other settings and are augmented in some studies by teacher report.

In terms of longer-term response to treatment, the case series data for risperidone are consistent with the improvements seen in the RCTs, with support for continued improvements extending to 6 months and beyond, but also with evidence of continued side effects.[33-37] RCT or case series data detailing either treatment response or adverse events extending beyond 6 months have not been published for aripiprazole or cyproheptadine. Two of the case series studies of SRIs are based upon durations of treatment longer than 6 months, but the general and sometimes qualitative ratings of change in these studies are difficult to compare with the results of the RCTs to understand if medication responses reported in RCTs are likely to be durable.[11, 222]

Among the sensory and auditory integration studies reviewed here, treatment responsiveness was not measured in the therapy setting. Parent, teacher, and clinician ratings were obtained in two studies, measuring sensory symptoms in one study, and behaviors and autism symptoms in a second. In a third study, language-related outcome was measured on two standardized assessments of language abilities. In this case, while the assessments were not within the treatment protocol, further information regarding language use in communicative bids would be useful in clarifying generalizability of findings. One did not report an outcome measure at all, thus generalizability of potential effects was not possible. The single study of music therapy used some parent report measures and some standardized assessments of joint attention which allowed some generalization of treatment effects to outside context (i.e., on parent report) or an alternate measurement setting (i.e., direct assessment). Findings regarding emotional and motivational responsiveness with the treating therapists and regarding increase eye contact and turn taking in session are not generalizable; assessments with other examiners, in different settings, and with different toys would be useful in clarifying with purported increase in emotional synchrony observed with music therapy generalizes outside of the treatment context.

KQ6. Drivers of Treatment Effects

No studies were identified to answer this key question.

KQ7. Treatment Approaches for Children Under Age Two at Risk for Diagnosis of ASD

This section presents the results of our literature search and findings regarding the use of treatment approaches in younger children who are at high risk of developing autism based upon behavioral, medical, or genetic risk factors. Studies located typically included participants whose mean age exceeded 24 months; however, the studies address interventions which can be used with children under age 2. The average age for diagnosis of ASD in the US is not until at least age three, but a reliable diagnosis may be possible as early as age two.[279-281] Research suggesting that early intervention can improve outcomes has compelled investigators to consider intervening in very young children.[20]

We identified four papers[8, 29, 145, 149] with unique study populations addressing treatment approaches for very young children. Three studies were conducted in the US[29, 145, 149] and one in the UK.[8] Two of the studies were prospective case series,[145, 149] one was a non-randomized controlled trial,[8] and one was a randomized controlled trial.[29] Table 27 summarizes outcomes for studies considered to be fair or good quality and employing comparison groups.

The RCT[29] and non-randomized trial[8] were completed in a clinic setting with instruction to continue with parents at home. All children in the RCT met DSM-IV criteria as well as criteria on ADOS and Toddler Diagnostic Interview for diagnosis confirmation; the mean age of participants in the treatment and control groups was 23 months. The non-randomized trial[8] employed parent training techniques to teach social communication skills and included children with a mean age of 38 months in the intervention group and 34 months in the control group.

One of the case series describes an evaluation of techniques to train personnel to provide ESDM-based therapy and included children with a mean age of 33 months.[149]The second case series[145] was completed in the home and classroom and focused on social-communication and language outcomes; children assessed in the study were between 18 and 36 months. Among studies in this section, 2 were considered fair quality and 2 were considered poor. The Dawson et al.[29] randomized controlled trial evaluated the effectiveness of the Early Start Denver Model (ESDM), for young children with ASD. ESDM, a comprehensive, manualized intervention that blends ABA with developmental and relational approaches, was designed to be used with children as young as 12 months, delivered in the home, and to utilize parents as well as trained therapists

After two years of intensive intervention (31 hours of intervention per week, 15 from a therapist and 16 from parents) children receiving ESDM displayed significantly larger gains in IQ (when compared with a community sample receiving 18 hours of individual and group intervention). Children in the experimental group also demonstrated significantly larger gains in terms of adaptive behavior skills (i.e., all areas except socialization) than controls. The authors also reported greater diagnostic shifts (i.e., from Autistic Disorder to PDD-NOS for seven (29.2 percent) children in the ESDM group and for one (4.8 percent) child in the A/M group; two (8.3 percent) children in the ESDM group and five (23.8 percent) children in the A/M group experienced a diagnosis change from PDD-NOS to ASD); however, these shifts were not matched with clinically significant improvements in terms of ADOS severity scores nor measurements of restricted and repetitive behaviors (i.e. RBS scores).

While no replication of this study has been conducted, the model had been subject to an early effectiveness trial[149] wherein the research team compared distance learning vs. live instruction

for community-based therapists implementing intervention and training parents. Results suggest that both modalities of learning were effective in teaching therapists to implement and train parents, with significant child gains over time and across modalities; however, results also suggested that implementation with fidelity required specific and explicit supervision. Thus, while promising in terms of treatment efficacy and extension to a younger population of children with ASD, training demands for broad implementation appear substantial. Further, the average age for enrollment was very close to two years of age. As such, concerns about how this model would apply to children closer to one year of age remain.

In another evaluation of an early intervention approach, parents of 51 preschool-aged children suspected of ASD (mean age, intervention group=38 months, mean age, control group= 34 months) participated in the Hanen More than Words program, as created by the Hanen Center either immediately (n= 26) or after a delay (n= 25).[8] The program focused on weekly group instruction in enhancing interactions and facilitating communication. In addition to 20 hours of group intervention, parents received individual in-home feedback on three occasions. Operationalization of 'suspected ASD' was identification of language delay and some aspect of concern about social behavior by a pediatrician and/or a speech and language therapist. Ultimately, this resulted in inclusion of children within intervention and control groups without ASD, with the authors grouping PDD-NOS and other developmental concerns under a category of 'non-core autism' (NCA). After the intervention period, reported language use was substantially higher for the intervention group, with both the core autism and NCA children demonstrating improvements. Parent use of taught strategies was also higher in the intervention group than in the comparison group but only for the children with core autism. No group differences were found for ADOS scores or behavior issues. Notably, more children in the intervention group had ASD, and the intervention group also received more 'substantial intervention' outside of the treatment context. Thus, while demonstrating potential benefit for parent training in social communication for young children with ASD, the unique impact of this program for specific children remains unclear.

Wetherby and colleagues'[145] prospective case series served as a preliminary study for the Early Social Interaction (ESI) Project, which emphasizes a parent-implemented individualized curriculum in a natural environment. The authors found significant within-group differences from pre- to post-test for 11 of the 13 social-communication measures on the CSBS-DP in the ESI group (n=17). The post-ESI group performed significantly better than the third-year contrast group (n=18) on three measures of social signals, rate of communicating, three measures of communicative functions, and understanding. There were no significant differences between the groups on the three measures of communicative means and both measures of play. The third-year contrast group performed significantly better than the pre-ESI group on all three measures of communicative means and on actions to others in play, but there were no significant differences on the three measures of social signals, rate of communicating, the three measures of communicative functions, understanding, and inventory of actions. The percentage of children who were verbal was 5.9 percent in the pre-ESI group, 76.5 percent in the post-ESI group, and 55.6 percent in the third-year contrast group.

These findings suggest that the ESI project has a positive impact on ASD symptoms, but because the groups were unable to be compared at pretest, we cannot conclude whether the benefits were due to ESI or to normal maturation. Another limitation in the authors'

methodology is the lack of documentation of parental implementation in the home, given that the parents' involvement is a significant factor in the effectiveness of ESI treatment.

Table 27: Outcomes of interventions for children at risk for diagnosis of ASD

Author, Year Groups Study quality	Age,mean (months) ±SD Diagnostic category, N (%) Groups, N enrollment/N final	Key outcomes
Dawson et al.[29] 2010 Comprehensive developmental behavioral intervention **G1:** ESDM **G2:** Community-based interventions Quality: Fair	**G1+G2**: Intake: 38 Follow-up: 52 Autism: 39 (75) PDD-NOS: 9 (17) **G1**: 24/24 **G2**: 24/21	**1 yr outcomes:** • Significantly greater improvement in IQ for ESDM (154 vs 22 pts) than community-based • No adaptive behavior differences **2 yr outcomes:** • Significantly more improvement in ESDM group vs. community-based on IQ; receptive language, and expressive language • Adaptive behavior improvements in both groups (all domains except socialization) • No change in ADOS severity scores or repetitive behavior • Diagnostic shift greater for ESDM group
McConachie et al.[8] 2005, UK **G1**: More than Words (MW) **G1a**: MW, participants with autism dx **G1b**: MW, participants with PDD-NOS or other childhood developmental disorder, **G2**: Wait list control **G2a**: Wait list control, participants with autism dx **G2b**: Wait list control: participants with PDD-NOS or other childhood developmental disorder Quality: Fair	**G1**: 38.12 (6.54) **G2**: 34.96 (6.68) **G1**: Autism: 17 (65) NCA: 9 (35) **G2**: Autism: 12 (48) NCA: 13 (52) **G1**: 26/26 **G1a**: 17/17 **G1b**: 9/9 **G2**: 21/21 **G2a**:12/12 **G2b**:13/13	• Reported language use was substantially higher for G2 with both the core autism (on average 50 words) and NCA groups demonstrating improvements • No group differences were found for ADOS scores or behavior issues

ADOS=Autism Diagnostic Observation Schedule, ESDM=Early Start Denver Model, NCA=non core autism

Chapter 4. Discussion

In this chapter, we summarize our findings about therapies for children with autism spectrum disorders, which derive from our systematic review of the literature for seven key questions. We provide an overview of the state of the literature by intervention type, a description of the strength of evidence for each major intervention-outcome combination and describe major issues and gaps in the current body of evidence.

Methods for applying strength of evidence assessments are established in the EPC Methods Guidance[132] and are based on consideration of four domains: risk of bias, consistency in direction of the effect, directness in measuring intended outcomes, and precision of effect. Within the risk of bias domain, we expected areas of moderate evidence to have at least one RCT with a "good" quality rating; areas of high strength of evidence had at minimum two good RCTs. In addition, to be considered "moderate" intervention-outcome pairs needed a positive response on two out of the three domains other than risk of bias.

At this point, we assessed the SOE, took into consideration the number of studies and range of study designs and downgraded if we felt it was appropriate. Table 37 documents assessments for each domain of the major intervention-outcome combinations. Overall SOE assessments are provided in the synthesis tables in this section.

Outcomes and Strength of Evidence of Therapies

Effectiveness of Behavioral Interventions

Categories of behavioral intervention studies included early intensive intervention studies, social skills approaches, play and interaction-based approaches, interventions focused on commonly associated conditions, and studies of additional behavioral interventions. Tables 28 through 36 summarize effectiveness findings.

Early/Intensive behavioral interventions. We located 38 papers[4-8, 18-32, 133-150] comprising 34 unique studies addressing early/intensive interventions. The literature on the range of early and intensive behavioral intervention published in the past 10 years is characterized by a small number of well-controlled studies conducted (five), substantial methodologic weaknesses in study conduct, and likely substantial confounding in the majority of the studies that is poorly addressed in analyses. Nonetheless, the existing research suggests, with moderate strength of evidence, that intensive UCLA/Lovaas and Early Start Denver Model interventions (greater than 30 hours per week) may confer greater improvements in cognitive performance, language skills, and adaptive behavior skills than the broadly defined eclectic treatments that are often available to children in the community.

At present, these approaches have demonstrated effect in RCTs when implemented by both professionals and parents. Data from observational and non-controlled studies also have demonstrated improvement for children receiving EIBI/ABA treatments compared with eclectic treatments. Positive outcomes have been most commonly observed in these studies when EIBI/ABA approaches are systematically delivered by expert providers, including well-supervised and trained parents, over fairly lengthy intervals of time (> 1 year). Not all children receiving early intensive intervention, however, demonstrate rapid gains, with some data suggesting that many children will continue to display prominent areas of impairment [4] and that subgroups may account for a majority of the changes observed.

Further, improvements are most often demonstrated in cognitive abilities and educational attainment, but less consistently in adaptive, social, and challenging behaviors. Of note, however, even children who have meaningful improvement in specific areas (most often in cognitive skills) often continue to have substantial impairment in other areas of adaptive, social, and behavioral functioning. This sustained level of impairment, along with a lack of longer-term outcomes data, make it difficult to assess whether treatment-related changes can modify long-term functional and developmentally appropriate adaptive independence across settings and over the course of development.

To date, studies have failed to adequately characterize the subpopulation of children who experience positive response to intervention, although it is clear that positive outcomes are most prominent in some children but not others. One of the most powerfully replicated findings in the available literature is that substantial and varying proportions of children do not seem to demonstrate robust changes in response to early and intensive behavioral interventions.

The challenge in interpreting results in this category of literature may also be attributed to the fact that although authors assert their use of EIBI/ABA generally, there is an overwhelming paucity of detail provided on the degree to which studies adhere to the method cited. Many of the studies are inadequately described, fail to include fidelity and treatment adherence measurements and procedures, and may in fact be ultimately delivering very different interventions. As a result, the body of literature categorized in this report as "early/intensive behavioral" is so disparate that conclusions cannot be easily drawn from the observational studies.

There also are no studies available that directly compare the effects of different treatment approaches (for example, no direct comparison of UCLA/Lovaas and ESDM), and there are few data on practical effectiveness or feasibility beyond research studies, so questions remain about whether reported findings would be observed on a larger scale within communities.

Beyond specific and intensive early interventions, less intensive interventions to provide parent training for bolstering social communication skills and managing challenging behaviors may be useful for younger children with ASD, particularly to improve social communication, language use, and potentially symptom severity.[5-8] However, while parent training programs can modify parenting behaviors during interactions, data are limited about their contribution to specific child improvements in the short- and long-term beyond simple language gains for some children.

In sum, there have been to date very few well-controlled trials and those conducted have used small samples; drastically different treatment approaches (i.e., developmental to intensive behavioral), intensity (12 hours over 3 months vs. 30 hours over 1 week), and duration (weeks to years); varied inclusion and baseline assessment criteria; children of varying ages (intake age ranging from 18 months to 7 years); and different outcome measurements over different periods of time (weeks to years). Nonetheless, improvements occur in some aspects of language, communication, cognitive ability, adaptive behaviors, challenging behaviors, and potentially improved educational attainment for some preschool and early school-aged children with ASD who receive intensive intervention. Strength of evidence is lower to support possible effects in children receiving low-intensity intervention, including parent training, but these approaches are promising and warrant further study.

Table 28. Synthesis of results of studies of early intensive/developmental approaches

Intervention	Study design/Quality	Key findings and Strength of Evidence
ABA-based approaches (including ESDM, UCLA/Lovaas-based intervention and other EIBI variants)	3 RCTs / 1 good,[18] 2 fair[4, 29] 3 Non-randomized trials / 3 fair,[25, 30, 133] 5 Prospective cohorts / 3 fair,[27, 32, 146] 2 poor[21-22] 2 Retrospective cohorts / 2 poor[134, 148] 8 Prospective case series / 1 fair,[135] 7 poor [19-20, 24, 137, 142, 145, 149] 6 Retrospective case series / 6 poor[23, 28, 136, 141, 143, 150]	• Young children receiving high intensity interventions (>30 hours a week for 1-3 years by well trained therapists) display improvements in areas of cognitive, language, adaptive functioning • Subgroups of children display only a moderated response to this intervention, with data not yet clearly describing this subgroup • Improvements in cognitive, language, and adaptive behavior skills are seen over 2 years of ESDM intervention for young children with ASD • ESDM findings are not yet replicated and it is unclear how core ASD symptoms change in response to tx • Strength of evidence for UCLA/Lovaas-based intervention in affecting cognitive, educational, and adaptive outcomes and ASD symptom severity is moderate and high for language outcomes • Strength of evidence for ESDM-based intervention in affecting cognitive, language, and adaptive outcomes insufficient
Parent training	2 RCTs / 2 fair[5-6] 2 Non-randomized controlled trials / 1 poor,[7] 1 fair[8] 3 Prospective case series / 3 poor[139-140, 147]	• There is some indication of short-term improvements in language, social, and adaptive skills for children whose parents receive training in these areas • Data do not yet demonstrate long-term functional improvements across domains for any specific form of training • Strength of evidence for changing core ASD deficit areas is low

ASD=Autism Spectrum Disorders; EIBI=early intensive behavioral intervention; ESDM=Early Start Denver Model; tx=treatment; UCLA=University of California, Los Angeles

Strength of evidence. The strength of evidence for the effect of UCLA/Lovaas-based intervention in affecting cognitive, educational, and adaptive outcomes as well as the severity of ASD symptoms is moderate, with 1 good quality RCT available, inconsistency of positive impact for certain measurements within studies, and direct measurement of the effect of the intervention on the outcomes of interest. The strength of evidence of the UCLA/Lovaas model on language is high, based on consistent and precise outcome measures and direct measurement of effects (Table 28).

With only 2 studies available (1 fair quality RCT), there are insufficient data at this time to assess the strength of evidence for the Early Start Denver Model on adaptive behavior, ASD symptom severity, IQ, and language.

The evidence for parent training interventions was low with few studies, only one of which was an RCT of fair quality. Furthermore, outcomes assessed in these studies were frequently short-term, indirect (intermediate) measures.

Social skills training. We located 15 papers addressing interventions targeting social skills.[152-166] Although all of the studies of social skills interventions reported some encouraging results, most have not included objective observations of the extent to which social skills improvements generalize and are maintained within everyday peer interactions. In addition, the current research focuses almost exclusively on high functioning children with autism, which excludes the majority of children within this diagnostic classification. The quality of the studies was poor to fair, although some promising results may suggest benefit for a subgroup of high functioning children. No two studies evaluated the same intervention, making it impossible to know whether observed results are likely to be consistently observed.

Comprehensive interventions directed to both children and their parents were associated [156, 163]) with improvements in social cognition, including executive function and anger management. The other RCT that involved parents was a less comprehensive program (Children's Friendship Training[158]), and resulted in some improvement in social skills related specifically to friendship. According to parents, children hosted more play dates, had better self-control, and engaged in fewer minimally socially interactive activities during play dates, and reported less loneliness and greater popularity.

The Social Stories intervention helped children improve their skills in playing board games[162] and although positive effects were observed with other interventions, those studies had poor quality and warrant further examination with more rigorous study designs if they are to be used in practice.[152-155, 157, 159-161, 165-166]

Strength of evidence. The strength of the evidence of social skills interventions affecting social outcomes is low (Table 29). Of 15 RCTs, 7 were fair in quality and none was good. All studies did demonstrate benefit on at least one outcome measure but a lack of consistency in outcome measures makes it impossible to assess consistency or precision. Most studies relied on report of intermediate rather than ultimate outcomes.

Table 29. Synthesis of results of social skills interventions

Intervention	Study design/Quality	Key findings and Strength of Evidence
Group-format	6 RCTs / 3 fair[152, 156, 158], 3 poor[160, 163, 166] 1 Retrospective cohort / 1 poor[165] 5 Prospective case series / 3 fair,[155, 157, 161] 2 poor[153, 159]	• High functioning children with ASD improved on various social outcomes, however whether or not the tx group made improvements in specific social skills (such as emotion recognition, theory of mind, and observed peer interactions) varied depending on the study • Strength of evidence on social outcomes is low
Individual-format	1 RCT / 1 fair[162] 2 Prospective case series / 1 fair,[154] 1 poor[164]	• Improvements in targeted social skills for treated participants • Strength of evidence on social outcomes is low.

ASD=autism spectrum disorders; RCT=randomized controlled trial; tx=treatment

Play- and interaction-based interventions. Among the 14 papers (12 unique study populations) addressing play-/interaction-based interventions[167-180] addressed here, the strength of evidence is insufficient to low, although there may be some suggestion that[177-179] interventions encouraging children to imitate adults in appropriate behaviors can produce better outcomes in motor activity and interaction with adults (i.e., touching, looking at, and being in proximity) than contingently responsive intervention. Interventions using either a joint attention approach or symbolic play are equally effective in improving responsive joint attention or expressive language. The combined results of these studies suggest that both the joint attention and symbolic play interventions generalize across people (i.e., mothers) with respect to specific skills, and that generalization of joint attention skills to a new stimulus is more likely to occur in children receiving the joint attention intervention.

As in the early intensive intervention literature, parent training in play-based interventions shows some promise for reducing challenging behavior and warrants further study. Very preliminary outcomes from four case series of relationship-focused interventions suggest improvement is possible in play and language skills and social interactions. However, each study in the review measured a different outcome.

Strength of evidence. Although there were at least two RCTs available for most categories of play interventions (parent-focused, relationship-based, imitation, joint attention and symbolic play), no RCTs were of good quality. The strength of evidence for the effectiveness of imitation-focused interventions on social behavior outcomes was low as was the strength of evidence for joint attention-focused interventions on joint attention outcomes (Table 30). The strength of evidence for parent-focused play-based interventions in modifying challenging behavior was similarly low, as neither of the two RCTs available was of good quality. There was insufficient evidence to evaluate the outcomes of the relationship-focused interventions on social skills and behaviors. Only four studies (all case series) fell into this category and there was little consistency among the outcomes measured.

Table 30. Synthesis of results of studies of play-/interaction-based interventions

Intervention	Study design/ Quality	Key findings and Strength of Evidence
Parent focused therapies	2 RCTs / 1 fair,[175] 1 poor[167-168]	• Problem behavior and hyperactivity declined for the treated group • Adaptive behavior increased for the treated group • Parent reports indicated that the treated group appeared more typical following intervention • Strength of evidence for effectiveness in affecting challenging behavior is low
Imitation	3 RCTs / 3 poor[177-179]	• Children in imitation tx groups showed more interaction with adults compared with those in contingent response groups • Strength of evidence for the effect on social behavior is low

Table 30. Synthesis of results of studies of play-/interaction-based interventions (continued)

Intervention	Study design/ Quality	Key findings and Strength of Evidence
Joint attention and symbolic play	2 RCTs / 2 poor[170-171] 1 Prospective case series / 1 poor[172]	• Joint attention and symbolic play equally effective in improving responsive joint attention or expressive language • Greater improvement in outcomes predicated on increased joint attention in the joint attention groups • Strength of evidence for effectiveness of joint attention intervention in affecting joint attention outcomes is low
Relationship-focused interventions	2 Prospective case series / 2 poor[174, 180] 2 Retrospective case series / 2 poor[173, 176]	• Positive outcomes in terms of acquiring pivotal behaviors noted, but no comparison groups • Insufficient evidence to determine strength of the evidence.

RCT=randomized controlled trial

Behavioral interventions for commonly associated conditions. We identified 11 studies reported in 12 papers [36, 56-57, 181-189] that addressed behavioral interventions focused on symptoms commonly associated with ASD. Most studies of the use of behavioral interventions to address commonly associated conditions are limited to high-functioning children with ASD who are at least school age. These studies evaluated behavioral treatments for commonly occurring comorbid symptoms in ASD, including anxiety, anger management difficulties, and challenging behaviors; all report promising results, with caveats concerning study quality.

Interventions included cognitive behavioral therapy in individual and group formats, parent training, and teacher training to address target symptoms. CBT-based treatments varied across studies and were generally adapted from existing manuals to be more amenable for use in children with ASD, who were expected to have difficulty with interventions emphasizing cognitive restructuring and emotion understanding components. Several studies suggested that CBT-based interventions were effective in reducing anxiety symptoms in children with comorbid anxiety disorders. After treatment, many children no longer met diagnostic criteria for anxiety disorders [183-184] and significant numbers showed reduced anxiety symptoms.[57, 183-184] One study also suggested that a CBT-based treatment for anxiety also improved parent report of their children's social skills.[183-184]

This category of intervention also included various parent training approaches to decrease challenging behaviors. Results of two studies combining parent training with risperidone treatment suggested that adding parent training to medication increased adaptive behavior and decreased non-compliance, hyperactivity, and irritability in children.[36, 185] Another set of parent training studies suggested that training parents improved both the frequency and intensity of a child's challenging behaviors, with a weekly individual session model being slightly more effective than a one-day workshop model, though both trainings were more effective than a wait list control.[187-188] While the literature regarding CBT and parent training for decreasing comorbid anxiety, anger management, and externalizing symptoms is promising, results should be interpreted cautiously; parents completed the majority of questionnaires to assess symptoms before and after treatment and reporting biases were not assessed.

Strength of evidence. The strength of evidence for a positive effect of CBT-based, parent-training, and teacher-training interventions on comorbid symptoms was moderate, with consistent positive findings regarding improvement in anxiety, anger, and challenging behavior levels (Table 31). Nonetheless, available RCTs were of fair quality and measurements of intermediate outcomes were typically imprecise.

Table 31. Synthesis of results of studies targeting behaviors commonly associated with ASD

Intervention	Study design/ Quality	Key findings and Strength of Evidence
CBT for anxiety	4 RCTs / 2 fair,[183-184] 2 poor[56, 182, 189] 1 Non-randomized trial / 1 fair[57]	• Decrease in anxiety symptoms in treated groups • Reduction in number participants meeting criteria for anxiety disorders • Improvement in social skills in treated children • Strength of evidence for a positive effect on comorbid symptoms was moderate, with consistent positive findings regarding improvement in anxiety
CBT for anger management	1 RCT / 1 fair[181]	• Reduction in parent-reported instances of anger in treated group • More anger management strategies developed by treated participants • Strength of evidence for a positive effect on comorbid symptoms was moderate, with consistent positive findings regarding improvement in anger and challenging behavior levels
Parent and teacher training	1 RCT / 1 fair[36] 1 prospective cohort / 1 poor[187-188] 2 prospective case series / 1 fair,[185] 1 poor[186]	• Less severe challenging behaviors in children taking risperidone whose parents participated in parent training • Reduced number and intensity of challenging behaviors, with parent training in individual sessions more effective than in a workshop setting • Reduction in targeted challenging behaviors in classroom • Strength of evidence for a positive effect on comorbid symptoms was moderate, with consistent positive findings regarding improvement in anxiety, anger, and challenging behavior levels •

CBT=cognitive behavioral therapy; RCT=randomized controlled trial

Additional behavioral interventions. Three studies[192-194] of additional behavioral interventions (neurofeedback, sleep workshops) met our inclusion criteria. These interventions showed some promising results but are limited by small sample sizes, short-term follow-up and largely parent-reported outcomes without additional independent assessments of symptom change. Neurofeedback research in ASD is in the early stages with few controlled studies. The RCTs included had small sample sizes (less than 60 treated children total), unclear diagnostic procedures, and no follow-up beyond the immediate 20- to 36-session treatment period..[192-193] A movement toward improved rigor can be seen in the broader range of measures used in the later studies and improved reporting of some methodologic elements. One pilot case

series[194]demonstrated some effectiveness for behavioral techniques in promoting good sleep habits for children with ASD, including those with limited receptive language.

Strength of evidence. With few studies of additional behavioral interventions, all of poor quality, there is insufficient evidence to evaluate the relative effect of other behavioral interventions on targeted outcomes including ASD symptom severity, problem and repetitive behaviors, and sleep concerns (Table 32). Nonetheless, some interventions show promise and should continue to be evaluated

Table 32. Synthesis of results of studies of other behavioral interventions

Intervention	Study design/ Quality	Key findings and Strength of Evidence
Neurofeedback	2 RCTs / 2 poor[192-193]	• Some improvements on broad measures of ASD severity • Insufficient evidence to determine strength of the evidence.
Sleep workshops	1 Prospective case series / 1 poor[194]	• Some effects on sleep habits but night wakings not affected • Insufficient evidence to determine strength of the evidence.

ASD=autism spectrum disorders; RCT=randomized controlled trial

Effectiveness of Educational Interventions

The TEACCH program is the most widely studied educational intervention, but the majority of research on it took place prior to the date cutoff for our review. Thus, only four studies met our criteria for inclusion.[196-199] In this newer research, the program continues to demonstrate improvements among children in gross motor, eye-hand coordination, and cognitive measures. In other studies, a developmentally center-based intervention was associated with improvements over no treatment, and the inclusion of a home-based component had an additive effect beyond center-based instruction alone.

Among the studies evaluating the setting and the type of instructional strategy, one study[9] found that children in both a home-based early intensive behavioral intervention and an autism-based nursery program improved at similar rates, but that there were child characteristics including IQ and receptive language at baseline that were strong predictors of progress. An additional study[10] suggested that home-based ABA teaching interventions were more effective than those in a school-based intervention borrowing from TEACCH, and a home-based portage program.

Strength of evidence. The strength of evidence for the effect of the TEACCH intervention on cognitive verbal outcomes is moderate, based on moderate risk of bias (2 prospective cohorts; 1 good and 1 fair quality), consistency in the direction of effect, and direct measurement of the effect of the intervention on the outcomes of interest (Table 33). These findings are based on the studies that meet our criteria for publication from 2000 to present.

The strength of evidence for the effect of broad-based educational strategies (seven studies[9-10, 202-206]) on socialization and communication (VABS), IQ and educational functioning was low; there was one RCT of good quality available, but further research is needed. There was insufficient evidence to evaluate the outcomes of computer-based programs on language and communication. Only two studies[200-201] (both of poor quality) fell into this category and there was little consistency between the outcomes measured in each.

Table 33. Synthesis of results of educational interventions

Intervention	Study design/ Quality	Key findings and Strength of Evidence
TEACCH	2 Prospective cohorts / 1 good,[196] 1 fair[198] 2 Prospective case series / 2 poor[197, 199]	• All treated groups improved in gross motor skills and cognitive performance • Inconclusive outcomes for fine motor skills, perception, daily living skills, imitation, and socialization. • Strength of evidence for effect on cognitive verbal outcomes is moderate
Broad-based approaches	1 RCT / 1 good[204] 1 Non-randomized trial / 1 poor[206] 3 Prospective cohorts / 3 fair[9-10, 205] 1 Prospective case series / 1 poor[203] 1 Retrospective case series / 1 poor[202]	• Combination of home- and center-based program compared with a center-based only program improved IQ and behavior. • ABA and nursery programs showed higher gains compared with the portage program in educational functioning and adaptive behavior. • More time intensive interventions produced greater improvements in intellectual and educational functioning, and adaptive behavior. However, this effect was tempered by higher levels of parental stress. • Strength of evidence for effect on socialization and communication skills is low
Computer-based approaches	1 RCT / 1 poor[200] 1 Prospective case series / 1 poor[201]	• Increases in verbal expressions after participating in multi-media program. • Greater recall of nouns after computer-based training as compared with teacher-led instruction. • Insufficient evidence to determine strength of the evidence.

ABA=applied behavior analysis; IQ=intelligence quotient; RCT=randomized controlled trial; TEACCH= Treatment and Education of Autistic and Related Communication-handicapped Children

Effectiveness of Medical Intervention

Although no current medical interventions demonstrate clear benefit for social or communication symptoms in ASD, a few medications show benefit for repetitive behaviors or associated symptoms. Given that many children with ASD are currently treated with medical interventions,[72-74] there is strikingly little evidence to support clear benefit for most medical interventions, especially in the realm of interventions such as restrictive diets and supplements. We located 17 papers from eight studies addressing antipsychotic medications;[33-35, 37, 207-210, 211, 212-218] five studies addressing SRIs;[11-12, 221-223] six publications[13-17, 227] from four studies evaluating stimulants and other medications for hyperactivity; eight studies addressing secretin;[228-235] and 15 papers (14 unique studies) addressing dietary and other medical interventions.[98, 236-249]

The clearest evidence favors the use of medications to address challenging behaviors (Table 34). Risperidone and aripiprazole are the two best-studied medications in ASD, with the

corresponding pharmaceutical companies funding at least one RCT for each. Each medication now has at least two RCTs demonstrating improvement in a parent-reported measure of challenging behavior that includes emotional distress, aggression, and self-injury. A parent-reported hyperactivity and non-compliance measure also showed significant improvement. Although it was not the primary target behavior addressed in these studies, the core ASD symptom domain of repetitive behavior also showed improvement with both risperidone and aripiprazole. Both medications also cause significant side effects, including marked weight gain, sedation, and risk of extrapyramidal symptoms. When considered in aggregate, risperidone and aripiprazole are efficacious but are associated with significant side effects that limit their use to patients with severe impairment or risk of injury.

Table 34. Synthesis of results of medical studies

Intervention	Study design/Quality	Key findings and Strength of Evidence
	Antipsychotics	
Risperidone vs. placebo	4 RCT / 1 good,[33, 35, 207-212] 3 fair[34, 213-215] 1 prospective case series / 1 poor[37]	• Improvements in challenging behavior and repetitive behavior • Adverse effects, including weight gain, sedation and extrapyramidal effects • Strength of evidence for reducing challenging behavior and repetitive behavior is high • Strength of evidence for adverse events is high; common side effects include weight gain, sedation, and extra-pyramidal effects
Aripiprazole vs.placebo	2 RCT / 2 good[216-217]	• Improvements in challenging behavior and repetitive behavior • Adverse effects, including weight gain, sedation and extrapyramidal side effects • Strength of evidence for reducing challenging behavior and repetitive behavior is high Strength of evidence for adverse events is high; common side effects include weight gain, sedation, and extra-pyramidal effects
Cyproheptadine added to haloperidol vs. haloperidol and placebo	1 RCT / 1 fair[218]	• Behavioral improvement reported but without indicating specific domains • Strength of evidence for reducing challenging behavior and repetitive behavior is high
	SRIs	
Fluoxetine vs. placebo	1 RCT / 1 fair[221] 1 Retrospective case series / 1 poor[222]	• Greater change in repetitive behavior with fluoxetine compared with placebo • Strength of evidence for SRIs to decrease repetitive behavior is low • Strength of evidence for adverse events is low

Table 34. Synthesis of results of medical studies (continued)

Intervention	Study design/Quality	Key findings and Strength of Evidence
SRIs		
Citalopram vs. placebo	1 RCT / 1 good[223] 1 Prospective case series / 1 fair[12]	• No significant difference between the groups on repetitive behavior • Significant but clinically small reduction in challenging behavior in the tx group compared with placebo • Genotype effect on improvement in challenging behavior • Strength of evidence for effect of SRIs to reduce repetitive behavior is low • Strength of evidence for adverse events is low
Various SRIs (including sertraline,citalopram, paroxetine, fluvoxamine)	1 Retrospective case series / 1 poor[11]	• 40/89 subjects ranked as “much improved” • Strength of evidence for effect of SRIs to reduce repetitive behavior is low • Strength of evidence for adverse events is low
Stimulants and other medications to treat hyperactivity		
Stimulants	1 RCT / 1 good[13-15] 2 Retrospective case series / 2 poor[16, 227]	• Improvement in hyperactivity and non-compliance • Adverse events, including increases in challenging behavior and loss of appetite • Strength of evidence for effectiveness in affecting hyperactivity is moderate • Strength of evidence around adverse events is also moderate
Guanfacine	1 Retrospective case series / 1 poor[17]	• Symptom improvement observed for hyperactivity, inattention, insomnia, and tics • Strength of evidence for effectiveness on hyperactivity and inattention is insufficient
Secretin		
Secretin vs. placebo	7 RCTs / 2 good,[231-232] 5 fair[228-230, 233-234] 1 Prospective case series / 1 poor[235]	• No studies showed significantly greater improvements in the secretin group; • No difference for porcine or synthetic secretin. • Strength of evidence is high for lack of effectiveness in affecting language, cognition, behavior, communication, autism symptom severity, and socialization

Table 34. Synthesis of results of medical studies (continued)

Intervention	Study design/Quality	Key findings and Strength of Evidence
Dietary interventions		
Dietary interventions and supplements	4 Prospective case series / 4 poor[236-237, 239-240]	• Some studies showed improvements with iron supplementation, magnesium and vitamins, fish oil, evening primrose oil and ketogenic diet • No studies had comparison groups and all were poor • Insufficient evidence to determine strength of evidence
Other interventions		
Various Medical Interventions	4 RCTs / 1 good,[246] 3 fair[241-242, 245] 1 Prospective case series / 1 poor[248] 1 Retrospective case series / 1 poor[238]	• Early promise for omega 3 fatty acids, melatonin, L-carnosine, and piracetam • 85% of parents reported decrease in or resolution of sleep problems with melatonin; problems returned in some children.[238] • One good RCT of hyperbaric oxygen showed benefit on general ratings and social and challenging behaviors • No effect for cholinesterase inhibitors (donepezil) on language or behavior • Insufficient evidence in any one category
Various Medical Interventions showing no benefit	4 RCTs / 1 good[98], 2 fair[244, 249], 1 poor[243, 247]	• Amantadine, oral immunoglobulin, and the chelating agent DMSA showed no benefit in single RCTs • Insufficient evidence to determine strength of the evidence for any one of the various medical interventions

DMSA=dimercaptosuccinic acid; RCT=randomized controlled trial; SRI=serotonin reuptake inhibitor

A few medical interventions have been studied in either single or multiple RCTs that provide adequate evidence that they show little promise for further study. Secretin has been exhaustively studied in multiple RCTs with clear evidence that it lacks benefit in ASD. Amantadine, N-dimethylglycine, oral immunoglobulin, and the chelating agent DMSA showed no benefit in single RCTs.

Other medical interventions have also been evaluated in single RCTs and show promise for further study. Methylphenidate improved hyperactivity in the ASD population in an RCT, and a follow-up analysis suggested possible improvements in a measure of social communication. An RCT of hyperbaric oxygen treatment showed benefit on general ratings of improvement, as well as a number of specific measures of social and challenging behavior.

The SRI fluoxetine showed benefit for repetitive behavior in a single cross-over RCT; although this effect was driven by only one arm of the study.[221] An RCT of the SRI citalopram[223] showed no benefit for repetitive behavior but possible improvement in challenging behavior.

A few additional treatments show promise in case series or other studies, including omega 3 fatty acids,[240] melatonin,[238] L-carnosine,[241] guanfacine,[17] cyproheptadine,[218] and piracetam.[245] Quite a number of other medical interventions in frequent use in ASD have little to no evidence

to argue for or against their use. It is hoped that clinicians using these untested medical treatments will publish case series data to allow the field to evaluate which treatments show enough promise to merit further study.

Also lacking in the literature are comparisons of medical interventions with behavioral interventions and combinations of the two, 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,[282-284] but only two studies of adequate size have considered combination treatment with risperidone and behavioral treatment, and these studies lacked an arm that considered behavioral treatment alone, in addition to lacking a placebo control.

One of the largest problems in the medical intervention literature is the paucity of reliable measures of change in ASD. Most studies to document treatment effects have relied upon the Aberrant Behavior Checklist, Community version (ABC-C), which has been very useful in measuring challenging behavior and hyperactivity/noncompliance. Unfortunately, however, the ABC-C does not effectively measure core features of autism, nor does it provide an appropriate gauge of attention, anxiety, or mood symptoms. Other measures have less data supporting their reliability or validity.

Overall, the average quality of the literature on medical interventions was higher than the average for behavioral interventions. Several factors could account for this, including the higher limit on minimum sample size that we set for medical interventions. We felt that the higher risk involved in a child with ASD taking a medication, pursuing a restricted diet, or participating in another medical intervention warranted a more rigorous standard supporting possible benefit. Nonetheless, the data on individual medical interventions continue to be sparse with the exception of risperidone and aripripazole.

Strength of evidence. We rated the strength of evidence for the effect of atypical antipsychotic medications on challenging behavior and repetitive behavior to be high (Table 34). There were a total of 6 RCTs in this area, three of which had good quality and the other three fair. They produced consistent and precise estimates of effect. By the same token, strength of evidence around adverse events is also high, with common side effects including weight gain, sedation and extra-pyramidal effects. One RCT of good quality supported by case series was available to evaluate the effects of stimulants on hyperactivity, and we assessed SOE for this relationship to be low. Side effects were, again, common, with low strength of evidence for their association with stimulants. With only one good quality RCT available, and an additional RCT of fair quality, we consider the strength of evidence for the ability of SRIs to reduce repetitive behavior to be low as well. SRIs were also studied for their effect on challenging behavior, but the one good RCT on SRIs did not focus on this outcome. The direction of the effect was inconsistent given that worsening of behavior can be an adverse effect of the treatment, and we assessed the SOE for this relationship to be low. Evidence of adverse effects with SRIs (decreased sleep and increased energy) was based on low strength of evidence (2 RCTs, one of which was good) with variability in how the outcomes were measured. The strength of evidence for the effectiveness of guanfacine for the treatment of hyperactivity and inattention as well as for harms in children with PDDs is insufficient, with one poor retrospective case series available.

It is clear from existing research that secretin is not effective in affecting language, cognition, behavior, communication, autism symptom severity, and socialization skills, and the strength of evidence for this lack of effectiveness is high. With seven RCTs with fair to good quality scores

and one case series contributing to this evidence base, future studies are unlikely to change the estimate of effect for this treatment.

With a wide range of interventions employed among the dietary and other medical interventions, range of outcomes assessed including general symptom severity, challenging behaviors, sleep difficulties, and language and communication, and the predominance of poor and fair quality results in this subset of the literature, there is insufficient evidence to evaluate the relative effect of any of the other medical interventions reviewed on the outcomes targeted. Nonetheless, some interventions show promise and should continue to be evaluated

Effectiveness of Allied Health Interventions

Studies in this category included those addressing language, sensory and auditory integration, and music therapy among others.

Language and speech. Our search identified eight publications focused on speech and language interventions (PECS and RPMT),[250-257] representing four distinct study populations Both interventions were effective at increasing the number of words used by children early after intervention (up to 3 months) but neither showed maintenance of improvements over the longer term. In addition, children most likely to benefit from RPMT in increasing joint attention had demonstrated at least 7 acts of joint attention in the pre-intervention assessment. A second RCT [255] of teacher training in PECS found that treatment was associated with a decrease in severity on the ADOS-G RSI score at 10 months. Scores did, however, remain well above the cutoff for autism, and this delayed effect is difficult to interpret. There was no significant effect of treatment on either of the standardized language tests at any time-point.

Sensory and auditory integration. We located seven papers,[123, 258-263] comprising five unique studies addressing sensory or auditory integration, but only one study examined sensory integration therapy in a meaningful way, finding improvement in sensory symptoms following 24 sessions conducted according to Sensory Diet procedures. This finding is consistent with a handful of previous studies, summarized in a prior review,[119] though other studies of sensory integration procedures reviewed in that article did not show positive treatment effects. In part, the inconsistency in outcomes in this area may be related to methodological difficulties in applying strict treatment procedures and rigorous evaluation to an intervention that is by nature child-led.

Evidence from studies in this review was insufficient to rate the strength of evidence related to auditory integration training for improving language skills, challenging behaviors, or cognitive ability in low functioning children with autism. While earlier studies (reviewed in Baranek, 2002[119]) suggested some positive outcomes associated with auditory integration, newer, well-designed studies described here contradict older findings in showing no improvements in the treatment groups. The two studies reviewed here utilized different auditory integration methods, with neither method yielding a positive result in randomized control crossover design studies. These studies suggest that auditory integration training is not effective for improving one-word receptive and expressive language or challenging behaviors in children with autism, though future research could clarify whether these treatments might be effective for other areas of difficulties, in which case the two studies reviewed here may not have used outcome measures most sensitive to capturing change.

In sum, there have been few studies in the past decade examining the effectiveness of allied health interventions with sufficient sample size to consider closely (Table 35), although these

approaches are often pursued by parents of children with autism. It will be important for future research to prioritize studying these treatments using rigorous methodologies to clarify whether (or for what outcomes) these treatments may be effective.

Table 35. Synthesis of results of allied health studies

Intervention	Study design/ Quality	Key findings and Strength of Evidence
Language and speech interventions		
PECS, RPMT	2 RCT / 1 good,[250-253] 1 poor[255] 1 Non-randomized controlled trial / 1 poor[254, 257] 1 Prospective case series / 1 poor[256]	• Mixed results for language acquisition • Observed increases in language have not been maintained long term or after tx discontinuation • Children most likely to benefit from RPMT in increasing joint attention had demonstrated at least 7 acts of joint attention in the pre-intervention assessment • Strength of evidence for language interventions (PECS and RPMT) is low
Sensory/auditory interventions		
Sensory integration interventions	1 RCT / 1 poor[258] 1 Prospective case series / 1 poor[259-260]	• Some improvements in sensory problems in tx groups; however, poor quality studies limit conclusions • Strength of evidence for effect is insufficient
Auditory integration interventions	2 RCTs / 2 fair[261-262]	• Receptive or expressive language, cognitive skills, problem or adaptive behaviors did not improve significantly in the tx groups • Insufficient evidence to determine effects on language, adaptive behavior, and challenging behaviors
Music and play therapy interventions	1 RCT / 1 poor[123, 263]	• Significantly more joint attention following music therapy • Increased engagement during music therapy relative to play sessions • Insufficient evidence to determine effects on social skills outcomes
Varied allied health interventions	1 RCT / 1 poor[268] 1 Non-randomized controlled trial / 1 poor[266] 5 Prospective case series / 5 poor[264-265, 267, 269-270]	• Some improvements in sensory measures, language, social interaction, challenging behaviors with some therapies • Improvements in motor skills while wearing prism lenses • Improvements in feeding behaviors • Small gains in words read using colored overlays • Small, short term studies • Insufficient evidence to determine strength of the evidence

PECS=Picture Exchange Communication System; RCT=randomized controlled trial; RPMT= Responsive Education and Prelinguistic Milieu Training; tx=treatment

Allied health-additional studies. We found seven studies[264-270] addressing disparate additional allied health interventions. Insufficient evidence is available to assess these interventions, including animal-assisted occupational therapy, prism lenses, and systematic

feeding training.

Strength of evidence for allied health interventions. The strength of evidence for an effect of both sensory integration therapy and music therapy was insufficient, as there was only a single RCT of poor quality in each; while measurement of the effect of interest (i.e., sensory problems) was direct, there was unknown consistency (Table 35). Evidence was insufficient to assess the effects of auditory integration on language, based on few available RCTs, though their outcomes were consistent in finding no effect of treatment on language. Strength of evidence is also affected by imprecise measurement of outcomes, though measurement of the effect of the intervention was direct. Evidence was also insufficient to evaluate the effects of auditory integration on adaptive and challenging behavior outcomes. Strength of evidence for language interventions (specifically, PECS and RPMT) is low for language acquisition at this time, in part due to too few studies available. In particular, although short-term benefits are demonstrated in language acquisition they are not durable. With a wide range of interventions employed among other allied health interventions, all of poor quality, there is insufficient evidence to evaluate the relative effect of any of these interventions on targeted outcomes including adaptive behavior, sensory and motor skills, social skills, and language.

Effectiveness of CAM Interventions

Much of the CAM research (six studies[271-276]) meeting our inclusion criteria is preliminary (Table 36). Escalona and colleagues brief trial of massage therapy[275] suggests a potential role for massage in promoting sleep and behavioral improvement in children with ASD. The Silva qigong massage studies[273-274, 276] report improvements in sensory processing, including reducing aversion to touch, and gains in adaptive behavior; these studies also illustrate methodologic growth with a move to blinded assessments by teachers in addition to parent report and videotaping of selected treatment sessions to assess fidelity. Pilot studies of acupuncture suggest potential effects on language[271] and social skills[272] based on small sample sizes and treatment duration of six weeks[272] and nine months.[271]

Overall, diagnostic techniques and participant characteristics, including concomitant therapies, are poorly reported, though interventions are typically well-described. There was little consistency in outcome measures reported across studies, and most studies relied on parent report. While several RCTs are represented, randomization methods are generally not clearly described and sample sizes are small. Adverse effects were not explicitly assessed in any study. Further research in massage and acupuncture modalities will benefit from clearer description of participant characteristics and study methods.

Table 36. Synthesis of results of CAM studies

Intervention	Study design/ Quality	Key findings and Strength of Evidence
Massage	3 RCTs / 1 fair,[274] 1 poor[275-276] 1 Prospective case series / 1 poor[273]	• Some improvements in sensory, adaptive behaviors, social skills, and language measures • Short term, small studies (mean 25 participants/study), largely employing parent reported outcome measures • Insufficient evidence to determine strength of the evidence

Table 36. Synthesis of results of CAM studies (continued)

Intervention	Study design/ Quality	Key findings and Strength of Evidence
Acupuncture	2 RCTs / 1 fair,[271] 1 poor[272]	• Small effects on language measured with unvalidated tools • Adverse effects not addressed • Insufficient evidence to determine strength of the evidence

RCT=randomized controlled trial

Strength of evidence. We found very few studies of complementary and alternative medicine, so evidence in this area also is insufficient to evaluate effects on outcomes assessed including sleep, language, social skills, sensory difficulties, and adaptive behavior (Table 36).

Assessment of Domains for Strength of Evidence

Table 37 documents assessments for each domain (risk of bias, consistency, directness, and precision) pertaining to strength of evidence for each of the major intervention-outcome combinations in this review. As noted in the EPC Methods Guidance, 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 one study is available. Directness is a reflection of the relationship between the intervention and the ultimate health outcome of interest. Precision is an assessment of certainty around the effect observed.

Table 37. Intervention, strength of evidence domains, and strength of evidence for key outcomes

Intervention	Domains Pertaining to Strength of Evidence (SOE):				SOE
	Risk of Bias	Consistency	Directness	Precision	
Adaptive behavior					
Behavioral, UCLA/Lovaas	Medium	Inconsistent	Direct	Precise	Moderate
Behavioral, ESDM	Medium	Inconsistent	Direct	Imprecise	Insufficient
Allied health, AIT	Medium	Consistent	Direct	Imprecise	Insufficient
Allied health,Other	*	Unknown (single studies)	*	*	Insufficient
CAM, Massage	High	Consistent	Indirect	Imprecise	Insufficient
Adverse events/harms					
Medical, Antipsychotics	Low	Consistent	Direct	Precise	High
Medical, SRIs	Medium	Inconsistent	Direct	Imprecise	Low
Medical, Stimulants	Medium	Consistent	Direct	Imprecise	Moderate
Medical, Guanfacine	High	Unknown (single study)	Indirect	Imprecise	Insufficient

Table 37. Intervention, SOE Domains, and SOE for Key Outcomes (continued)

Intervention	Domains Pertaining to Strength of Evidence (SOE):				SOE
	Risk of Bias	Consistency	Directness	Precision	
Anger					
Behavioral, CBT (commonly associated conditions)	Medium	Consistent	Direct	Precise	Moderate
Behavioral, Parent & teacher training (commonly associated conditions)	Medium	Consistent	Direct	Precise	Moderate
Anxiety					
Behavioral, CBT (commonly associated conditions)	Medium	Consistent	Direct	Precise	Moderate
Behavioral, Parent & teacher training (commonly associated conditions)	Medium	Consistent	Direct	Precise	Moderate
ASD symptom severity					
Behavioral, Lovaas	Medium	Inconsistent	Direct	Precise	Moderate
Behavioral, ESDM	Medium	Inconsistent	Direct	Imprecise	Insufficient
Behavioral, Other--Neurofeedback	High	Consistent	Indirect	Imprecise	Insufficient
Medical, Secretin	Low	Consistent	Direct	Precise	High (lack of effectiveness)
Medical, Dietary & other	High	Inconsistent	Direct	Imprecise	Insufficient
Educational					
Behavioral, UCLA/Lovaas	Medium	Inconsistent	Direct	Precise	Moderate
Educational, Broad-based	High	Inconsistent	Direct	Imprecise	Low
Hyperactivity/inattention					
Medical, Stimulants	Medium	Consistent	Direct	Imprecise	Moderate
Medical, Guanfacine	High	Unknown (single study)	Indirect (retrospective)	Imprecise	Insufficient
IQ/cognitive					
Behavioral, UCLA/Lovaas	Medium	Inconsistent	Direct	Precise	Moderate
Behavioral, ESDM	Medium	Inconsistent	Direct	Imprecise	Insufficient
Educational, TEACCH	Medium	Consistent	Direct	Imprecise	Moderate
Educational, Broad-based	High	Inconsistent	Direct	Imprecise	Low
Medical, Secretin	Low	Consistent	Direct	Precise	High (lack of effectiveness)
Allied health, AIT	Medium	Consistent	Direct	Imprecise	Insufficient
Joint attention					
Behavioral, Joint attention/symbolic play (play/interaction based)	High	Consistent	Direct	Precise	Low

Table 37. Intervention, SOE Domains, and SOE for Key Outcomes (continued)

Intervention	Domains Pertaining to Strength of Evidence (SOE):				SOE
	Risk of Bias	Consistency	Directness	Precision	
Language/communication					
Behavioral, UCLA/Lovaas	Medium	Consistent	Direct	Precise	High
Behavioral, ESDM	Medium	Inconsistent	Direct	Imprecise	Insufficient
Behavioral, Parent training (early intensive behavioral)	High	Inconsistent	Direct	Precise	Low
Educational, TEACCH	Medium	Consistent	Direct	Imprecise	Moderate
Educational, Broad-based	High	Inconsistent	Direct	Imprecise	Low
Educational, Computer-based	*	Unknown (single studies)	*	*	Insufficient
Medical, Secretin	Low	Consistent	Direct	Precise	High (lack of effectiveness)
Medical, Dietary & other	High	Inconsistent	Mixed (some direct, some indirect)	Imprecise	Insufficient
Allied health, Auditory integration	Medium	Consistent	Direct	Imprecise	Insufficient
Allied health, PECS/RPMT	Medium	Consistent	Indirect	Imprecise	Low
Allied health,Other	*	Unknown (single studies)	*	*	Insufficient
CAM, Acupuncture	High	Consistent	Indirect	Imprecise	Insufficient
Motor/sensory					
Allied health, Sensory integration	High	Unknown (single study)	Direct	Precise	Insufficient
Allied health,Other	*	Unknown (single studies)	*	*	Insufficient
CAM, Massage	High	Consistent	Indirect	Imprecise	Insufficient
Challenging behavior					
Behavioral, Parent-focused (play/interaction-based)	High	Inconsistent	Indirect	Imprecise	Low
Behavioral, CBT (commonly associated conditions)	Medium	Consistent	Direct	Precise	Moderate
Behavioral, Parent & teacher training (commonly associated conditions)	Medium	Consistent	Direct	Precise	Moderate
Behavioral, Other--Sleep	High	Unknown (single study)	Indirect	Imprecise	Insufficient
Medical, Antipsychotics	Low	Consistent	Direct	Precise	High
Medical, SRIs	High	Consistent	Direct	Imprecise	Low
Medical, Dietary & other	High	Inconsistent	Mixed (some direct, some indirect)	Imprecise	Insufficient
Allied health, AIT	Medium	Consistent	Direct	Imprecise	Insufficient

Table 37. Intervention, SOE Domains, and SOE for Key Outcomes (continued)

Intervention	Domains Pertaining to Strength of Evidence (SOE):				SOE
	Risk of Bias	Consistency	Directness	Precision	
Repetitive behavior					
Behavioral, Parent training (early intensive behavioral)	High	Inconsistent	Indirect	Unknown	Low
Behavioral, Other--Sleep	High	Unknown (single study)	Indirect	Imprecise	Insufficient
Medical, Antipsychotics	Low	Consistent	Direct	Precise	High
Medical, SRIs	Medium	Inconsistent	Direct	Imprecise	Low
Sleep					
Behavioral, Other--Sleep	High	Unknown (single study)	Indirect	Imprecise	Insufficient
Medical, Dietary & other	High	Inconsistent	Indirect	Imprecise	Insufficient
CAM, Massage	High	Consistent	Indirect	Imprecise	Insufficient
Social skills/social behaviors					
Behavioral, Parent training (early intensive behavioral)	High	Inconsistent	Indirect	Imprecise	Low
Behavioral, Social skills	Medium	Inconsistent	Direct	Imprecise	Low
Behavioral, Imitation (play/interaction based)	High	Consistent	Direct	Precise	Low
Behavioral, Relationship-focused (play/interaction-based)	*	Unknown (single studies)	*	*	Insufficient
Educational, Broad-based	High	Inconsistent	Direct	Imprecise	Low
Medical, Secretin	Low	Consistent	Direct	Precise	High (lack of effective-ness)
Allied health, Music therapy	High	Unknown (single study)	Indirect	Imprecise	Insufficient
Allied health,Other	*	Unknown (single studies)	*	*	Insufficient
CAM, Acupuncture	High	Consistent	Indirect	Imprecise	Insufficient

*Insufficient number of studies to determine; AIT=auditory integration therapy; CAM=complementary and alternative medicine; CBT=cognitive behavioral therapy; ESDM=Early Start Denver Model; PECS=Picture Exchange Communication System; RPMT= Responsive Education and Prelinguistic Milieu Teaching SRI=serotonin reuptake inhibitor; TEACCH=Treatment and Education of Autistic and Communication-related Handicapped Children; UCLA=University of California, Los Angeles

KQ2: Modifiers of Treatment Outcomes

Understanding what characteristics of young children with autism (i.e., specific ASD related difficulties and skills), treatments (e.g., type, duration, intensity), and aspects of larger systems (e.g. family, community) influence response to treatments is important to match individual children to optimal treatment modalities and for assessing applicability of existing research. However, few of the reviewed articles assess moderating characteristics and even fewer conducted analyses to determine whether measures of such characteristics account for individual variability in outcome. This is particularly important given that heterogeneity in outcome is common.

The most commonly noted characteristics as potential modifiers in the study of behavioral interventions are treatment intensity and approach (e.g. parent-led versus clinician-led) as well as baseline measures of child characteristics, including IQ, language and verbal skills and severity of the autistic disorder. No studies were available to explicitly examine the impact of training or experience of the individual providing the intervention.

Several investigations have noted that pretreatment IQ and language predicts IQ at follow-up in EIBI/ABA studies.[18-22] However, other studies have suggested having a lower IQ at initiation of treatment is related to increased change in IQ over time [23] or failed to find a relationship between IQ and change in response to intervention.[24-26] IQ and verbal ability also predict treatment outcomes in educational interventions. Baseline language/communication skills may also correlate with treatment success, with studies generally suggesting a benefit for communication skills, including changes in ASD classification associated with baseline language skills in an ABA approach.[21, 24] Similarly, social skills studies have found verbal skills, either verbal comprehension (using the Verbal Comprehension Index) or expressive communication skills to be associated with greater improvements in social skills.

Data on the degree to which earlier age of treatment initiation is associated with better outcomes with EIBI/ABA is conflicting; studies suggesting a preference for early intervention may be confounded by type of treatment.[27]

Finally, there is some evidence that specific constellations of symptoms related to ASD may be important in understanding response to treatment. Social responsiveness and imitation skills have been suggested as skills that may predict improved treatment response in EIBI/ABA treatment,[18] whereas 'aloof' subtypes of ASD have been suggested to be associated with less robust changes in IQ,[135] and lower baseline symptom tallies have also been related to specific gains.[19] Other studies have seen specific improvement in EIBI/ABA for children with PDD-NOS vs. Autistic Disorder diagnoses,[4] which may be indicative of baseline symptom differences. However, many other studies have failed to find a relationship between autism symptoms and treatment response.

In the medical literature, some characteristics of the family and child were found to be useful in predicting treatment success, including a history of psychiatric diagnoses in the family, early verbal skills in the child,[11] and, potentially, genotype for predicting lack of treatment response.[12] Several studies of stimulant use highlighted differences in effectiveness by diagnosis type[13-17] finding that children with Asperger syndrome were typically more responsive to psychostimulant treatment than those with autistic disorder. The presence of co-morbid intellectual disability was associated with lower treatment response in one study.[17]

KQ3: Early Results in the Treatment Phase That Predict Outcomes

Information about early response to treatment, or lack thereof, could guide treatment selection, implementation, and modification. The reviewed literature offers almost no information about what specific observations of children that might be made early in treatment to predict long-terms outcome and response. There is some evidence that early response to both EIBI/ABA and ESDM intervention in terms of changes in IQ over the first year of treatment predicts, or accounts for, longer-term change in IQ.[18, 29] However, findings also suggest that while gains in the cognitive domain might be accounted for primarily within the first year of

treatment, changes in adaptive behavior in response to these same interventions may occur over a longer time frame[18, 29-31] if they occur at all.[32]

KQ4: End of Treatment Effects That Predict Outcomes

No studies analyzed the ability of end of treatment outcomes to predict longer term functional outcomes in children.

KQ5: Generalization of Treatment Effects

Few studies included in this review explicitly measured generalization of effects seen in treatment conditions to either different conditions or locations. The majority of studies in the behavioral interventions targeting associated conditions did not measure outcomes in the treatment context (i.e., within therapy sessions or groups). Outcomes were primarily assessed using parent, self, and/or teacher report of targeted symptoms (e.g., anxiety, externalizing behaviors) at home, at school, and in the community, suggesting that those interventions conducted in a clinical setting for which measured outcomes were positive may generalize in the sense that they achieve outcomes in the "natural setting" of the child. On the other hand, in most cases, these outcomes are parent reported and not confirmed with direct observation. Behavioral intervention studies uniformly failed to measure outcomes beyond the intervention period, and therefore, we cannot assume that effects are maintained over time.

For medical studies, data across classes of medications are likely to be transferable outside of the clinic setting, primarily because the outcome measures used in these studies rely on parent report of the subjects' behavior in the home and other settings and are augmented in some studies by teacher report. In terms of longer-term response to treatment, the case series data for risperidone are consistent with the improvements seen in the RCTs, with support for continued improvements extending to 6 months and beyond, but also with evidence of continued side effects.[33-37]

KQ6: Drivers of Treatment Effects

No studies were identified to answer this question.

KQ7: Treatment Approaches in Children under Age Two at Risk for ASD

Research on very young children is preliminary but promising, with only four studies identified in our review.[8, 29, 145, 149] One was a fair quality study[29] that suggested benefit for the use of ESDM in young children, with diagnostic shifts in close to 30 percent of children (but still on the autism spectrum) and improvements in adaptive behavior. The observed diagnostic shifts, however, were not associated with clinically significant improvements in terms of ADOS severity scores or other measures. There is a critical need for the development of interventions directed to toddlers that takes into account the diagnostic uncertainty at this age. Therefore, we considered the strength of evidence in this area currently insufficient, pending additional data.

Quality Considerations

To better understand methodologic challenges facing the field of autism research as a whole, we analyzed the distribution of quality scores for the medical and behavioral (including educational studies). Studies in other categories were too few in number to do this analysis.

Just over half (60 percent behavioral; 66 percent medical) did employ a group design (i.e., included a comparison group); of the group design studies, 60 percent of behavioral and 92 percent of medical studies were randomized. Although almost all (89 percent behavioral; 100 percent medical) adequately described their intervention, few (30 percent behavioral; 37 percent medical) provided any measure of fidelity or adherence. Only 24 percent of behavioral studies reported differences in or held steady concomitant interventions that might have served as confounders of the observed effect. Outcome measures were almost always valid (93 percent behavioral; 92 percent medical); 24 percent of behavioral studies reported outcomes coded by individuals blinded to the intervention status, compared with 63 percent of medical studies.

Of particular note in the quality assessment is lack of adequate characterization of participant populations. Fewer than 20 percent of behavioral studies and only 33 percent of medical studies reported using a combination of clinical DSM-IV with the ADOS and/or ADI-R to diagnose or confirm diagnoses of ASD. Almost 40 percent of behavioral studies either did not use or did not report use of the DSM-IV or ADOS. Analytic approaches were problematic with 56 percent of behavioral and 71 percent of medical studies conducting using appropriate statistical approaches. Quality scores for each study in this report are presented in Appendix H.

Applicability

By definition, autism spectrum disorders are heterogeneous. Characterizing a "typical" child with an ASD is not possible, although certain symptoms are central to the range of disorders on the spectrum. Individual therapies are developed and tested to ameliorate specific symptoms or groups of symptoms, often in a fairly circumscribed subset of children, but because the conditions are often truly pervasive, finding outcome measures that capture overall improvement as well as change on individual factors is challenging. Ideally, research on therapies for ASD should target children most likely to benefit from a particular focus; thus details on the PICOTS for each intervention category are provided in Appendix I to support translation of our findings and assessment of the applicability of each for differing circumstances and children.

Furthermore, although interim, clinically based improvement is important, longer term functional outcomes are the goal for autism therapy. We calculated the proportion of studies that provided measures of outcomes obtained outside of a clinical environment (e.g. in the home or school); 70 percent of behavioral studies and 40 percent of medical studies did so. In terms of follow-up for assessing durability of effects, 17 percent of behavioral and 5 percent of medical studies report on outcomes collected at least 3 months after treatment ended. Additional research is needed on the degree to which changes observed in clinical settings translate to functional outcomes in children's natural environment and over time.

Behavioral Interventions

Studies of ABA-based interventions were conducted primarily in preschool children (i.e. typically children from ages 2-7) and as such questions of how such approaches apply to and

benefit younger children with (≤ 2) or at-risk for ASD remain. The cognitive, language, and adaptive behavior profiles of participants included in these studies were generally in line with those seen in the community (i.e., typically marked by substantial impairment/delay, but with some children with more intact early cognitive/language profiles).

The range of approaches studied, however, may not always match exactly what is available in practice. That is, the studies were often either conducted in highly controlled environments (e.g., university supported intervention trials) or in environments where it might not be easy to infer the actual methodology or driving mechanisms of the interventions themselves (i.e., non-manualized approaches). Thus, individuals wishing to infer the potential results of clinical practice based on the available research need to assess carefully the degree to which the study methods matched those available and used in practice. Two of the primary intensive behavioral intervention programs (UCLA/Lovaas and ESDM) publish and/or employ manuals for intervention, but implementing them requires sophisticated training and oversight that will continue to make translation to common practice difficult.

Studies of parent training interventions for preschool children, often with an ABA-based approach, aligned with current practice and the target populations that are typically referred for these services. Training programs often included components to improve social communication skills such as joint attention, play-based interactions, and pragmatic language approaches; interventions were conducted for approximately 1-4 hours/week with parents asked to introduce learned techniques within natural settings. Several programs offer manualized versions of training that can be adopted in other settings with appropriate training.

Most studies of social skills interventions targeted elementary school aged children (between 6 and 13 years old). Only one study targeted younger children (4 to 6 years old); although such interventions may be important in this younger age group. Most also excluded children with IQs below 60 and 6 of the studies targeted children with high functioning ASD or who were diagnosed with Asperger disorder only. Therefore, evidence on social skills interventions is likely applicable to older, higher functioning children only. Similarly, CBT for commonly associated conditions was targeted toward older children who were high-functioning, some with Asperger disorder only or excluded those with intellectual disabilities. The effectiveness of both of these types of interventions in other groups of children with ASD is currently unknown.

Studies of play-based interventions were generally conducted in children whose ages ranged from 3 to 12 years and were conducted in clinic settings; further research is needed to assess the utility of these approaches outside of the clinic environment.

Medical Interventions

In the medical literature, study participants were generally recruited from non-primary care populations that may not represent wider populations of children with ASD because they may be seeking a higher level of care 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. Some studies also expanded their inclusion criteria to include children with Asperger syndrome or PDD-NOS.

For some medications, age could be an important modifier of treatment, which should be considered in future studies. As one example, SRIs were reported to be helpful for repetitive

behaviors in adults in a previous RCT, but more recent data in children shows less clear evidence for benefit.

In addition to the limitations of the actual populations studied, some characteristics of the family and child were found to be useful in predicting treatment success within individual studies as noted in the discussion on modifiers. These might be helpful in determining the degree to which research on a given medical intervention is applicable to a given child. These include family history, cognitive profile, and, potentially, genotype, for predicting treatment response. Specific diagnosis within the autism spectrum could also be a modifier, with studies of psychostimulant medications suggesting better response in children with Asperger syndrome than other ASDs.

Review of Systematic Reviews

Because we limited our review to studies published after the year 2000, we reviewed existing systematic review literature so as not to lose important information published previously. Our findings in the current review concur with findings in the previously available reviews in that some evidence supports effectiveness of early intervention approaches and interventions such as CBT.

Most of the reviews generally concluded that the evidence base for EIBI is inadequate, noting variability in treatment and intervention, limited follow-up, lack of comparative studies, need for replication, and unclear inclusion and exclusion criteria.[46, 285-286] Meta-analyses from Reichow[287] and Eldevik,[288] reported more positive results, noting strong evidence for EIBI's effects in some children.[287-288] Eldevik's meta analysis of nine studies found an average large effect size for IQ change (1.103, 95 percent CI [CI=.871, 1.335]) and medium effect size for change on the VABS composite score (.660, 95 percent CI [CI=.41, .90]). The meta-analysis from Reichow and Wolery,[287] including studies exclusively based on Lovaas' treatment manuals or replicating the UCLA/Lovaas model and computing mean effect size based on change in the EIBI group only, also reported a large effect size of .69 for IQ change and mean difference effect sizes suggesting greater gains for children receiving EIBI compared with those receiving minimal behavioral intervention, usual treatment, or eclectic treatment. Each of these reviews, however, notes significant concerns about the included studies, such as limited accounting for the effects of maturity, lack of equivalent groups, uncertain treatment fidelity, and small sample sizes. Several authors also noted the need for studies comparing EIBI to other approaches that have been similarly empirically tested.

Across all the reviews, areas noted for improvement in the literature included the need for more RCTs, though investigators acknowledge the difficulty of conducting RCTs with interventions of such complexity and ethical issues of withholding treatment for comparison purposes. Additional areas for improvement noted in reviews included the need for larger sample sizes; longer follow-up to allow for evaluation of the durability of effects; greater treatment fidelity; improved reporting of methodological and participant characteristics; and greater consistency in treatment approaches and outcomes measurement.

In terms of the quality of the reviews themselves, we assessed the reviews to be of generally good quality, though some elements of reporting were inconsistent across reviews. For example, few reviews[46, 285, 289-290] explicitly reported author conflicts of interest, though, for example, investigators in one meta-analysis were authors of papers included in the analysis. Use of an *a priori* design was not always clearly stated though generally implied, and we considered review

designs *a priori* if a standardized approach appeared to be employed. Similarly, methods for reviewing abstracts and the full papers of studies were not always clearly described (e.g. use of dual reviewers), and six out of 10 reviews provided a complete (ample enough to likely permit replication) description of search terminology.[285-286, 289-292] Appendix G presents more information on our assessment of recent reviews.

Future Research

State of the Literature

Research on treatment approaches for autism has emerged primarily in the past two decades, and we focused our review on the last decade. Like any young research field, the body of evidence on therapies to treat core and concomitant symptoms of autism is characterized by a predominance of small studies with no comparison groups, a smaller set of nonrandomized cohort studies, and a very small set of RCTs. Only 13 of 149 of the studies were rated as good, although we see a clear evolution in the field toward greater rigor. Within our review, studies of medical interventions were more likely to be rated of higher quality; although our decision to require a higher number of subjects (30) in studies of medical interventions may have contributed to this difference.

Gaps in Areas of Research

Several treatment approaches show promise in early research, but remain understudied in more rigorous designs. In the behavioral literature, these include ABA-based EIBI interventions[4, 18, 25-26, 31-32, 133, 293] (e.g. UCLA/Lovaas model and variants), the Early Start Denver Model,[29], and parent trainings (e.g. PRT, More than Words,[8] Early Social Interaction,[145] etc.). In the medical literature, these include cyproheptadine,[218] omega 3 fatty acids,[240] melatonin,[238] L-carnosine,[241] and piracetam.[245]

Data on modifiers of effectiveness even in those interventions with good evidence is a promising field of study, and preliminary data suggest that some interventions, including intensive behavioral interventions, are likely to be most effective when targeted to yet undefined subgroups of children. Early research suggests child characteristics, such as baseline cognitive, language, and adaptive skill, may modify aspects of treatment outcome; however, such broad assessment characteristics to date have provided limited information in making predictions of what treatments will work best for individual children (i.e., some children with similar profiles related to these characteristics show varied responses). Specifically, there is promise for research focusing on identifying additional characteristics, such as pharmacogenetic questions as well as biological and genetic modifiers of effectiveness of non-medical interventions, that might be useful in personalizing treatment approaches.

Behavioral interventions are by their nature often multi-component, and data on whether specific functional components of the interventions drive effectiveness are currently unavailable. Component analyses in this field would be productive for refinement of intervention approaches and for assessing applicability and generalizability of the results.

Along those lines, we found few studies providing specific evidence of the generalization of interventions (the maintenance of effects when factors such as the setting, individual providing the intervention, or situational factors are changed). It is essential for families of children with

autism to understand the degree to which intervention effects observed in a clinical setting are likely to translate to functional behavior changes in their child's natural setting.

Further, as proposed treatments methods often rely heavily upon parents as coordinating influences and/or primary interventionists, examination of the characteristics of families that modify treatment appears another area for potential examination.

In the social skills literature, we identified several studies[156-157, 161, 163-164, 166] that were the first report of the particular intervention and these are candidates for replication. Most focused on group interventions and more consideration of the potential for family oriented or individual intervention is warranted. This literature overall focuses almost entirely on high functioning children with ASD, and it would be helpful to consider whether social skill interventions have potential for a broader range of individuals. There was also a tendency in this area to focus on intermediate outcomes (e.g. recognition of facial expressions) with little information on whether these translate to longer term functional outcomes.

The intensity of the treatment process and the diverse needs of children with autism point to a substantial need for health services research on accessibility and feasibility of providing effective interventions to enough children to meet the need that is present and growing. A few studies in this literature made preliminary strides in addressing these issues, but studies that specifically measure the role of setting, provider and other factors would strongly benefit our ability to inform implementation practices. In line with this need, we recommend future consideration of the ways in which the cultural context of the child and family may affect applicability or effectiveness of specific interventions.

In the medical literature, there is a need for properly-designed, appropriately-powered randomized, controlled trials of a number of interventions that have been inadequately studied to date. Some of the strongest studies 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 has also funded some large-scale studies of a few medical interventions, but publicly funded studies of medications for ASD are few and more are warranted.

Importantly, the marked improvements in challenging behaviors seen with risperidone and aripiprazole support the study of other atypical antipsychotic medications that do not cause as much weight gain or liability to metabolic disorders. Additionally, medications for hyperactivity and inattention symptoms deserve further scrutiny in autism. Dosing information remains inadequate in the stimulant literature and is particularly important for balancing positive outcomes with potential harms. The data on serotonin reuptake inhibitors are scattered and contradictory, with a particular need to consider modifiers such as age (childhood versus adult, see Posey et al.[294] and pharmacogenetics.[12] The largest published trial of an SRI, citalopram, found no effect at all on repetitive or compulsive behavior but found a possible effect on challenging behavior (ABC-C-I) that warrants follow up in a study with challenging behavior as a focus.[223] A number of other medical interventions are worthy of further study, including hyperbaric oxygen,[246] which was studied in a single RCT by providers with a significant conflict of interest.

In addition to the need for further study of interventions with some existing research, there is a tremendous need for research on medical interventions with no existing research.[295] Clinicians who employ medical interventions without an existing research base are encouraged to publish case series data to allow researchers to evaluate which treatments are worth studying in RCTs.

Given that behavioral interventions are the mainstays of autism treatment, studies examining the effects of coupling medical and behavioral interventions are crucial to match the typical experience of most children with ASD. Emerging data in other arenas, including anxiety and mood disorders, suggests that medications and behavioral treatments may act in synergy to produce benefit, including studies on SRIs and cognitive-behavioral therapy,[282-284] as well as recent studies on the use of cognitive enhancers to potentiate cognitive behavioral therapy.[296]

Methodologic Issues

A high proportion of studies in this review (38 percent) fail to use a comparison group, and while substantial strides have been made in the analysis of single subject designs, measurement of efficacy and effectiveness requires group studies. Nonetheless, even in group design studies, sample size of the current research is frequently insufficient to draw conclusions, and larger, multisite trials are needed across all treatment modalities. There also was a strong tendency for authors to present data on numerous outcomes without adjusting for multiple comparisons, and to fail to report the outcome that was the primary outcome of *a priori* interest and on which sample size calculations were based (when they were present). This may suggest a level of publication bias in which results are published on a select group of outcomes that show the most effect. We attempted, but were unable, to identify a clear primary intended outcome in almost all of the papers.

We encourage investigators to provide adequate detail as they describe their interventions to allow for replicable research. In ideal circumstances, manuals are published and referenced, but many studies made general references to their use of an underlying approach (e.g., ABA) without specifying the ways in which they used the technique or modifications they made to the original, published use of it.

Characterization of the study population was often inadequate, with 114 of 149 studies failing to use or report "gold standard" diagnostic measures (clinical DSM-IV-based diagnosis plus ADI-R and/or ADOS) for the participants. Because ASD is a spectrum disorder, it is difficult to assess the applicability of interventions when the population in which they were studied is poorly defined or described. Authors often do not consider diagnostic criteria in selecting participants for their studies; nor do they fully describe the children who do participate. Perhaps more importantly, because the myriad causes of ASD are unknown, even children with the same diagnosis may have distinct genetic or other “causes” that could affect treatment effectiveness. It will be critical for future research to better characterize participants, ideally from both genotypic and phenotypic bases.

Similarly, the choice of comparison groups in the studies that employed group design was uneven. A number of studies used comparison groups that were clearly inappropriate for observing group differences in treatment effect (e.g., comparing treatment in children with autism to typically developing peers or to children with a different developmental disorder), and for those studies we could only use the pre-post case series data available in the group with autism, limiting the ability to comment on effectiveness.

We identified more than 100 distinct outcome measures used in this literature base, not accounting for subscales of many of these. The use of so many and such disparate outcome measures makes it nearly impossible to synthesize the effectiveness of the interventions, and some consensus is necessary in the field to move comparative effectiveness research forward, and to provide a sense of expected outcomes of the interventions. At the same time, the means

for assessing outcomes should include increased focus on use of observers or reporters masked to the intervention status of the participant, and where some outcomes are measured in a masked fashion but others not, more emphasis should be placed on those that are.

Duration of treatment and follow up was generally short, with few studies providing data on long term outcomes after cessation of treatment. Future studies should extend the follow up period and assess the degree to which outcomes are durable. Few studies adequately accounted for concomitant interventions that might confound observed effectiveness and this should be standardized in future research.

Conclusions

The literature regarding therapies for children with autism spectrum disorders is of highly variable quality and in many specific areas sparse and inconclusive. A few conclusions can be drawn, however. In the behavioral literature, there is some evidence to support early and intensive behavioral intervention, including three randomized studies of intensive (i.e., interventions provided >30 hours per week) and comprehensive (i.e., addressing numerous areas of functioning) approaches. These included two UCLA/Lovaas focused approaches and one developmentally focused ESDM approach. Both approaches demonstrated greater improvements in cognitive performance, language skills, and adaptive behavior skills when compared with broadly defined eclectic treatments, in subgroups of children.

At present, these approaches have demonstrated effect when implemented by professionals, parents, and combinations thereof. Not all children receiving such interventions (most specifically the UCLA/Lovaas method) demonstrate rapid gains, with some available data suggesting that many children will continue to display prominent areas of impairment[4] and that subgroups may account for a majority of change within certain samples. There are no studies directly comparing effects of different treatment approaches (for example, no direct comparison of UCLA/Lovaas and ESDM) and little evidence of practical effectiveness or feasibility beyond research studies, so questions remain about whether reported findings would be observed on a larger scale within communities. Furthermore, the studies conducted have used small samples, drastically different treatment approaches and duration and different outcome measurements. Nonetheless, improvements occur in some aspects of language, cognitive ability, adaptive behavior, challenging behaviors and potentially improved educational attainment for some children.

Strength of evidence is low for the effects of social skills training for older children or play and interaction-based approaches for younger children. Cognitive behavioral therapy for associated conditions such as anxiety also has moderate strength of evidence supporting positive outcomes, with outcomes almost always reported by parents.

There is moderate strength of evidence for improvements in cognitive outcomes with educational interventions, particularly the TEACCH intervention and broad-based approaches based on ABA principles.

Evidence was insufficient at this time to support the use of sensory or auditory integration or complementary and alternative medicine approaches and low to speech and language interventions

It seems likely based on preliminary evidence that subgroups of children are more amenable to many of the interventions available. These include, potentially, groups defined by initial IQ, language and verbal skills as well as severity of the ASD for both medical and behavioral

interventions. Current evidence is insufficient, however, to adequately identify and target children most likely to benefit from specific interventions.

Data are similarly lacking for information about early changes in the treatment phase that could predict successful outcomes, end of treatment outcomes that predict later, functional success, or the generalizability of outcomes beyond the treatment setting. Some very early research on interventions for young toddlers (less than 2 years of age) is promising, but preliminary and challenged by the uncertainty of diagnoses at this age.

A few medications show benefit for repetitive behaviors or associated symptoms, with the clearest evidence favoring risperidone and aripiprazole, both studied in RCTs and showing evidence of improvement in problem and repetitive behavior. Significant side 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

A few other medical interventions show some promise for future research, including stimulants for hyperactivity and SRIs. Others are clearly not efficacious and warrant no further study, including secretin and DMSA for chelation.

Importantly, the literature lacks comparisons of medical interventions with behavioral interventions and combinations of the two, 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,[282-284] but only two studies of adequate size have considered combination treatment with risperidone and behavioral treatment, and these studies lacked an arm that considered behavioral treatment alone, in addition to lacking a placebo control.

In sum, evidence to support therapies for children with autism is uneven, but the field is developing. There are substantial needs for continuing improvements in methodologic rigor in the field and for larger, potentially multi-site, studies of existing interventions that extend our current knowledge. In sum, research to support therapies for children with autism is sparse, with ranging strength of evidence, but the field is developing. The needs are substantial for continuing improvements in methodologic rigor in the field and for larger, multi-site studies of existing interventions that extend our current knowledge. Finally, better characterization, both phenotypically and genotypically, of children in these studies to target treatment plans better is imperative.

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List of Acronyms/Abbreviations

3TPRF	“The Three Things” Parent Rating Form
ABA	Applied Behavior Analysis
ABC	Aberrant Behavior Checklist
ABC-C	Aberrant Behavior Checklist-Community
ABC-C-H	Aberrant Behavior Checklist-Community Version Hyperactivity Subscale
ABC-C-I	Aberrant Behavior Checklist-Community-Irritability Subscale
ABC-C-S	Aberrant Behavior Checklist-Community-Stereotyped Behaviors Subscale
ABC-P	Aberrant Behavior Checklist-Parent
ABLLS	Assessment of Basic Language and Learning Skills
AD	Asperger Disorder
ADHD	Attention Deficit Hyperactivity Disorder
ADI	Autism Diagnostic Interview
ADI-R	Autism Diagnostic Interview-Revised
ADIS	Anxiety Disorders Interview Schedule
ADIS-C/P	Anxiety Disorders Interview Schedule-Child and Parent versions
ADOS	Autism Diagnostic Observation Schedule
ADOS-G	Autism Diagnostic Observation Schedule-Generic
ADOS-R	Autism Diagnostic Observation Schedule-Revised
AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
ADI-R	Autism Diagnostic Interview-Revised
AIT	Auditory Integration Training
APPEFE-PC	Assessment of Perception of Emotion from Facial Expression and from Posture Cues
AS	Asperger Syndrome
ASD	Autism Spectrum Disorders
ASIEP-2	Autism Screening Instrument for Educational Planning-Second Edition
ASQ	Autism Screening Questionnaire
ASSQ	Autism Spectrum Screening Questionnaire
ATEC	Autism Treatment Evaluation Checklist
atm	atmospheric pressure
AWP/C	Approach/Withdrawal Problems Composite (PDDBI subscale)
BARS	Barnes Akathisia Rating Scale
BAS	British Abilities Scale
BAS II	British Abilities Scales-Second Edition
BASC	Behavior Assessment System for Children
BASC-PRS	Behavior Assessment System for Children-Parent Rating Scales
BASC-TRS	Behavior Assessment System for children-Teacher Rating scales
BDI-Cognitive	Behavioral Descriptive Interviewing-Cognitive
BID	Twice a day
BPD	Bipolar Disorder
BPVS	British Picture Vocabulary Scale
BRIEF	Behavior Rating Inventory of Executive Function
BRS	Bayley Behavior Rating Scale

BSI	Behavior Symptoms Index subscale of the Behavior Assessment System for Children
BSID	Bayley Scales of Infant Development
BSID-II	Bayley Scales of Infant Development®-Second Edition
BSID-R	Bayley Scales of Infant Development-Revised (also BSID-II-Second Edition)
BSQ	Behavior Screening Questionnaire
C	Control Group
CABAS	Comprehensive Application of Behavior Analysis to Schooling
CAM	Complementary and Alternative Medicine
CARS	Childhood Autism Rating Scale
CAST	Childhood Asperger Syndrome Test
CATS	Children's Automatic Thoughts Scale
CBCL	Achenbach Childhood Behavior Checklist
CBRS	Child Behavior Rating Scale
CBT	Cognitive Behavioral Therapy
CCBSQ	Classroom Child Behavioral Symptoms Questionnaire
CCEI	Children’s Center for Early Intervention, Inc.
CCIF	Child and Caregiver Information Form
CDD	Childhood Disintegrative Disorder
CEBI	Children’s Eating Behavior Inventory
CELF-II	Clinical Evaluation of Language Fundamentals-Second Edition
CFT	Children’s Friendship Training
CGAS	Children's Global Assessment Scale
CGI	Clinical Global Impression Scale
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impressions-Severity
CHAT	Checklist of Autism in Toddlers
ChIA-P	Children's Inventory of Anger-Parent Form
CI	Confidence Interval
CINAHL	Cumulative Index of Nursing and Allied Health Literature
CPEP-R	Chinese Version of the PEP-R
CPM	Coloured Progressive Matrices
CPRS	Children’s Psychiatric Rating Scale
CPRS-R	Conners’ Parent Rating Scale-Revised
CRS-R	Conners' Rating Scales-Revised
CSBS	Communication and Symbolic Behaviour Scales
CSBS-DP	Communication and Symbolic Behavior Scales Developmental Profile
CSHQ	Children's Sleep Habits Questionnaire
CSR	Clinical Severity Rating Scale
CTS	Children’s Toddler School
CTSRQ	Classroom Teachers' Stress Reactions Questionnaire
CYBOCS	Child Yale Brown Obsessive Compulsive Scale
CYBOCS-PDD	Children’s Yale-Brown Obsessive Compulsive Scales-Pervasive Developmental Disorders
DANVA	Diagnostic Analysis of Non-Verbal Accuracy; short forms
DANVA2	Diagnostic Analysis of Nonverbal Accuracy2
DANVA-2-AF	Diagnostic Analysis of Non-Verbal Accuracy-2, Adult Facial Expressions

DAS	Differential Abilities Scale
DBC	Developmental Behavior Checklist
DF	Degrees of Freedom
DH	Donepezil hydrochloride
DIR	Developmental, Individual Differences, Relationship-based
DMSA	Dimercapto Succinic Acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition
DTG	Delayed Treatment Group
DTT	Discrete Trial Training
DTVP-II	Developmental Test of Visual Perception-Second Edition
EBASAS	Extended Basic Academic Skills Assessment System
ECBI	Eyberg Child Behavior Inventory
ECO	Early Childhood Outcomes
EEG	Electroencephalogram
EIBI	Early Intensive Behavioral Intervention
ELAP	Early Learning Accomplishments Profile
ELM	Early Language Milestone
EOWPVT	Expressive One-Word Picture Vocabulary Test
EOWPVT-R	Expressive One-Word Picture Vocabulary Test-Revised
EOWVT	Expressive One Word Vocabulary Test
EPC	Evidence-based Practice Center
EPS	EIBI Performance Scale
ERIC	Educational Research Information Clearinghouse
ERSSQ	Emotion Regulation and Social Skills Questionnaire
ESCS	Early Social Communication Scales
ESCSA	Early Social Communication Scales Assessment
ESDM	Early Start Denver Model
FEAS	Functional Emotional Assessment Scale
FH	Family history
FISH	Family Inventory of Sleep Habits
FSIQ	Full Scale Intelligence Quotient
GADS	Gilliam Asperger's Disorder Scale
GARS	Gilliam Autism Rating Scale
GARS-SI	Gilliam Autism Rating Scale-Social Interaction Subscale
GBRS	Global Behavior Rating Scale
GI	Gastrointestinal
GIFT	Group Intensive Family Training
GSQ	Gastrointestinal Symptoms Questionnaire
HAD	High-functioning Autistic Disorder (or HF-Autism)
HFA	High Functioning Autism
HFASD	High Functioning Autism Spectrum Disorder
HFASSQ	High Functioning Autism Spectrum Screening Questionnaire
HKBABS	Hong Kong Based Adaptive Behavioral Scales
HSQ	Home Situations Questionnaire
Hx	History

IBI	Intensive Behavioral Intervention
ID	Intellectual Disability
IGOH	Oral Human Immunoglobulin
IOWA	Iowa Social Competence Scales: Preschool form
IQ	Intelligence Quotient
ITG	Immediate Treatment Group
ITSEA	Infant Toddler Social Emotional Assessment
IV	Intravenous
JA	Joint Attention
JAFA	Joy and Fun Assessment
JDTP	Junior Detective Training Program
kg/d	kilograms per day
LAP-R	Learning Accomplishment of Profile-Revised
LIPS	Leiter International Performance Scale
LIPS-R	Leiter International Performance Scale-Revised
LOCF	Last observation carried forward
LUFAP	Lancashire Under Fives Autism Project
MAD	Major Affective Disorder
MASC	Multidimensional Anxiety Scale for Children
MBRS	Maternal Behavior Rating Scale
MCDI	Mac Arthur Communication Development Inventories
MCHAT	Modified Checklist for Autism in Toddlers
M-CIA	Mother-Child Interaction Assessment
M-COPM	Modified Canadian Occupational Performance Measure
MDI	Mental Development Index
Mdn	Median
MEU	Methylphenidate Equivalency Units
mg	milligrams
mg/kg/d	milligrams per kilogram per day
MGH	Massachusetts General Hospital
MGIS	Modified Global Impression Scale
MPH	Methlyphenidate
MPS	Merrill-Palmer Scale of Mental Tests
MSEL	Mullen Scales of Early Learning
MYAP	Multisite Young Autism Project
n, N	number
NC	Non-categorical
NCA	Non Core Autism (PDD-NOS or other early childhood developmental disorder such as specific language disorder)
NCBRF	Nisonger Child Behavior Rating Form
NCBRF-P	Nisonger Child Behavior Rating Form-Parent
NIDOCD	National Institute for Deafness and Other Communication Disorders
NMDA	N-methyl-D-aspartate
NR	Not reported
NRCT	Non randomized controlled trial

NS, ns	Not (statistically) Significant
NTG	No Treatment Group
NVDQ	Non-verbal Developmental Quotient
NVIQ	Non-Verbal IQ
OCD	Obsessive Compulsive Disorder
OT	Occupational Therapist
P	P value
PAQ	Parental Attribution Questionnaire
PBCL	Preschool Behavior Checklist
PCI	Proportional Change Index
PCIT	Parent Child Interaction Therapy
PCQ	Parental Concerns Questionnaire
PDD	Pervasive Developmental Disorder
PDDBI	Pervasive Development Disorder Behavior Inventory
PDD-BI	Pervasive Developmental Disorder-Behavior Inventory
PDD-NOS	Defining Pervasive Developmental Disorder-Not Otherwise Specified
PECS	Picture Exchange Communication Systems
PEI	Pupil Evaluation Inventory
PEP	Psycho-educational Profile
PEP-DQ	PsychoEducational Profile-Developmental Quotients
PEP-R	Psycho-educational Profile-Revised
PFQ	Parent Feelings Questionnaire
PHS	Piers-Harris Self-Concept Scale
PIAT-R	Peabody Individual Achievement Test-Revised
PIC	Personality Inventory for Children
PIC-2	Personality Inventory for Children II
PIQ	Performance IQ
PLS	Preschool Language Scale
PLS-3	Preschool Language Scale-3
PLS-III	Preschool Language Scale-Third Edition
PPVT	Peabody Picture Vocabulary Test (PPVT-III-Third Edition)
PRQ	Parent's Rating Questionnaire
PRT	Pivotal Response Training
PSI	Parenting Stress Index
PSI-III	Parenting Stress Index-Third Edition
PSI-SF	Parenting Stress Index-Short Form
PSOC	Parenting Sense of Competence Scale
PT	Parent Training
PTA	Parental Treatment Adherence
PUFA, PUFAs	Polyunsaturated Fatty Acids
PVCS	Pre-Verbal Communication Schedule
QD	Once a day
qEEG	Quantitative Electroencephalogram
QPQ	Quality of Play Questionnaire
QRS	Questionnaire on Resources and Stress

QRS-F	Friedrich Short-form of the Questionnaire on Resources and Stress
QST	Qigong Sensory Training
RAD	Reactive Attachment Disorder
RBS-R	Repetitive Behavior Scale-Revised
RC	Response-Cost
RCMAS	Revised Children's Manifest Anxiety Scale
RCT	Randomized Controlled Trial
RDLS	Reynell Developmental Language Scales
REXSCA/C	Receptive/Expressive Social Communication Abilities Composite (PDDBI subscale)
RLRS	Ritvo-Freeman Real Life Rating Scale
ROWPVT	Receptive One-Word Picture Vocabulary Test
RPMT	Responsive Education and Prelinguistic Milieu Teaching
RSI	Relative Strength Index
RUPP	Research Units on Pediatric Psychopharmacology
SAEC	Social Adjustment Enhancement Curriculum
SAS	Severity of Autism Scale
SOE	Strength of Evidence
S-B	Stanford-Binet
SBCQ	Self-report Social and Behavioral Communication Questionnaire
SB-FE	Stanford-Binet Intelligence Scale-Fourth Edition
SB-IV	Stanford Binet Intelligence Scale-Fourth Edition
SCARED	Screen for Child Anxiety and Related Emotional Disorders
SCAS	Spence Children's Anxiety Scale
SCDS	MGH YouthCare Social Competency/ Social Skill Development Scale
SCPQ-P	Social Competence with Peers Questionnaire-Parent
SCPQ-PU	Social Competence with Peers Questionnaire-Pupil
SCQ	Social Communication Questionnaire
SD	Standard Deviation
SDQ-Parent	Strengths and Difficulties Questionnaire-Parent Report
SDSC	Sleep Disturbance Scale for Children
SECA	Sensory Evaluation Form for Children with Autism
SEM	Standard Error of the Mean
SIB-R	Scales of Independent Behavior Revised
SIT	Sensory Integration Therapy
SLP	Student Learning Profile
SMS-SQ	Social Maturity Scale-Social Quotients
SORF	Systematic Observation of Red Flags
SOS	Secretion Outcome Survey
SP	Sensory Profile
SPA	Structured Play Assessment
SRI/SRIs	Serotonin Reuptake Inhibitors
SRS	Social Responsiveness Scale
Ss	Skillstreaming Survey
SSA	Special support assistants
SSC	Social Skills Checklist

SSQ	Social Skills Questionnaire
SSQ-P	Social Skills Questionnaire-Parent
SSRC	Sense and Self-Regulation Checklist
SRIs	Serotonin Reuptake Inhibitors
SSRS	Social Skills Rating System
SSRS-P	Social Skills Rating Scale-Parent Version
SSRS-T	Social Skills Rating Scale-Teacher Version
SST	Social Skills Training
STAT	Screening Tool for Autism in Two-Year-Olds
Stress- RS	Stress- Restraint Stress
SULP	Social Use of Language Programme
SWQ	Social Worries Questionnaire
SWQ-P	Social Worries Questionnaire-Parent
TABS	Temperament and Atypical Behavior Scale
TD	Treatment Difference
TEACCH	Treatment and Education of Autistic and Communication-related Handicapped Children
TEP	Technical Expert Panel
TID	Three times a day
TOM	Theory of Mind
TONI	Test of Non-Verbal Intelligence
TOPS	Test of Problem Solving
Tx, tx	treatment
UCLA	University of California Los Angeles
UK	United Kingdom
VABS	Vineland Adaptive Behavior Scale
VABS- Survey	Vineland Adaptive Behavior Scale-Survey Form
VABS-ABC	VABS adaptive behavior composite
VABS-CD	VABS communication domain
VABS-SD	VABS socialization domain
VCAA	Visuomotor Coordination Ability Assessment
VCI	Verbal Comprehension Index
VIQ	Verbal IQ
VR-TIS	Virtual Reality- Tangible Interaction System
WASI	Wechsler Abbreviated Scale of Intelligence
WIAT	Wechsler Individual Achievement Test
WISC-III	Wechsler Intelligence Scale for Children-III
WISC-R	Wechsler Intelligence Scale for Children-Revised
WMS	Walker-McConnell Scale of Social Competence and Social Adjustment
WPPSI-III/R	Wechsler Preschool and Primary Scale of Intelligence-Third Edition/ Revised
WPPSI-R	Wechsler Preschool and Primary Scale of Intelligence-Revised
WSQ	Wing Subgroups Questionnaire